

Large pK_a Shifts of α -Carbon Acids Induced by Copper(II) Complexes

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Abstract: A series of synthetic receptors (**4–6**) incorporating metal ions, specifically copper(II), were examined for their ability to enhance the acidity of active methylene compounds. The copper(II) complexes were observed to reduce the pK_a of 1,3-diketone carbon acids in acetonitrile by as much as 12 pK_a units. The relatively large pK_a re-

duction achieved by the complex is attributed to the electrostatic interaction between the anionic π system of the enolate and the copper(II) ions. The

Keywords: acidity • copper complexes • enzyme models • N ligands • receptors

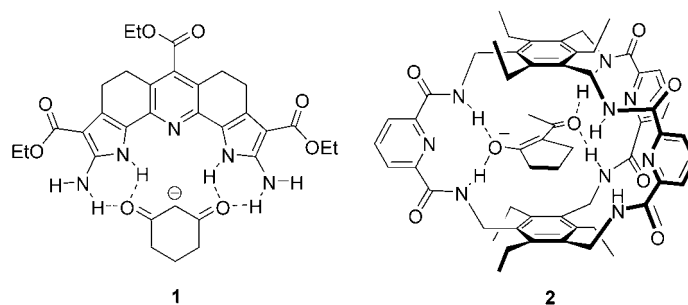
cage structure and hydrogen bonding sites in receptors **4** and **5** lead to a very modest further enhancement of the acidity relative to that with **6**. This study provides insight into the way in which metalloenzymes stabilize an enolate intermediate.

Introduction

The catalytic function of enzymes relies on the preferential stabilization of a transition state compared to a substrate.^[1] Preferential stabilization of an enolate intermediate results in the depression of the pK_a of a carbon acid substrate, allowing deprotonation by a relatively weak base in an enzyme active site. For example, yeast enolase utilizes an active site lysine ($pK_a \sim 10$) to catalyze the dehydration of 2-phospho-D-glycerate (PGA) to produce phosphoenolpyruvate by the abstraction of a proton α to a carboxylic acid ($pK_a \sim 32$) in PGA.^[2] Several enzymatic studies have focused on determining the mechanism through which enolate stabilization is achieved in enolases,^[2] racemases,^[3] and aldolases.^[4] These enzymes share a common feature: the use of a transition-metal ion in the active site. It has been proposed for each of these classes of enzymes that the metal ion plays a pivotal role in stabilizing the negative charge on the transition state and intermediate enolate during substrate deprotonation.

The use of hydrogen bonds to stabilize enolate intermediates has been proposed, but to date, organic models have

not been able to account for the 10-unit or more pK_a shifts often observed in enzyme catalysis. For example, polyaza cleft **1** was designed to form hydrogen bonds directed toward the oxygen lone pairs of carbon acids (Scheme 1).^[5]



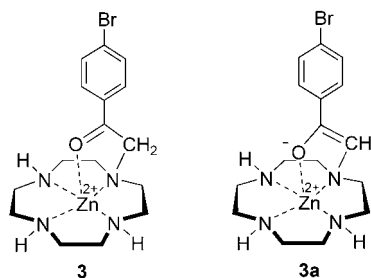
Scheme 1. Synthetic receptors **1** and **2** and their idealized binding modes for 1,3-cyclohexanedione and 2-acetylcyclopentanone, respectively.

Hydrogen bonding was proposed to reduce the pK_a of active methylene compounds by withdrawing electron density away from the enolate intermediate. A modest reduction of 1.0 unit in the pK_a of 1,3-cyclohexanedione was obtained with receptor **1**. Subsequently, it was proposed that hydrogen bond geometry is crucial to achieving a larger reduction in the pK_a of carbon acids, as supported by studies of 4-chlorobenzoyl-Co-A-dehalogenase. A crystal structure of this enzyme revealed hydrogen bonds oriented towards the π system of a thioester carbonyl enolate.^[6] Host **2** was de-

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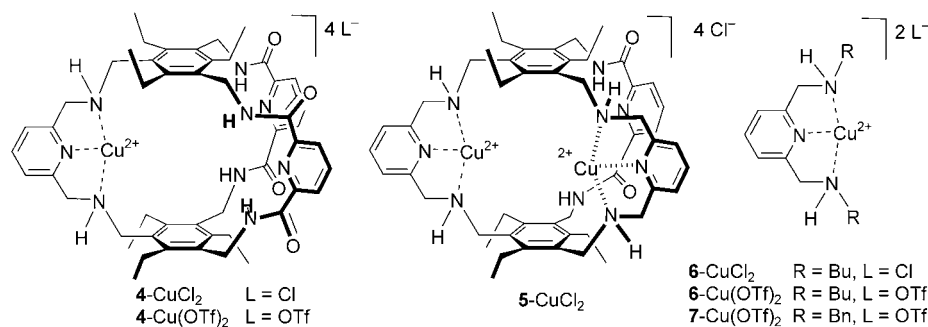
signed to bind the enolate of 2-acetylcyclopentanone with amide hydrogen bonds directed towards the π system of the enolate because this is where the negative charge resides in the enolate.^[7] A pK_a shift of 2.9 units was obtained with receptor **2** and 2-acetylcyclopentanone. These results suggest that hydrogen bond geometry plays a significant role in enolate stabilization. However, traditional hydrogen bonds alone are insufficient to decrease the pK_a of carbon acids in enzyme active sites. The possibility of stabilization by low barrier hydrogen bonds^[8] or cooperative effects between hydrogen bonds and electrostatic effects with metal ions cannot be ruled out.^[3a]

Synthetic models have been designed to explain the pK_a reduction in enzymatic systems based on the use of metal coordination. It has been established that aldol condensations are in part catalyzed in the active site of class II aldolases by a zinc ion ligated by the imidazole groups of three histidines.^[9] In these enzymes, zinc functions as a Lewis acid, activating methylene groups α to a carbonyl towards deprotonation by withdrawing negative charge from the carbonyl oxygen in the transition state. Kimura et al. proposed a model system for class II aldolases to study how much the acidity of a hydrogen α to a carbonyl may be increased through coordination of the zinc(II) center.^[10] The model system, 4-bromophenacyl-pendant zinc cyclen (**3**), specifical-



ly sought to determine how the formation of the enediolate by a relatively weak base (glutamic carboxylate) at physiological pH is possible in the active site of class II aldolases. A reduction in the pK_a of the methylene hydrogen of 10 pK_a units was found. The large pK_a shift is explained by the coordination of the carbonyl to the dicationic zinc center, as **3a** was isolated from solution. Such large enhancement in the pK_a of a carbon acid suggests that metal binding may be much more influential in reducing the pK_a of carbon acids in enzyme active sites than hydrogen bonding.

We have designed a series of synthetic receptors (**4–6**) (Scheme 2) and examined the carbon acidity of active meth-



Scheme 2. Copper (II) complexes of synthetic receptors (**4–7**) used to study the effects of metal coordination on the pK_a of active methylene compounds.

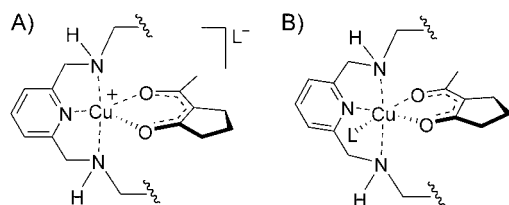
ylene compounds in the presence of copper(II) complexes of these receptors. The enolates of active methylene compounds were used in our studies in order to compare our results with those obtained using receptors **1** and **2**. Upon comparison of the pK_a values of 2-acetylcyclopentanone in the presence of receptors **4** and **5** and with our results with receptors **1** and **2**, it was concluded that the use of metal ions greatly enhances the acidity of carbon acids, and that the additional hydrogen bonding sites only lead to a modest further enhancement.

