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FEATURE ARTICLE

Dynamic anion recognition by macrocyclic polyamines in neutral pH aqueous solution: development from static anion complexes to an enolate complex

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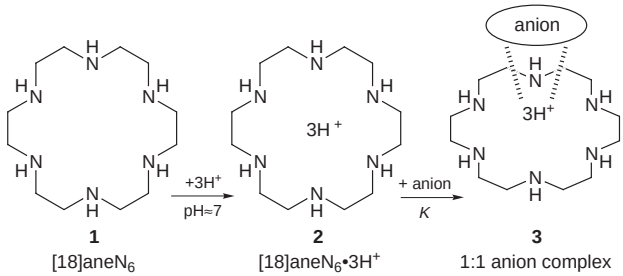
Multiprotonated macrocyclic polyamines are useful host molecules for anion guests at neutral pH in aqueous solution. An intramolecular uracil anion complex with a diprotonated macrocyclic tetraamine recently provided a unique example of electrostatic stabilization of the uracil N^1 anion at neutral pH, which may be relevant to the facile glycosylation and deglycosylation of uracil at N^1 in DNA. Macrocyclic polyamine complexes with Zn^{2+} possess strong anion affinities and hence can deprotonate weak acids at neutral pH to bind with the resulting conjugate bases: *e.g.* $H_2O \rightarrow HO^-$, $ROH \rightarrow RO^-$, $ArSO_2NH_2 \rightarrow ArSO_2NH^-$, $RCONHR' \rightarrow RCON^-R'$, $RCONHCOR' \rightarrow RCON^-COR'$. The Zn^{2+}–conjugate base complexes act as catalytic nucleophiles (*i.e.* HO^-–Zn^{2+}, RO^-–Zn^{2+}), fluorescence sensors ($ArSO_2NH^-$–Zn^{2+}), and thymine or barbital recognition hosts, which are often found in zinc–enzyme functions. Enolate anion complex formation has recently been observed in intramolecular interaction of carbonyl oxygen with Zn^{2+}.

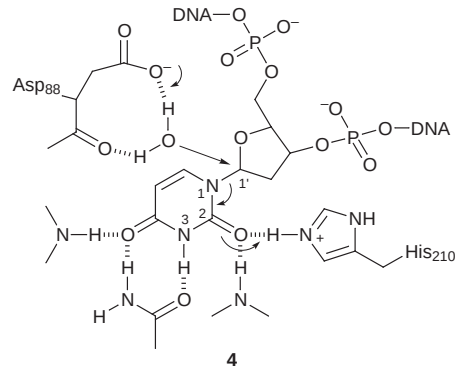
1 Anion complexes with multiprotonated macrocyclic polyamines

Macrocyclic polyamines have long been demonstrated to be good host molecules for polyanions (*e.g.* di- and tri-carboxylates, phosphates, carbonates) and form stable 1 : 1 complexes at neutral pH in aqueous solution, where macrocyclic polyamines are multiprotonated and highly charged.[1–10] For instance, the hexaazamacrocyclic polyamine [18]aneN$_6$ **1** which has pK_a values of 10.2, 9.2, 8.7, 4.1, < 2, and < 2, is mostly present in the [18]aneN$_6$·3H$^+$ form **2** at pH *ca.* 7, which binds with citrate^{3-} (log K = 2.4), AMP^{2-} (log K = 3.3), or ATP^{4-} (log K = 6.4) in 1 : 1 anion complexes **3** (Scheme 1).[2,5] Electrostatic and hydrogen bonding interactions account for the fairly strong complexation.



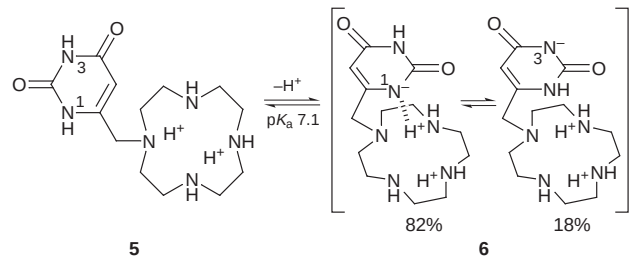
Scheme 1

Enolization of carbonyl compounds is crucial in a wide variety of key reactions in biochemical transformations; enzymes include aldolase, racemase and isomerase. Of special interest is how weak bases of enzymes (*e.g.* imidazole, aspartate or glutamate), with pK_a values < 7, can effectively abstract a proton from carbonyl substrates having much higher pK_a values and there must be some mechanism which lowers pK_a values of the methylene protons adjacent to a carbonyl group.[11] Uracil–DNA glycosylase (UDGase), which disrupts the N(1)–C(1′) bond (see **4**) at neutral pH, is an example of one



