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Review

Anion recognition using dimetallic coordination complexes

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Contents

Abstract

This article describes advances made over the past 3 years in anion recognition using coordination complexes, with a specific focus on dimetallic architectures that utilize a bridging mechanism. The formation of coordination complexes is a relatively straightforward method of constructing fluorescent and colorimetric chemosensors and imaging agents, and a particularly effective way to develop indicator displacement assays that operate in water. These assays are likely to find increased application in various aspects of analytical and environmental chemistry, as well as biomedical imaging and drug discovery. Significant progress in phosphoesterase mimics has been made, and concomitant with the increased mechanistic insight, is the discovery of a catalyst that cleaves phosphodiesters with poor *O*-alkyl leaving groups. Also discussed is a macrocyclic coordination complex whose shape and supramolecular function is pH-dependent.

Keywords: Anion coordination; Metal coordination; Fluorescence sensing; Indicator displacement assay; Macrocycle; Zinc; Copper; Dipicolylamine; Nucleotides; Phospholipids; Dyes

1. Introduction

Anion recognition continues to be a major research goal for many supramolecular chemistry groups around the world [1]. As the field matures there is an increasing emphasis on synthetic receptors that operate in aqueous solution [2]. This is because most of the important biomolecular targets such as peptides, nucleotides, phospholipids, and carbohydrates are anionic compounds. However, anion recognition in water is an extremely challenging task for a number of reasons. For a start, anions are strongly hydrated and any complexation process that involves anion dehydration will likely have to pay a large energetic penalty [3]. It is particularly difficult to develop anion recognition systems that form hydrogen bonded complexes in aqueous solvent, for the obvious reason that the water competes strongly for the hydrogen bonding sites. Compared to cations, anions are larger and they come in wide range of different geometries such as spherical, linear, trigonal, tetrahedral, octahedral, etc. This means that synthetic anion receptors are likely to be larger than cation receptors and they should also have complementary shapes. From a supramolecular chemistry perspective, it is not surprising that there are so few low-molecular-weight natural

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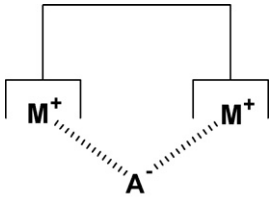
products with anion binding ability. The structures of several anion binding proteins are known; indeed there are examples of phosphate and sulfate binding proteins that only utilize hydrogen bonding [4]. However, in these cases, the anion binding sites are typically buried deep inside the protein structures. Thus, it seems that uncharged, hydrogen bonding synthetic receptors for anions must be designed with structural features that protect the binding sites from the aqueous environment. Although, a few successful examples have been reported, most notably by the group of Kubik et al. [2,5], a potential limitation with this approach is the requirement for relatively large molecules with sophisticated architectures and potentially time-consuming syntheses. Because of these drawbacks, there is a need to boost affinity by incorporating additional bonding interactions that are more competitive in aqueous environments. One common approach is to combine hydrogen bonding with electrostatic attraction. The group of Schmuck and Geiger has been particularly active on this topic in recent years, and they have developed a series of effective carboxylate receptors that operate in water [6]. An alternative bonding interaction is direct coordination of the anion to a cationic metal center that in turn is simultaneously coordinated to an organic scaffold [7]. This recognition strategy takes advantage of the fact that water is a strong hydrogen bonding agent but a relatively poor Lewis base. Thus, water interferes less with anion recognition systems that are based on anion coordination to Lewis acidic metal cations. Since the enthalpy of a single coordination bond is usually quite high, it is relatively easy to construct structurally simple coordination complexes that have sub-millimolar affinities for anions. In many cases, these affinities are good enough for practical use, e.g., in indicator displacement assays. Structurally more complicated versions of these recognition systems can often be constructed in a modular fashion using readily accessible building blocks.

The current field of anion recognition using metal coordination complexes has roots in classical coordination chemistry [8]. A large number of metal complexes are known to form coordination bonds in water, and in many cases the bonding is so strong that the interactions are essentially irreversible. However, irreversible bonding is not useful in most types of supramolecular devices; rather the need is for metal complexes with vacant coordination sites that can form reversible bonds to anions with dissociation constants in the millimolar to nanomolar range. Typically, the rates of association and dissociation need to be fast on the laboratory scale, with half-lives that are less than one second. In terms of receptor design, a common approach is the chelating strategy illustrated in Scheme 1, where an organic scaffold with coordinating atoms (typically nitrogens) holds two metal centers at a specific distance, so they can be bridged by a target anion. When the scaffold is a macrocycle, the bridged structure is sometimes referred to as a cascade complex [9,10]. In terms of the recognition mechanism, there are two limiting cases to consider. In one case, the scaffold binds the metal cations so strongly that the complex can be considered as a single molecular unit with two Lewis acidic sites whose separation is controlled by the length and rigidity of the scaffold. The alterative mechanism is when the scaffold has an inherently weak affinity for one or both of the metal cations. However, the presence of a suitable bridging anion induces a three-component assembly to occur that brings together the scaffold, metal cations, and bridging anion. While the difference between these two association mechanisms is subtle, it has important implications for the successful operation of certain types of molecular devices. An example that will be discussed below is fluorescent sensing, where the anion-induced binding of both metal cations to the scaffold is the event that triggers an increase in fluorescence emission. This type of signal switch would not work if both metal cations were irreversibly coordinated to the scaffold.

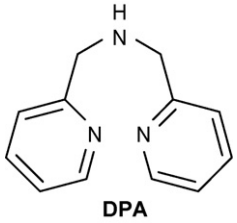


Scheme 1. Anion recognition by a dimetallic coordination complex. The organic scaffold may also be a macrocycle.

The purpose of this article is to describe advances made over the past 3 years in anion recognition using coordination complexes. Moreover, the specific focus is on dimetallic architectures that utilize the bridging mechanism that is shown in Scheme 1. Readers who are looking for a more extensive description of receptors with Lewis acid centers are directed to other articles in this special issue [1], and a recent comprehensive review on molecular recognition of anions in aqueous solution [2].

