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Molecular Recognition of Thymine and Uracil in Water by an Amino-, Amido-, and Carboxymethyl-functionalized Pyridinophane

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A new water soluble 26-membered macrocyclic pyridinophane functionalized by amide and carboxymethyl groups has been synthesized in a single step reaction and characterized by elemental analysis, mass spectrometry (FAB$^+$), UV-vis, fluorescence, and ^{1}H NMR spectroscopy as well as single-crystal X-ray diffraction analysis. Its complexation properties with the nucleobases thymine and uracil have been explored in aqueous media by performing ^{1}H NMR titration experiments and potentiometric studies. The binding constants of the 1:1 host-guest complexes were determined as $10^3\,M^{-1}$ by proton NMR and 10^2–$10^3\,M^{-1}$ by potentiometry. Semiempirical molecular modelling studies have shown that the nucleobases are included within the cavity of the macrocyclic receptor and that the complexes are stabilized by hydrogen bonding.

Keywords: Binding constant; Cyclophanes; Host-guest complex; Molecular recognition; NMR; Thymine; Uracil

INTRODUCTION

Important efforts have been made to study molecular recognition of nucleobases and their derivatives in different organic solvents [1–9] and in water [10–23]. For this purpose different types of receptors have been used, such as synthetic macrocycles [3–6,17,18], ferroceptors [1,2,9], Zn(II) complexes [20–23], porphyrin [19] and sapphyrin conjugates [24]. The most examined nucleobases are nucleotides [9,12–14,17,18,21], nucleosides [12,13], and derivatives having aliphatic chains in different positions [1–8,10], but there are few studies of free nucleobases and other related molecules such as caffeine and theophylline in water [19]. The measured binding constants are in the range 0.0138–$4.5 \times 10^4\,M^{-1}$ in chloroform and 2–$7 \times 10^7\,M^{-1}$ in water. Both in organic [4] and aqueous solvents [14] the complex (host-nucleobase) formation occurs mainly through complementary hydrogen bonding and aromatic stacking interactions.

In this work, we report on the structural characterization of a pyridinophane derived from 2,6-diaminopyridine and ethylenediaminotetracetic (EDTA) dianhydride, **1** and its molecular recognition properties toward thymine and uracil in water (Chart 1). Cyclophane **1** has two aromatic groups in the macrocyclic ring system and, in addition, three different functional groups, i.e. amino and amide functions in the cyclophane framework and carboxymethyl groups as pendant arms. The two 2,6-diamidopyridine fragments in this system can be used to bind pyrimidine nucleobases and their derivatives as it has been shown in former studies [6,19]. These structural features allow the formation of host-guest complexes with uracil and thymine, due to the combined effect of a hydrophobic interaction between the aromatic groups of the host and guest molecules and electrostatic interactions between $-CO_2^-$ and $-NH_3^+$ groups of the host and the polar groups of the guest.

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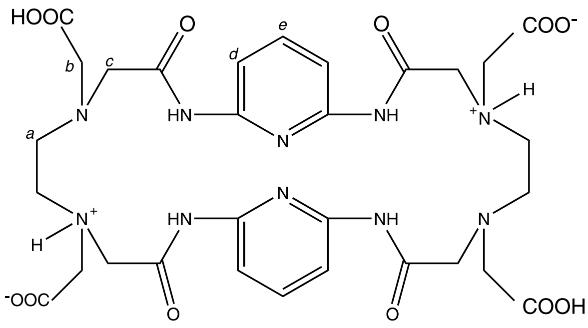

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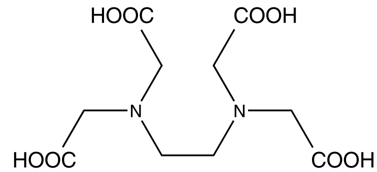

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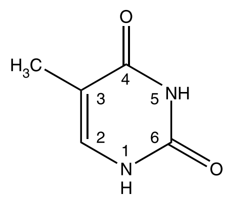
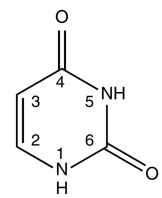


thymine



uracil

CHART 1 Chemical structures of the hosts and guests molecules studied in this work.