of these enzymes.[12,13] The amide carbonyl group C^2=O must be activated (probably by hydrogen bonding with protonated His$_{210}$), so as to lower the electron density of the uracil group to allow a concerted nucleophilic attack by a water molecule (activated by Asp$_{88}$) on the C$^{1'}$ atom. Concerning this mechanism, chemical questions arise: how much is the product uracil anion stabilized by the protonated imidazole or how is uracil N^{1}H selectively deprotonated for activation in the reverse reaction to form the glycosyl bond at neutral pH. These questions are translated into whether the uracil N^{1}H (pK_a *ca.* 9.5) can be rendered more acidic.

In order to address such basic chemical questions, we synthesized a diprotonated cyclen-attached uracil **5**.[14] It is remarkable to find that the uracil N^{1}H group of **5** (Scheme 2) is



Scheme 2

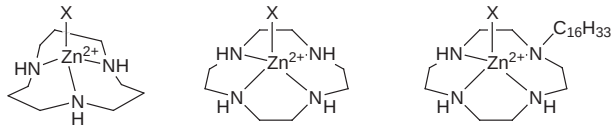
readily deprotonated to the anionic species **6** in aqueous solution [pK_a = 7.14 at 25 °C (I = 0.1)]. The lowered pK_a by more than two units is due to an electrostatic stabilization of the conjugate base (N^1)$^-$ anion by the diprotonated cycle at physiological pH. Furthermore, the negative charge is highly localized at N^1 (82% according to UV and NMR studies), under the strong influence of cyclen NH$^+$. At higher pH where the two protons are removed from the cyclen, the negative charge at N^1 becomes delocalized and the (N^3)$^-$ anionic tautomer becomes more predominant (18% at pH → 63% at pH 12.5).

This simple model may illustrate how easily the uracil N^1H can be deprotonated so as to be a good leaving group in deglycosylation and also to be a good nucleophile for glycosylation at neutral pH. The uracil N^1 site should be especially subject to the electrostatic effect by protonic acids. Thus, uracil may be appropriately chosen for the DNA repair mechanism.

2 Dynamic anion complexes by interaction of macrocyclic polyamine–zinc(II) complexes with water and alcohols

When a strong Lewis acid such as a divalent metal ion replaces protons in macrocyclic polyamine cavities, more acidic macrocyclic molecules are obtained. This is particularly true for Zn^{2+}, which along with Cu^{2+} is one of the strongest Lewis acids, and is characteristically non-directional (no ligand field effect) owing to its d^{10} electronic state (*cf.* the directional d^9 Cu^{2+} ion[15–19]) and Zn^{2+} can be regarded as a condensed multiproton site. The Zn^{2+} ion complexes in four-, five- or six-coordinate structures. Taking full advantage of the properties of Zn^{2+} and rigid macrocyclic configurations, one can design appropriate zinc(II) complexes as host molecules for anions. In this connection, it should be noted that halogen ions X^- or inorganic hydrogen phosphate $HOPO_3^{2-}$ bind to Zn^{2+} at active centers of zinc enzymes to inhibit the enzymatic activities and that zinc enzymes are active towards anionic substrates (*e.g.* $HOCO_2^-$ for carbonic anhydrase, $ROPO_3^{2-}$ for alkaline phosphatase) or neutral molecules (with weak acidity) that are developed into anionic reaction intermediates or transition states [*e.g.* amides for carboxypeptidase, CO_2 (or H_2CO_3) for carbonic anhydrase].[20] Thus, zinc(II) macrocyclic polyamine complexes can be static as well as dynamic receptor molecules for anions, showing more versatile behavior than mere protonated macrocyclic polyamines or other conventional organic anion receptors.[21–23]

The most revealing example is ready deprotonation of water bound to Zn^{2+} in macrocyclic polyamines (**7a** ⇄ **7b** + H^+ and **8a** ⇄ **8b** + H^+), as reflected in the pK_a values (7.3 and 7.9,



