Supramolecular Assembling of Dizinc Macrocyclic Complexes with Thymine and Uracil — The Role of Intra- and Intermolecular Hydrogen Bonding

Carla Bazzicalupi,[a] Andrea Bencini,*[a] Emanuela Berni,[a] Antonio Bianchi,*[a]
Samuele Ciattini,[a] Claudia Giorgi,[a] Piero Paoletti,*[a] and Barbara Valtancoli*[a]

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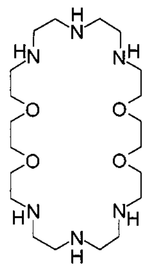
A binuclear Zn$^{\mathrm{II}}$ complex with an oxa-aza macrocyclic ligand can bind two deprotonated thymine or uracil moieties, giving versatile building blocks for the assembly of supramolecolar structures, by hydrogen bond pairing of the nucleobases.

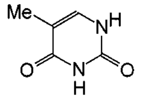
Introduction

In the last few years a great deal of interest has been devoted to the recognition of nucleobases, nucleosides and nucleotides by synthetic receptors in aqueous solutions,[1-11] due both to their use as mimic systems for enzymes and to their potential medical application. Particular attention has been focused on the role of nucleobases in the recognition process, since these molecules possess several functions which can be used for hydrogen bonding and/or metal binding. Metal complexes are often chosen as receptors for these substrates. Recent work by Kimura[8-11] has shown that thymine derivatives containing an imide CO−NH−CO moiety (such as AZT or thymidine), are strongly bound by Zn$^{\mathrm{II}}$ complexes with cyclen-based macrocycles (cyclen = 1,4,7,10-tetraazacyclododecane), through a recognition process which involves deprotonation of the imide function, metal binding by the deprotonated nitrogen and hydrogen bonding between the CO functions and two complementary amine groups of the macrocyclic unit. This "three-point" binding mode accounts for the selective binding of thymine derivatives with respect to cytosine ones, which don't contain an "imide" moiety.

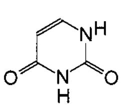
Several zinc enzymes, however, contain two Zn$^{\mathrm{II}}$ ions in their active site. At the same time, binuclear metal complexes with macrocyclic ligands are potential receptors for nucleobases.[10] The particular topology of these ligands, in fact, may force the two metal centres into close proximity where they can act as multipoint binding sites for substrate molecules or anions.[12,13] Ligand **L** presents two almost independent binding moieties — the two triamine chains — separated by two weakly coordinating polyoxa chains.[14] In its dizinc complex each metal is bound by a triamine unit and presents an unsaturated coordination sphere. This complex, therefore, may be a promising receptor for nucleobases, such as thymine (TH) or uracil (UH).



L



Thymine



Uracil

Results and Discussion

Thymine and uracil binding to the dizinc complex $[\mathrm{Zn_2}\mathbf{L}]^{4+}$ was studied by means of potentiometric measurements in aqueous solutions. This complex displays similar binding features towards thymine and uracil. We found, in fact, that it forms stable 1:1 and 1:2 complexes with both deprotonated thymine and uracil at neutral or slightly alkaline pH's. Deprotonation and simultaneous binding of thymine and uracil to the $[\mathrm{Zn_2}\mathbf{L}]^{4+}$ complex takes place at neutral pH, to give the 1:1 complexes $[\mathrm{Zn_2}\mathbf{L}\mathrm{T}]^{3+}$ or $[\mathrm{Zn_2}\mathbf{L}\mathrm{U}]^{3+}$ {log K = 5.3(1) and 5.0(1) for the equilibria $[\mathrm{Zn_2}\mathbf{L}]^{4+} + \mathrm{T}^- = [\mathrm{Zn_2}\mathbf{L}\mathrm{T}]^{3+}$ and $[\mathrm{Zn_2}\mathbf{L}]^{4+} + \mathrm{U}^- = [\mathrm{Zn_2}\mathbf{L}\mathrm{U}]^{3+}$, respectively}. These complexes are formed in the pH range 6.5−9, with a maximum percentage of ca. 20% at pH 7.5 in solutions containing $[\mathrm{Zn_2}\mathbf{L}]^{4+}$ and TH or UH in a 1:1 molar ratio. This process is followed at slightly alkaline pH's by deprotonation and binding of a second nucleobase, leading to the assembly of the $[\mathrm{Zn_2}\mathbf{L}\mathrm{T_2}]^{2+}$ and $[\mathrm{Zn_2}\mathbf{L}\mathrm{U_2}]^{2+}$ complexes {log K = 5.0(1) and 4.7(1) for the equilibria $[\mathrm{Zn_2}\mathbf{L}\mathrm{T}]^{3+} + \mathrm{T}^- = [\mathrm{Zn_2}\mathbf{L}\mathrm{T_2}]^{2+}$ and $[\mathrm{Zn_2}\mathbf{L}\mathrm{U}]^{3+} + \mathrm{U}^- = [\mathrm{Zn_2}\mathbf{L}\mathrm{U_2}]^{2+}$, respectively}, which contain two deprotonated nucleobases. These species are formed in the pH range 7−10.5 (maximum percentage ca. 60% at pH 9). It is of interest to note that, for both thymine and uracil, the constant for the addition of the first deprotonated nucleobase is almost equal to that for the addition of the second one, suggesting that each nucleobase is coordinated, almost independently, by one Zn$^{\mathrm{II}}$ ion of the $[\mathrm{Zn_2}\mathbf{L}]^{4+}$ complex.

