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Dynamic Multi-Component Hemiaminal Assembly

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Abstract

A simple approach to generating *in situ* metal templated tris-(2-picolyl)amine-like multi-component assemblies with potential applications in molecular recognition and sensing is reported. The assembly is based on the reversible covalent association between di-(2-picolyl)amine and aldehydes. Zinc ion is the best for inducing assembly among the metal salts investigated, while 2-picolinaldehyde is the best among the heterocyclic aldehydes studied. Although an equilibrium constant of $6.6 \times 10^3 \text{ M}^{-1}$ was measured for the assembly formed by 2-picolinaldehyde, di-(2-picolyl)amine, and zinc triflate, the equilibrium constants for other systems are in the 10^2 M^{-1} range. X-ray structural analysis revealed that zinc adopts a trigonal bipyramidal geometry within the assembled ligand. The diversity and equilibrium of the assemblies are readily altered by simply changing concentrations, varying components, or adding counter anions.

Keywords

reversible covalent bond; dynamic combinatorial library; component exchange; multi-component assembly; hemiaminal

Introduction

Dynamic combinatorial libraries (DCLs)^[1] used for receptor creation and subsequent molecular recognition have often employed reversible covalent bond formation.^[2] One of the most widely explored reversible associations is imine or hemiaminal formation from carbonyls and primary amines. Mohr^[3] and Zimmerman^[4] developed a series of trifluoroacetyl based reactants. Upon nucleophilic addition to the carbonyls, the trifluoroacetyl form is converted into the hemiaminal form.^[5] Besides this strategy, dynamic imine formation between carbonyls and primary amines has also been incorporated into various systems by Lehn,^[6] Sanders,^[7] Chin^[8] and others.^[9]

The reaction between carbonyls and secondary amines results in hemiaminals, enamines, or iminium salts.^[10] However, secondary amines are more sterically bulky and thereby often less nucleophilic than primary amines, and hence, their addition reactions are more sluggish. As a result, secondary amines have not been as extensively explored as primary amines within the context of reversible covalent bond chemistry.^[11] Yet, the reversible reaction of secondary amines with carbonyls would lead to a further increase in the chemical diversity applicable to DCLs.

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The use of DCLs for creating metal-ligand complexes could be applied to chemical sensing^[12] and metal mediated catalysis.^[13] As one example, tris-(2-picolyl)amine (TPA) ligands bind a variety of metal ions, including Ni^{2+} , Co^{2+} , Cu^{2+} , Zn^{2+} , and Fe^{2+} , with high affinity.^[14] Canary and coworkers studied chiral TPA derivatives for the purpose of identification of absolute configuration.^[15] Our group has incorporated the TPA motif into sensing ensembles for detection and differentiation of phosphate anions.^[16] Further, copper-TPA complexes have been used to promote atom transfer radical polymerization reactions.^[17] DCLs of TPA ligands could be applied to these same ends.

We are initiating a project to create reversible covalent bond assembly templated by metals for ultimate use in cross-reactive arrays.^[18] In this regard, our group recently explored the use of 2-picolinaldehyde (2-PA) and derivatives as electrophilic agents for condensation with primary amines^[19] or secondary alcohols.^[20] A driving force for imine or acetal formation was the loss of water. However, loss of water is not an option for the reaction of secondary amines with 2-PA unless iminium salts are formed with the assistance of a Brønsted acid, and as a result, the reactions tend to lead to hemiaminals. Therefore, we postulated that the reaction of 2-PA and di-(2-picolyl)amine (DPA) had the potential to afford a dynamic metal templated assembly that creates TPA-like ligand systems (Eq. 1).