7a X = OH_2 **b** X = OH^- Zn^{2+}-[12]aneN_3

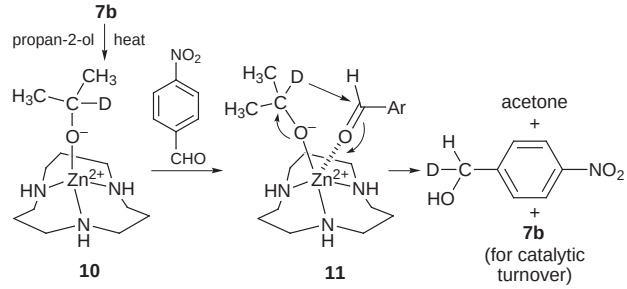
8a X = OH_2 **b** X = OH^- Zn^{2+}-cyclen

9a X = OH_2 **b** X = OH^-

respectively).[24,25] Alternatively, one can view the HO^- anion binding to Zn^{2+}, which is measured in terms of the anion affinity constant K ($10^{6.7}$ and $10^{6.1}$ dm^3 mol^{-1}, respectively). Although HO^-–Zn^{2+} bonds are fairly strong they are characteristically labile. In line with their pK_a values, HO^-–Zn^{2+} complexes are appreciably and rapidly generated at physiological pH, which then act as nucleophiles toward carboxyesters, β-lactam and phosphoesters for catalytic hydrolyses.[24–27] When appended with a hexadecyl group (see **9**), the HO^- anion complex is generated as readily (pK_a = 7.6 for **9a** ⇄ **9b** + H^+) and the resulting anion can migrate into Triton X-100 micelles, whereby the Zn^{2+}-bound OH^- becomes more desolvated and its nucleophilicity towards lipophilic esters such as tris(4-nitrophenyl) phosphate is 290 times stronger than HO^-–Zn^{2+} of **8b**.[28]

It is of interest to point out that the anion affinity of Zn^{2+} is of central importance in the active center of zinc enzymes such as carbonic anhydrase (CA).[17] In the forward (CO_2 hydration) and reverse ($HOCO_2^-$ dehydration) reactions, two anionic reactants OH^- (a good nucleophile toward CO_2) and $HOCO_2^-$ (a substrate) always compete for Zn^{2+}. The successful binding to Zn^{2+} depends on the pH of the medium (*i.e.* concentration of OH^-) and $HOCO_2^-$. This equilibrium then determines the direction of the enzyme reaction: at higher pH hydration of CO_2 and at lower pH dehydration of $HOCO_2^-$ predominate. The 12-membered macrocyclic triamine ([12]aneN_3) zinc(II) complex **7a** (pK_a = 7.3 at 25 °C) has for the first time mimicked such pH-dependent CA behavior of CO_2 hydration and $HOCO_2^-$ dehydration at physiological pH.[29]

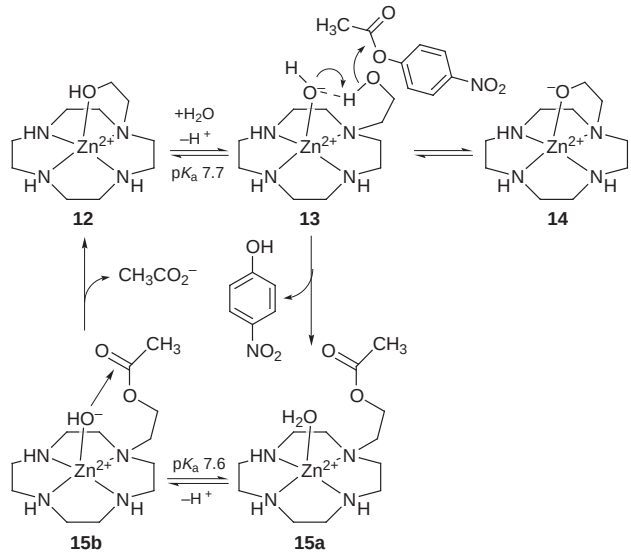
The Zn^{2+}-bound OH^- anion can also behave as a catalytic base. When propan-2-ol was heated with catalytic amounts of **7b** in dimethylformamide in the presence of 4-nitrobenzaldehyde or *N*-methyl nicotinamide, hydride transfer occurred from propan-2-ol to 4-nitrobenzaldehyde (yielding 4-nitrobenzyl alcohol) or *N*-methyl nicotinamide (yielding 1,4-dihydronicotinamide).[30] The reaction mechanism (Scheme 3) was