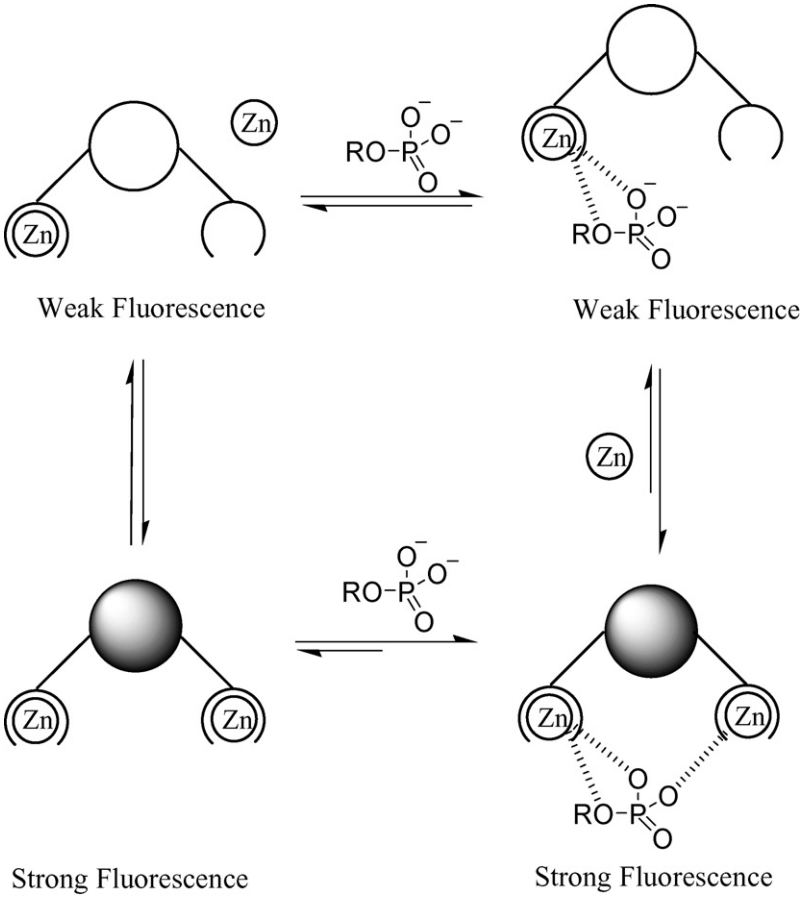
2. Dimetallic coordination complexes

The dipicolylamine (DPA) ligand, was first reported by Kabzinska [11]. The ligand in known to form stable complexes with numerous metal cations but Zn^{2+}-DPA complexes are popular for molecular recognition. Zinc(II) is a particularly attractive metal cation for chemosensing because unlike other metal cations, it does not quench the fluorescence of an attached dye and it is not redox active. The three nitrogens of a DPA ligand can coordinate strongly to a Zn^{2+} cation, with an association constant around $10^7\ M^{-1}$ in water, leaving one or perhaps two vacant coordination sites for an anionic guest. Furthermore, it is synthetically straightforward to incorporate multiple DPA units into a single organic scaffold.



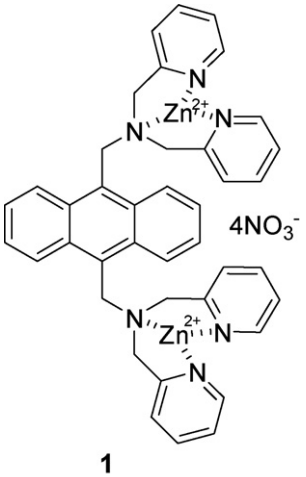
2.1. Chemosensors and imaging agents

In recent years, the group of Hamachi and coworkers has developed a number of effective recognition systems using



Scheme 2.

dimetallic coordination complexes with two DPA units incorporated into an organic scaffold [12]. One of the first examples is receptor **1**, an anthracene derivative with two appended Zn^{2+}-DPA units [13]. This compound is an effective fluorescent sensor of dianionic phosphate derivatives, especially peptides with phosphotyrosine residues. The phosphate guests form bridging 1:1 complexes with stabilities around 10^4 to $10^6\,M^{-1}$. Upon binding, the fluorescence intensity of the sensor increases by about a factor of four. Monoanionic phosphate esters and other inorganic monoanions such as halide and carboxylate do not elicit a significant change in fluorescence intensity. Detailed mechanistic studies indicate that the fluorescent enhancement is due to a three-component assembly mechanism. The organic scaffold in compound **1** has a strong affinity for the first Zn^{2+} ($K_1 \sim 10^7\,M^{-1}$) but a much poorer affinity for the second Zn^{2+} ($K_2 \sim 10^5\,M^{-1}$). Thus, at the concentration required for fluorescence measurement (1 μM) there is a significant amount of mono-zinc complex that is weakly fluorescent due to quenching by photoinduced electron transfer (PET) from the uncomplexed benzylic nitrogen. Association of a dianionic phosphate guest induces the second Zn^{2+} to coordinate to the DPA unit which decreases PET quenching, and results in increased fluorescence (Scheme 2). This anion association process has been characterized using calorimetry, and found to be endothermic with a large positive entropy change [14].



1

Subsequent work by Smith and coworkers has shown that Zn^{2+}-DPA complex **1** is also an effective fluorescent sensor of bilayer membrane surfaces that are enriched with anionic phospholipids such as phosphatidylserine (Fig. 1) [15]. The sensing mechanism is similar to the process described above, but in this case it is the anionic membrane surface that attracts the second Zn^{2+} to the sensor and attenuates the PET quenching (Scheme 3) [16]. This sensing system was incorporated into fluorescent and

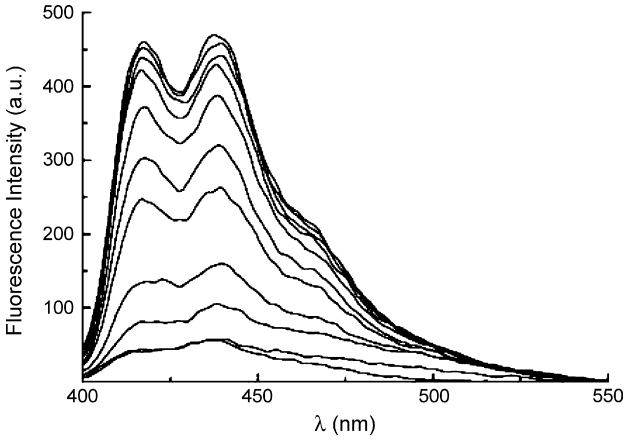
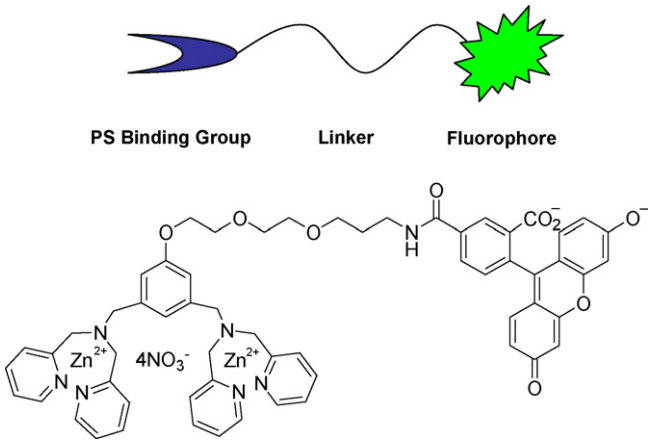


Fig. 1. Fluorescence emission (ex 380 nm) of **1** increases upon addition of POPC:POPS (50:50) vesicles.

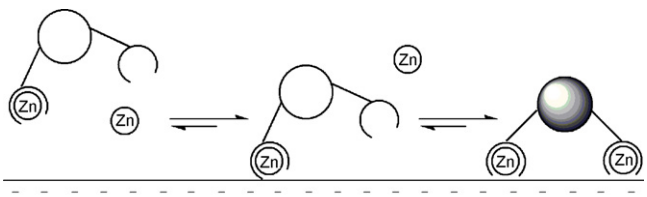


Scheme 4. Design of second generation apoptosis sensor, **2**.