Results and Discussion

Design criteria: Our receptor design is a bicyclic host that may bind an anionic guest through charge-pairing with one or two bound divalent metal centers and hydrogen bonding, with the two binding interactions behaving cooperatively to induce pK_a shifts. As illustrated in Scheme 2, receptors **4** and **5** incorporate amide hydrogen bond donors, as modeled from receptor **2**. Whereas receptor **2** utilizes three pyridine-2,6-dicarboxylic acid diamide moieties, receptor **4** utilizes two pyridine-2,6-dicarboxylic acid diamide moieties for hydrogen bond formation and one 2,6-bis(aminomethyl)pyridine moiety for binding a metal ion inside the macrocycle. Receptor **5** utilizes one pyridine-2,6-dicarboxylic acid diamide moiety for hydrogen bond formation and two 2,6-bis(aminomethyl)pyridine moieties for binding metal ions. The similar macrocyclic scaffolds of our receptors allow a direct comparison with carbon acid pK_a shift results obtained by using receptor **2**. Receptor **6** was designed to bind enolates exclusively through metal coordination to examine the effect of the cage structure in inducing pK_a shifts in active methylene enolates, and may also allow an evaluation of cooperative effects of metal interactions and hydrogen bonding in hosts **4** and **5**.

The 2,6-bis(aminomethyl)pyridine or similar triaza moieties are known to bind metal ions, such as copper(I), copper(II), and zinc(II).^[11] Copper(II) was used in our host design because it can adopt a trigonal-bipyramidal or octahedral geometry with triaza ligands geometrically similar to those used in receptors **4** and **5**.^[12,13] This kind of Cu^{II} complexes is

known to form chelates with oxygen-containing ligands such as (benzyloxy)acetaldehyde.^[13] Therefore, an enolate will be bound in the equatorial position on the metal and hence lie parallel to the host aromatic rings (Scheme 3). This orienta-



Scheme 3. Schematic representation of the (A) trigonal bipyramidal or (B) octahedral Cu^{II} center in the possible structures of the receptor-enolate complexes.

tion may position an enolate bound within the macrocycle for simultaneous hydrogen bonding and additional metal coordination.

Synthesis: The syntheses of receptors **4** and **5** may be accomplished by joining two hexasubstituted benzene rings, 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene with 2,6-disubstituted pyridine linkers (Scheme 4). A hexasubstituted benzene ring is used to arrange the functional groups on the 1, 3, and 5 positions to one face of the benzene ring.^[14]

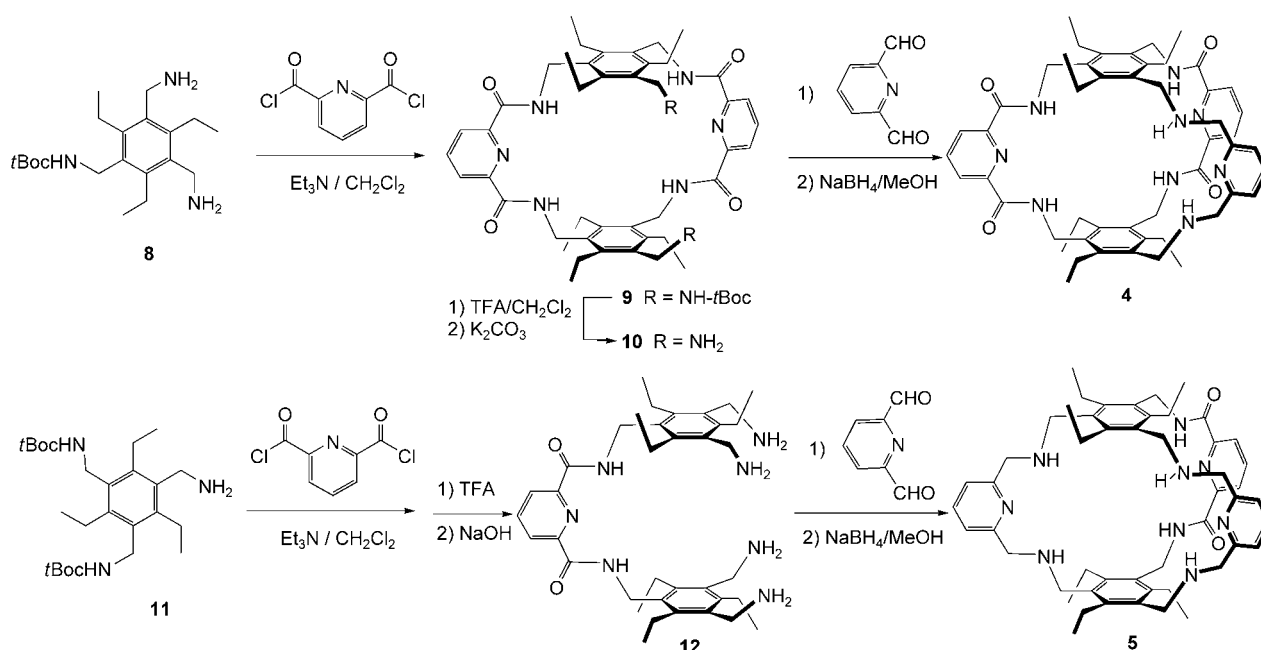
Mono-*t*Boc-protected 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**8**) was allowed to react with 1,6-pyridinedicarbonyl dichloride giving a double linked cleft **9**. Removal of the *t*Boc protecting groups in **9** with trifluoroacetic acid in dichloromethane afforded **10**. The two free amino groups

in **10** were coupled by reductive amination with 2,6-pyridinedicarboxaldehyde giving the final cage-like receptor **4** in 80% yield.

Similarly, two equivalents of di-*t*Boc-protected 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**11**) were coupled by reaction with 2,6-pyridine dicarbonyl dichloride. Removal of the *t*Boc protecting groups with trifluoroacetic acid followed by ion exchange chromatography yields cleft **12**. The synthesis of cage-like receptor **5** is completed by nucleophilic substitution of the primary amines of the cleft to two equivalents of 2,6-pyridinedicarboxaldehyde followed by reductive amination in which the imine groups are converted to secondary amines. The reaction is carried out in toluene at high dilution.

The acyclic ligands 2,6-bis(*n*-butylaminomethyl)pyridine (**6**) and 2,6-bis(benzylaminomethyl)pyridine (**7**) were synthesized by the reductive amination of 2,6-pyridinedicarboxaldehyde with *n*-butylamine or benzylamine.

Binding studies: To initiate our studies with receptors **4–6**, it was necessary to determine the binding stoichiometry between the receptors and metal ions. Copper(II) has been used in similar macrocyclic receptors and the binding stoichiometry determined by spectroscopic methods.^[11] The binding stoichiometry of receptors **4–6** with copper(II) salts was determined by the mole ratio method,^[15] by monitoring the absorbance increase of the ligand-copper(II) complexes by spectrophotometric titrations (Figure 1). The titration curves clearly reveal that receptors **4** and **6** form 1:1 complexes with $\text{Cu}(\text{OTf})_2$, whereas receptor **5** forms a 1:2 complex with CuCl_2 . The binding stoichiometry is in accordance with the number of 2,6-bis(aminomethyl)pyridine chelating moieties in the receptors. The sharp turning points on the ti-



Scheme 4. Synthesis of receptors **4** and **5**.