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EXPERIMENTAL

Materials and Spectroscopic Measurements

All reagents were purchased from Aldrich and used as received. ^{1}H NMR spectra were recorded in D_2O at 400 MHz at a probe temperature of 20°C on a Varian UNITY INOVA 400 or Bruker AVANCE instruments using sodium 3-(trimethylsilyl)-propanesulfonate (DSS) as internal reference. The pH of each sample was determined after the NMR measurement employing an Aldrich long-stem thin pH electrode, which was calibrated with standard aqueous buffers. The UV-Vis spectra were recorded at 25°C on a Hewlett Packard 8453A diode array spectrophotometer and the fluorescence spectra were measured on a FluoroMax SPEX spectrofluorometer. FAB mass spectra were obtained on a JEOL JMS-SMX102A equipment.

Synthesis of 1

A dimethylformamide (DMF) solution (50 mL) containing 1.00 g of 2,6-diamino-pyridine was slowly added to 2.32 g of EDTA dianhydride in 250 mL of DMF under vigorous stirring for 2 hours. Any solid formed was removed by filtration and the filtrate was concentrated to a viscous liquid (ca. 10 mL). Addition of ethanol (20 mL) to the liquid gave a pale yellow solid, which was separated by filtration and identified as **1**. The ethanolic filtrate was concentrated to 5 mL, whereupon 2 mL of water were added, and the resulting solution was left to stand in a refrigerator to form pale yellow crystals of **1** which were suitable for an X-ray single crystal diffraction analysis. Yield 14%. Anal. Calc. for $C_{30}H_{38}N_{10}O_{12}(H_2O)_5$: C, 43.42; H, 5.95; N, 16.88%; found: C, 43.46; H, 6.15; N, 16.75%. ^{1}H NMR (D_2O—Na_2CO_3, pH 10.5, 400 MHz, reference DSS): $\delta = 2.82$ (s, 8H, H_a), 3.23 (s, 8H, H_b), 3.48 (s, 8H, H_c), 7.40 (d, 4H, H_d), 7.63 (t, 2H, H_e). ^{13}C NMR (D_2O—Na_2CO_3, pH 10.5, 100 MHz, reference DSS) $\delta = 53.6$ (C_a), 59.4, 59.2 (C_b, C_c), 111.3 (C_d), 141.1 (C_e), 148.7 (C_f), 173.9 (CONH), 179.1 (CO^{2-}). MS (FAB^+) $m/z = 731$ $[M + H]^+$.

Potentiometric Studies

Potentiometric titrations of **1** were carried out at 298.1 ± 0.1 K using KCl 0.1 M as supporting electrolyte in a sealed-jacketed vessel under nitrogen with a piston type burette and a Thermo Orion model 920Aplus pHmeter equipped with an Orion 8102U combination electrode. The glass electrode was calibrated as a hydrogen-ion concentration probe by titration of previously standardized amounts of $HClO_4$ with CO_2-free NaOH solutions. The equivalent point was determined by Gran's method, which gives the ionic product of water (pKw = −13.95). The computer program HYPERQUAD [25,26] was used to calculate the protonation and stability constants. The pH range investigated was 3–11 and the concentration of nucleobases and the cyclophane ranged from 1×10^{-3} to 5×10^{-3} M with guest:host molar ratios varying from 2.5:1 to 1:1.