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[a] Department of Chemistry, University of Florence,
Via Maragliano 77, 50144 Florence, Italy
Fax: (internat.) +39-055/354-845
E-mail: benc@chim1.unifi.it

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The crystal structure of the $[Zn_2\mathbf{L}T_2]^{2+}$ cation (Figure 1a) shows that two deprotonated thymine units are coordinated to the two metal centers and lie on opposite sides with respect to an ideal plane containing the macrocycle oxygen atoms. The metals are symmetry related [Zn···Zn′ = 7.667(5) Å] and present a distorted trigonal bipyramidal coordination geometry, with the equatorial plane defined by the "lateral" N(1) and N(3) amine groups of the macrocycle and the deprotonated N(3t) nitrogen of thymine, with a rather short Zn−N(3t) bond length [1.948(6) Å], due to the anionic nature of this donor. The "central" nitrogen N(2) of the triamine unit and an oxygen [O(1)] of the polyoxa chain occupy the apical positions and are bound at longer distances [Zn(1)−N(2) = 2.143(9) Å, Zn(1)−O(1) = 2.398(7) Å] than the other three coordinated nitrogens. The Zn^{II} ion and the two lateral amine groups lie on the plane of the thymine ring [max. deviation 0.325(7) Å for N(1)]. Such a complementary disposition allows the formation of two rather strong hydrogen bonds between the two carbonyl oxygens of thymine and the coordinated N(1) and N(3) amine groups of the macrocycle [N(1)···O(2t) = 3.02(1) Å; N(3)···O(4t) = 3.39(2) Å]. Furthermore, deprotonation of the imide nitrogen develops negative charges at the carbonyl functions, which become better acceptors for the N−H hydrogens. The match of the complementary binding sites of receptor and substrate allows the formation of a tight $(CO)_2N(3t)-ZnN(1)N(3)$ unit and may account for the remarkably high stability in aqueous solution of the present dizinc complex with deprotonated thymine.

Thymine, however, possesses another binding site, the N(1t) nitrogen, which can be used for hydrogen bonding. Besides intramolecular hydrogen bonding, inspection of the crystal packing revealed the formation of hydrogen-bond pairing between the thymine units of different $[Zn_2\mathbf{L}T_2]^{2+}$ complexes. The ORTEP drawing of the crystal packing for the $[Zn_2\mathbf{L}T_2]^{2+}$ complex (Figure 1b) clearly shows that each thymine unit is associated through two symmetry-related strong hydrogen bonds [N(1t)···O(2t) 2.769(9) Å] with a thymine moiety of a different binuclear complex. Consequently, the $[Zn_2\mathbf{L}T_2](ClO_4)_2$ complexes are assembled into infinite pillars of $[Zn_2\mathbf{L}T_2]^{2+}$ units, joined together through a centrosymmetrical hydrogen bond network.

