

# Unusual Ligand Isomerization Dictated by Coordination Requirements of the Metal Ion: A Double-Bond Shift in Cu(II)-Assisted Template Condensation between Diacetylpyridine and a Tripodal Tetramine

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Received January 6, 1999

This paper reports a new effect in template-directed Schiff base condensation, a “fine-tuning” of the macrocyclic structure in accordance with the precise coordination requirements of the metal ion. The nature of the metal template determines the outcome of Schiff base condensation between a difunctional carbonyl component (2,6-diacetylpyridine) and a trifunctional amine component (tris(3-aminopropyl)amine, trpn). Both Cu(II) and Ni(II) facilitate [1 + 1] condensation with the formation of macrocyclic products in 50–60% yield, but single-crystal X-ray diffraction reveals that the chemical structure of the major product is metal-ion dependent. In the nickel(II) complex  $[\text{Ni}(\text{L}_{\text{sym}})]^{2+}$ , the C=N double bonds are conjugated with the pyridine ring, as expected from the structure of the starting diacetylpyridine. In contrast, the copper(II) ion caused isomerization of the macrocyclic ligand, with one of the C=N double bonds migrating into the initially saturated six-membered chelate ring forming  $[\text{Cu}(\text{L}_{\text{asym}})]^{2+}$ . The second product isolated, in small quantities, from the copper(II)-templated condensation has been characterized as an isomeric symmetric macrocycle  $[\text{Cu}(\text{L}_{\text{sym}})]^{2+}$ . In the case of the zinc(II) template, no macrocyclic product has been isolated; instead, a zinc(II) complex of the starting tetramine,  $\text{Zn}(\text{trpn})\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ , was recovered and structurally characterized. An unusual double-bond migration in the course of Cu(II)-directed template condensation is governed by the coordination requirements of the central metal ion. The asymmetric ligand isomer is more flexible than its symmetric counterpart and can therefore better accommodate the five-coordinate central metal ion. This effect is more pronounced for the copper(II) complex than for the nickel(II) complex, because of shorter in-plane M–N distances in the former, as follows from the X-ray structure determination. The position of the double bond in the macrocyclic ring influences the spectral properties of the copper(II) complexes and the ionization constants of the amino group in the side arm.

## Introduction

Template Schiff base condensations between dicarbonyl compounds and diamines are among the simplest and most popular methods for macrocycle synthesis. The size and preferred coordination geometry of the metal ion control the structure of the condensation products.<sup>1,2</sup> This effect is especially pronounced when rigid building blocks are used, and relatively rigid macrocycles are formed. In such cases conformational changes within the macrocyclic ligand are limited, and little adjustment of the coordination sphere geometry is possible. Examples of rigid, planar, conjugated dicarbonyl building blocks include 2,6-diacetyl- and 2,6-diformylpyridine. Indeed, both [1 + 1] and [2 + 2] condensations with diamines are well documented for pyridine-containing carbonyl compounds.<sup>3–6</sup>

The two possible product types ([1 + 1] and [2 + 2]) have dramatically different macrocyclic ring sizes, and preferential formation of one over the other is determined by the metal ion used. Another type of coordination geometry adjustment also found for pyridine-containing macrocycles involves a “ring contraction” rearrangement<sup>3,7–9</sup> of ligands with large ring sizes. These effects can be viewed as “coarse tuning” of the macrocycle structure by the template metal ions.

This paper reports a new effect in template-directed Schiff base condensation, a “fine-tuning” of the macrocyclic structure in accordance with the precise coordination requirements of the metal ion. We have demonstrated an unusual double-bond migration in the course of Cu(II)-directed template condensation between diacetylpyridine and tris(3-aminopropyl)amine (trpn), leading to the formation of an otherwise thermodynamically unfavorable ligand  $\text{L}_{\text{asym}}$  (Figure 1). X-ray structures of the asymmetric copper(II) complex  $[\text{Cu}(\text{L}_{\text{asym}})]^{2+}$ , the symmetric nickel(II) complex  $[\text{Ni}(\text{L}_{\text{sym}})]^{2+}$ , and the zinc(II) complex with the tripodal tetramine  $[\text{Zn}(\text{trpn})]^{2+}$  are reported. The position of the double bond in the macrocyclic ring influences the

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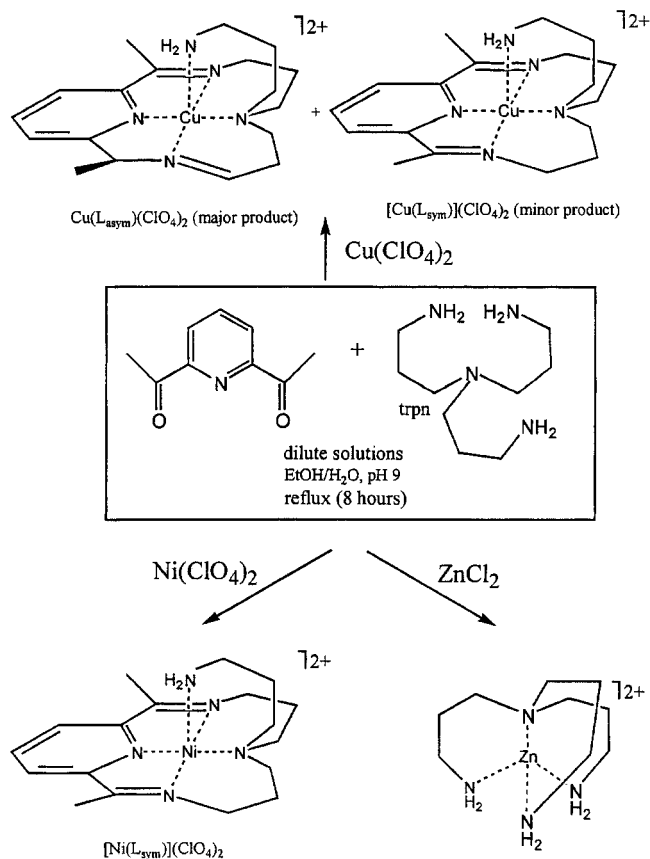
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**Figure 1.** Outcome of the template condensation between 2,6-diacetylpyridine and tris(3-aminopropyl)amine in the presence of different metal ions. Isolated products are shown.

spectral properties of the copper(II) complexes and the ionization constants of the amino group in the side arm.