(Eq. 1)

Results and Discussion

Design

2-Picolinaldehyde (2-PA) does not react with DPA to any detectable extent in acetonitrile at room temperature to form the tripyridine system **1** (Eq. 1). However, electrophilic activation of 2-acylpyridine analogs toward weak nucleophiles, such as alcohols, by both Brønsted and Lewis acids *via* chelation control, has been recently reported by us^[20] and Lehn.^[21] We therefore set out to examine the ability of metal based Lewis acids to facilitate DPA addition. DPA is a known metal ligand, and chelation of the secondary amine to a metal would impede nucleophilic addition to an aldehyde. Thus, a careful balance between aldehyde activation and coordination of the metal to the DPA must be created in order to shift the equilibrium toward the formation of complex **1**: MX_n (Scheme 1).

Metal salts screen

We screened a series of metal salts using 2-PA and DPA in a 1: 1: 1 stoichiometry. The reaction mixture was stirred overnight and studied by ^1H NMR and ESI-MS, and the results are listed in Table 1.

In the case of $\text{Zn}(\text{OTf})_2$, a substantial amount of complex was formed. The decrease of the 2-PA aldehyde signal at 10 ppm in conjunction with appearance of two new resonances at 5.4 and 6.2 ppm suggests that a new covalent bond was formed between the carbonyl carbon of 2-PA and the secondary amine nitrogen of DPA, producing a hemiaminal. Moreover, four doublets ($J \sim 17$ Hz) between 3.8 and 5.0 ppm suggest that all four benzylic methylene

hydrogens are diastereotopic, indicative of formation of a stereocenter in **1**:MX_n. The m/z in ESI-MS corresponds to the metal salt complex minus one counter anion.

Several factors affect the extent of assembly. The effect of metal salts on the extent of assembly follows the trend: Zn(OTf)₂ > Zn(ClO₄)₂ > Fe(OTf)₂ >> Cu(OTf)₂ and Eu(OTf)₃. The extent is apparently dependent on several factors. First, the strength of Lewis acidity toward carbonyl activation plays a crucial role. Cu²⁺, Zn²⁺, and Fe²⁺ have different Lewis acidity. Triflate is a softer anion than perchlorate, and as a result, Zn(OTf)₂ is a stronger Lewis acid than Zn(ClO₄)₂. Second, the preferred coordination geometry of the metal has a significant impact on complex formation. Both Zn²⁺ and Cu²⁺ are known to be able to adopt the five coordinated trigonal bipyramidal geometry, while Fe²⁺ and Eu³⁺ prefer an octahedral geometry.^[22] Third, the binding affinity of DPA to metal ions affects assembly formation. The binding constants between DPA and Cu²⁺ is much higher than DPA and Zn²⁺ (logK₁ in water is 14.4 and 7.6 for Cu²⁺ and Zn²⁺ respectively^[14]), and therefore, the reaction between DPA and 2-PA is impeded in the presence of Cu²⁺.

Further, the stability constants (logK) of TPA with Zn²⁺ and Cu²⁺ in aqueous solution are 11.0 and 16.2 respectively.^[14] Because TPA derivatives are much better ligand than DPA derivatives for zinc (logK 11.0 and 7.6), we postulate that formation of the more stable metal complex is a major driving force for this three-component assembly. However, the difference in binding affinity between TPA and DPA with copper is much smaller (logK 16.2 and 14.4). Lastly, the effect of molecular sieves was minor presumably because no water is lost during complex formation, eliminating such loss as a driving force for complex formation.

Temperature and concentration dependence experiments

After confirming the three-component assembly, we sought to evaluate if an equilibrium exists. To do that, isolated crystals of **1**:Zn(ClO₄)₂ were dissolved in CD₃CN. The reappearance of an aldehyde signal at 10 ppm with time confirms that this three-component assembly dissociated and is a reversible process. The reversibility was further explored by temperature dependent NMR measurements (Figure 1). The dissociation of the assembly increased as the temperature was elevated, and decreased again upon cooling.