The assembly of this supramolecular architecture can also be ascribed to the macrocyclic structure of **L**, which keeps two Zn-thymine units at rather close distance. At the same time, the well-known ability of thymine to give hydrogen bonds with other nucleobases (a different thymine unit in the present case) allows the formation of the pillared structure presented by the $[Zn_2\mathbf{L}T_2](ClO_4)_2$ complex.

The crucial role played by both intra- and intermolecular hydrogen bonding in this assembling process is confirmed by the crystal structure of the dinuclear Zn^{II} complex with uracil, which presents the same binding sites as with thymine (Figure 2).

In the $[Zn_2\mathbf{L}U_2]^{2+}$ complex, each metal displays a trigonal bipyramidal coordination geometry, very similar to that found in the thymine complex. The N(3u), N(1) and N(3) nitrogens define the basal plane, while the N(2) and O(1) donors, at the apical positions, are coordinated at longer distances. Figure 2 clearly shows the optimal matching between the N(1)−Zn−N(3) unit of the receptor and the $CO-N(3u)^{-}-CO$ imide function, leading, once again, to an enhanced receptor-substrate interaction through the formation of a strong Zn−N(3u) bond [1.93(1) Å] and two N(1)···O(2u) and N(3)···O(4u) hydrogen bonds [3.05(2) and 3.16(2) Å, respectively]. As in the case of thymine, intermolecular hydrogen bond pairing between two symmetry related uracil units of two different dizinc clusters [N(1u)···O(2u), 2.84(2) Å] leads to the formation of infinite pillars of $[Zn_2\mathbf{L}U_2]^{2+}$ complexes (Figure 2b).

To the best of our knowledge, the $[Zn_2\mathbf{L}T_2](ClO_4)_2$ and $[Zn_2\mathbf{L}U_2](ClO_4)_2$ complexes are the first structurally characterized dizinc assemblies containing two thymine or uracil units.

The present structures suggest that binuclear Zn^{II} macrocyclic complexes with nucleobases may be used as building blocks for supramolecular structures, due to the versatile hydrogen bonding ability of these molecules. Intramolecular hydrogen bonds, in fact, give a significant contribution to the stability of the binuclear dithymine or diuracil adducts. At the same time, intermolecular hydrogen bonding of different binuclear complexes contributes to generate the as-