### Experimental Section

The reagents were obtained from Aldrich, except for 2,6-diacetylpyridine (Fluka) and tris(3-aminopropyl)amine (Strem), and used as received.

**Template Condensation between 2,6-Diacetylpyridine and Tris(3-aminopropyl)amine (Trpn).** Trpn (1 mmol) was dissolved in 200 mL of water and mixed with a solution of 1 mmol of a metal salt ( $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ , or  $\text{ZnCl}_2$ ) in 50 mL of water. To the resulting solution (dark-blue for the copper salt, light-blue for the nickel salt, and colorless for the zinc salt) was added 1 mmol of 2,6-diacetylpyridine dissolved in 300 mL of ethanol over a period of 10 min. The mixture was stirred at reflux for 8 h, cooled to ambient temperature, and left overnight. During reflux, the color changed from blue to dark blue-violet in the case of copper(II) (some brown solid was also formed in this system) and from light blue to peach in the case of nickel(II); no color change was observed for the zinc complex, but the reaction mixture became slightly turbid.

**CAUTION!** Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with great caution.

**Isolation of Two Isomeric Copper Macrocycles,  $[\text{Cu}(\text{L}_{\text{sym}})](\text{ClO}_4)_2 \cdot 1.5\text{H}_2\text{O}$  and  $[\text{Cu}(\text{L}_{\text{asyim}})](\text{ClO}_4)_2$ .** The reaction mixture was filtered and rotary evaporated to about  $1/10$  of its initial volume. Upon cooling to room temperature, blue solid was deposited. It was filtered, washed with minimal amounts of cold water and cold ethanol, washed with ether, and then air-dried. The material (0.06 g, 10%) was purified by dissolution in a minimal amount (ca. 2 mL) of acetonitrile, removal of the undissolved brown and white impurities by filtration, and precipitation of the blue complex by slow addition of ethanol followed by slow partial evaporation of the solvents. The resulting material was isolated by suction filtration and characterized as  $[\text{Cu}(\text{L}_{\text{sym}})](\text{ClO}_4)_2 \cdot$

$1.5\text{H}_2\text{O}$ . Anal. Calcd for  $\text{C}_{18}\text{H}_{32}\text{N}_5\text{Cl}_2\text{O}_{9.5}\text{Cu}$ : C, 35.74; H, 5.33; N, 11.58. Found: C, 35.78; H, 5.03; N, 11.41. FAB MS (positive FAB in nitrobenzyl alcohol): 378 ( $\text{CuL}^+$ ), 477 ( $\text{CuLClO}_4^+$ ), isotopic pattern corresponds to the proposed formulation. IR (KBr disks): 1622, 1585  $\text{cm}^{-1}$ .

After removal of the blue solid from the original reaction mixture by filtration, the resulting solution was mixed with 5 mmol of  $\text{NaClO}_4$  dissolved in 5 mL of water. Slow evaporation of the solvent at ambient temperature and pressure produced a dark-blue crystalline compound, which was filtered, washed with a minimal amount of water, and dried in vacuo, yielding 0.30 g (52%) of the complex,  $[\text{Cu}(\text{L}_{\text{asyim}})](\text{ClO}_4)_2$ . Anal. Calcd for  $\text{C}_{18}\text{H}_{29}\text{N}_5\text{Cl}_2\text{O}_8\text{Cu}$ : C, 37.41; H, 5.06; N, 12.12. Found: C, 37.16; H, 5.07; N, 11.88. FAB MS (positive FAB in nitrobenzyl alcohol): 378 ( $\text{CuL}^+$ ), 477 ( $\text{CuLClO}_4^+$ ), isotopic pattern corresponds to the proposed formulation. IR (KBr disks): 1680, 1620, 1585  $\text{cm}^{-1}$ .

**Isolation of  $[\text{Ni}(\text{L}_{\text{sym}})](\text{ClO}_4)_2$ .** The reaction mixture obtained after Schiff base condensation was rotary evaporated to about 50 mL ( $1/10$  of its initial volume). Upon cooling, red microcrystalline material precipitated out of solution. It was filtered, washed with cold ethanol, and dried in the air. Sodium perchlorate (5 mmol) was added to the filtrate, and the filtrate was concentrated to a volume of 10 mL. The precipitate which formed was filtered, washed with cold ethanol, and air-dried. The two portions of the solid gave identical IR spectra, with absorptions at 1585 (s), 1621 (s), and 1665 (w)  $\text{cm}^{-1}$ , indicating preferential formation of the symmetric isomer, slightly contaminated with an asymmetric isomer. They were combined, and the complex was recrystallized from hot water, producing 0.34 g (60%) of dark-red needles. Anal. Calcd for  $\text{C}_{18}\text{H}_{29}\text{N}_5\text{Cl}_2\text{O}_8\text{Ni}$ : C, 37.73; H, 5.06; N, 12.22. Found: C, 37.63; H, 4.96; N, 12.18. FAB MS (positive FAB in nitrobenzyl alcohol or thioglycerol/glycerol): 373 ( $\text{NiL}^+$ ), 472 ( $\text{NiLClO}_4^+$ ). IR (KBr disks): 1621, 1585  $\text{cm}^{-1}$ .