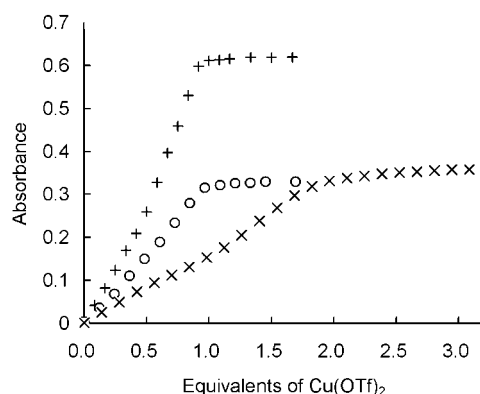


Figure 1. Titrations of free hosts with $\text{Cu}(\text{OTf})_2$ in acetonitrile: (x) absorbance at 640 nm of 1.5 mM **5**; (o) absorbance at 570 nm of 2.0 mM **4**; (+) absorbance at 620 nm of 3.0 mM **6**.

tration curves suggest high association constants of the receptors with copper(II) salts. Limited by the sensitivity of absorbance spectral method and the formation of two-ligand-one-copper complexes when less than one equivalent of copper(II) was presented, no binding constant was obtained from the titration curves. Based on these stoichiometry studies, the copper(II) complexes of **4–6** were made in situ by mixing a receptor solution with one or two equivalents of a copper(II) salt.

The enolates of active methylene compounds 2-acetylcyclopentanone (**13**) and 1,3-cyclopentane dione (**14**) were selected for binding studies with receptors **4**, **5**, and **6** in order to make a direct comparison with our previous results for receptors **1** and **2**.^[5,7] In our previous studies, the active methylene compounds were selected due to their increased functionality, and therefore an increased number of potential binding sites, compared with monocarbonyl compounds. Additionally, active methylene compounds have lower pK_a values than monocarbonyl compounds.

The binding mode of enolates with the copper complexes of receptors **4**, **5**, and **6** was studied with UV/Vis spectroscopic titrations (Figure 2, Figure 3, Figure 4). Although an aqueous medium is optimal for the titrations, acetonitrile is also an acceptable solvent because its dielectric constant (37.5) is proposed to mimic the interior of an enzyme active site.^[5] Additionally, a direct comparison may be made with the results of pK_a shift experiments with receptors **1** and **2**, also performed in acetonitrile. UV/Vis spectral change in the titrations of copper(II) complexes of **4** and **6** with sodium enolate **13** are shown in Figure 2 and Figure 3. The titration curves in Figure 3 reveal that the copper(II) centers in the complexes can bind one or two molecules of **13** dependent on the amount of the enolate added. The receptor ligands **4** or **6** did not dissociate from the copper(II) center by addition of the enolate, revealed by a control titration of $\text{Cu}(\text{OTf})_2$ with the enolate in the absence of the receptors that showed completely different absorbance spectra from those titrations in the presence of the receptors. The clear isosbestic points in Figure 2 and sharp turning points at one equivalent in Figure 3 suggest that the first binding constant (K_1) is

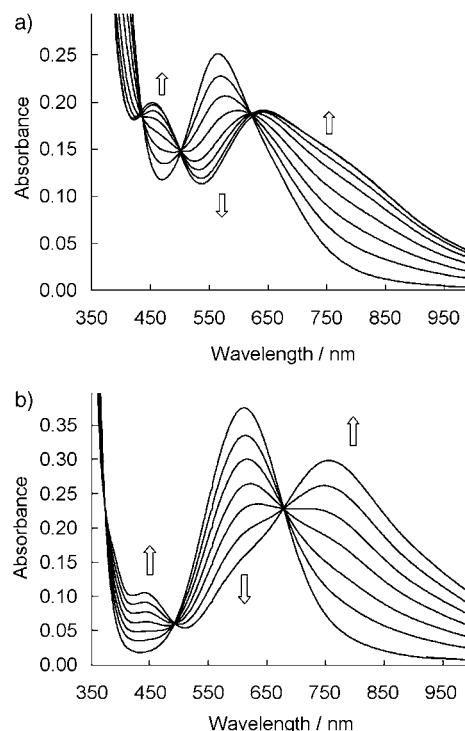


Figure 2. Absorption spectral change of a 2.0 mM solution of **4**- $\text{Cu}(\text{OTf})_2$ (a) or **6**- $\text{Cu}(\text{OTf})_2$ (b) in acetonitrile upon addition of up to one equivalent of **13**- $\text{Na}^+ \cdot [15]\text{crown-5}$. For clarity, spectra of adding more than one equivalent of enolate **13** were not shown because of the formation of a 1:2 complex.

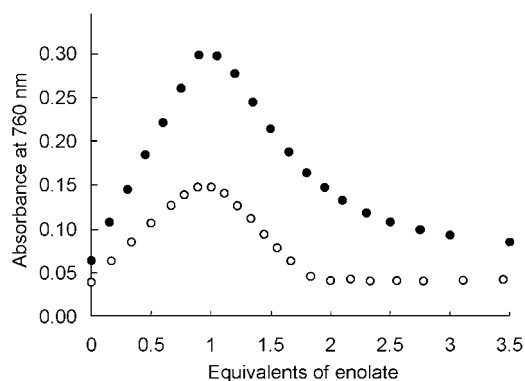


Figure 3. Absorbance at 760 nm of a 2.0 mM solution of **4**- $\text{Cu}(\text{OTf})_2$ (open circle) or **6**- $\text{Cu}(\text{OTf})_2$ (closed circle) in acetonitrile upon addition of **13**- $\text{Na}^+ \cdot [15]\text{crown-5}$.

much greater than the second binding constant (K_2). Therefore, when only one equivalent or less of the enolate is present, the systems can be treated simply as 1:1 complexes. The binding mode of the enolate of 1,3-cyclopentane dione (**14**) with the copper complexes of **4** and **6** are very similar to that of **13**.

A 2:1 binding stoichiometry was found from a decrease in absorbance of the binuclear copper(II) complex of receptor **5** at 460 nm upon titration of sodium enolate **13** in acetonitrile, as shown in Figure 4.

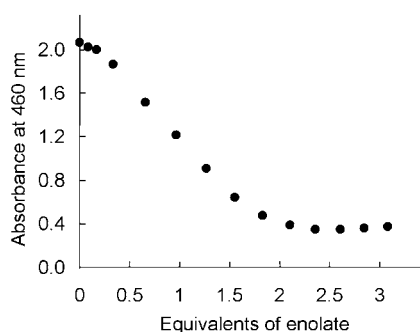


Figure 4. Titration curve for the **5**-CuCl₂ (2.09 mM) and **13**- Na⁺·[2.2.1]cryptand in acetonitrile.

Crystal structure: Extensive efforts were made trying to prepare crystals of the copper(II) complexes of **4–6** by slow evaporation of their methanol, water, or dichloromethane solutions. However, only extremely small needles that were not suitable for X-ray analysis were obtained. To solve this problem, 2,6-bis(benzylaminomethyl)pyridine (**7**) was synthesized, because it is structurally more rigid than its butyl analogue **6**. Slow evaporation of a dichloromethane solution of **7** and Cu(OTf)₂ in 1:1 molar ratio gave the complex as blue needles. X-ray analysis showed that the complex is **7**-Cu(OTf)₂·H₂O (Figure 5). The geometry of the copper(II)

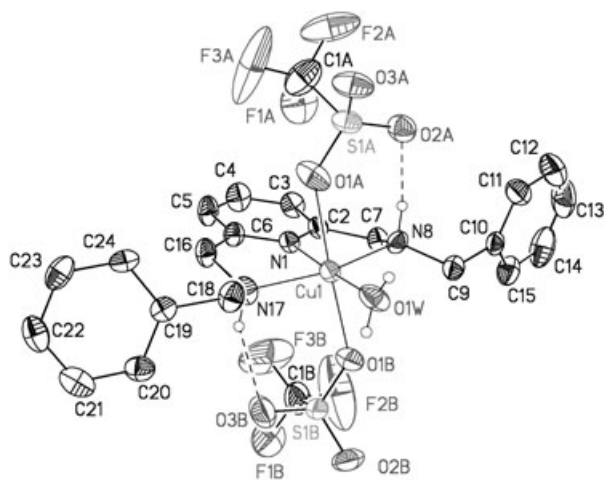


Figure 5. Molecular structure of **7**-Cu(OTf)₂·H₂O (ORTEP plot; 50% probability). Most hydrogen atoms have been removed for clarity. Dashed lines are indicative of H-bonding interactions. Selected interatomic distances [Å]: Cu1–N1 1.927(3), Cu1–N8 2.062(4), Cu1–N17 2.062(4), Cu1–O1A 2.479(4), Cu1–O1B 2.352(4), Cu1–O1W 1.945(3), N8–O2A 3.065(6), N17–O3B 2.996(5).

center is octahedral. The three nitrogen atoms of **7** and an oxygen atom of water coordinate to copper are in an approximate plane. The two triflate anions make the other two coordination bonds sitting on the axis. Each triflate forms a hydrogen-bond with the NH group with N–H···O distance of 3.00 to 3.07 Å.