^{1}H-NMR Titrations

All guests and hosts molecules were dissolved in phosphate buffer (D_2O, pH = 7.6, 5×10^{-2} M), whereby in the case of the cyclophane and EDTA

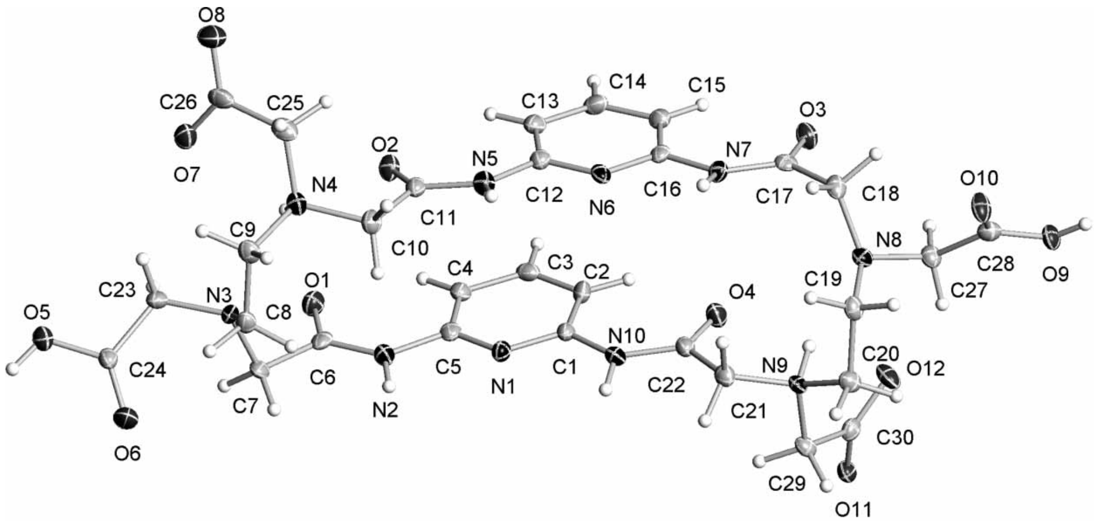

FIGURE 1 Molecular structure of macrocycle **1**, showing that the zwitterionic character found in solution is maintained in the solid state.

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hosts a minimum of solid Na_2CO_3 was added and the pH adjusted to 7.6. Low concentration titrations were performed adding 4 aliquots of 2×10^{-2} M guest stock solutions to 1.5×10^{-3} M solutions of the macrocycle. For the high concentrations experiments, the guest was added as solid to NMR tube. The experimental data were fitted using non-linear least-squares regression with Microcal Origin 5 program. Only aliphatic host protons were used for fitting and the binding constants obtained were averaged.

X-ray Crystallography

X-ray diffraction studies were performed on a BRUKER-AXS APEX diffractometer with a CCD area detector (λMo Kα = 0.71073 Å, monochromator: graphite) Frames were collected at $T = 100$ K via ω- and Φ- rotation at 10 s per frame (SMART [27]). The measured intensities were reduced to F^2 and corrected for absorption with SADABS (SAINT-NT [28]). Structure solution, refinement and data output were carried out with the SHELXTL-NT program package [29]. C—H hydrogen atoms were placed in geometrically calculated positions using a riding model. The N—H and O—H hydrogen atoms have been localized by difference Fourier maps, but their D—H distances and U_{iso} factors have been fixed (0.86 Å for N—H, 0.84 Å for O—H, $U_{iso} = 1.5$ times the U_{equiv} value of the neighboring donor atom).

Crystal data for **1**: $C_{30}H_{38}N_{10}O12\ 7H_2O$, $M_r = 856.82\ \mathrm{gmol}^{-1}$, $0.18 \times 0.20 \times 0.21\ \mathrm{mm}^3$, triclinic, space group $P1$, $a = 9.3502(8)$, b = 10.8768(10), $c = 11.4491(10)$ Å, $\alpha = 113.512(2)°$, $\beta = 104.356(2)°$, $\gamma = 102.129(2)°$, $V = 969.76(15)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.467$, $2\theta_{max} = 25$, 3397 independent reflections, $R_1 = 0.0370$ for 3397 reflections with $I > 2\sigma(I)$ 0.0577 and $wR_2 = 0.1395$ and $wR_2 = 0.083$ for all data, 556 parameters.