**Isolation of  $[\text{Zn}(\text{trpn})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ .** The reaction mixture was filtered, rotary evaporated to a volume of 30 mL, and cooled in a refrigerator. The white microcrystalline product which precipitated was filtered off, washed with a minimal amount of water, and air-dried. Yield: 0.13 g (36%). Anal. Calcd for  $\text{C}_9\text{H}_{28}\text{N}_4\text{O}_2\text{Cl}_2\text{Zn}$ : C, 29.97; H, 7.83; N, 15.54. Found: C, 29.83; H, 7.93; N, 15.71. Attempts to isolate condensation products from the filtrate through addition of excess  $\text{NaClO}_4$  failed. FAB MS of the reaction mixture did not show any peak corresponding to the macrocyclic products.

**Potentiometric Measurements. Materials.** All aqueous solutions were prepared using deionized and distilled water. Stock solutions of the metal complexes (0.5 mM) were prepared with a background of 0.100 M  $\text{KNO}_3$ . The protonation constant of each complex's side arm was determined potentiometrically in a Metrohm jacketed glass reaction vessel, equipped with a magnetic stirrer and fitted with a Metrohm 6.0238.000 combination electrode filled with 3 M NaCl. Atmospheric  $\text{CO}_2$  was excluded from the potentiometric apparatus using a steady stream of nitrogen. The potential of the cell was measured with a Metrohm Titrino 736 titration system. The amount of carbonate present in the base and  $\text{pK}_w$  were calculated from titration of a strong acid ( $\text{HNO}_3$ ) with a strong base (KOH) according to Gran's method.<sup>10</sup> The  $\text{pK}_w$  of the solvent medium was found to be 13.65.

**Procedure.** To 10 mL of stock solution of complex were added 25 mL of  $\text{KNO}_3$  and 0.3 mL of  $\text{HNO}_3$  solution. The above mixture was titrated with KOH (0.1007 M). The titrations were carried out at  $25.0 \pm 0.1$  °C, and at least three independent titrations were performed for each complex. Direct titration of the complexes with acid was also done, producing the same results. Protonation constants were calculated by means of the pH-titration program BETA,<sup>11</sup> which is a nonlinear least squares refinement FORTRAN program based on the ORGLS subroutine.<sup>12,13</sup>

**X-ray Crystal Structure Analysis.** Crystal data and the most relevant experimental parameters for the three crystal structures (**I**,  $[\text{Ni}(\text{L}_{\text{sym}})](\text{ClO}_4)_2$ ; **II**,  $[\text{Cu}(\text{L}_{\text{asyim}})](\text{ClO}_4)_2 \cdot 0.5\text{H}_2\text{O}$ ; **III**,  $[\text{Zn}(\text{trpn})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ )

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**Table 1.** Crystal Data and Structure Refinement

	I	II	III
empirical formula	C <sub>18</sub> H <sub>29</sub> Cl <sub>2</sub> N <sub>5</sub> NiO <sub>8</sub>	C <sub>18</sub> H <sub>30</sub> Cl <sub>2</sub> Cu-N <sub>5</sub> O <sub>8.50</sub>	C <sub>9</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> Zn
fw	573.07	586.91	360.62
space group	P2 <sub>1</sub> /n	P2 <sub>1</sub> /c	P2 <sub>1</sub> /n
unit cell dimens			
<i>a</i> , Å	7.9599(17)	16.676(4)	8.290(2)
<i>b</i> , Å	15.620(3)	9.238(2)	12.650(3)
<i>c</i> , Å	19.695(3)	17.460(4)	15.690(3)
β, deg	100.439(17)	112.03(2)	99.22(3)
<i>V</i> , Å <sup>3</sup>	2408.3(8)	2493.4(10)	1624.1(6)
<i>Z</i>	4	4	4
ρ <sub>calcd</sub> , g cm <sup>-3</sup>	1.581	1.563	1.475
μ, mm <sup>-1</sup>	1.081	1.145	1.842
<i>F</i> (000)	1192	1216	760
indep reflns/parameters	4213/332	3315/361	2641/187
GOF on <i>F</i> <sup>2</sup>	1.040	1.011	0.997
final <i>R</i> indices [ <i>I</i> > 2σ( <i>I</i> )]	0.065	0.060	0.050

**Table 2.** Selected Bond Lengths (Å) and Angles (deg) for I–III

	I (M = Ni)	II (M = Cu)	III	
			Zn–N1	
M–N1	2.082(5)	2.061(6)	Zn–N1	1.993(5)
M–N2	1.958(5)	1.944(5)		
M–N3	2.056(5)	2.015(5)	Zn–N3	2.000(5)
M–N4	2.037(5)	1.993(5)	Zn–N4	2.098(4)
M–N5	2.054(5)	2.186(5)	Zn–N2	1.984(5)
N1–C9	1.296(8)	1.284(9)		
N1–C8	1.460(8)	1.438(9)		
N3–C3	1.465(7)	1.251(8)		
N3–C2	1.274(8)	1.486(9)		
N2–M–N4	171.2(2)	167.6(2)		
N2–M–N3	78.5(2)	79.1(2)		
N3–M–N4	100.7(2)	94.7(2)	N3–Zn–N4	97.2(2)
N2–M–N1	78.6(2)	78.7(2)		
N4–M–N1	100.0(2)	101.9(2)	N4–Zn–N1	99.87(19)
N3–M–N1	153.9(2)	146.6(2)	N3–Zn–N1	116.0(2)
N2–M–N5	89.9(2)	97.2(2)		
N4–M–N5	98.8(2)	94.9(2)	N4–Zn–N2	98.0(2)
N3–M–N5	95.8(2)	109.0(2)	N3–Zn–N2	121.9(2)
N1–M–N5	96.6(2)	98.3(2)	N1–Zn–N2	115.9(2)
N1–C9–C10	115.5(5)	114.5(6)		
N1–C8–C7	113.0(6)	110.9(6)		
N3–C2–C1	115.5(5)	106.8(5)		
N3–C3–C4	124.1(7)	113.2(5)		