Efforts to make crystals of receptor–copper(II)–enolate complexes were not successful.

Deprotonation studies: A key step in enzyme catalysis with an enolate intermediate is the deprotonation of carbon acid substrates using peptide bases with much lower conjugate acid pK_a values than the substrate. It was shown in experiments with receptors **1** and **2** that bases with lower conjugate acid pK_a values than the active methylene compounds 1,3-cyclohexanedione and 2-acetylcyclopentanone, respectively, could be used to deprotonate the carbon acids in the presence of the receptors and induce complex formation.^[5,7] The stabilization of the enolate of the carbon acids results in the observed pK_a shifts in acetonitrile.

UV spectroscopy was used with receptors **4**, **5**, and **6** to determine the extent of deprotonation of 2-acetylcyclopentanone and 1,3-cyclopentanedione in the presence of systematically selected bases. The strategy for selective deprotonation of the parent active methylene compound in the presence of the receptor is to optimize the base such that the pK_a of the conjugate acid of the base is lower than that of the carbon acid, but close to the pK_a of the carbon acid receptor complex. Sterically hindered amine or pyridine bases, whose conjugate acid pK_a values in acetonitrile have been previously reported, were used in our studies to induce complex formation between our receptors and the enolates **13** and **14**. Table 1 lists the enolates and organic bases (**15–18**)

Table 1. pK_a values of the conjugate acids of enolates and organic bases.

Compound	Number	pK _a in CH ₃ CN	pK _a in H ₂ O
	13	25.4 ^[7]	7.8 ^[17]
	14	19.2 ^[5]	4.5 ^[18]
	15	18.2 ^[5]	11.25 ^[19]
	16	14.2 ^[20]	6.81 ^[21]
	17	13.4 ^[5]	7.03 ^[22]
	18	–	4.95 ^[23]

used in the titrations with their conjugate acid pK_a values in both water and acetonitrile.

Figure 6 illustrates a UV/Vis titration study of 2-acetylcyclopentanone with organic bases in the presence of receptor **6**-Cu(OTf)₂. Titration of a 1:1 mixture of **6**-Cu(OTf)₂ and 2-acetylcyclopentanone with 1,2,2,5,5-pentamethylpiperidine (**15**) resulted in a spectral change (Figure 6a) almost identical to that of the titration of **6**-Cu(OTf)₂ with enolate

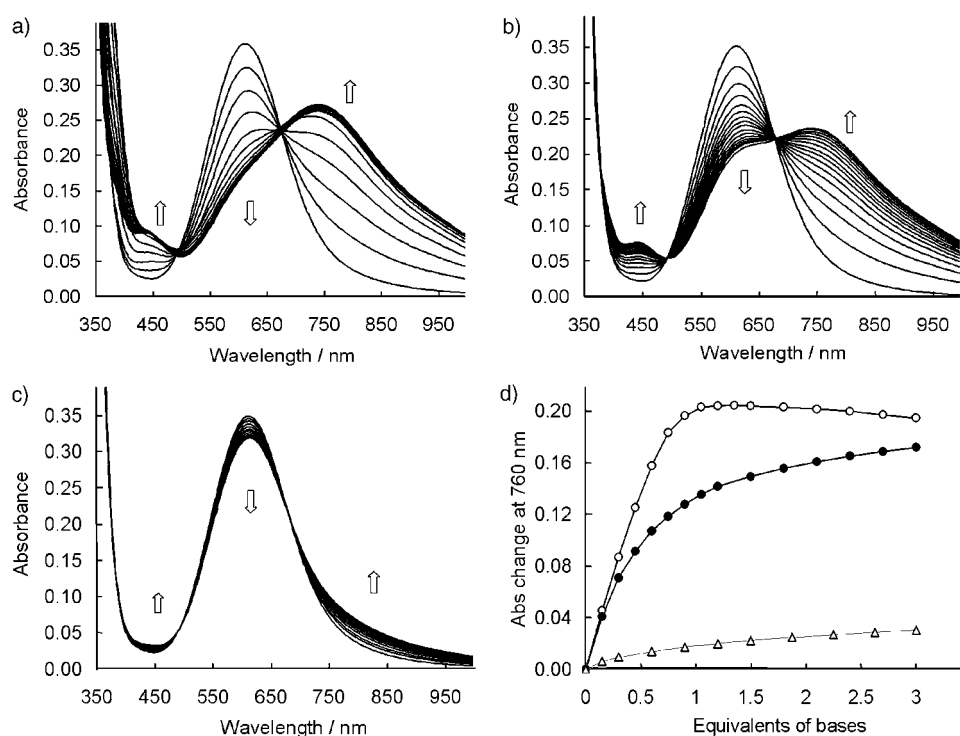


Figure 6. UV/Vis spectra of 2.0 mM **6**-Cu(OTf)₂ in the presence of one equivalent of 2-acetylcyclopentanone in acetonitrile upon titration of (a) **15**, (b) **17**, and (c) **18**. Plot d shows the absorbance changes at 760 nm of the titrations by **15** (○), **17** (●), and **18** (△).

13 (Figure 3), revealing that one equivalent of **15** can nearly quantitatively deprotonate 2-acetylcyclopentanone in the presence of the receptor complex. Titrations with weaker bases 2-dimethylaminopyridine (**17**) (Figure 6b) and 2,6-di-*tert*-butylpyridine (**18**) (Figure 6c) also caused similar but smaller spectral changes.

Figure 6d further illustrates that one equivalent of 2-dimethylaminopyridine (**17**) with a conjugate acid pK_a of 13.4 in acetonitrile is capable of deprotonating 61 % of 2-acetylcyclopentanone (pK_a of 25.4 in acetonitrile) to form an enolate complex with receptor **6**-Cu(OTf)₂ under the titration conditions. The observed pK_a of the substrate carbon acid (SH) was calculated from the deprotonation ratio and the pK_a^{BH} of the base (BH⁺) to be 13.0 using Equation (1) (for details, see Experimental Section).

$$pK_a = pK_a^{BH} - \log\left(\frac{[S^-][BH^+]}{[SH][B]}\right) \quad (1)$$

The pK_a of 2-acetylcyclopentanone is therefore shifted by 12.4 by the presence of **6**-Cu(OTf)₂, as its normal pK_a is 25.4 in acetonitrile.

