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A Zinc(II)-organized Molecular Receptor as a Catalyst for the Cleavage of Amino Acid Esters

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The Zn^{II} complex of ligand **1a**, a derivative of TREN bearing three 3-hydroxyphenyl units at the amines of its arms, acts as a transacylation catalyst of the *p*-nitrophenyl ester of 4-pyridinecarboxylic acid.

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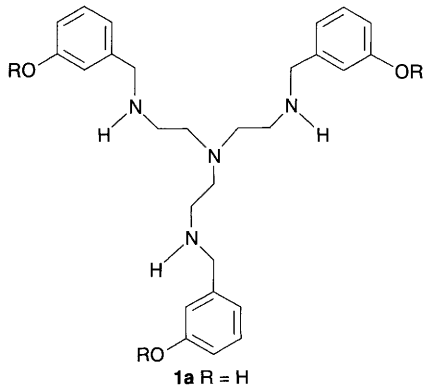
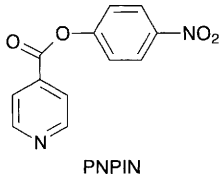
Transition metal ions play a relevant role in biological systems being involved in the catalytic sites of metalloenzymes and in the organization and stabilization of the structures of proteins and nucleic acids.[1] Synthetic systems exploiting these abilities of transition metal ions, in particular their catalytic properties, have been investigated and reported.[2] There has been considerable recent interest in the use of these ions for the organization of small molecules[3,4] and, hence, for the generation of new supramolecules[5] entailing new functions and properties.

We here report how the simple derivative of tris(2-aminoethyl)amine (TREN)[6] **1a**, may assume, upon complexation of a Zn^{II} ion, a basket-like structure, bind substrates in water and, eventually, cleave them in a transacylation process. Compound **1a**, as well as its *O*-methoxy analogue **1b**, obtained by reacting TREN with 3-hydroxybenzaldehyde (3-methoxybenzaldehyde for **1b**) and subsequent reduction of the imine derivative,† binds Zn^{II} quite strongly[7] at pH > 6.5. The tetramine derivative, which otherwise possesses a flexible structure, following complexation with the metal ion assumes a well-defined geometry with the metal ion at the bottom of a cavity roughly defined by the three aromatic residues, as confirmed by the X-ray single crystal structure‡ obtained for **1b** and shown in Fig. 1. The crystallographic analysis reveals that the Zn^{II} ion assumes, in the complex, a trigonal bipyramid coordination geometry with four coordination positions occupied by the four nitrogens of the ligand and the fifth apical position occupied by Cl^-. In this trigonal bipyramid the Zn atom lies *ca.* 0.35 Å above the plane defined by the three secondary-amine nitrogens. The three aromatic residues lying above the same plane form a ill-defined cavity, at least in the crystal. From an examination of the crystal packing diagram it appears that the organization of this molecule is owing to the Zn^{II} ion complexation and not to lattice packing effects. In aqueous solution, because of hydrophobic interactions, the aromatic groups may be forced to approach each other in a calix-like arrangement and the chloride ion occupying the apical position of coordination to Zn^{II} may be exchanged with other coordinating species such as a water molecule. In fact the pH titration curve of ligands **1a** and **1b** in the presence of one equivalent of $Zn(NO_3)_2$ reveals the presence of a Zn^{II}-bound water molecule with a pK_a *ca.* 8.2. The reported pK_a values, in different complexes,[8] for water molecules coordinated to a Zn^{II} ion lie in the range 7–9, in agreement with the value here observed. The same pH titration curve shows that, in the case of the **1a**·Zn^{II} complex, one of the three phenolic hydroxy groups has a particularly low[9] pK_a of *ca.* 8.5.

The rate of cleavage of the *p*-nitrophenyl ester of 4-pyridinecarboxylic acid (PNPIN) at pH = 8.3 was measured in the presence of **1a**·Zn^{II} and, for sake of comparison, with **1b**·Zn^{II} and TREN·Zn^{II}. The data are reported in Table 1. At [**1a**·Zn^{II}] = 1×10^{-3} mol dm^{-3} the rate of cleavage of PNPIN is ten times faster than the OH^--catalysed process. The log k_ψ *vs.* pH profile for the cleavage process gives a pK_a of *ca.* 8.5 for the nucleophilic species in agreement with the above-mentioned titration experiments. Rate acceleration is not observed in the case of **1b**·Zn^{II} or TREN·Zn^{II}. Only a modest effect is observed in the presence of TREN·Zn^{II} and 3 equiv. of phenol, accounting for the nucleophilicity of this latter at the operational pH. Clearly the acceleration observed requires: (*a*) the phenols