are reported in Table 1. Single crystals of **I** were obtained by recrystallization from methanol, **II** was recrystallized from water, and **III** was recrystallized from ethanol/water. Single-crystal intensity measurements were collected at room temperature with a Siemens R3m/V diffractometer, using Mo Kα radiation with a graphite monochromator. Lattice parameters for **I–III** were obtained using least squares refinement of the angles of 24 reflections with 22° < 2θ < 28°. Intensities were collected using the θ/2θ scan mode. Absorption corrections were applied to the data set of each crystal using a ψ scan technique. The structures were solved by direct methods with successive Fourier syntheses.<sup>14</sup> Full-matrix least squares refinement was performed using SHELXL-97<sup>15</sup> with anisotropic thermal parameters for all non-hydrogen atoms. Selected bond distances and angles are listed in Table 2. All hydrogen atoms except those attached to the oxygen atoms in **III** were located at calculated positions and were not refined. The water molecule with an occupancy of 0.5 causes disorder of the two perchlorate ions in **II**. The side chain appears to be disordered in **I**.

## Results and Discussion

The template condensation between diacetylpyridine and trpn leading to the formation of macrocyclic Schiff base complexes

was first suggested by Keypour and Stotter in 1979.<sup>16</sup> In our current investigation, we have further examined this reaction in the presence of Ni<sup>2+</sup>, Cu<sup>2+</sup>, and Zn<sup>2+</sup> metal ions (Figure 1). This reaction was studied for several reasons:

(1) It is synthetically important, because it is expected to produce monofunctionalized pyridine-containing macrocyclic complexes. Interest in macrocycles with pendant arms is growing on account of their unique coordination and structural properties, their utility in enzyme mimicking studies, and their rapidly growing applications as radiopharmaceuticals and magnetic resonance imaging reagents.<sup>17–19</sup> The pendant primary amino group can also be used to attach the macrocycles to other small molecules<sup>20</sup> or to monoclonal antibodies.<sup>21,22</sup> Five-coordinate complexes derived from pyridine-containing macrocycles are promising for oxygen and peroxide activation.<sup>23–25</sup>

(2) The reaction is synthetically challenging, because the presence of a third primary amino group in tripodal tetramine, trpn, may cause synthetic complications. These include 3 + 2 condensation leading to cryptand formation (observed, for example, in analogous condensations between 2,6-diformylphenol and trpn<sup>26</sup>) and several kinds of polymerization processes. Extensive investigations of monofunctionalized pyridine-containing complexes by Kaden<sup>27,28</sup> and Alcock and Moore<sup>29–33</sup> did not reveal these difficulties, because, in their rigorous synthetic approach, the functional group in the pendant arm (such as 2-methylpyridine or *N,N*-dimethylethylamine) was chosen to be unreactive toward the carbonyl groups of 2,6-diformylpyridine.

(3) The reaction is likely to produce target [1 + 1] macrocycles. There was an indication in the literature that [1 + 1] condensation indeed occurs in dilute solutions of trpn and 2,6-diacetylpyridine with Ni(II) or Cu(II) as template; the detailed reaction conditions were not, however, provided, and the structures of the products had not been determined.<sup>16</sup> An analogous template reaction between *N,N,N',N'*-tetra(aminoethyl)ethylenediamine and diacetylpyridine has been reported, giving rise to a pentaza macrocyclic manganese complex bearing two primary amino pendant arms.<sup>34</sup>

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(4) It is difficult to satisfy the diverse coordination requirements of different metal ions incorporated into rigid Schiff base pyridine-containing macrocycles with an additional donor atom in the side arm. Analogous reduced ligands are flexible and adopt a variety of conformations, producing both tetragonal-pyramidal and trigonal-bipyramidal metal complexes.<sup>30–33</sup> How will the unsaturated ligands accommodate different metal ions, using highly restricted conformational space? In this regard, the structures of Schiff base complexes formed in template condensations are of particular interest.

Experimentally, trpn complexes of Cu(II), Ni(II), or Zn(II) were formed in situ, followed by condensation with 2,6-diacetylpyridine. In order to prevent polymerization processes, dilute solutions were used (2 mM). The conditions necessary for 1:1 complexation between trpn and Cu(II), Ni(II), and Zn(II) salts (in aqueous solution) are known from the potentiometric measurements.<sup>35–37</sup> The final pH of the Cu(II)–amine solution was 9.0, indicating that the four-coordinate complex is the predominant species in solution.<sup>37</sup> The condensations with 2,6-diacetylpyridine were conducted in a water/ethanol solvent system, under reflux, over a period of 8 h. The major products were characterized by FAB mass spectrometry, C,N,H analysis, IR and UV–vis spectroscopy, and X-ray crystallography. Spectroscopic characterization complemented the X-ray data in that (1) it demonstrated that single crystals of each complex chosen for X-ray studies had the same composition as the bulk materials and (2) it can be used, in the future, for rapid identification of the condensation products.