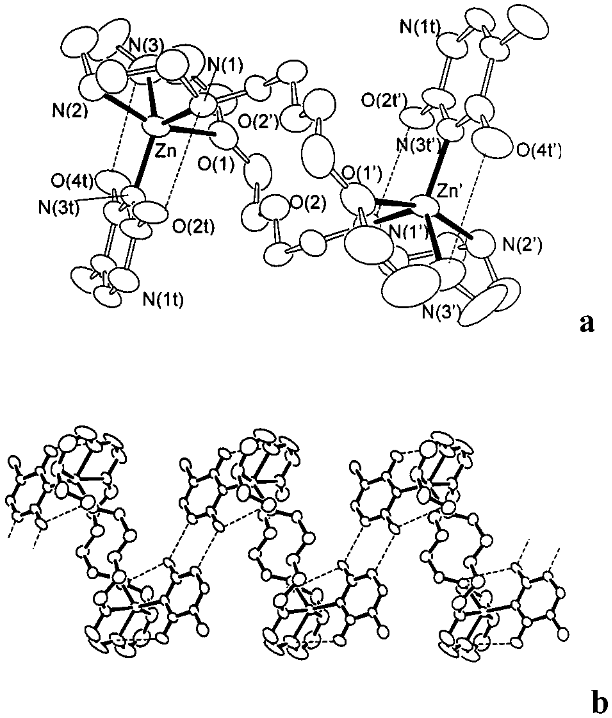

Figure 1. (a) ORTEP drawing of the $[Zn_2\mathbf{L}T_2]^{2+}$ cation; (b) crystal packing for $[Zn_2\mathbf{L}T_2](ClO_4)_2$ displaying the intramolecular hydrogen bonds and the hydrogen bond pairing between thymine units of different $[Zn_2\mathbf{L}T_2]^{2+}$ complexes (perchlorate anions are omitted for clarity); selected bond lengths (Å) and angles (°): Zn−N(3t) 1.948(6), Zn−N(3) 2.034(9), Zn−N(1) 2.070(7), Zn−N(2) 2.143(9), Zn−O(1) 2.398(7); N(3t)−Zn−N(3) 129.0(4), N(3t)−Zn−N(1) 119.2(3), N(3)−Zn−N(1) 111.5(4), N(3t)−Zn−N(2) 105.0(3), N(3)−Zn−N(2) 83.6(4), N(1)−Zn−N(2) 84.7(3), N(3t)−Zn−O(1) 94.5(3), N(3)−Zn−O(1) 74.5(4), N(1)−Zn−O(1) 96.5(3), N(2)−Zn−O(1) 156.9(3), Zn···Zn′ 7.667(5)

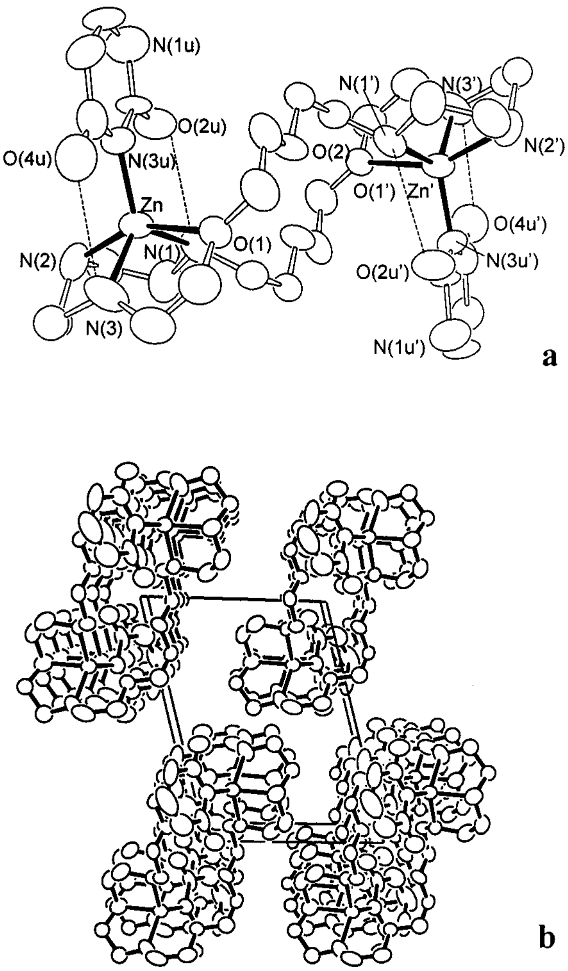

Figure 2. (a) ORTEP drawing of the $[Zn_2\mathbf{L}U_2]^{2+}$ cation; (b) crystal packing for $[Zn_2\mathbf{L}U_2](ClO_4)_2$ [view normal to (011)], displaying the pillared structure of $[Zn_2\mathbf{L}U_2]^{2+}$ cations (perchlorate anions are omitted for clarity); selected bond lengths (Å) and angles (°): Zn−N(3u) 1.93(1), Zn−N(3) 2.04(1), Zn−N(1) 2.08(1), Zn−N(2) 2.11(1), Zn−O(1) 2.462(8); N(3u)−Zn−N(3) 121.9(5), N(3u)−Zn−N(1) 120.0(4), N(3)−Zn−N(1) 117.0(5), N(3u)−Zn−N(2) 111.2(4), N(3)−Zn−N(2) 83.5(5), N(1)−Zn−N(2) 84.9(4), N(3u)−Zn−O(1) 94.1(4), N(3)−Zn−O(1) 73.4(4), N(1)−Zn−O(1) 92.1(3), N(2)−Zn−O(1) 152.3(4), Zn···Zn′ 7.799(2)

sembly of supramolecular architectures based on infinite pillars of $[Zn_2\mathbf{L}T_2]^{2+}$ or $[Zn_2\mathbf{L}U_2]^{2+}$ units.

Further investigations on different nucleobases are in progress.