Similarly, the deprotonation studies of 2-acetylcyclopentanone and 1,3-cyclopentanedione in the presence of our other copper(II) complexes of **4** and **5** were performed and the results are listed in Table 2. The pK_a shifts induced by the complex receptors are related to the counterions and the structures of the ligands and carbon acids. The Cu(OTf)₂ complexes of **4** and **6** induce a pK_a shift of about 12.4–

12.7 units on 2-acetylcyclopentanone, whereas the CuCl₂ complexes induce 7.0–7.6 unit shifts on the same acid. The pK_a shift of 1,3-cyclopentanedione (5.7 units) induced by the Cu(OTf)₂ complexes of **4** and **6** is about 7 units smaller than that of 2-acetylcyclopentanone. Comparable or slightly larger pK_a shifts were found for the copper(II) complexes of the cage-like molecule **4** relative to the acyclic simple molecule **6**. Binuclear complex **5**-2(CuCl₂) induces a significantly bigger pK_a shift than mononuclear complex **4**-CuCl₂ (10.6 versus 7.6) on 2-acetylcyclopentanone. Hence, the two metals in **5** are cooperative. The shifts of 5.7–12.7 units listed in Table 2 are comparable with the 10 unit pK_a shift found by Kimura et al. with receptor **3**, which similarly utilizes a metal cation to activate a carbonyl and subsequently reduce the pK_a of the α methylene proton.^[10]

Table 2. pK_a shifts of 2-acetylcyclopentanone (ACP) and 1,3-cyclopentanedione (CP) induced by Cu^{II} complex receptors in acetonitrile at 25 °C.

Carbon acid (2.0 mM)	Receptor (2.0 mM)	Base (2.0 mM)	Deprotonation ratio ^[a] [%]	pK_a	pK_a shift ^[b]
ACP	4 -Cu(OTf) ₂	17	68	12.7	12.7
ACP	6 -Cu(OTf) ₂	17	61	13.0	12.4
ACP	4 -CuCl ₂	15	61	17.8	7.6
ACP ^[c]	5 -CuCl ₂ ^[d]	16 ^[e]	39	14.8	10.6
ACP	6 -CuCl ₂	15	45	18.4	7.0
CP	4 -Cu(OTf) ₂	17	47	13.5	5.7
CP	6 -Cu(OTf) ₂	17	48	13.5	5.7

[a] The ratio of enolate complex concentration related to the initial concentration of the ketone ACP or CP. [b] The pK_a difference of the carbon acid in the absence or presence of the Cu^{II} receptor. [c] 2.14 mM. [d] 0.97 mM. [e] 2.91 mM.

The above trends shown in Table 2 can be explained based on the thermodynamic cycle of receptor(R)-substrate(SH) binding illustrated in Figure 7 in which two routes to the bound substrate anion are shown. The first path, K_1 – K_2 , represents deprotonation of the substrate before binding to the host. In the second path, K_4 – K_3 , host–substrate binding occurs prior to deprotonation. Equilibrium constant K_1 denotes the acid dissociation constant of the free carbon acid, whereas K_3 signifies that of the substrate bound by the receptor. The ratio of the acid dissociation constants, K_3/K_1 , is equal to the ratio of the binding constants of the substrate

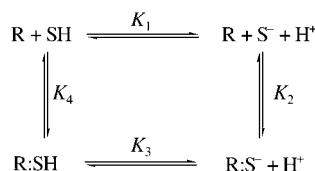


Figure 7. Thermodynamic cycle for substrate (SH) association and substrate deprotonation in the presence of a receptor (R).

and enolate with the receptor, K_2/K_4 . The binding constants (K_4) of 2-acetylcyclopentanone with receptors in acetonitrile were measured by UV/Vis titrations to be $87(\pm 23)\text{M}^{-1}$ with **4**-Cu(OTf)₂, $19(\pm 9)\text{M}^{-1}$ with **6**-Cu(OTf)₂, $36(\pm 12)\text{M}^{-1}$ with **4**-CuCl₂, and $<10\text{M}^{-1}$ with **6**-CuCl₂. The relatively narrow range of K_4 values suggests that the $\text{p}K_{\text{a}}$ shifts are mainly determined by the K_2 values which are the binding constants of the enolates with the receptors. Therefore, the large shift in the $\text{p}K_{\text{a}}$ of the carbon acids in the presence of our copper(II) host complexes is attributed to strong charge-pairing or coordination interaction between the enolate anion and metal center. The enolate–metal interaction is in competition with the association of the counterion with the metal complex. Because chloride has a much stronger interaction with copper(II) than triflate, the $\text{p}K_{\text{a}}$ shifts induced by the CuCl₂ complexes of **4** and **6** are around five units lower than those induced by the Cu(OTf)₂ complexes (Table 2).

The very similar $\text{p}K_{\text{a}}$ shifts induced by the copper(II) complexes of the cage-like molecule **4** and the acyclic simple molecule **6** suggest that O–Cu coordination bonds are dominant binding forces between the diketone enolates and the receptors. No significant cooperative hydrogen-bonding or solvophobic interaction attributed to the amide linkages and cage-like cavity in **4** were observed under the experimental conditions in acetonitrile. Enolates of 1,3-diketones are well-known ligands for copper(II). Enolate of 2-acetylcyclopentanone can form a six-membered chelating ring with a metal center leading to strong binding. The binding of the enolate of 1,3-cyclopentanedione, however, is much weaker because the orientation of the two oxygen atoms fixed on the ring is not favorable for chelation. Therefore, the $\text{p}K_{\text{a}}$ shifts of 1,3-cyclopentanedione induced by the copper(II) complex receptors are much smaller than that of 2-acetylcyclopentanone (Table 2). Because the binding of enolates with receptors is in competition with the counterions of copper(II), the receptors with noncoordinating counterions such as triflate can bind an enolate stronger and therefore induce a bigger $\text{p}K_{\text{a}}$ shift than those with coordinating counterions such as chloride.

Conclusion

The use of receptors **4**, **5**, and **6** incorporating metal ions, specifically copper(II), has been shown to reduce the $\text{p}K_{\text{a}}$ value of 1,3-diketone carbon acids in acetonitrile by as much as 12 $\text{p}K_{\text{a}}$ units. The relatively large reduction in $\text{p}K_{\text{a}}$

value achieved by the complex is attributed to the electrostatic or coordination interaction between the anionic π system of the enolate and the copper(II) center. As in the active site of class II aldolases, electrostatic induction is more effective in stabilizing highly reactive intermediates and inducing $\text{p}K_{\text{a}}$ shifts of carbon acids than traditional hydrogen bonds.

Experimental Section

General considerations: ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 400 or Varian Unity Plus 300 spectrometer. UV/Vis measurements were performed on a Beckman DU-70 UV/Vis spectrometer. Low-resolution and high-resolution mass spectra were measured with Finnigan TSQ70 and VG Analytical ZAB2-E instruments, respectively. 1-[[[(1,1-Dimethylethoxy)carbonyl]aminomethyl]-3,5-bis(aminomethyl)-2,4,6-triethylbenzene (**8**) and 1,3-bis[[[(1,1-Dimethylethoxy)carbonyl]aminomethyl]-5-aminomethyl-2,4,6-triethylbenzene (**11**)] were synthesized according to reference [16]. All other chemicals were purchased from Aldrich or Acros and used without further purification.