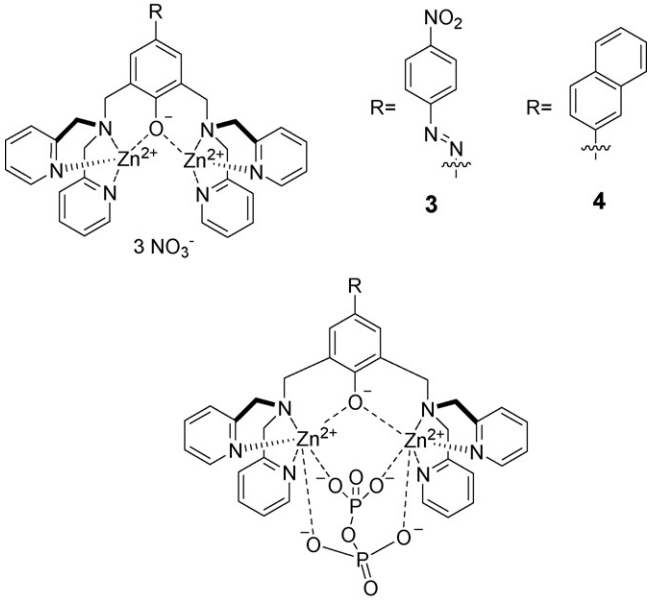
flow cytometry assays that identify mammalian cells undergoing apoptosis. A hallmark of apoptosis is the appearance of phosphatidylserine on the membrane surface [17]. The sensor selectively binds to these phosphatidylserine-enriched cell surfaces and makes them fluorescent.

While **1** shows a 10-fold increase in fluorescence in the presence of phosphatidylserine containing vesicles, the excitation at 380 nm is not compatible with the lasers in most flow cytometers which limits the general utility in cellular assays. To alleviate this problem, a second generation design was developed that uses a linker to connect a phosphatidylserine binding unit (a Zn^{2+}-DPA coordination complex) to a fluorophore (Scheme 4). A number of different fluorophores and linkers were prepared and evaluated [18]. One example is compound **2** which is an effective stain for apoptotic cells and can be employed with common flow cytometers [19]. The Hamachi group has also developed conjugates of Zn^{2+}-DPA with attached fluorophores. For example, they have recently shown that a dansyl derivative with two appended Zn^{2+}-DPA units can act as a fluorescent sensor for phosphate derivatives when it is in the presence of a hydrogel network [20]. The fluorescent response is due to complexation-induced transfer of the solvatochromic dye from bulk aqueous into a more hydrophobic region near the hydrogel network.

A structurally related design of Zn^{2+}-DPA sensors has been developed by Hong and coworkers (Scheme 5) [21]. In this case, the scaffold includes a phenoxide that provides a central oxygen atom to preorganize the binding pocket formed by the two Zn^{2+}-DPA units. The phenoxide also forms a conjugation pathway that electronically connects the anion association site to the chromophore. Compound **3** is a colorimetric sensor, whereas, compound **4** is a fluorescent sensor. Both receptors are selective for pyrophosphate in water even in the presence of other phosphate-containing compounds anions such as phosphate and ATP. X-ray crystallography indicates that the pyrophosphate forms the tetradentate complex shown in Scheme 5. The UV spectrum of azo-derivative **3** is red-shifted when pyrophosphate is added. This is attributed to a weakening of the bond between the phenoxide oxygen and Zn^{2+}, which increases electron density in the *p*-nitrophenylazo chromophore. A similar explanation is used to rationalize the increase in fluorescence intensity of **4** when it binds to pyrophosphate. Thus, in contrast to the three-component assembly mechanism utilized by sensor **1**, sensors **3** and **4** act like a single molecular unit with two permanently attached Lewis acidic sites. Furthermore, calorimetry data indi-



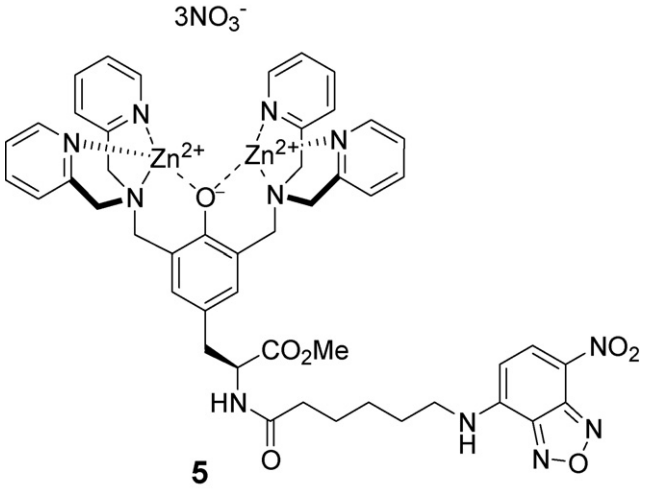
Scheme 3.



Scheme 5. Association of pyrophosphate to Zn^{2+}-DPA sensors.

cates that this anion association process is essentially driven by enthalpy [22].

Recently, the Smith group has made an amino acid version of this receptor system. An amino acid scaffold is attractive for the obvious reason that it can be easily incorporated into peptides. The tyrosine derivative **5** with a fluorescent NBD label was evaluated for its ability to interact with bilayer membranes [23]. Not only does it selectively associate with vesicles containing anionic phospholipids, it also translocates through the bilayer membrane. The translocation mechanism is currently under investigation.



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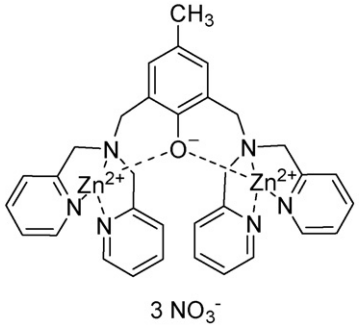
In recent years, a number of fluorescent dyes with appended DPA units have been investigated as zinc sensors. One example is the fluorescein-derived sensor, Zinpyr-1 developed by Lippard and coworkers [24]. The fluorescence increases 3–5-fold upon complexation of Zn^{2+} which inhibits a PET quenching pathway. X-ray crystallography reveals that the Zn^{2+} ions are bound not only to the DPA units but also to the adjacent phenoxides on the fluorescein, as shown in Scheme 6. Recently, Yoon and coworkers demonstrated that this Zn^{2+}-Zinpyr-1 complex acts as a fluorescent sensor for pyrophosphate in water at physiological pH [25]. Their proposed mechanism for the binding of pyrophosphate is shown in Scheme 6. They propose that the pyrophosphate ligand bridges the Zn^{2+} metal centers and breaks coordination with the phenoxide oxygens on the fluorescein. This result suggests that the zinc binding ability of Zinpyr-1 is anion dependent. The effect, if any, of this anion dependence on the performance of Zinpyr-1 as a biological zinc sensor was not addressed.

2.2. Chemosensing ensembles for indicator displacement assays

Synthetic receptors, especially those that employ metal centers, are well-suited for development into indicator displacement assays. The method has been reviewed extensively recently [26,27], and is only considered here in the context of dimetallic coordination complexes. In short, the assay employs a receptor that can form a reversible complex with a fluorescent or UV dye (the indicator). Treatment of a receptor/indicator ensemble with a high affinity analyte (in this case an anion) results in displacement of the indicator which elicits a measurable change in fluorescence or UV absorbance. Receptors with metal centers are particularly effective because direct coordination of the indicator can induce large changes in its photophysical properties [28].