Our results clearly demonstrate that the nature of the metal template determines the outcome of Schiff base condensation between a difunctional carbonyl component (diacetylpyridine) and a trifunctional amine component (trpn) (Figure 1). Both Cu(II) and Ni(II) facilitate formation of macrocyclic products in 50–60% yield, but single-crystal X-ray diffraction reveals that the chemical structure of the major product is metal-ion dependent. In the nickel(II) complex, the C=N double bonds are conjugated with the pyridine ring, as expected from the structure of the starting diacetylpyridine (Figure 2). In contrast, the copper(II) ion caused isomerization of the macrocyclic ligand, with one of the C=N double bonds migrating into the initially saturated six-membered chelate ring (Figure 3). To the best of our knowledge, this type of isomerization has not been reported previously for Schiff base macrocyclization reactions. It should be noted, however, that other types of isomerization are typical for pyridine-containing macrocycles.<sup>3–9</sup> In the case of the zinc(II) template, we were unable to isolate a macrocyclic condensation product; instead, a zinc(II) complex of the starting tetramine, Zn(trpn)Cl<sub>2</sub>·2H<sub>2</sub>O, was recovered and structurally characterized. A possible reason for the cyclization to fail is the tetrahedral structure of the Zn(trpn) complex, which provides no vacant coordination site for diacetylpyridine to approach the metal ion and position itself favorably for [1 + 1] condensation.

Analytical and FAB mass-spectroscopic data for all three of the isolated copper(II) and nickel(II) complexes indicate that the compounds resulted from [1 + 1] condensation reactions. An IR of the crystalline nickel complex contains an absorption at 1621 cm<sup>-1</sup>, typical for the C=N stretch for the azomethine group conjugated with an aromatic ring. The crystalline copper(II) complex (the major product of the Cu-templated condensa-

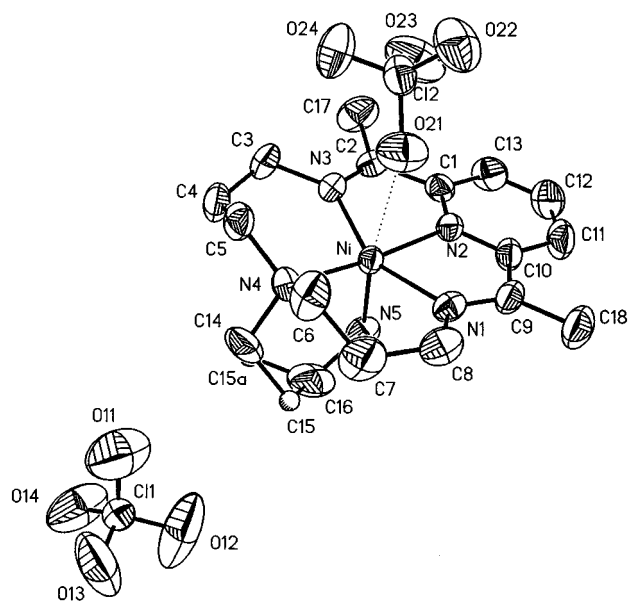


Figure 2. Crystal structure of [Ni(L<sub>sym</sub>)](ClO<sub>4</sub>)<sub>2</sub> (I).

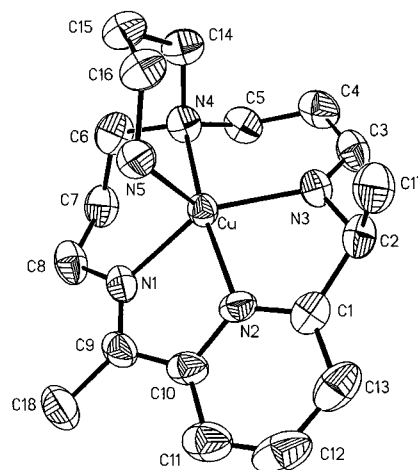


Figure 3. Crystal structure of [Cu(L<sub>asym</sub>)](ClO<sub>4</sub>)<sub>2</sub>·0.5H<sub>2</sub>O (II). Perchlorate anions and water molecule are omitted for clarity.

tion) shows two strong absorbances at 1680 and 1620 cm<sup>-1</sup>, consistent with the presence of two inequivalent C=N groups in the macrocyclic ligand, L<sub>asym</sub>. The IR spectrum of the second copper(II) complex (the minor product in the condensation reaction) is nearly identical to the spectrum of [Ni(L<sub>sym</sub>)](ClO<sub>4</sub>)<sub>2</sub>, with a single C=N stretch observed at 1622 cm<sup>-1</sup>. This suggests that the second copper(II) complex is an isomeric compound, Cu(L<sub>sym</sub>)<sup>2+</sup>, which has both C=N bonds conjugated to the pyridine ring.

**Description of the X-ray Structures.** In both macrocyclic complexes, [Ni(L<sub>sym</sub>)](ClO<sub>4</sub>)<sub>2</sub> (I) and [Cu(L<sub>asym</sub>)](ClO<sub>4</sub>)<sub>2</sub>·0.5H<sub>2</sub>O (II), the five nitrogen donor atoms of the macrocyclic ligands are coordinated to the metal ions in a tetragonal-pyramidal fashion, with the amine nitrogen from the pendant arm occupying the axial position (Figures 2 and 3). The coordination number of the copper ion in complex II is 5. The oxygen atom closest to the copper center is O6, belonging to a disordered perchlorate counterion. The occupancy factor for O6 is 0.5, and the Cu–O6 distance of 3.27 Å is too long to be considered a bond. In contrast, for I, *d*(Ni–O21) is short enough (2.66 Å) to be considered a weak coordinative bond, making the overall coordination number 5 + 1. The X-ray structure of I is very similar to that described previously for an analogous nickel(II)

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complex having a pyrrolidinyl group in the side arm.<sup>31</sup> Although all Ni–N distances are somewhat shorter for **I**, the Ni–O(ClO<sub>4</sub>) distance is 0.27 Å longer in **I** than in Alcock's Schiff base complex.<sup>31</sup> The Cu–N(macrocycle) bonds in **II** are significantly shorter than the corresponding Ni–N(macrocycle) bonds in **I**, while the axial Cu–N(pendant arm) bond (2.186 Å) is significantly elongated due to Jahn–Teller distortion and is ca. 0.1 Å longer than the corresponding Ni–N(pendant arm) bond (2.054 Å) (Table 2).