Given that an equilibrium can be established, we set out to explore the kinetics of assembly. At concentrations above 30 mM, the equilibrium was reached after 48 h, while at lower concentrations, the assembly took longer to reach equilibrium with a lower ratio of final complex to reactants (Figure 2). Additionally, the effects of different solvents on the assembly were studied. In addition to CD₃CN; DMSO, D₂O, and CD₃OD were used. Each showed some evidence of complex formation, but all to a lower extent than acetonitrile. Because of this, acetonitrile was used in all other studies.

Equilibrium constants

The next step was to measure equilibrium constants for assembly. Because 2-PA, DPA, and adduct **1** can be either free or zinc bound, multiple equilibria exist in the solution (Scheme 1). However, because both DPA and TPA are better ligands than 2-PA, we made the assumption that at higher concentrations the non-reactive DPA is predominately bound to zinc, and as a result, the equilibrium of the assembly formation was simplified to a two-component system:

$$K = [\text{Zn-1}] / \{[2\text{-PA}][\text{Zn-DPA}]\} \quad (\text{Eq. 2})$$

All the concentrations in the equation can be deduced from the total concentration of each reactant and the integrals in ¹H NMR spectra. Since a 1: 1: 1 stoichiometry of 2-PA, DPA,

and $\text{Zn}(\text{OTf})_2$ was used, the concentrations of Zn-DPA and 2-PA are the same based on mass balance. As a result, we can simplify Eq. 2 to Eq. 3:

$$K = [\text{Zn-1}] / [\text{2-PA}]^2 \quad (\text{Eq. 3})$$

The equation was then rearranged using the mass balance of 2-PA as well as the ratio of $[\text{Zn-1}]$ to $[\text{2-PA}]$, a value which can be readily calculated from the ^1H NMR data (Eqs. 4, 5, and 6).

$$[\text{2-PA}] + [\text{Zn-1}] = [\text{2-PA}]_{\text{total}} \quad (\text{Eq. 4})$$

$$R = [\text{Zn-1}] / [\text{2-PA}] \quad (\text{Eq. 5})$$

$$K = R(1+R) / [\text{2-PA}]_{\text{total}} \quad (\text{Eq. 6})$$

The apparent equilibrium constant for the complex formation from 2-PA, DPA, and $\text{Zn}(\text{OTf})_2$ in acetonitrile is estimated to be around $6.6 \times 10^3 \text{ M}^{-1}$, which is surprisingly high considering that no reaction is detected between 2-PA and DPA at room temperature without the addition of zinc salt.

Aldehydes screen

In order to explore the scope of the assembly process, 2-picolinaldehyde derivatives and other nitrogen containing heterocyclic aldehydes were studied. The assembly reactions were conducted in CD_3CN with a 1: 1: 1 mixture of aldehyde, DPA, and $\text{Zn}(\text{OTf})_2$. The data for these experiments is listed in Table 2. In all cases, zinc mediated assembly is observed, but to different extents. ESI-MS confirmed the formation of zinc assemblies. Because these complexes are labile under MS conditions, the ratio of assembled complexes over starting materials is different between NMR and ESI-MS. The electrophilicity of the carbonyl, the donating ability of the ligand, and sterics were all found to have an impact on complex formation. The significantly different equilibrium constants between 5-bromo-pyridine-2-carboxaldehyde and 3,5-dibromo-pyridine-2-carboxaldehyde is best explained by the steric repulsion between 3-Br and the resulting tertiary center in the complex. Substitution at pyridine position 6 also decreases the binding. Similar sterics based arguments can be made for quinoline-2-carboxaldehyde and isoquinoline-3-carboxaldehyde. The lower extent of assembly with thiazole-2-carboxaldehyde and imidazole-2-carboxaldehyde is probably due to their lower electrophilicity than 2-picolinaldehyde.