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-247223. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; E-mail: deposit@ccdc.cam.ac.uk, www:http://www.ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

The reaction between EDTA dianhydride and 2,6-diaminopyridine gave a so far not reported pyridinocyclophane, in which two diamine and two EDTA units are linked by four amide bonds. The formation of the macrocycle was confirmed by elemental analysis, mass spectrometry (FAB$^+$), ^{1}H NMR spectroscopy and single-crystal X-ray diffraction analysis. In its acid form the cyclophane is only slightly soluble in water, however, in form of the sodium salt it is water-soluble. The three different functional groups present in the receptor, i.e. amino, amide and pendant and carboxylate groups, contribute to the water-solubility, and are potential molecular recognition sites for nucleobases.

Molecular Structure of 1

Figure 1 shows the molecular structure of pyridinophane **1**. The 26-membered macrocycle shows a $\pi-\pi$-interaction between the pyridine rings, with an interplanar distance of 3.45 Å that is close to the 3.40 Å predicted for the optimum face-to-face stack of aromatic molecules, and a displacement of

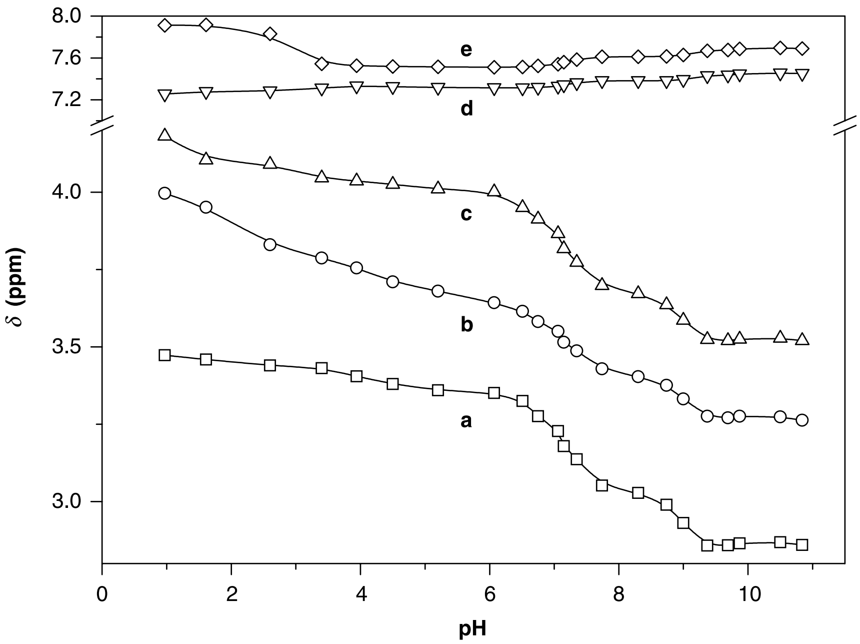

FIGURE 2 ^{1}H NMR chemical shifts of the protons in **1** as pH function (labels as Chart 1).

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the centroids by 1.8 Å [30]. The closest C—C distance between opposite pyridine rings is 3.34 Å for C(3)···C(13). The molecular planes of the amide bonds are almost coplanar with the aromatic rings, indicating that the π-electrons of the pyridine moieties are conjugated with the amide groups. Hydrogen atoms close to the amine nitrogen atoms N(4) and N(9), and the carboxyl oxygen atoms O(5) and O(9) were located by difference Fourier maps, indicating that these atoms are protonated. Further evidence for this assignment is provided by the fact that the C—O distance of the protonated oxygen atom is approximately 0.1 Å longer than the C—O distance of unprotonated oxygen (C(24)—O(6)), whereas in the carboxylate groups C(26)O(8)O(7) and C(30)O(11)O(12), the two C—O distances are ≈1.25 Å and their difference is not larger than 0.03 Å. Therefore, **1** can be formulated as $[MH_4]^0$, in which two N-carboxymethyl groups have the dipolar (or zwitterion) form, $>NH^+CH_2CO_2^-$, and the other two have the neutral form $>NCH_2CO_2H$.