Scheme 3

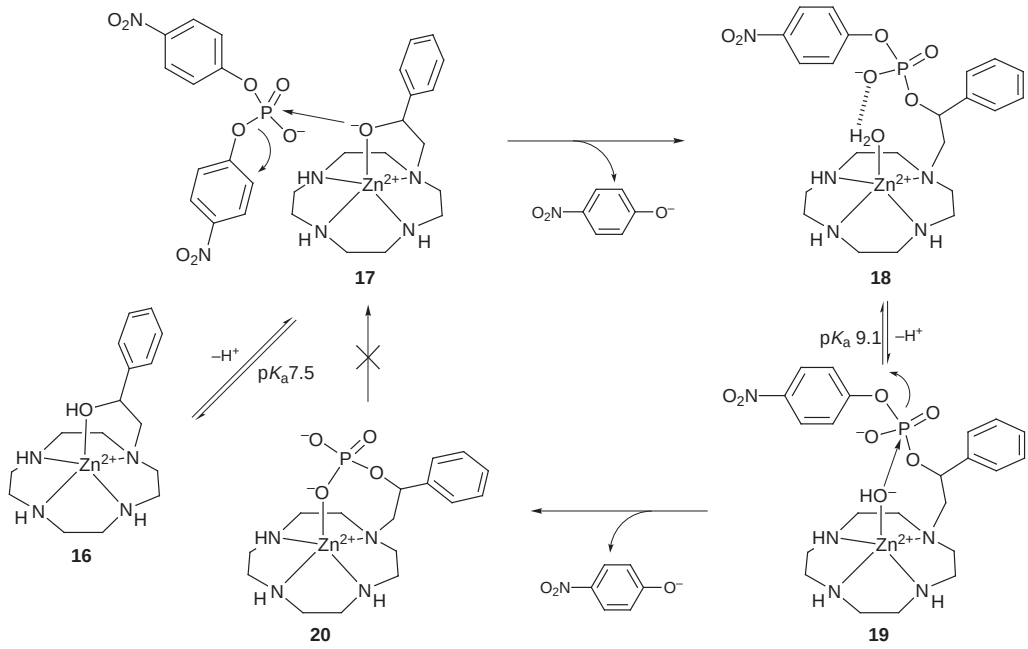
established by using $(CH_3)_2CDOH$. An essential step is generation of an alkoxide at the acidic Zn^{2+} center (**10**), which still leaves the fifth coordination site open for the other reactants coordinating through carbonyl oxygen to permit hydride transfer in the aldehyde-bound complex **11**. This system is a good model for Zn^{2+}-containing alcohol dehydrogenase.

With an alcohol-pendant zinc(II)–cyclen complex **12**, deprotonation occurs with a pK_a value of 7.7 in aqueous solution (Scheme 4).[31] Available evidence supports the HO^-–Zn^{2+}



Scheme 4

structure **13** rather than Zn^{2+}–alkoxide complex **14**. In terms of reactivity, the pendant alcohol in **13** is more nucleophilic than a reference Zn^{2+}-bound OH^- complex **8b**. The product from the reaction of **13** (at pH > 8) with 4-nitrophenyl acetate was exclusively an acetyl-transferred complex **15a**. The pendant acetate in **15a** immediately undergoes hydrolysis by the proximate Zn^{2+}-bound HO^- in **15b** which is immediately generated (pK_a = 7.6). Another alcohol–pendant Zn^{2+} complex **16** is at equilibrium with its monodeprotonated complex **17** in neutral aqueous solution with a pK_a value of 7.5 (Scheme 5).[32] In this case, the alkoxide-bound complex **17** rather than an