Structural analysis

A crystal for X-ray diffraction analysis was grown by the slow diffusion of diethyl ether into a solution containing 1: 1: 1 $\text{Zn}(\text{ClO}_4)_2$, 2-PA, and DPA in acetonitrile. The resulting structure is shown in the top panel of Figure 3. The zinc atom adopts a trigonal bipyramidal geometry around the three pyridine nitrogens, which have almost identical distances to the zinc center (Zn-N1 2.04, Zn-N2 2.04 and Zn-N3 2.07 Å), but the bond distance between the tertiary amine nitrogen and zinc center is slightly longer (2.20 Å). A solvent molecule is also bound to zinc (Zn-N 2.07 Å) in the axial position (angle N1A-Zn-N4 176.97). The N1-Zn-N4, N2-Zn-N4, and N3-Zn-N4 bond angles are 79.68, 80.30, and 79.12 respectively, suggesting that the bipyramidal geometry of the metal center is only slightly distorted.

A crystal structure of the product derived from the assembly of thiazole-2-carboxaldehyde, DPA, and $\text{Zn}(\text{ClO}_4)_2$ indicates that the binding mode is similar to that shown for 2-PA (Figure 3 bottom panel). The bond between the tertiary amine nitrogen and zinc center is

again longer (2.25 Å) than the other four Zn-N bonds (Zn-N1 2.04 Å, Zn-N3 2.06 Å, Zn-N4 2.04 Å, Zn-N1A 2.07 Å). The N1-Zn-N2, N3-Zn-N2, and N4-Zn-N2 bond angles are 78.89, 78.50, and 79.45 respectively.

Component exchange

After confirming reversible covalent bond assembly with several aldehydes, we set out to explore dynamic exchange. Component exchange is one of the most important characteristics of a dynamic combinatorial system, because compound diversity and complexity can be readily generated.^[1] After equilibrium was reached between thiazole-2-carboxaldehyde (~ 60 mM), DPA and zinc triflate (1: 1: 1 molar ratio), a second aldehyde, 2-picolinaldehyde (1 equiv.), was added to the solution. The ¹H NMR spectra taken after 20 hours showed that peaks indicative of 2-picolinaldehyde derived assembly appeared while the corresponding peaks from thiazole-2-carboxaldehyde derived assembly decreased dramatically (Figure 4). Moreover, peaks corresponding to thiazole-2-carboxaldehyde increased. A similar exchange was observed with 5-bromo-pyridine-2-carboxaldehyde and 2-picolinaldehyde, as well as at lower concentration (~ 10 mM). The results demonstrate that component exchange is occurring with these complexes.

Anion competition experiments

Because there was a difference in the extent of assembly between Zn(OTf)₂ and Zn(ClO₄)₂, we investigated counter ion effects on the already assembled structures. Various anions, such as AcO⁻, Cl⁻, Br⁻, I⁻, and PF₆⁻, were tested to see if they would shift the equilibrium of the system. The varied Lewis basicity and coordinating affinity of the anions toward zinc are expected to have different effects on the assembly.

Tetrabutylammonium salts were added into a 1: 1: 1 mixture of 5-bromo-pyridine-2-carboxaldehyde (~ 22 mM), DPA, and Zn(OTf)₂ at equilibrium in CD₃CN (~ 78% assembly). Equilibrium was reached after standing overnight, and an increase in the amount of assembly was observed after addition of Cl⁻, Br⁻, and I⁻ (Figure 5 top panel). This effect was likely due to stabilization of the zinc complex by halogen coordination in the axial position. Acetate can bind to the zinc and stabilize the complex, but it can also reduce the Lewis acidity of the metal. These processes seem to offset as there is no apparent change in the amount of assembly formed. The non-coordinating PF₆⁻ has no effect on the assembly formation. Except for PF₆⁻, each anion binding to the zinc complex was observed by peak shifts in the ¹H NMR spectra (see Supporting Information). The relatively larger shift of peaks in the presence of Cl⁻, Br⁻, and I⁻ and smaller shift in the presence of AcO⁻ are consistent with the data shown in Figure 5.