1a R = H
1b R = Me



PNPIN

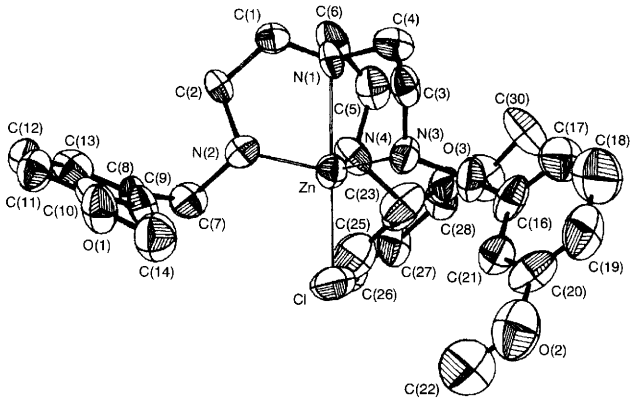


Fig. 1. ORTEP view of the molecular structure of one of the two independent molecules of **1b**·Zn^{II}. The thermal ellipsoids are at the 50% probability level and the hydrogen atoms are omitted for clarity. The other molecule present in the cell unit (not shown) has a different conformation owing to the relative orientation of one phenyl ring (highlighted by the bold dihedral angle). Selected bond distances (Å) and bond angles (°) for the two independent molecules of **1b**·Zn^{II} (the first value refers to the shown structure): Zn(1)–N(1) 2.30(1) 2.23(1), Zn(1)–N(2) 2.05(1) 2.10(1), Zn(1)–N(3) 2.07(1) 2.10(1), Zn(1)–N(4) 2.09(1) 2.12(1), Zn(1)–Cl(1) 2.311(5) 2.337(5), Cl(1)–Zn(1)–N(2) 101.0(5) 99.9(4), Cl(1)–Zn(1)–N(3) 97.3(4) 96.8(4), Cl(1)–Zn(1)–N(4) 100.9(4) 100.6(4), N(2)–Zn(1)–N(3) 109.2(5) 110.8(4), N(2)–Zn(1)–N(4) 125.1(5) 123.4(4), N(3)–Zn(1)–N(4) 117.0(6) 118.2(5), N(1)–Zn(1)–N(2) 79.0(5) 80.8(5), N(1)–Zn(1)–N(3) 80.7(5) 80.9(5), N(1)–Zn(1)–N(4) 80.8(5) 80.9(5), Cl(1)–Zn(1)–N(1) 177.8(3) 177.4(4), Cl(1)–Zn(1)–N(2)–C(7) –33(1) –36(1), Cl(1)–Zn(1)–N(3)–C(15) 64(1) 63(1), Cl(1)–Zn(1)–N(4)–C(23) –37(1) –41(1), N(2)–C(7)–C(8)–C(9) –67(1) –68(1), N(3)–C(15)–C(16)–C(21) **72(1)–107(1)**, N(4)–C(23)–C(24)–C(29) 102(1) 103(1).

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covalently bound to TREN as an integral part of the molecular receptor, and (*b*) the free phenolic hydroxy groups. This also rules out the action of a Zn^{II}-bound water molecule as a nucleophile. The plot k_ψ *vs.* [**1a**·Zn^{II}] shows the saturation behaviour characteristic of a kinetic process subsequent to a binding equilibrium.[10] From the analysis of this profile we evaluate the following parameters: $K_b = 440 \pm 40$ dm^3 mol^{-1} for PNPIN binding to the metalloreceptor and $k_{lim} = 1.3 \times 10^{-2}$ s^{-1} for the rate constant of the fully bound substrate. Evidence in favour of an association pre-equilibrium between **1a**·Zn^{II} and PNPIN, as a requisite for the subsequent reaction, comes from the inhibition of the rate acceleration observed in the presence of increasing amounts of 4-methylpyridine which may successfully compete with PNPIN for the occupation of the metalloreceptor cavity *via* Zn^{II} coordination. Control experiments showed that this latter has no effect on the OH^--catalysed reaction.

The above results point to a mechanism involving the binding of the substrate to the metalloreceptor *via* the coordination of the pyridine nitrogen to the Zn^{II} ion followed by the transacylation of one of the phenolic hydroxy groups (see Fig. 2). The proposed transacylation mechanism clearly resembles that operative in the case of cyclodextrins,[11] though it occurrs at a much lower pH because of the higher acidity of one of the phenolic hydroxy groups in the present system. ^{1}H NMR experiments performed in CD_3CN–D_2O at the apparent§ pD = 8 with a 1 : 1 mixture of PNPIN and **1a**·Zn^{II} allowed the detection of the formation of the transacylation intermediate. This latter eventually hydrolyses to 4-pyridinecarboxylic acid and **1a**·Zn.