Experimental Section

General Remarks: Compound **L** and $[Zn_2\mathbf{L}](ClO_4)_4$ were prepared as previously described.[14]

$[Zn_2\mathbf{L}T_2](ClO_4)_2$: Crystals of the $[Zn_2\mathbf{L}T_2](ClO_4)_2$ complex were obtained in 82% yield by slow evaporation of an aqueous solution containing $[Zn_2\mathbf{L}](ClO_4)_4$ (0.001 M) and TH (0.002 M) at pH 8. − $C_{30}H_{56}Cl_2N_{10}O_{16}Zn_2$ (1014.49): C 35.52, H 5.56, N 13.81; found C 35.7, H 5.7, N 14.0.

$[Zn_2\mathbf{L}U_2](ClO_4)_2$: This compound was prepared in 87% yield in a similar manner as already described for $[Zn_2\mathbf{L}T_2](ClO_4)_2$. − $C_{28}H_{52}Cl_2N_{10}O_{16}Zn_2$ (986.44): C 34.09, H 5.31, N 14.20; found C 34.2,H 5.3, N 14.1.

Potentiometric Measurements: All potentiometric measurements (pH = $-\log[H^+]$) were carried out in 0.1 M NMe_4NO_3 (pK_w = 13.83 at 298.1 K) at 298.1 K, by using the method and procedure from ref.[14] The nucleobase:[Zn^{II} complex] molar ratio was varied from 0.3 to 5 in order to better ascertain the stoichiometry of the adducts. The computer program HYPERQUAD[15] was used to calculate the addition constants from e.m.f. data.

X-ray Crystallographic Study: $[Zn_2\mathbf{L}T_2](ClO_4)_2$: $C_{30}H_{56}Cl_2N_{10}O_{16}Zn_2$, M = 1014.48, triclinic, $P\bar{1}$, a = 9.305(6) Å, b = 9.612(4) Å, c = 13.170(5) Å, α = 103.17(3)°, β = 100.94(4)°, γ = 100.53(4)°, V = 1094.2(9) $Å^3$, T = 298 K, Z = 1, calculated density 1.540 Mg/m^3. Data collection with an Enraf Nonius CAD4 diffractometer, graphite-monochromated Mo-K_α radiation, crystal size 0.3 × 0.25 × 0.1 mm, θ-2θ scan, $2\theta_{max}$ = 50°, μ = 1.295 mm^{-1}, 4500 reflections collected, 3719 unique (R_{int} = 0.1355) which were used in all calculations, absorption correction by psi-scan method, transmission factors 0.72−0.82, data/parameters 3719/272, final R indices $R1$ = 0.0838 [$I > 2\sigma(I)$], $wR2$ = 0.2711. All hydrogen atoms were introduced in calculated positions.

$[Zn_2\mathbf{L}U_2](ClO_4)_2$: $C_{28}H_{52}Cl_2N_{10}O_{16}Zn_2$, M = 986.44, triclinic, $P\bar{1}$, a = 9.405(1) Å, b = 9.443(1) Å, c = 12.457(2) Å, α = 103.46(1)°, β = 96.81(1)°, γ = 100.53(1)°, V = 1042.7(2) $Å^3$, T = 298 K, Z = 1, calculated density 1.571 Mg/m^3. Data collection with a Siemens P4 diffractometer equipped with a rotating anode, graphite-monochromated Cu-K_α radiation, crystal size 0.15 × 0.1 × 0.1 mm, θ-2θ scan, $2\theta_{max}$ = 110°, μ = 3.280 mm^{-1}, 2688 reflections collected, 2173 unique (R_{int} = 0.0684) which were used in all calculations, absorption correction by psi-scan method, transmission factors 0.61−0.72, data/parameters 2173/261, final R indices $R1$ = 0.0810 [$I > 2\sigma(I)$], $wR2$ = 0.2278. All hydrogen atoms were introduced in calculated positions.

Both structures were solved using the direct methods of the SIR97 program[16] and refined by full-matrix least-squares on F^2 by means of the SHELXL-97 program.[17]

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-149822 {$[Zn_2\mathbf{L}T_2](ClO_4)_2$} and -149823 {$[Zn_2\mathbf{L}U_2](ClO_4)_2$}. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

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