When identical conditions were used except for thiazole-2-carboxaldehyde (~ 22 mM) in place of 5-bromo-pyridine-2-carboxaldehyde, the equilibrium was reached very slowly, with less than 10% assembly formed after six days (Figure 5 bottom panel). However, a dramatic increase in assembly formation was observed after halogen anions or acetate was added, although reaching equilibrium was still slow. The percentage of assembly after six days is 63%, 50%, 37%, and 56% for Cl⁻, Br⁻, I⁻, and AcO⁻ respectively. Because the equilibrium constants for assembly from thiazole-2-carboxaldehyde and 5-bromo-pyridine-2-carboxaldehyde with zinc triflate and DPA are similar (Table 2), the percentage of assembly at equilibrium should be comparable. As a result, we postulate that the increase in assembly with anions is due to a kinetic effect *via* stabilization of intermediates. As expected, the non-coordinating PF₆⁻ has no effect on the assembly formation.

Conclusion

In summary, we have discovered a metal mediated dynamic multi-component assembly to generate tripodal tris-(2-picolyl)amine-like complexes *in situ*. Both the Lewis acidity and coordination mode of the metal center influence complex formation, with zinc being the best among those investigated. A series of nitrogen containing aromatic heterocyclic aldehydes were tested, with 2-picolinaldehyde being the best. The stability of the metal complexes provides the driving force for the assembly. NMR, ESI-MS, and X-ray structural analysis confirm assembly, wherein the zinc adopts a trigonal bipyramidal geometry. Component exchange and counter anion effects demonstrate the dynamic nature of these assemblies. The system is reversible, and as a result, further expands the scope of dynamic covalent bond chemistry. Applications of this assembly process in library creation and molecular recognition are ongoing.

Experimental Section

General

^1H NMR and ^{13}C NMR spectra were recorded from The University of Texas at Austin NMR facility. Mass spectra were obtained from The University of Texas at Austin mass spectrometry facility. X-ray data was obtained from The University of Texas at Austin X-ray diffraction facility. Reagents were of the best grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate.

Assembly formation and dynamics

The assembly was prepared *in situ* without further purification. A mixture of aldehyde (1 equiv.) and metal salt (1 equiv) was dissolved in acetonitrile. To this solution, was added di-(2-picolyl)amine (1 equiv). The mixture was stirred at room temperature overnight. For component exchange and anion competition experiments, 1 equiv. of a second aldehyde or tetrabutylammonium salt was added to the assembly solution of a 1: 1: 1 mixture of aldehyde, di-(2-picolyl)amine and zinc salt in CD_3CN . The assembly solution was characterized by ^1H NMR and ESI-MS, and the percentage of assembly was calculated.

Structural analysis

Crystals for X-ray analysis were grown by the slow diffusion of diethyl ether into a solution containing **1**: $\text{Zn}(\text{ClO}_4)_2$ in acetonitrile. The crystals were collected by vacuum filtration, washed with diethyl ether and dried under vacuum. ^1H NMR (400 MHz, CD_3CN): δ = 8.82-8.72 (m, 3H; pyridine *CH*), 8.25 (dt, J = 7.8, 1.6 Hz, 1H; pyridine *CH*), 8.17 (dt, J = 7.8, 1.6 Hz, 1H; pyridine *CH*), 8.11 (dt, J = 7.8, 1.6 Hz, 1H; pyridine *CH*), 8.05-8.01 (m, 1H; pyridine *CH*), 7.76-7.64 (m, 4H; pyridine *CH*), 7.62-7.58 (m, 1H; pyridine *CH*), 5.67 (d, J = 6.8 Hz, 1H; *CHOH*), 5.44 (d, J = 6.8 Hz, 1H; *CHOH*), 4.77 (d, J = 16.8 Hz, 1H; CH_2), 4.28 (d, J = 16.8 Hz, 1H; CH_2), 4.01-3.91 ppm (m, 2H; CH_2). ^{13}C NMR (150 MHz, CD_3CN): 157.7, 156.4, 156.3, 149.5, 149.3, 149.2, 143.7, 143.2, 143.0, 127.0, 126.4, 126.3, 126.3, 126.2, 125.4, 84.8, 54.4, 51.8 ppm. HRMS (ESI): m/z for **1**: $\text{Zn}(\text{ClO}_4)$ ($\text{C}_{18}\text{H}_{18}\text{ClN}_4\text{O}_5\text{Zn}$), calcd: 469.0252; found: 469.0247.