1,6-Bis(*n*-butylaminomethyl)pyridine (6): A mixture of 2,6-pyridinedicarboxaldehyde (117 mg, 0.867 mmol), *n*-butylamine (0.188 mL, 1.91 mmol), and 3 Å molecular sieves (ca. 20 beads) in anhydrous methanol (4 mL) was stirred at room temperature for 3 h under argon. NaBH₄ (150 mg, 4.0 mmol) was added. The reaction mixture was stirred for 4 h and filtered through celite. The filtrate was concentrated by evaporation and acidified by adding 1 N HCl to decompose the excess borohydride. The mixture was adjusted to strongly basic by adding 10% aqueous NaOH solution (ca. 5 mL), and then extracted with dichloromethane (3 × 10 mL). The organic layers were combined, washed once with water (5 mL), dried over MgSO₄, evaporated under reduced pressure, and dried in vacuum to give a pale yellow oil (0.210 g) in 97% yield. ¹H NMR (400 MHz, CDCl₃, TMS): δ = 7.58 (t, ³J(H,H) = 7.6 Hz, 1H), 7.16 (d, ³J(H,H) = 7.6 Hz, 2H), 3.88 (s, 4H), 2.65 (t, ³J(H,H) = 7.2 Hz, 4H), 1.93 (br s, 2H), 1.56–1.48 (m, 4H), 1.36 (p, ³J(H,H) = 7.3 Hz, 4H), 0.92 ppm (t, ³J(H,H) = 7.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 155.38, 132.67, 116.26, 51.24, 45.34, 28.26, 16.43, 9.96 ppm; HRMS (CI): m/z : 250.22807 (calcd for C₁₅H₂₈N₃ ([M+H]⁺): 250.22832).

1,6-Bis(benzylaminomethyl)pyridine (7): Compound **7** was synthesized by using the same procedure as for **6** from 2,6-pyridinedicarboxaldehyde (126 mg, 0.93 mmol) and benzylamine (200 mg, 1.87 mmol) as a pale yellow oil (288 mg) in 98% yield. ¹H NMR (250 MHz, CDCl₃, TMS): δ = 7.57 (t, ³J(H,H) = 7.6 Hz, 1H), 7.36–7.23 (m, 10H), 7.16 (d, ³J(H,H) = 7.6 Hz, 2H), 3.90 (s, 4H), 3.83 (s, 4H), 2.21 ppm (br s, 2H); ¹³C NMR (62.5 MHz, CDCl₃): δ = 159.12, 140.10, 136.65, 128.26, 128.11, 126.82, 120.33, 54.36, 53.42 ppm; HRMS (CI): m/z : 318.19699 (Calcd for C₂₁H₂₄N₃ ([M+H]⁺): 318.19702).

7,23-Bis(*N'*-*t*-Boc-aminomethyl)-6,8,22,24,34,36-hexaethyl-3,11,19,27,33,35-hexaazopentacyclo[27.3.1.1^{5,9}.1^{13,17}.1^{21,25}]hexatriacont-1(33),5,7,9(36),13,15,17(35),21,23,25(34),29,31-dodecaene-2,12,18,28-tetrone (9): A solution of 1-[[[(1,1-dimethylethoxy)carbonyl]aminomethyl]-3,5-bis(aminomethyl)-2,4,6-triethylbenzene (**8**) (0.647 g, 1.85 mmol) and triethylamine (2.6 mL, 19 mmol) in dry dichloromethane (150 mL) was cooled with an ice-water bath under argon. With stirring, 1,6-pyridinedicarboxyl dichloride (0.378 g, 1.85 mmol) was added in one portion as a solid. The reaction solution was stirred at 0°C for 30 min and then at room temperature for 2 h. The reaction mixture was concentrated by evaporation under reduced pressure to about 5 mL. Ethyl acetate (10 mL) was added to facilitate the precipitation of triethylamine hydrochloride. The precipitate was removed by filtration. The filtrate was concentrated by evaporation and subjected to column chromatography (silica gel, CH₂Cl₂/acetone 100:5 to 100:30 v/v) to give an off-white solid in 46% yield (0.410 g). R_f = 0.6 (silica gel, CH₂Cl₂/acetone 4:1 v/v); ¹H NMR (400 MHz, CDCl₃, TMS): δ = 8.45 (d, ³J(H,H) = 8.0 Hz, 4H), 8.07 (t, ³J(H,H) = 7.6 Hz, 2H), 7.22 (br s, 4H), 4.68 (d, ³J(H,H) = 4.4 Hz,

8H), 4.42 (br s, 6H), 2.75 (q, $^3J(\text{H,H})=7.5$ Hz, 8H), 2.66 (q, $^3J(\text{H,H})=7.5$ Hz, 4H), 1.44 (s, 18H), 1.24–1.16 ppm (m, 18H); ^{13}C NMR (100 MHz, CDCl_3): $\delta=163.41, 155.25, 148.66, 144.84, 144.57, 138.98, 131.18, 125.77, 79.79, 38.39, 28.37, 23.47, 22.94, 16.75, 16.05$ ppm; HRMS (CI): m/z : 961.55559 (calcd for $\text{C}_{54}\text{H}_{73}\text{N}_8\text{O}_8$ ($[\text{M}+\text{H}^+]$): 961.55514).

7,23-Bis(aminomethyl)-6,8,22,24,34,36-hexaethyl-3,11,19,27,33,35-hexaazopentacyclo[27.3.1.1^{5,9}.1^{13,17}.1^{21,25}]hexatriaconta-1(33),5,7,9(36),13,15,17(35),21,23,25(34),29,31-dodecaene-2,12,18,28-tetrone (10): A solution of **9** (385 mg, 0.401 mmol) in dichloromethane–trifluoroacetic acid (1:1 (v/v); 5 mL) was stirred at room temperature for 4 h and then concentrated by evaporation under reduced pressure to remove most of the acid. The resulting oil was redissolved in dichloromethane (10 mL) and washed with 20% K_2CO_3 aqueous solution. The aqueous phase was separated and extracted with dichloromethane (2×10 mL). The organic layers were combined, dried over Na_2SO_4 , evaporated to dryness, and dried in vacuum to give a pale pink solid (290 mg) in 95% yield. ^1H NMR (400 MHz, CDCl_3 , TMS): $\delta=8.44$ (d, $^3J(\text{H,H})=7.6$ Hz, 4H), 8.04 (t, $^3J(\text{H,H})=7.8$ Hz, 2H), 7.85 (br s, 4H), 4.65 (br s, 8H), 3.89 (s, 4H), 2.75 (q, $^3J(\text{H,H})=7.3$ Hz, 8H), 2.59 (q, $^3J(\text{H,H})=7.3$ Hz, 4H), 1.80 (br s, 2 NH_2 and H_2O), 1.23–1.13 ppm (m, 18H); ^{13}C NMR (62.5 MHz, CDCl_3): $\delta=163.73, 148.85, 143.84, 143.38, 138.65, 131.15, 125.59, 39.01, 38.54, 22.90, 16.56, 15.96$ ppm; HRMS (CI): m/z : 761.45092 (calcd for $\text{C}_{44}\text{H}_{57}\text{N}_8\text{O}$ ($[\text{M}+\text{H}^+]$): 761.45028).