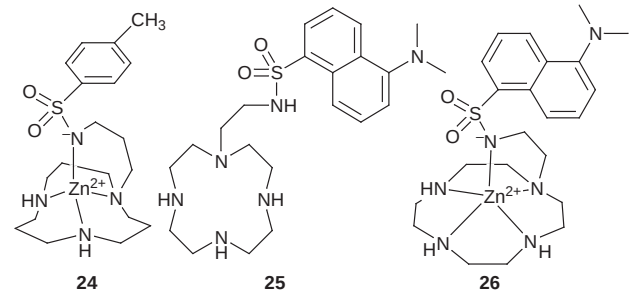
Scheme 5

equivalent **13**-type complex is predominant in alkaline solution. The alkoxide anion complex was isolated and its X-ray crystal structure was determined. The Zn^{2+}-bound alkoxide ion in **17** is again a better nucleophile than HO^-–[zinc(II)–cyclen] **8b**. The alkoxide complex **17** reacted with a phosphodiester to yield an isolable 'phosphate-transfer' product **18**, which is then subject to intramolecular attack by an immediately generated Zn^{2+}-bound OH^- in **19**. The reactions led eventually to a very stable Zn^{2+}-bound phosphomonoester anion complex **20**. Here, we see the appearance of various anions each having different dynamic behaviour in neutral aqueous solution during the reaction processes.

A dinuclear zinc(II) cryptate **21** is a potential receptor of phosphomonoester dianions such as 4-nitrophenyl phosphate (NP^{2-}), although the two Zn^{2+} ions (separated at a distance of 3.42 Å) in the cryptate appear coordinatively saturated in a rigid five-coordinate configuration.[33] However NP^{2-} can transiently bind to **21** at pH *ca.* 6 in aqueous solution to give **22** and cleavage of the P–O ester bond by nucleophilic attack of one of the apically coordinated NH groups yields the phosphoramide product **23** (Scheme 6). The driving force for the recognition by the two Zn^{2+} centres in **22** arises from formation of the stable zinc(II)–phosphate O^- bonds in **23**.

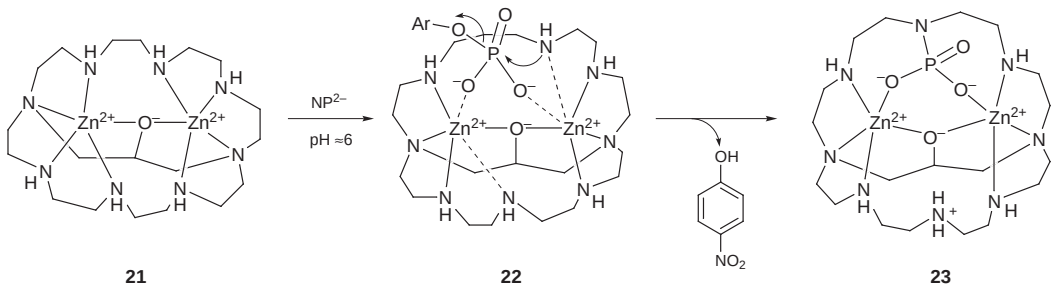
3 Application of anion complexes for recognition of Zn^{2+} and weakly acidic neutral molecules

Just like H_2O and alcohols, other weak acids, *e.g.* aromatic sulfonamides (pK_a *ca.* 10) are deprotonated at physiological pH by macrocyclic polyamine zinc(II) complexes. The recognition



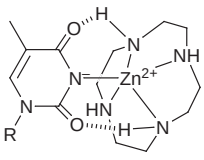
of the deprotonated sulfonamide anion by Zn^{2+} in **24** is a good chemical model designed to explain the inhibition of carbonic anhydrase by aromatic sulfonamides.[34] Attachment of a dansylamide pendant to cyclen **25** has led to a very sensitive and selective fluorescent probe for Zn^{2+} at neutral pH in aqueous solution (owing to formation of **26**).[35] The Zn^{2+}-dependent fluorescence with 5 μM **25** (at pH 7.3) is quantitatively responsive to 0.01–5 μM concentrations of Zn^{2+}, and is unaffected by the presence of mM concentrations of biologically important metal ions such as Na^+, K^+, Ca^{2+} and Mg^{2+}. The zinc fluorophore **25** forms a far more stable 1 : 1 Zn^{2+} complex (K_d = 6×10^{-13} mol dm^{-3} at pH 7.8) than any previously prepared zinc fluorophore[36] and can be regarded as a new prototype of zinc fluorophore.