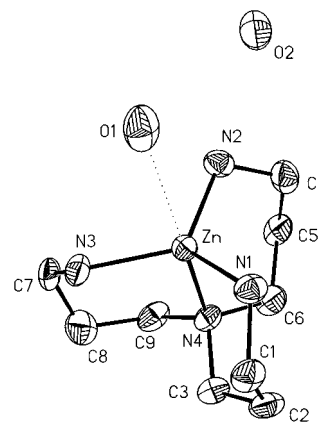
The fragment of the macrocyclic ligand in **I** which contains the pyridine ring and adjacent azomethine groups is essentially planar, with C(9)–N(1) and C(2)–N(3) distances typical of double bonds (Table 2). In contrast, the copper(II) ion caused isomerization of the macrocyclic ligand, with one of the C=N double bonds migrated into an initially saturated six-membered chelate ring, producing Cu(L<sub>asym</sub>)<sup>2+</sup>. Indeed, the C9 atom is trigonal planar, and the N1–C9 bond length (1.284(9) Å) is characteristic for an azomethine double bond, while the C2 carbon atom is clearly tetrahedral, with the N3–C2 bond length (1.486(9) Å) typical of a C–N single bond. At the same time, the neighboring bond N3–C3 is short (1.251(8) Å), indicating a double bond between these two atoms. Bond angles about the C3 carbon atom are typical of a trigonal-planar, sp<sup>2</sup> carbon (Table 2). Analytical and FAB mass-spectroscopic data also support the presence of two double bonds in the molecule, indicating a double-bond migration, but not double-bond reduction.

The double-bond migration observed in the copper(II) complex produces two additional stereocenters in the molecule (carbon atom C2 and nitrogen atom N4). According to the crystallographic data, the only diastereoisomer isolated has both the methyl group (C17 in Figure 3) and the pendant arm on the same "face" of the macrocycle. Since the complex crystallizes in a centrosymmetric space group (*P*2<sub>1</sub>/*c*), two enantiomers (*RS* and *SR*) coexist in the crystal lattice, and spontaneous resolution of enantiomers is impossible. Isolation of a single diastereoisomer may indicate that the double-bond migration in the copper(II) complex is stereoselective. Moderate isolated yield of the complex **II**, however, does not allow for definitive conclusions on the stereoselective nature of the double-bond-migration reaction. This issue will be addressed in our future research.

The water of hydration in **II** is connected via weak hydrogen bonds to both perchlorate ions: *d*(O9–O8) = 2.84 Å and *d*(O9–O4) = 2.62 Å.

The coordination geometry of zinc(II) in its complex with the tripodal tetramine trpn ([Zn(trpn)]Cl<sub>2</sub>·2H<sub>2</sub>O, **III**) is that of a distorted tetrahedron (Figure 4, Table 2). Neither the chloride anions nor the water molecules are bound to the Zn(II) ion in **III**: the closest contact with any potential donor atom, other than amine nitrogens, is Zn–O(1) (2.91 Å).

Possible reasons for the preferential formation of different products in the condensation between 2,6-diacetylpyridine and tris(3-aminopropyl)amine in the presence of different metal ions follow from analysis of the coordination geometries of the copper(II) and nickel(II) macrocycles (Table 2). To accommodate the short in-plane copper–nitrogen bonds, the macrocycle in the copper(II) complex isomerizes, which allows for greater flexibility within the pyridine–azomethine fragment of the molecule. This hypothesis is supported by molecular mechanics calculations (augmented MM2, as implemented in the CAChe molecular modeling package<sup>38</sup>). These calculations



**Figure 4.** Crystal structure of [Zn(trpn)]Cl<sub>2</sub>·2H<sub>2</sub>O (**III**). Chloride anions are omitted for clarity.

**Table 3.** Ligand Strain Energy in "Symmetric" and "Asymmetric" Isomeric Macrocyclic Complexes (Figure 1): The Results of Molecular Mechanics (MM2/CAChe) Calculations

complex	energy, kcal/mol	
	optimized complex, MN <sub>5</sub> fixed, M deleted	optimized ligand, N <sub>5</sub> fixed
NiL <sup>2+</sup>		
sym (real structure)	40.01	37.65
asym (hypothetical, "Cu-like")	37.67	35.47
CuL <sup>2+</sup>		
sym (hypothetical, "Ni-like")	40.30	38.56
asym (real structure)	33.34	31.80