2,16,18,32,45,47-Hexaethyl-5,13,21,29,34,42,44,46,48-nonaazaheptacyclo[15.15.11.1^{3,31}.1^{7,11}.1^{15,19}.1^{23,27}.1^{36,40}]octatetraconta-1,3(45),7,9,11(48),15,17,19(47),23,25,27(46),31,36,38,40(44)-pentadecaene-6,12,22,28-tetrone (4): In a 250-mL flask equipped with a Dean–Stark trap, a solution of 2,6-pyridinedicarboxaldehyde (51 mg, 0.38 mmol) and **10** (288 mg, 0.38 mmol) in benzene (150 mL) and methanol (5 mL) was refluxed for 1 h under argon. The reaction mixture was concentrated to about 50 mL by distillation off the solvents and then cooled to room temperature. Anhydrous methanol (39 mL) and NaBH_4 (140 mg, 3.7 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 4 h and evaporated to dryness. The residue was partitioned into dichloromethane (15 mL) and 1 N NaOH aqueous solution (10 mL). The aqueous phase was extracted with dichloromethane (2×10 mL). The organic layers were combined, dried over MgSO_4 , evaporated to dryness. The residue was separated by column chromatography on silica gel (dichloromethane/acetonitrile/methanol 100:30:(0–10) v/v) to give a white solid (260 mg) in 80% yield. ^1H NMR (400 MHz, CDCl_3 , TMS): $\delta=8.49$ (d, $^3J(\text{H,H})=7.8$ Hz, 4H), 8.04 (t, $^3J(\text{H,H})=7.8$ Hz, 2H), 7.72 (br s, 4H), 7.59 (t, $^3J(\text{H,H})=7.6$ Hz, 1H), 7.08 (d, $^3J(\text{H,H})=7.6$ Hz, 2H), 4.75 (dd, $^2J(\text{H,H})=15.0$, $^3J(\text{H,H})=4.7$ Hz, 4H), 4.65 (dd, $^2J(\text{H,H})=15.0$, $^3J(\text{H,H})=4.0$ Hz, 4H), 4.08 (s, 4H), 3.84 (s, 4H), 2.94–2.82 (m, 4H), 2.68–2.60 (m, 8H), 2.61 (br s, 2H), 1.25–1.15 ppm (m, 18H); ^{13}C NMR (100 MHz, CDCl_3): $\delta=163.97, 158.01, 149.00, 144.77, 144.45, 138.48, 136.50, 134.30, 130.71, 125.99, 120.26, 55.72, 47.90, 38.65, 23.04, 16.18, 15.81$ ppm; HRMS (CI): m/z : 864.49280 (calcd for $\text{C}_{51}\text{H}_{62}\text{N}_9\text{O}_4$ ($[\text{M}+\text{H}^+]$): 864.49248).

Pyridine-2,6-dicarboxylic acid bis[3,5-bis(aminomethyl)-2,4,6-triethylbenzylamide] (12): To a round-bottomed flask equipped with an addition funnel, condenser and a Dean–Stark trap, was added **11** (3.04 g, 6.76 mmol) in benzene. The solution was refluxed and the water removed. The benzene was then removed in vacuo and the residue dissolved in anhydrous THF (50 mL); previously distilled over sodium and benzophenone ketyl and triethylamine (3.42 g, 33.8 mmol, previously distilled from calcium hydride). Anhydrous potassium carbonate was then added. 2,6-Pyridine dicarbonyl dichloride (0.69 g, 3.38 mmol) was added dropwise in anhydrous THF (25 mL). The reaction was monitored by thin layer chromatography. The solution was vacuum filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica, ethyl acetate). The Boc protecting groups were removed in an aqueous solution of trifluoroacetic acid (100 mL; 1:1 v/v) and dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under vacuum and the residue was dissolved in a minimum amount of water. Chloride anion exchange was accomplished by using Amberlite IRA-400 (Cl) to yield a white solid. Continuous extraction for the resulting solid from a 5 N solution of sodium hydroxide using dichloromethane gave **12** as a foamy

solid (3.9 g, 92%). ^1H NMR (300 MHz, CDCl_3 , TMS): $\delta=8.35$ (d, 2H, 7.9 Hz), 7.99 (t, 1H, 7.9 Hz), 7.54 (bs, 2H), 4.63 (d, $^3J(\text{H,H})=4.9$ Hz, 4H), 3.83 (s, 8H), 2.82 (q, $^3J(\text{H,H})=7.6$ Hz, 4H), 2.7 (q, $^3J(\text{H,H})=7.4$ Hz, 8H), 1.86 (bs, 8H), 1.2 ppm (t, $^3J(\text{H,H})=7.4$ Hz, 12H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=163.56, 149.33, 142.22, 139.08, 131.52, 125.58, 39.61, 38.44, 23.12, 17.06, 16.85$ ppm; IR (deposit from CDCl_3 on NaCl): $\tilde{\nu}=3294$ cm^{-1} (NH) and 1659 cm^{-1} (C=O); HRMS (CI $^+$): m/z : 630.449 (calcd for $\text{C}_{37}\text{H}_{56}\text{N}_7\text{O}_2$ ($[\text{M}+\text{H}^+]$): 630.449).

2,16,18,32,45,47-Hexaethyl-5,13,21,29,34,42,44,46,48-nonaazaheptacyclo[15.15.11.1^{3,31}.1^{7,11}.1^{15,19}.1^{23,27}.1^{36,40}]octatetraconta-1,3(45),7,9,11(48),15,17,19(47),23,25,27(46),31,36,38,40(44)-pentadecaene-6,12-dione (5): To a 500-mL round-bottomed flask equipped with an addition funnel, a condenser and a Dean–Stark trap was added **12** (0.500 g, 0.794 mmol) followed by toluene (550 mL). The solution was heated to reflux and the azeotrope of water was received over 4 Å molecular sieves in the Dean–Stark trap. To the solution was then added a solution of 2,6-pyridine dicarboxaldehyde (0.214 g, 1.59 mmol) in toluene (275 mL) over 6 h at room temperature. The reaction mixture was then heated to reflux for 18 h. The remaining dialdehyde was then added over 6 h and the solution again heated to reflux for 18 h. The solution was then cooled to room temperature and the toluene removed in vacuo. To residue was dissolved in anhydrous methanol (100 mL) under argon. To the solution was then added NaBH_4 (365 mg, 9.65 mmol). The solution was then stirred for three hours under argon. The reaction was quenched with water and the methanol removed in vacuo. The residue was dissolved in 1 N NaOH (100 mL) and extracted with dichloromethane (3×100 mL). The combined organic layers were washed with saturated brine, dried over MgSO_4 , filtered, and the solvent was removed under vacuum. The resulting solid was purified by column chromatography (silica, 1% ammonia-saturated methanol in dichloromethane) to yield **5** as a yellow solid (496 mg, 75%). ^1H NMR (300 MHz, CDCl_3 , TMS): $\delta=8.35$ (d, $^3J(\text{H,H})=7.4$ Hz, 2H), 8.16 (bs, 2H), 8.06 (t, $^3J(\text{H,H})=7.4$ Hz, 1H), 7.59 (t, $^3J(\text{H,H})=7.4$ Hz, 2H), 7.08 (d, $^3J(\text{H,H})=7.4$ Hz, 2H), 4.64 (d, $^3J(\text{H,H})=4.6$ Hz, 4H), 3.93 (s, 8H), 3.78–3.77 (m, 8H), 2.88–2.74 (m, 8H), 2.62–2.55 (m, 4H), 1.82 (s, 4H), 1.17–1.08 ppm (m, 18H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=164.4, 159.8, 150.3, 144.3, 138.8, 137.5, 135.22, 132.0, 129.3, 126.3, 120.9, 118.3, 56.2, 48.6, 38.7, 23.3, 23.2, 16.9, 16.6$ ppm; HRMS (CI $^+$): m/z : 836.534 (calcd for $\text{C}_{51}\text{H}_{66}\text{N}_9\text{O}_2$: 836.533).

Titration Studies

Stock solutions of 4–6 and their copper(II) complexes: 10.0 mM solutions of **4–6**, and 50.0 mM solutions of CuCl_2 and $\text{Cu}(\text{OTf})_2$ in acetonitrile were made separately in 10-mL flasks by weighing calculated amounts of the anhydrous compounds and adding HPLC grade acetonitrile to scale. 5.0 mM stock solutions of **4–CuCl₂**, **4–Cu(OTf)₂**, **5–2(CuCl₂)**, **6–CuCl₂**, and **6–Cu(OTf)₂** were made in 10-mL flasks by adding 5.00 mL of the 10.0 mM **4–6** solutions, calculated amounts (1.00 or 2.00 mL) of the 50.0 mM copper(II) salt solutions, and diluted with acetonitrile to scale.