Kim and coworkers have employed the dimetallic coordination complex **6** and the dye pyrocatechol violet **7** as a colorimetric sensing ensemble for inorganic phosphate and AMP [22]. Treatment of the ensemble with either of these two analytes results in a color change from yellow to blue. The utility of the assay was demonstrated by using it to monitor the kinetics of phosphodiesterases (PDEs) which are a class of hydrolases responsible for the degradation of cyclic adenosine 3′,5′-monophosphate (cAMP) and cyclic guanosine 3′,5′-monophosphate (cGMP) to form 5′-monophosphate of the corresponding nucleotides (AMP or GMP) (Scheme 7). This assay appears to have advantages over other methods which are more laborious and require isotopically labeled materials. Smith and coworkers developed a fluorescent version of this indicator displacement system by using the fluorescent, coumarin methylsulfonate, **8** [29]. The fluorescence of **8** is quenched when it binds to receptor **6**, and is restored when **8** is displaced by a suitable phosphate derivative. This fluorescent sensing ensemble was subsequently employed as a detection system for bilayer membranes that contain anionic phospholipids, especially phosphatidylserine [30]. In the best case, as little as 5% phosphatidylserine could elicit a fluorescent response. It appears that this displacement system can be used as a high-throughput assay for apoptosis. Following phosphatidylserine externalization on the surface of an apoptotic cell, the fluorescent indicator (I) is displaced from the receptor–indicator complex (R–I) by the phosphatidylserine headgroup (Scheme 8).



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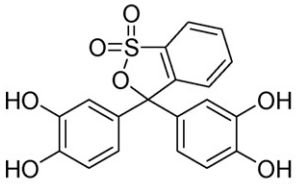

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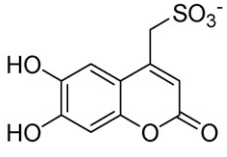
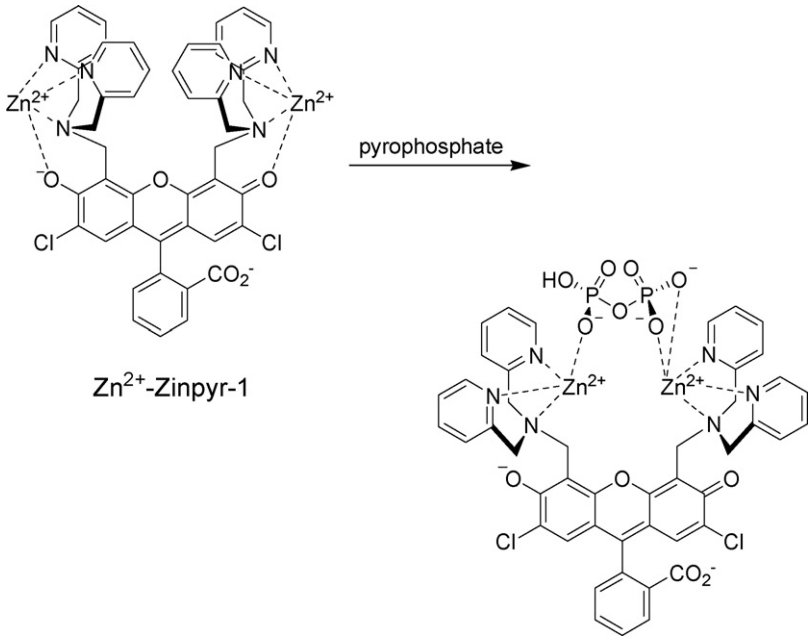


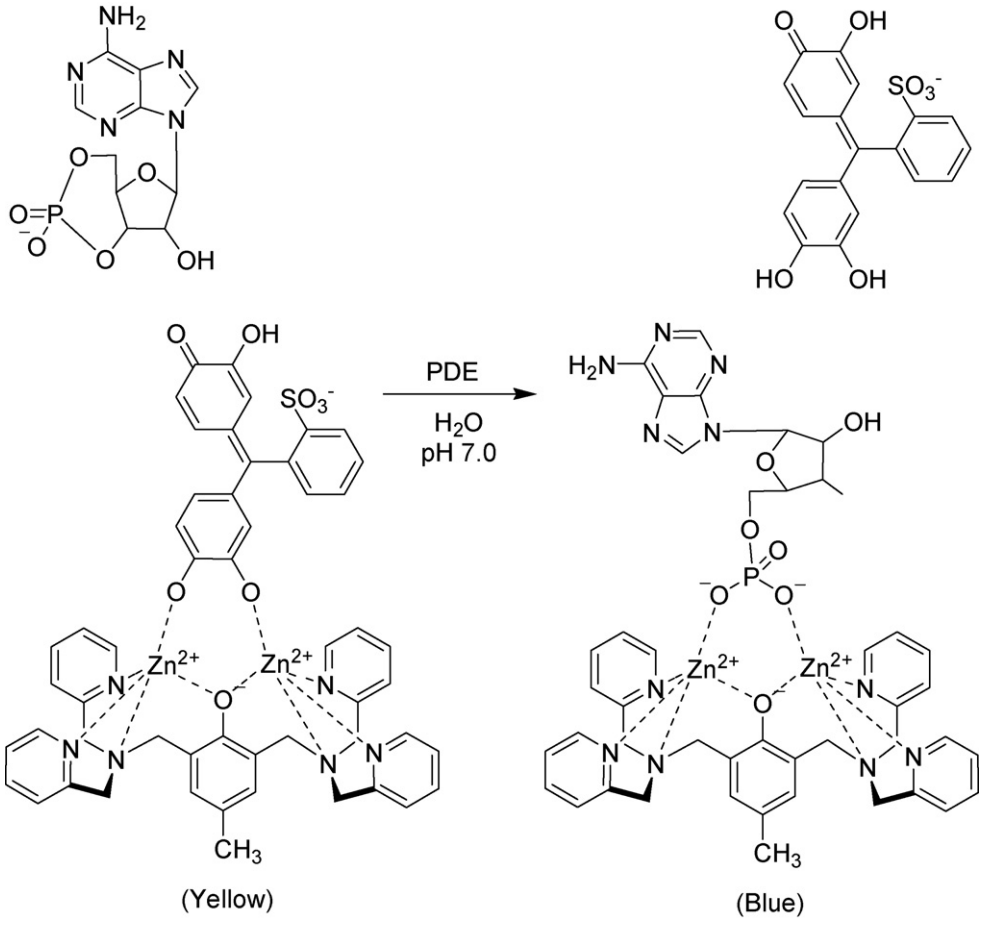
8

The group lead by Fabbrizzi has developed a number of indicator displacement assays in recent years. Most of their designs utilize copper(II) which is an effective quencher of a coordinated



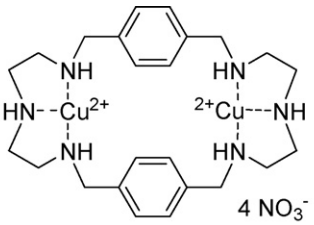
Scheme 6. Proposed mechanism for the binding of Zinpyr-1·Zn^{2+} and pyrophosphate.

fluorescent dye, and they have worked extensively with aza-macrocycles such as the dicopper(II) macrocycle **9** [31]. They have measured the association of **9** with three readily available fluorescent dyes **10**–**12**. The association constants are listed in Table 1 and cover a reasonably wide range. This makes it possible to select a receptor/indicator system with appropriate affinity for selective sensing a specific anion guest. For example, the data in Table 2, suggests that fluoresceine (**11**) (log $K_i = 5.9$) would



Scheme 7. Schematic representation of an AMP chemosensor using an indicator displacement assay.

be the indicator of choice for making a sensing system that was responsive to pyrophosphate (log $K = 7.2$) but not responsive to phosphate (log $K = 4.4$).