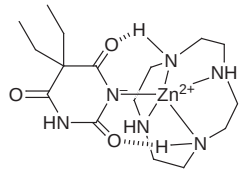
The zinc(II)–cyclen complex **8a** can act as a good anion receptor for imide-containing weakly acidic molecules at neutral pH in aqueous solution. Typical guests are thymidine (or



Scheme 6

uridine) and barbiturates, which are deprotonated and form 1 : 1 complexes **27a**[37] and **28**[38] upon interaction with **8a**. Complexes **27a** and **28** result from Zn^{2+} deprotonating the imide protons





27a R = 2'-deoxy-1'-ribosyl
b R = 3'-azido-2',3'-dideoxy-1'-ribosyl

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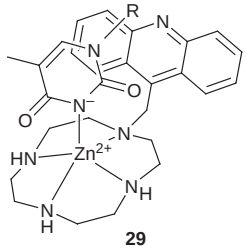

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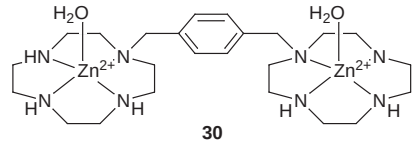
and the resulting Zn^{2+}–N^- (imide) bond is reinforced by the two complementary hydrogen bonds between the two imide oxygen atoms and two NH groups of cyclen; K_d values (at 25 °C) are 8×10^{-4} mol dm^{-3} for **27a** at pH 7.4 and 6×10^{-5} mol dm^{-3} for **28** at pH 8. The X-ray crystal structure of the AZT$^-$–[zinc(II)–cyclen] complex **27b** reinforces the stability of these complexes. The major stabilization comes from the Zn^{2+}–N^-(imide) bonding with the two hydrogen bonds providing a supplementary contribution. The zinc(II)–acridinylmethylcyclen complex binds 50 times more strongly with thymine, owing to an additional π–π stacking interaction (see **29**).[39] It is remarkable that zinc(II)–cyclen complexes preferentially recognize neutral thymine or uracil bases over biological anions such as phosphate monoanions in DNA or RNA.

In the light of the fact that zinc(II)–cyclen yielded only the 1 : 1 complex **28** with barbital, although barbital potentially has two imide donor sites, a bis[zinc(II)–cyclen] connected with a *p*-xylene bridge **30** was synthesized to match the dianionic barbital anion.[40] A number of host molecules (*e.g.* **31**[41]) have been synthesized for barbiturates; however, such barbiturate–host complexes are stable only in non-aqueous environments (*e.g.* $K_d = 10^{-2}$–10^{-6} in $CDCl_3$ for **31**): and they dissociate immediately in aqueous solution. Potentiometric pH titration of **30** and barbital (both at 1 mM) led to extremely facile deprotonation of the two imide groups at pH < 7, leading to the formation of the 1 : 1 complex barbital^{2-}–bis[zinc(II)–cyclen] **32**.[40] From an aqueous solution of an equimolar mixture of **30** and barbital at pH 8, a cyclic 2 : 2 complex **33** was isolated and characterized by X-ray crystal analysis. An NMR study of isolated **33** in 10% (v/v) D_2O–H_2O revealed the dissociation of **33** into the original target 1 : 1 complex **32**, establishing a dimerization constant K of $10^{3.4}$ dm^3 mol^{-1} for **32** + **32** ⇄ **33**. Thus, **30** was established to be an excellent host for barbital at neutral pH in aqueous solution.

The acridine-pendant complex, zinc(II)–acridinylmethylcyclen (*cf.* thymidine complex **29**) also acts as a selective host molecule for terephthalic acid by supramolecular self-assembly.[42] In neutral pH aqueous solution, zinc(II)–acridinylmethylcyclen yields a 1 : 1 complex with terephthalate with dissociation constant $K_d = 10^{-2.3}$ mol dm^{-3} at 25 °C. Despite its relatively weak affinity, crystalline **34** [a ternary complex of one terephthalate and two zinc(II)–acridinylmethylcyclen molecules] precipitated almost quantitatively when zinc(II)–acridinylmethylcyclen (10 mM) was mixed with terephthalic acid (5 mM) in an aqueous solution containing excess ClO_4 at pH 8.4. It was found that zinc(II)–acridinylmethylcyclen selectively separates terephthalate as insoluble



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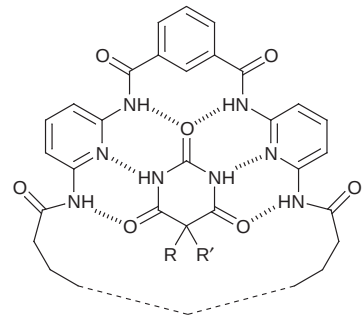
Bis(Zn^{2+}-cyclen)