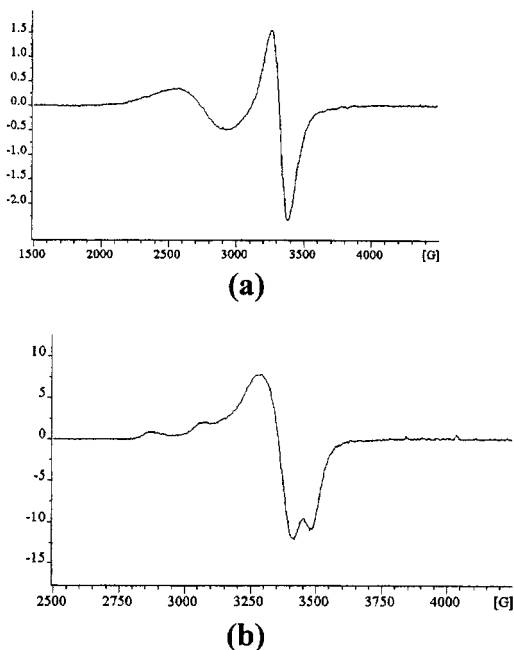
were designed to compare the strain energies of the two ligand isomers for both nickel and copper. X-ray atom coordinates for [Cu(L<sub>asym</sub>)]<sup>2+</sup> were used to generate the initial geometries for [Cu(L<sub>asym</sub>)]<sup>2+</sup> and for [Cu(L<sub>sym</sub>)]<sup>2+</sup>. Analogously, X-ray atom coordinates for [Ni(L<sub>sym</sub>)]<sup>2+</sup> were used to generate initial geometries for both [Ni(L<sub>sym</sub>)]<sup>2+</sup> and [Ni(L<sub>asym</sub>)]<sup>2+</sup>. All four structures were minimized using a conjugate gradient algorithm. The coordination sphere of the metal ion (MN<sub>5</sub>) was kept fixed in all these calculations. After the minimization converged, the metal ion was deleted, and the energy of the ligand in the optimized complexes was computed (Table 3). This approach eliminates the difficult problem of force field parameter development for the transition metal complexes. Alternatively, the free ligands, with all five nitrogen atoms fixed, were optimized, giving energy values very similar to those obtained for the optimized complexes (Table 3).

It should be noted that the energies computed in molecular mechanics minimization methods reflect unfavorable deviations of the molecule from ideal geometry, but do not explicitly include the favorable bonding energy of the molecule. In our case, for example, the resonance stabilization of the conjugated symmetric structure is not reflected in Table 3.

It is clear from Table 3 that the ligand strain energy is smaller for the isomer with a shifted double bond. The difference between symmetric and asymmetric isomers is much greater for the copper(II) complex (ca. 7 kcal/mol) than for the nickel(II) complex (ca. 2 kcal/mol). Consequently, the driving force for ligand isomerization is much greater in the case where copper(II) is the template metal ion.

**Pendant Arm Protonation Equilibria.** pH-dependent "on–off" equilibria involving the donor atom in the pendant arm are well-documented for monofunctionalized macrocyclic complexes.<sup>27,28,39–42</sup> We found that the aminopropyl group which is coordinated to the metal ion in the crystalline solid

(38) *Personal CAChe for Windows*, version 3.0; Oxford Molecular Group: Oxford, U.K., 1997.

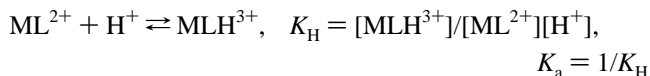


**Figure 5.** (a) EPR spectrum of  $[\text{Cu}(\text{L}_{\text{asym}})]^{2+}$  in  $\text{CH}_3\text{CN}$  (frozen glass, 77 K). (b) EPR spectrum of protonated  $[\text{Cu}(\text{L}_{\text{asym-H}})]^{3+}$  in  $\text{CH}_3\text{CN}$ /triflic acid (1 equiv) (frozen glass, 77 K).

**Table 4.** Protonation Constants (25 °C, 0.1 M  $\text{KNO}_3$ ) and UV–Vis Spectral Data for the Pentaaza Pyridine-Containing Macrocyces

complex	$\text{pK}_a$	absorption bands, $\lambda_{\text{max}}$ ( $\epsilon$ )	
		pH 3.0	pH 10.0
$\text{NiL}_{\text{sym}}^{2+}$	$6.46 \pm 0.03$	480 sh (174)	815 (19), 560 sh (54), 520 sh (70)
$\text{CuL}_{\text{asym}}^{2+}$	$7.34 \pm 0.04$	551 (148)	840 (69), 605 (175)
$\text{CuL}_{\text{sym}}^{2+}$	$8.24 \pm 0.06$	577 (181)	856 (61), 612 (198)

complexes,  $\text{NiL}_{\text{sym}}^{2+}$  and  $\text{CuL}_{\text{asym}}^{2+}$ , can also dissociate from the central metal ion in aqueous solutions. Potentiometric titrations of the three isolated macrocyclic complexes indicate the presence of one ionizable proton in each compound and allow for determination of the protonation constants (Table 4):



The color of the solutions also changes upon protonation: from peach to yellow for  $\text{NiL}_{\text{sym}}^{2+}$  and from blue to purple for both  $\text{CuL}_{\text{asym}}^{2+}$  and  $\text{CuL}_{\text{sym}}^{2+}$ . Isosbestic points are present in series of spectra recorded at different pH values (ranging from 2.5 to 10) for each individual complex, indicating one pH-dependent equilibrium in each system. The corresponding spectral changes, summarized in Table 4, confirm formation of square-planar four-coordinate complexes upon protonation of the aminopropyl group.<sup>28,40,42</sup> Additional evidence for a change in copper(II) coordination geometry upon protonation of the side arm can be found in the EPR spectra of  $\text{Cu}(\text{L}_{\text{sym}})^{2+}$  (Figure 5). The starting five-coordinate complex  $[\text{Cu}(\text{L}_{\text{sym}})](\text{ClO}_4)_2$ , dissolved in acetonitrile, gave an unresolved anisotropic spectrum (frozen glass), while the singly protonated species formed after

addition of 1 equiv of triflic acid to the above solution gave rise to hyperfine splitting typical of Cu(II) complexes with tetraazamacrocycles ( $g_{\parallel} = 2.170$ ,  $A_{\parallel} = 206.7 \times 10^{-4} \text{ cm}^{-1}$ ,  $g_{\perp} = 2.060$ ).