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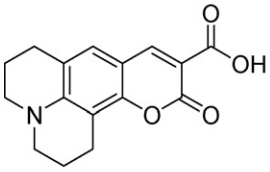

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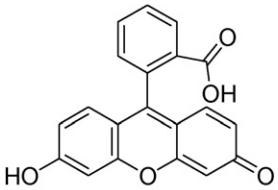

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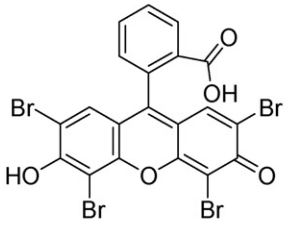
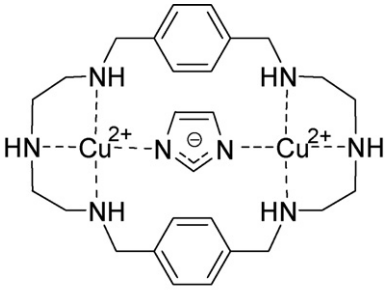


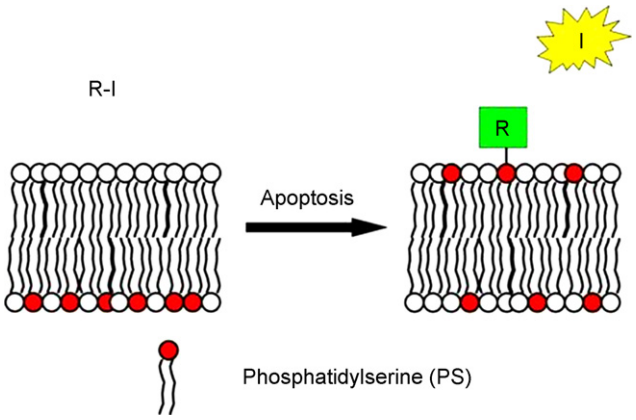
12

To design an indicator displacement system that is selective for the amino acid histidine, Fabbrizzi and coworkers needed to find a receptor/indicator pair that would be displaced by the imidazole side chain but not displaced by the carboxylate functionality that is present in all amino acids. They found that imidazole is bound tightly by the dimetallic macrocycle **9** (log $K > 7$) to give the bridged complex **13** [32]. Furthermore, eosine y (**12**) was an appropriate indicator for selective sensing of histidine. No other amino acid elicits an appreciable response with this chemosensing ensemble.



13

Bicyclic scaffolds such as **14** are known to form cascade complexes in aqueous solution with two transition metal cations bridged by small spherical anions such as F^- [33]. A more ellipsoidal scaffold such as **15** can also coordinate two transition metal ions and encapsulate rod shaped anions. For example, the



Scheme 8. Displacement assay for apoptosis: following phosphatidylserine externalization on the surface of an apoptotic cell, the fluorescent indicator (I) is displaced from the receptor–indicator complex (R–I) by the PS headgroup.

Table 1
Association constants (log K_i) for receptor **9** and three fluorescent indicators

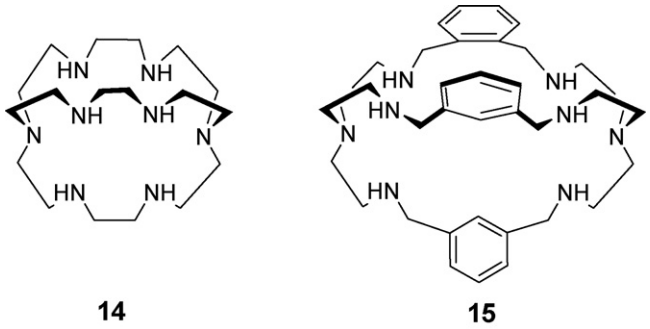
Indicator	log K_i
Coumarine (**10**)	4.5 ± 0.1
Fluoresceine (**11**)	5.9 ± 0.1
Eosine y (**12**)	7.2 ± 0.1

cage molecule **15** can coordinate two Cu(II) metal ions that can in turn bind anions such as N_3^-, NCO^-, and HCO_3^- leading to a stable inclusion complex [34]. A more recent design is the bicycle **16** with larger spacer groups between the tren functionalities. As a dimetallic receptor, it can form inclusion complexes with anions that have donor groups that are well separated from each other. Fabbrizzi prepared the dicopper(II) complex of **16** and measured its ability to encapsulate various dicarboxylates in water [35]. They employed an indicator displacement assay with a carboxyrhodamine dye as the indicator. Of the three isomers of benzenedicarboxylate, they found that the 1,4-isomer had the strongest association by almost four orders of magnitude. They also evaluated the selectivity for simple alkane dicarboxylates and found that a propyl and butyl spacer between the carboxylates produced association constants that were three orders of magnitude greater than ethyl and pentyl linkers. Another experiment demonstrated that L-glutamate binds strongly to

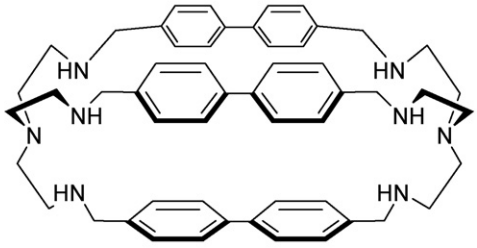
Table 2
Association constants (log K) for receptor **9** and several anions in aqueous solution at pH 7

	Coumarine **10**	Fluoresceine **11**	Eosine y **12**
PPi	>6.5	7.2 ± 0.2	7.2 ± 0.2
Pi	4.2 ± 0.1	4.4 ± 0.2	4.0 ± 0.2
NCO^-	–	4.7 ± 0.2	4.6 ± 0.2
N_3^-	–	4.0 ± 0.2	–
Cl^-, NO_3^-, SO_4^{2-}, acetate, benzoate	<3	<3	<3

the dimetallic receptor and can selectively displace 6-carboxytetramethylrhodamine as the indicator.