In conclusion we have shown that a simple derivative of *TREN* may, as a Zn^{II} complex, recognize an ester of the proper structure and geometry *via* the co-ordination to the Zn^{II} ion and act as a catalyst of its esterolysis at pH = 8.3. The Zn^{II} ion is not involved in the catalytic process; rather, it plays both the role of organizing the ligand and orienting the substrate in the supramolecular complex suggested to be the active species in the process. The system described here represents a prototype of a new class of relatively simple, metal-organized receptors.

Table 1 Observed pseudo-first order rate constants[a] (k_ψ, s^{-1}) for the cleavage of PNPIN at pH = 8.3, in 5×10^{-2} mol dm^{-3} EPPS [*N*-(2-hydroxyethyl)piperazine-*N*′-(3-propanesulfonic acid)] buffer at 25 °C in the presence of different additives

Complex[b]	Additive	$10^4 k_\psi$/s^{-1}
none	none	5.5
1a·Zn^{II}	none	53.0
1a·Zn^{II}	4-methylpyridine[c]	38.9
1b·Zn^{II}	none	7.0
TREN·Zn^{II}	none	5.5
TREN·Zn^{II}	phenol[d]	15

[a] Reactions were started by addition of 20–30 μl of a 2×10^{-3} mol dm^{-3} solution of substrate in MeCN and followed spectrophotometrically by monitoring the appearence of *p*-nitrophenoxide at 400 nm. [b] [Complex] = 1×10^{-3} mol dm^{-3} in all cases. [c] [4-Methylpyridine] = 6.5×10^{-2} mol dm^{-3}. [d] [Phenol] = 3×10^{-3} mol dm^{-3}.

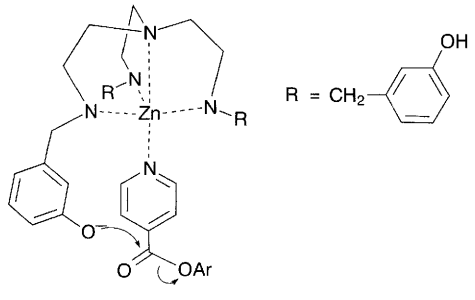

Fig. 2 Proposed mechanism for the cleavage of PNPIN by **1a**·Zn^{II}

Indeed, other activated esters of amino acids such as 3-pyridinecarboxylic and 4-imidazoleacrylic acids proved to be proper substrates for receptor **1a**. The kinetic effects were different from those here reported for PNPIN, suggesting some geometrical selectivity of the system. One may speculate that replacing the hydroxy groups with more powerful nucleophiles and decreasing the degrees of freedom of the moieties bound to the nitrogens of TREN may result in a more rigid and potentially more reactive system; work in this direction is in progress in our laboratory.

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Footnotes

† All new compounds gave correct elemental analyses (C, H, N) and the expected ^{1}H NMR spectra.

‡ *Crystal data* for **1b**·Zn^{II}: $C_{30}H_{42}Cl_3N_4O_3Zn \cdot 0.5H_2O$: M = 651.98, crystal size 0.1 × 0.1 × 0.2 mm, monoclinic, space group $P2_1/c$, a = 18.4920(20), b = 23.6260(20), c = 15.1050(20) Å, β = 90.30(0.10)°, V = 6599(1) Å^3, Z = 8, D_c = 1.31 g cm^{-3}, λ(Mo-Kα) = 0.71069 Å, μ(Mo-Kα) = 9.6 cm^{-1}, F(000) = 2744, scan type θ–2θ to 2θ = 56°, T = 293 K, 12556 reflections, 11598 unique (R_{int} = 0.06), no. of observations [$(F) > 3\sigma(F)$] 4259, total number of refined parameters 615, observations/variables 6.92, R = 0.10, R_w = 0.12, with $w = 1/[\sigma^2(F) + 0.005F^2]$. Data were collected on a automatic Philips PW 1100 diffractometer with standard software and the structure was solved with the Patterson Fourier Method. No absorption corrections were applied. All non hydrogen atoms, except C(52) and O(1)W, were refined anisotropically. Hydrogen atoms were located on a ΔF map but not refined. The high values of R obtained for the structure are owing to the presence of some molecular disorder, as revealed by the presence of two different conformations of the molecule in the unit cell (see caption to Fig. 1). This crystal has a pseudo-orthorhombic symmetry but the R_i value of 0.19 between h, k, l and $-h, k, l$ reflections and the two different conformations of the molecule found in the unit cell confirm the monoclinic system. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ Uncorrected pD reading in D_2O before mixing with CD_3CN.

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