Sodium enolate solutions of 13 and 14: The sodium enolate solutions were made freshly before each titration by mixing the ketones with one equivalent of sodium methoxide, because they are not stable, as revealed by development of yellow color and changes on ^1H NMR spectra upon standing. Then [15]crown-5 or [2.2.1]cryptand were added to complex the sodium cation and increase solubility. A 0.94 M sodium methoxide solution was made directly from 216 mg of sodium metal and anhydrous methanol in a 10-mL flask. The methoxide solution was transferred into a polyethylene bottle and kept under argon. The 200 mM solutions of $\text{Na}^+\text{--}13$ or $\text{Na}^+\text{--}14$ were made by mixing 0.667 mL of 300 mM 2-acetylcyclopentanone or 1,3-cyclopentanedione and [15]crown-5 (1:1 mol/mol) in acetonitrile with the 0.94 M NaOMe solution (0.213 mL) and diluted with acetonitrile to 1.00 mL.

General procedure for titrations: All the UV/Vis titrations were performed in a 1-cm quartz cell equipped with a silicon septum. The solutions to be titrated (1.00 mL) were made directly in the cell by adding calculated amounts of stock solutions and acetonitrile solvent using Hamilton gas-tight syringes. The solutions were mixed by shaking with hand. Absorbance spectrum of the titrand was recorded. Aliquots (usually 0.1 equivalents) of titrant were added, and spectra were recorded after each addition of the titrant. In the cases of titrations of copper(II) com-

plexes with the neutral ketones (2-acetylcyclopentanone or 1,3-cyclopentanedione) or their sodium enolates (**13** or **14**), the titrant solutions contained the copper(II) complexes at the same concentrations as the titrand solutions, so that the copper(II) complex concentrations kept constant during the titrations. In the cases of the copper(II) complexes and the ketones being titrated with the organic bases (**15–18**), no copper(II) complexes were presented in the titrant solutions. Instead, high concentration titrants (150 times of the titrand concentration) were used, and the absorbance spectra were corrected for the dilution caused by the addition of titrants that was usually less than 3% of the volume.

Calculation of the pK_a shifts: For the acid–base equilibrium between a carbon acid (the substrate SH) and a base (B), the pK_a of the carbon acid can be calculated from the deprotonation ratio (R) and the pK_a of the conjugate acid of the base (pK_a^{BH}) according to Equations (2) and (3).



$$pK_a = pK_a^{BH} - \log\{([S^-][BH^+])/([SH][B])\} \quad (3)$$

Since $R = [S^-]/[SH]^i$, we have $[BH^+] = [S^-] = R[SH]^i$, $[SH] = (1-R)[SH]^i$, and $[B] = [B]^i - R[SH]^i$, where $[SH]^i$ and $[B]^i$ are the initial total concentrations of the acid and base, Equation (3) becomes Equation (4).

$$pK_a = pK_a^{BH} - \log\{([R][SH]^i)^2/((1-R)[SH]^i([B]^i - R[SH]^i))\} \quad (4)$$

The deprotonation ratio (R) was obtained from two titrations. First, a solution of receptor-copper(II) complex was titrated with sodium enolate (**13** or **14**) to get the absorbance change caused by binding of one equivalent of the enolate (Figure 2 and Figure 3, for example). Second, in the presence of the receptor-copper(II) complex, the carbon acid was titrated with an organic base (Figure 6, for example) to determine the absorbance change caused by the formation of enolate complex in the presence of the base. Comparison of the absorbance changes in these two titrations gave the deprotonation ratio. For example, addition of one equivalent of enolate **13** into 2.0 mM **6**-Cu(OTf)₂ solution caused an absorbance change of 0.23 at 760 nm (Figure 3), and addition of one equivalent of organic base **17** into 2.0 mM 2-acetylcyclopentanone, which is the carbon acid of enolate **13**, and 2.0 mM **6**-Cu(OTf)₂ solution caused an absorbance change of 0.14 at the same wavelength (Figure 6d). Thus, the deprotonation ratio was $0.14/0.23 = 0.61$. The pK_a of **17** (pK_a^{BH}) is 13.4 in acetonitrile, and the initial concentrations of the carbon acid ($[SH]^i$) and base ($[B]^i$) were both 0.002 M. Therefore, the observed pK_a of 2-acetylcyclopentanone was calculated according to Equation (5).

$$pK_a = 13.4 - \log\{((0.61 \times 0.002)^2)/((1-0.61) \times 0.002 \times (0.002 - 0.61 \times 0.002))\} = 13.0 \quad (5)$$

X-ray structure analysis: Crystals of **7**-Cu(OTf)₂·H₂O were prepared as blue needles by slow evaporation of a solution of **7** (22 mg, 0.070 mmol) and Cu(OTf)₂ (25 mg, 0.070 mmol) in dichloromethane (0.5 mL). The data crystal was cut from a long needle and had approximate dimensions of $0.36 \times 0.11 \times 0.09$ mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoK α radiation ($\lambda = 0.71073$ Å). A total of 309 frames of data were collected using ω scans with a scan range of 1.1° and a counting time of 181 s per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 3. Data reduction was performed by using DENZO-SMN.^[24] The structure was solved by direct methods using SIR97^[25] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.^[26] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to $1.2 \times U_{eq}$ of the attached atom ($1.5 \times U_{eq}$ for methyl hydrogen atoms). The hydrogen atoms on the water molecule and on the nitrogen atoms were observed in a ΔF map and refined with isotropic displacement parameters. One hydrogen atom on O1W did not refine well, H1wb. The O–H bond length refined to below

Table 3. Crystal data and structure refinement for **7**-Cu(OTf)₂·H₂O.

empirical formula	C ₂₃ H ₂₅ CuF ₆ N ₃ O ₇ S ₂
formula weight	697.12
temperature [K]	153(2)
wavelength [Å]	0.71073
crystal system	orthorhombic
space group	$P2_12_12_1$
unit cell dimensions	
a [Å]	10.3304(2)
b [Å]	12.4782(2)
c [Å]	22.0691(5)
volume [Å ³]	2844.81(10)
Z	4
ρ_{calc} [Mg m ⁻³]	1.628
μ [mm ⁻¹]	1.001
$F(000)$	1420
crystal size [mm]	$0.36 \times 0.11 \times 0.09$
θ range for data collection	3.16 to 27.48°
index ranges	$-13 \leq h \leq 13$, $-16 \leq k \leq 16$, $-28 \leq l \leq 28$
reflections collected	6427
independent reflections	6427
completeness to $\theta = 27.48^\circ$ [%]	99.8
absorption correction	none
refinement method	full-matrix least-squares on F^2
data/restraints/parameters	6427/0/381
goodness-of-fit on F^2	1.003
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0491$, $wR2 = 0.0928$
R indices (all data)	$R1 = 0.1004$, $wR2 = 0.1112$
absolute structure parameter	0.007(16)
extinction coefficient	none
largest diff. peak and hole [eÅ ⁻³]	0.663 and -0.615

0.6 Å and its U_{iso} went negative. As a result, the O–H bond lengths were idealized at 0.8 Å by moving the H atom along its O–H bond vector. The subsequent H atom positions were refined riding on the oxygen atom position with U_{iso} set to $1.5 \times U_{eq}$ for the oxygen atom. The absolute structure was determined by the method of Flack.^[27] The Flack x parameter refined to $0.01(2)$ for the configuration given. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0372P)^2 + (0.387P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.111 , with $R(F)$ equal to 0.0491 and a goodness of fit, $S = 1.00$. Definitions used for calculating $R(F)$, $R_w(F^2)$ and the goodness of fit, S , are given below.^[28] The data were checked for secondary extinction but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the *International Tables for X-ray Crystallography* (1992).^[29] Figure 5 was generated by using SHELXTL/PC.^[30]

CCDC-247492 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/contents/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

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