14 **15**



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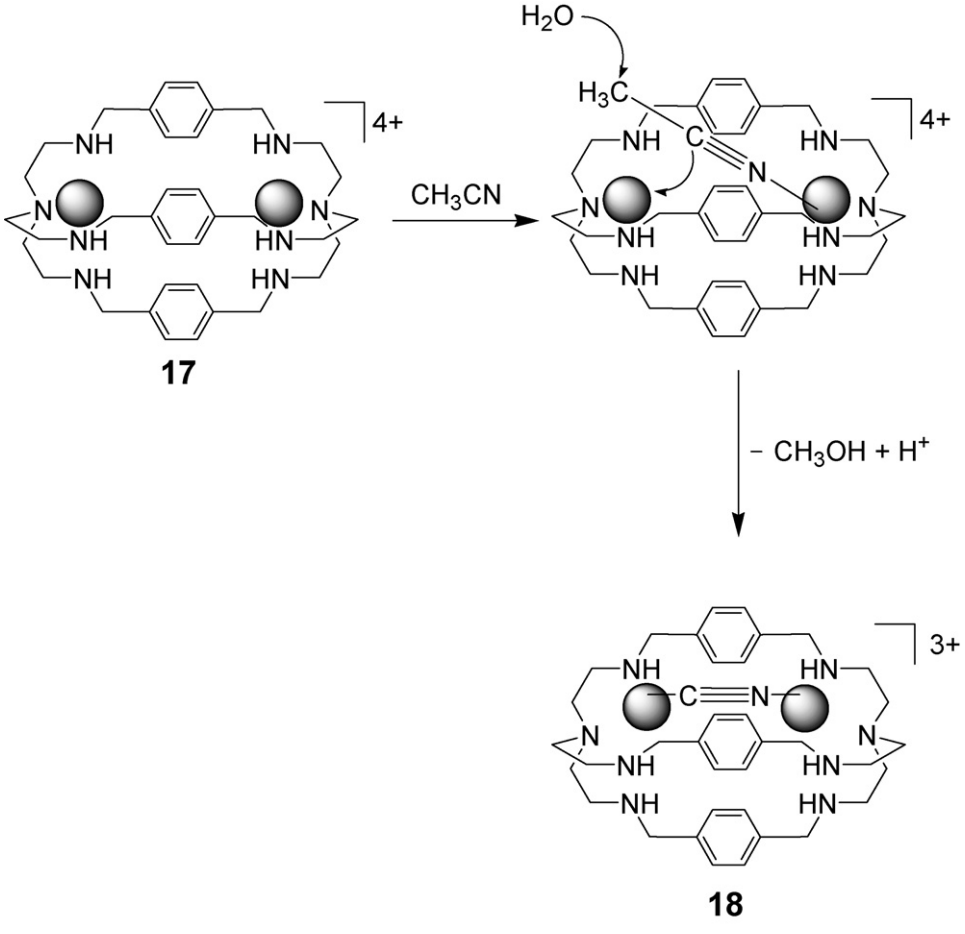
Independently, a similar dicarboxylate recognition study was conducted by Li et al. who examined a hexaazamacrocycle containing two copper(II) cations and found a binding selectivity for malonate [36].

2.3. Chemical catalysis

Dimetallic coordination complexes have recently been employed as catalysts of some important reactions in organic synthesis, however, the organic substrates for these molecular recognition systems are beyond the scope of this focused review on anion recognition [37,38].

2.3.1. C–C bond cleavage

An ongoing goal in organometallic chemistry is the development of new methods to cleave C–C bonds. The literature contains a few reports of C–C activation by transition metals including activation of nitrile containing compounds [39]. Recently, Lu et al. reported that an air-stable dinuclear copper(II) cryptate promotes room-temperature cleavage of the C–C bond in acetonitrile forming a stable cyanide bridged dinuclear copper(II) cryptate [40]. The reaction was achieved by simply dissolving the starting dinuclear copper(II) cryptate **17** in acetonitrile and slowly evaporating the solvent to yield complex **18** as confirmed by X-ray crystallography. The electronic spectrum of starting **17** shows a band a 699 nm indicating the presence of a compressed tetrahedral geome-



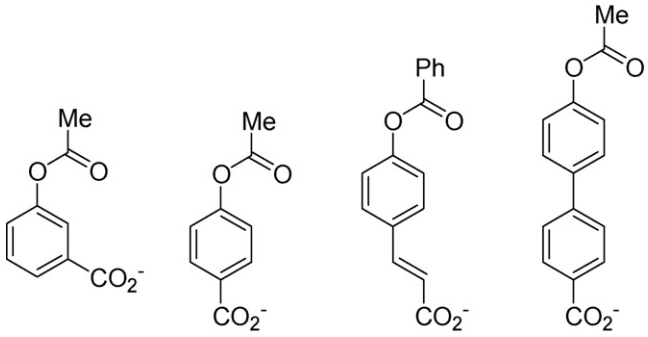
17 **18**

Scheme 9. Possible mechanism of C–C bond cleavage.

try about the copper(II). Upon the addition of acetonitrile, an absorption band at 887 nm appears indicating the trigonal bipyramidal species **18**. The mechanism in Scheme 9 is consistent with the experimental data. It is noteworthy that under the same reaction conditions there is no reaction between $[Cu(tren)](ClO_4)_2$ and acetonitrile. This demonstrates that the activation and subsequent cleavage of acetonitrile is a function of the high stability of the cyanide bridged dinuclear copper(II) cryptate **18**.

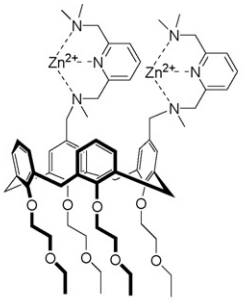
2.3.2. Ester hydrolysis

A significant number of enzymes have metal cations in their active-sites [2,41]. Therefore, it is not surprising that metal coordination complexes are often investigated as mimics of metalloenzymes [42]. A ubiquitous process in cell biology is hydrolysis of a phosphate diester, a reaction that is extremely slow at physiological pH and has to be catalyzed by protein or RNA catalysts. Typically, the active-site of a phosphoesterase enzyme contains two or three metal cations which provide: (a) Lewis acid activation of the electrophilic phosphodiester, (b) activation of the nucleophilic water, and (c) stabilization of the leaving group. Functional mimics of these active-site structures are important for understanding the role of the metal cations in the hydrolytic mechanism [43,44].



19 **20** **21** **22**

The multinational group of Reinhoudt and coworkers are engaged in an ongoing effort to develop coordination complexes as hydrolase mimics. Much of their work has employed calix[4]arene scaffolds in the cone conformation with multiple metal cations appended to the upper rim [45]. Recently, they have attempted to determine if the multiple metal centers can act in a cooperative fashion. For technical simplicity they re-examined a related series of calix[4]arene-based Zn^{2+} complexes for their abilities to catalyze the hydrolysis of carboxylic esters. The structures of the ester substrates, **19**–**22**, contain a carboxylate group which allows multipoint binding to dimetallic catalysts **23** and **24** and trimetallic **25**. The rates enhancements are a measure of the complementarity of shape and charge between substrate and catalyst. The rate of methanolysis catalyzed by the 1,2-vicinal dinuclear complex **23** was consistently higher with all substrates than the rate obtained with the 1,3-distal regioisomer **24**. In the most favorable cases, rates with catalyst **23** were enhanced by four orders of magnitude over the uncatalyzed reaction. Similar results were found for the methanolysis of a series of carboxylate-functionalized esters catalyzed by a bis(barium) complex [46]. Interestingly, the trimetallic catalyst **25** exhibited an increase in catalytic efficiency with substrates **20** and **21** compared to the best dimetallic catalyst **23**. This result is evidence for the simultaneous involvement of all three Zn^{2+} ions in **25**. Possible mechanisms for the dimetallic and trimetallic catalysis are shown in Scheme 10. The first step in both mechanisms is binding of the substrate to form a pre-reaction complex. The subsequent step(s) involves Lewis acid activation and nucleophile delivery. In the dimetallic systems, both of these functions are carried out by the same metal center. With larger substrates, the trimetallic catalyst is more efficient and these two functions are carried out by separate metal centers.