The protonation constants for the pendant amino groups coordinated to the metal ions in  $[\text{Cu}(\text{L}_{\text{asym}})]^{2+}$ ,  $[\text{Cu}(\text{L}_{\text{sym}})]^{2+}$ , and  $[\text{Ni}(\text{L}_{\text{sym}})]^{2+}$  are relatively high (Table 4), falling in the same pH range as the protonation constants for aminopropyl pendant arm attached to isocyclam copper(II) and nickel(II) complexes.<sup>40</sup> The pH range for the proton-dependent dissociation of the coordinated aminopropyl pendant arms is very convenient as it allows for switching between two different ligand binding modes under mild conditions. Shorter side arms, which form five-membered chelate rings with the central metal ion, are usually less susceptible to protonation and can only be protonated in acidic media (pH of about 2).<sup>40,42</sup> The same qualitative trend in relative stabilities of the coordinated *N,N*-dimethylaminopropyl and *N,N*-dimethylaminoethyl groups attached to the pyridine-containing macrocycles has also been reported by Alcock and Moore.<sup>29,31,33</sup>

The  $\text{pK}_a$  for  $\text{NiL}_{\text{sym}}^{2+}$  determined in this work compares well with the  $\text{pK}_a$  of 7.25 reported in the early communication by Keypour and Stotter.<sup>16</sup> Unlike Keypour et al., who found another minor transition with  $\text{pK} = 8.05$ , we have not observed any other protonation/deprotonation steps for the isomerically pure complex in the pH range from 3 to 10. It is possible that the second transition should be attributed to the admixture of a different isomer of the nickel(II) complex, rather than to ionization of the coordinated water molecule suggested in ref 16. This hypothesis is supported by the presence of two absorptions at 1665 and 1624  $\text{cm}^{-1}$  in the IR of the nickel(II) complex isolated by Keypour et al.<sup>16</sup> Our data indicate that the 1624  $\text{cm}^{-1}$  band belongs to  $\text{Ni}(\text{L}_{\text{sym}})^{2+}$ , while the band at 1665  $\text{cm}^{-1}$  is characteristic of the isomeric macrocycle having a nonconjugated C=N bond. Titration results for the two isomers of the Cu(II) complex (Table 4) suggest that relatively small variations in the macrocyclic structure can give rise to a significant difference in the  $\text{pK}_a$  of the pendant amino group. The higher  $\text{pK}_a$  for  $\text{CuL}_{\text{sym}}^{2+}$  corresponds to relief of the macrocycle steric strain upon protonation (and dissociation from the metal ion) of the aminopropyl group. This effect is smaller for the  $\text{CuL}_{\text{asym}}^{2+}$ , where the macrocyclic ring is more flexible, resulting in an order of magnitude smaller protonation constant of the amino group in the side arm. A second ionization process has been detected at high pH for the  $\text{Cu}(\text{L}_{\text{asym}})^{2+}$  ( $\text{pK}_a = 11.15 \pm 0.15$ ) and can be attributed to deprotonation of the coordinated water molecule. This high value is in agreement with  $\text{pK}$  values previously observed for the copper(II) and nickel(II) complexes with a parent tetraazamacrocycle CR (an analogue of  $\text{L}_{\text{sym}}$  lacking an aminopropyl pendant arm),<sup>43</sup> but not with the interpretation of the two ionization processes proposed by Keypour and Stotter.<sup>16</sup>

It is worth noting that the two copper(II) complexes studied in this work display qualitatively identical chemical behavior with respect to protonation/deprotonation of the pendant aminopropyl group, including very similar pH dependence of their visible spectra. At the same time, the quantitative characteristics, such as the positions of the absorption maxima in both deprotonated and protonated forms, or the values of the protonation constants, are somewhat different for the two complexes (Table 4). This is consistent with the assignment of structures for the two isomeric complexes, which both have an

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equatorial macrocyclic ligand bearing an aminopropyl side chain. Quantitatively, however, two ligand isomers are substantially different, with the asymmetric (rearranged) macrocycle characterized by a stronger ligand field ( $\lambda_{\max} = 612$  nm for  $\text{CuL}_{\text{sym}}^{2+}$  and 605 nm for  $\text{CuL}_{\text{asym}}^{2+}$ ; this difference is even more pronounced for the protonated square-planar complexes, with  $\lambda_{\max} = 577$  nm for  $\text{Cu}(\text{L}_{\text{sym}}\text{H})^{3+}$  and 551 nm for  $\text{Cu}(\text{L}_{\text{asym}}\text{H})^{3+}$ ) and an order of magnitude greater affinity for the axial amino group in the pendant arm ( $\text{p}K_{\text{a}} = 8.24$  for  $\text{CuL}_{\text{sym}}^{2+}$  and 7.34 for  $\text{CuL}_{\text{asym}}^{2+}$ ).

### Conclusions

A new type of metal ion control over the outcome of template [1 + 1] condensation reactions has been found. A fine-tuning of the coordination sphere of the central metal ion is accomplished by means of double-bond migration in the Schiff

base macrocycle. This process leads to the formation of a more flexible asymmetric macrocyclic ligand and is governed by the coordination requirements of the central metal ion.

**Acknowledgment.** The authors would like to thank Prof. D. H. Busch, Dr. M. Buchalova, Dr. J. McCormick, and Dr. R. Roesner for helpful discussions. Financial support from Tufts University (EVR-A) is gratefully acknowledged.

**Supporting Information Available:** Listings of all final positional and thermal parameters, full description of crystallographic data collection and refinement, and intramolecular bond lengths and angles for **I–III**. X-ray crystallographic files, in CIF format, for complexes **I–III**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

IC990027N