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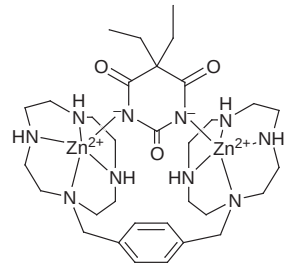

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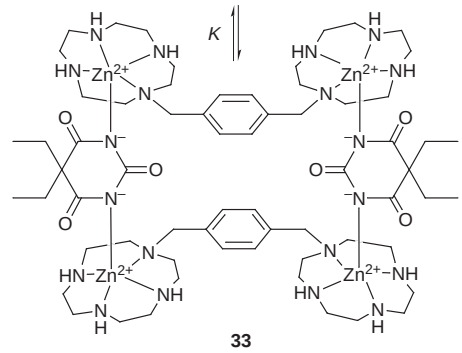

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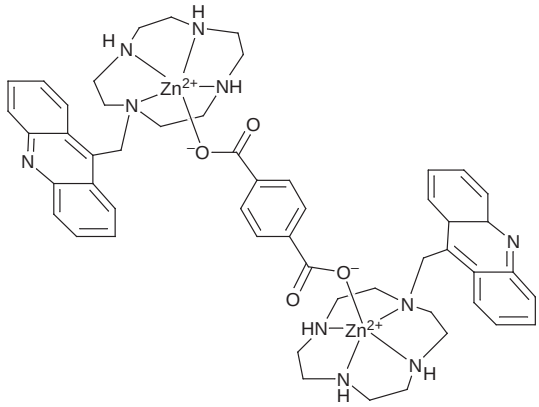
crystals of the 2 : 1 complex **34** from a mixture with its isomers (*o*- and *m*-phthalate). This is a consequence of the fact that **34** in the solid state is additionally stabilized by self-assembly in a highly ordered aggregate with π–π stacking (schematic representation **35**), as revealed by X-ray crystal analysis. Metal complexes with aromatic pendants like zinc(II)–acridinylmethylcyclen would be useful for the molecular recognition of other anionic molecules in aqueous media.

The recognition of thymine (or uracil) by zinc(II)–cyclens has been extended to a single-stranded polynucleotide poly(U) and double-stranded poly(U)–poly(A).[43–46] The affinity constant of zinc(II)–cyclen **8a** for each N^3-deprotonated uracil base in poly(U) is $K = 10^{5.1}$ dm^3 mol^{-1} at 25 °C, which is almost the same ($10^{5.2}$ dm^3 mol^{-1}) for the interaction of zinc(II)–cyclen and N^3-deprotonated uridine. This fact imples that zinc(II)–cyclen shows a negligible interaction with the monoanionic phosphodiester backbone of poly(U). Moreover, zinc(II)–cyclen disrupts U–A hydrogen bonds to unzip the duplex of poly(U)–poly(A) (see **36**), as demonstrated by the decreasing melting temperatures (T_m) of poly(U)–poly(A) in aqueous solution at pH 7.6 (5 mM Tris-HCl, 10 mM NaCl) with an increase in the concentration of zinc(II)–cyclen. A bidentate host molecule, bis[zinc(II)–cyclen] **30**, is a more potent zipper of the poly(U)–poly(A) double strand. Very recently, we have determined an



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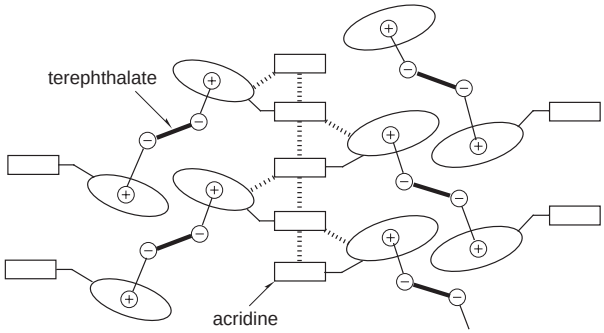

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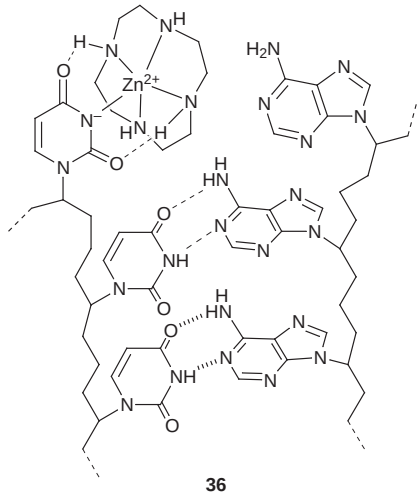