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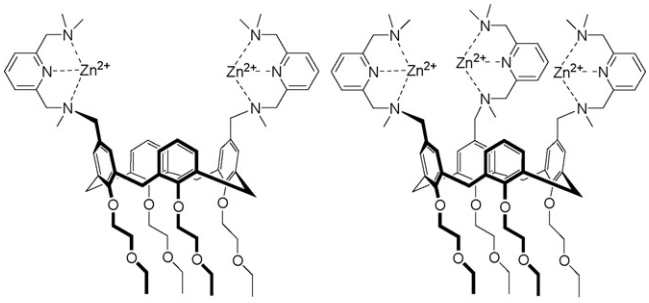
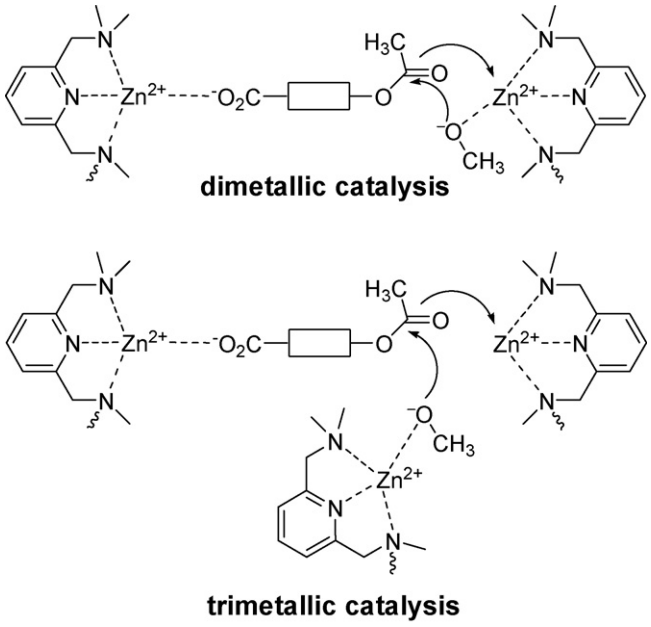


24 **25**

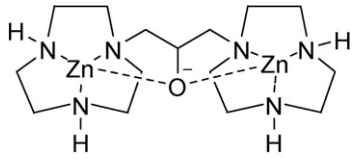
A number of other research groups around the world are pursuing phosphoesterase mimics. Several dimetallic designs have been reported over the past 3 years, with some achieving rate enhancements around 10^6 for model substrates with good leaving groups, and slightly lower enhancements (10^5) when RNA is the substrate [47]. Despite the continued progress, the mechanism for assisted RNA cleavage by synthetic catalysts (and natural catalysts) is still under debate, suggesting that further mechanistic studies are needed [48].

One system that has been studied in great detail is the internally bridged, dinuclear Zn(II) complex **26**. A series of recent papers by Richard and Morrow indicate that the two zinc cations in **26** act cooperatively to promote the cleavage reaction [49]. Intramolecular tethering of the cations by the central alkoxide ion has the effect of generating a highly charged core with unusual catalytic activity. These interactions help deprotonate the C-2 hydroxyl in a RNA substrate, and more importantly, stabilize the highly anionic, reaction transition state by around



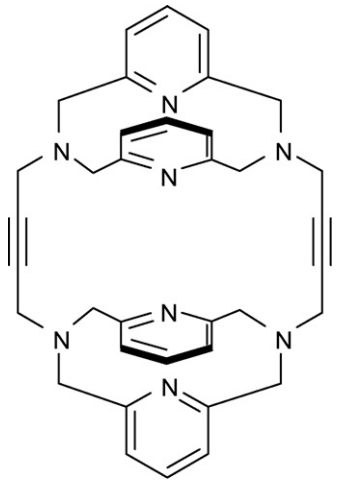
Scheme 10. Schematic mechanisms for dimetallic and trimetallic catalysts.

7–9.5 kcal/mol, which is about 50% of the stabilization observed with protein and RNA catalysts.



26

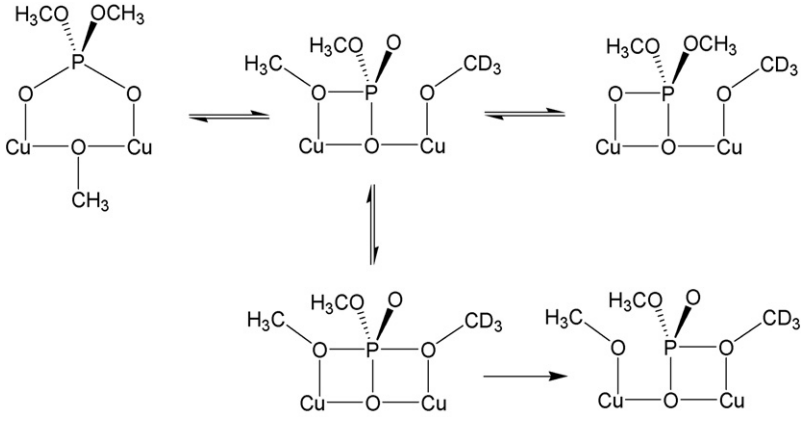
With regard to highly active phosphoesterase mimics, Krämer and coworkers have reported a full mechanistic study of the dinuclear macrocyclic Cu(II) complex of scaffold **27**, which strongly promotes the cleavage of dimethyl phosphate by alcohols [50]. The dimetallic complex appears to be an insightful model for mechanistic studies of phosphoryl transfer promoted by two metal centers. The proposed transesterification mechanism is shown in Scheme 11 (the macrocycle has been deleted for clarity) and achieves transition state stabilization in the same way as several phosphoryl transfer enzymes. The results support the idea that two metal centers are crucial for the function of many metalloenzymes. The work is a remarkable demonstration of a catalyst that can cleave phosphate diesters with poor *O*-alkyl leaving groups.