$\text{Zn}(\text{ClO}_4)_2$ mediated assembly from thiazole-2-carboxaldehyde and di-(2-picolyl)amine were prepared in acetonitrile. ^1H NMR and ESI-MS confirmed formation of desired complex with remaining starting materials. Crystals for $\text{Zn}(\text{ClO}_4)_2$ mediated assembly were grown in a similar fashion as mentioned above. The crystals were used directly for X-ray diffraction without chemical isolation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Equilibrium during proposed assembly

Figure 1. ^1H NMR spectra of the reaction of 2-picolinaldehyde, dipicolylamine, and zinc triflate in CD_3CN at various temperatures (from bottom to top: -40 , -20 , 0 , 20 , 27 , 40 , 60 , 75°C).

Figure 2. Concentration dependence of the assembly formation as monitored by ^1H NMR spectra taken every 24 hours for 7 days (1: 1: 1 stoichiometry of 2-PA, DPA and $\text{Zn}(\text{OTf})_2$).

Figure 3. X-ray structure of $\text{Zn}(\text{ClO}_4)_2$ assembly from 2-picolinaldehyde and dipicolylamine (top panel) and from thiazole-2-carboxaldehyde and dipicolylamine (bottom panel).

Figure 4. ^1H NMR spectra of the mixture of thiazole-2-carboxaldehyde (~ 60 mM), DPA, and $\text{Zn}(\text{OTf})_2$ in CD_3CN (bottom panel) and ^1H NMR spectra of the solution after the addition of 2-picolinaldehyde (1 equiv.) (top panel).

Figure 5.

The effect of various anions on assembly formed from a 1: 1: 1 mixture of 5-bromopyridine-2-carboxaldehyde (~ 22 mM), DPA, and Zn(OTf)₂ (top panel) and from a 1: 1: 1 mixture of thiazole-2-carboxaldehyde (~ 22 mM), DPA, and Zn(OTf)₂ (bottom panel).

Table 1

The effect of metal salt on assembly (1: 1: 1 stoichiometry of 2-PA, DPA and metal salt at ~ 60 mM; 3Å molecular sieves).

Metal Salt	Molecular Sieves Added	Complex%	ESI-MS (calcd.)	ESI-MS (found)
Zn(OTf) ₂	No	>90%	519.03	519.08
Zn(OTf) ₂	Yes	>90%	/	/
Zn(ClO ₄) ₂ ·6H ₂ O	No	83%	469.03	469.08
Zn(ClO ₄) ₂ ·6H ₂ O	Yes	85%	/	/
Fe(OTf) ₂	No	~39%	511.04	511.08
Cu(OTf) ₂	No	trace	518.03	517.92
Eu(OTf) ₃	No	trace	756.97	756.67

Table 2

The effect of aldehyde on assembly

Aldehyde	Equilibrium Constant (M ⁻¹)	ESI-MS (calcd.)	ESI-MS (found)
	6600	519.03	519.08
	230	596.94	597.00
	30	674.85	674.92
	70	549.04	549.08
	45	569.05	569.08
	220	569.05	569.17
	320	524.99	525.00

Aldehyde	Equilibrium Constant (M ⁻¹)	ESI-MS (calcd.)	ESI-MS (found)
900	508.02	508.08