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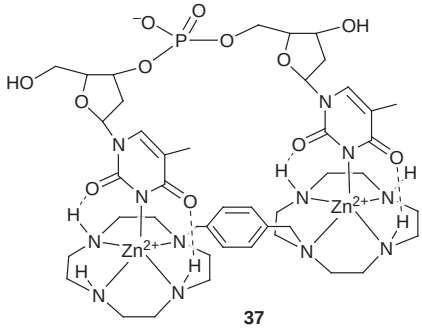

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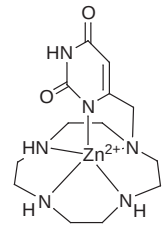
extremely strong interaction of bis[zinc(II)–cyclen] with thymidinylthymidine (TpT) in aqueous solution at pH 7.4 to yield a much more stable complex **37** *cf.* T$^-$–[zinc(II)–cyclen] **27a**.[47] The dissociation constant K_d of 10^{-6} mol dm^{-3} for **37** is almost 10^3 times smaller than that for **27a** ($K_d = 8 \times 10^{-4}$ mol dm^{-3}). This fact, along with the widened T–T plane distance (*ca.* 10 Å) determined by molecular mechanics calculation (MM2) well accounts for the more effective disruption of the poly(U)–poly(A) double strand by **30**. Thus, **30** can act as a useful TpT sequence-selective ligand in biochemical applications.

In section 1, it was stated that uracil N^{1}H is two orders of magnitude more acidic when proximate to a diprotonated macrocyclic tetraamine (see **5** and **6**). When Zn^{2+} is used in place of the two protons in **5**, the acidic Zn^{2+} in the cyclen exerts an even stronger effect on the deprotonation of the uracil N^{1}H to below pH 5.[14] The resulting zinc(II) complex **38** contains a very stable Zn^{2+}–(N^1)$^-$ coordination bond.



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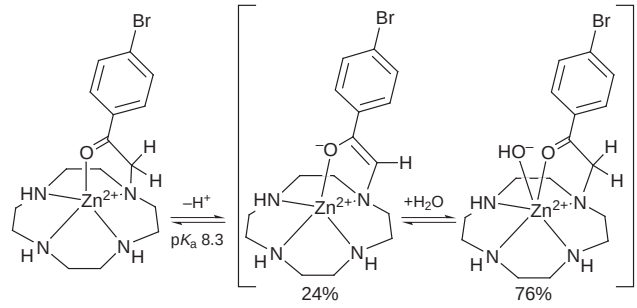
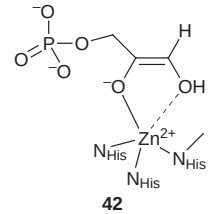
Finally, the acidic Zn^{2+} centre in the substituted cyclen ligand 1-(4-bromophenacyl)-1,4,7,10-tetraazacyclododecane **39** has recently been found to deprotonate a methylene hydrogen adjacent to the carbonyl group to yield an enolate complex **40** in aqueous solution (Scheme 7), which is in equilibrium with an



39 **40** **41**

Scheme 7

equivalent OH$^-$-bound complex **41** (ratio of **40**:**41** = 24:76).[48] Surprisingly, its pK_a value is as low as 8.3 at 25 °C (I = 0.1, $NaNO_3$), which is probably the first successful identification of enolate formation in aqueous solution. It is of interest to note that type II aldolase is a zinc enzyme, which also forms an enolate-bound zinc(II) complex (see **42**).[20]



42

4 Conclusions

This article illustrates that macrocyclic polyamines either in multiprotonated forms or in zinc(II) complexes act as static anion receptors in aqueous solution. The macrocyclic 12-membered N_3– or N_4–Zn^{2+} complexes can, moreover, recognize netural molecules having weak acid protons to yield stable

anion complexes. These anion complexes possess dynamic functions as exemplified by HO^{-}–Zn^{2+} and RO^{-}–Zn^{2+} acting as strong nucleophiles for catalytic hydrolysis of esters or as bases for thymine recognition. This basic principle has been further developed to hydride transfer reactions from Zn^{2+}-bound alkoxides, a Zn^{2+} sensor, DNA base recognition, or stabilization of unusual anions such as enolate in aqueous solution.

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Notes and References

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