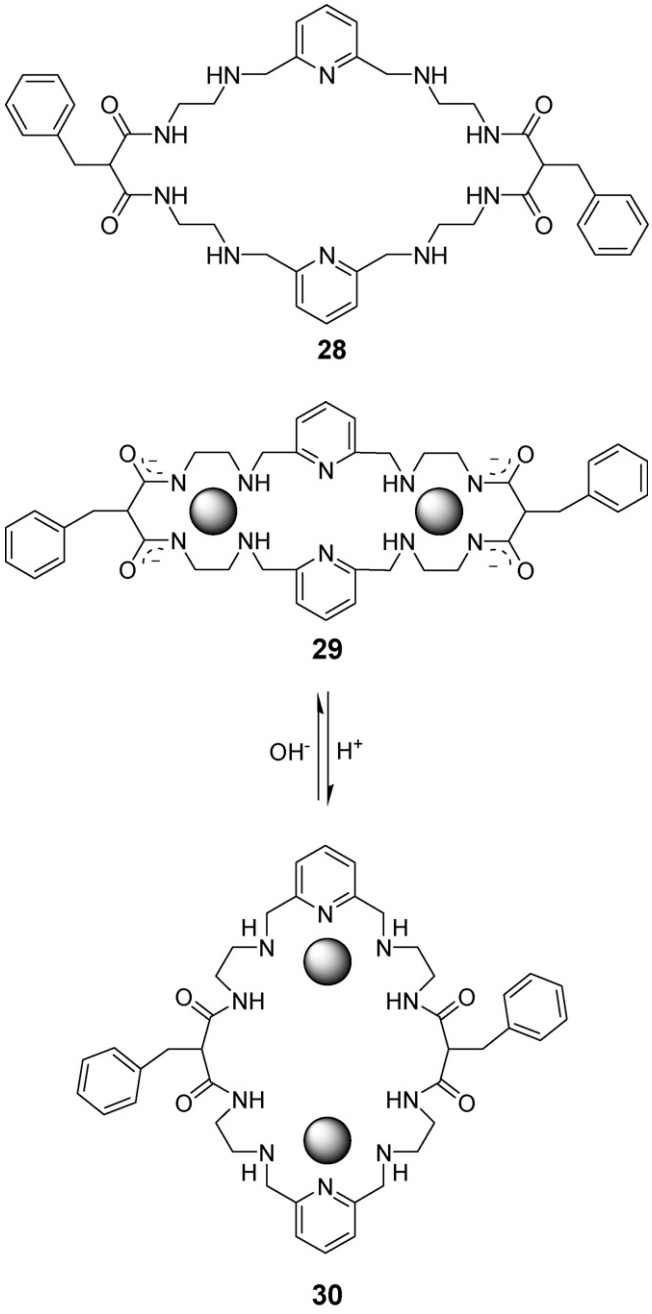
27

2.4. Switchable binding

One of the goals of the emerging field of molecular machines is to develop supramolecular systems with controllable recognition properties [51]. One approach is to design synthetic receptors with shapes that can be switched by external stimuli. Most examples in the literature use photoisomerization to accomplish this task [52]. Recently, Fabbrizzi and coworkers described a dimetallic coordination complex with a binding selectivity that can be switched by changes in pH. Macrocycle **28** is capable of binding two Cu^{2+} ions by either tetradentate diamide–diamine coordination or by tridentate pyridine–diamine coordination. Potentiometric and spectrophotometric titrations of the complex after the addition of two molar equivalents of Cu^{2+} ions showed two different copper containing species as a function of pH. A band at 660 nm predominates from pH 3 to 9.5. Above pH 9.5, the band at 660 nm decreases and a band appears centered on 515 nm. The structures, **29** and **30**, that produce this

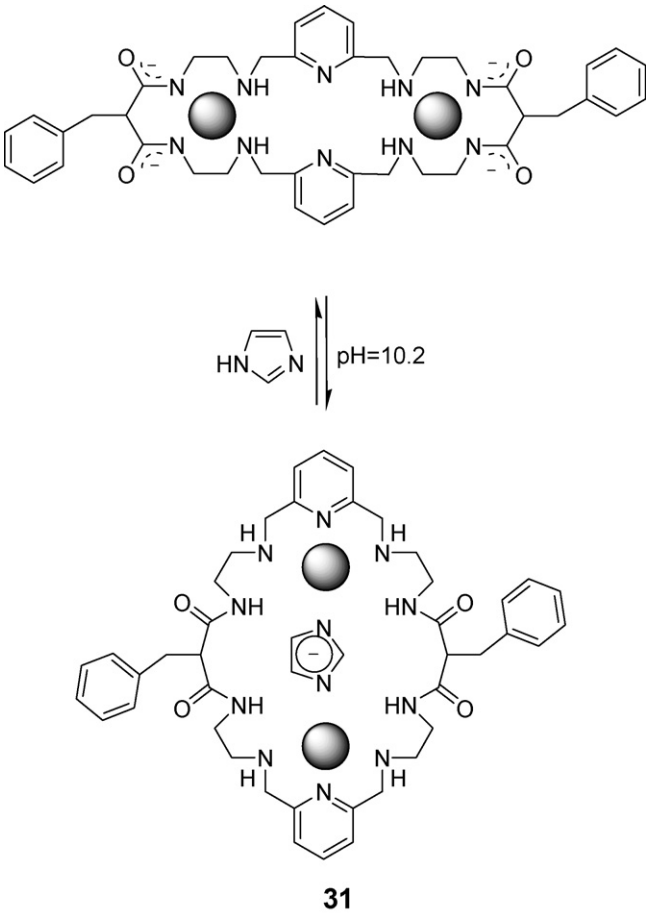


Scheme 11. Proposed mechanism of transesterification. The macrocyclic scaffold has been omitted for clarity.



Scheme 12. pH dependant translocation of Cu^{2+} ions.

pH dependence are shown in Scheme 12. In basic conditions, the Cu^{2+} complex is four-coordinated square-planer (**29**) thus making the Cu^{2+} coordinatively saturated. At acidic pH, complex **30** is three-coordinated by the ligand and water completes the coordination sphere. Since the coordinated water can easily be displaced by a stronger ligand, this system is considered to be in its "open" form where it can bind a bidentate guest in bridging fashion. The ability of a bidentate guest to bridge both Cu^{2+} centers and form a cascade complex is controlled by the distance between the metal centers, making this receptor system a good candidate to be a switchable sensor. The complexation behavior of the copper complex was investigated with several potential bridging substrates including dicarboxylates,



Scheme 13. Imidazole-induced translocation of Cu^{2+} ions.

phosphates, azide, and imidazolate. At pH 7, in all cases except azide, the $[Cu_2(ligand)(OH)]^{3+}$ species was predominant and a 1:1 adduct was observed. The presence of imidazole was then tested, because of previous work in the area of histidine detection, and it was found that complex **31** predominates from pH 6.0 to 10.0. Spectrophotometric titrations were performed and provided evidence for imidazole-induced translocation of the Cu^{2+} ions between different coordination sites as shown in Scheme 13. This switchable coordination system shows a high degree of guest selectivity. At a fixed pH of 10.2, the addition of various bridging anions including N_3^-, PO_4^{3-}, $P_2O_7^{4-}$, and $C_2O_4^{2-}$ as well as glycine, arginine, proline, glutamate, ADP, and ATP produces no spectrophotometric response. On the other hand, the addition of histidine and histamine gives the same response as imidazole. It appears that the selectivity stems from the stability of the $\{Cu^{2+}–(Im^-)–Cu^{2+}\}$ complex which overcomes the energetic penalty for translocating the two Cu^{2+} metal centers.

3. Summary

In the near future, interest in coordination complexes as anion receptors will continue for a number of reasons. (a) It is a relatively straightforward to convert coordination complexes into fluorescent and colorimetric chemosensors and imaging agents, and it is a particularly effective way of developing indicator

displacement assays that operate in water. These sensing assays are likely to find increased application in various aspects of analytical and environmental chemistry, as well as biomedical imaging and drug discovery. (b) Significant progress in esterase mimics continues to be made, and concomitant with the increased mechanistic insight is the likelihood that biomedically useful catalysts will be produced, including molecules that are capable of cleaving RNA with sequence selectivity. (c) There is increasing interest in constructing molecular systems with controllable shape and supramolecular function. One of the long-term goals is to produce molecular machines with programmable functions; however, the fabrication of these complicated nanoscale devices will require continued development of synthetic methods. Metal coordination is an excellent way to achieve reversible and self-correcting assembly with a wide range of accessible geometries [53]. It is increasingly possible to design coordinative building blocks that spontaneously assemble into large, highly complicated, and functional molecular structures [54–56].

Acknowledgment

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