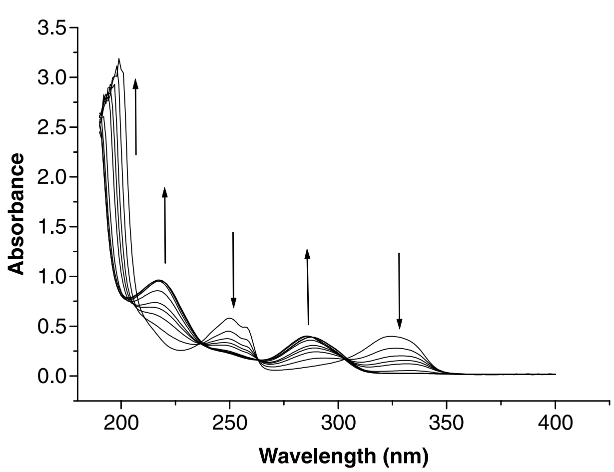

FIGURE 3 Absorption spectra of **1** (2×10^{-5} M) in water as pH function in the range of 5.46 to 0.95. The arrows indicate the spectral changes with increasing pH.

Protonation of 1 in Solution

Only four of the ten expected protonation constants were determined by potentiometric titrations as $\log K_1 = 7.40$ (standard deviation = 0.02), $\log K_2 = 6.49$ (0.02), $\log K_3 = 3.57$ (0.05) and $\log K_4 = 3.39$ (0.05). Due to the low solubility of the ligand in solutions with a pH lower than 3, a fifth protonation constant could be determined by spectroscopic measurements (*vide infra*). The protonation sites can be readily assigned from the pH dependence of the ^{1}H NMR signals that is shown in Fig. 2. In the pH range 6–9 the CH_2 hydrogen atoms (signals labeled *a*, *b*, and *c*, Chart 1) that are adjacent to the amino nitrogen atoms undergo a large downfield shift caused by the deshielding effect upon protonation, and therefore K_1 and K_2 correspond to the protonation of two of the amino groups. Further protonation occurs between pH 5 and 2 and in this case the signals for the protons adjacent to carboxyl and/or carboxylate groups (labeled *b*) move to lower field, while proton *a* and *c* do not suffer significant shift. Therefore, constants K_3 and K_4 were assigned to the protonation of the carboxylate groups, proofing that compound **1** shows a twofold zwitterionic character also in solution. At pH values lower than 2 the aromatic

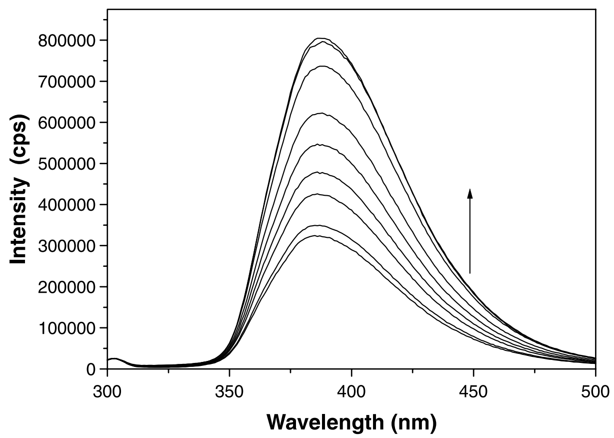

FIGURE 4 Emission spectra of **1** (2×10^{-5} M) in water as pH function in the range of 2.57 to 0.5. The arrow indicates the spectral changes with decreasing pH.

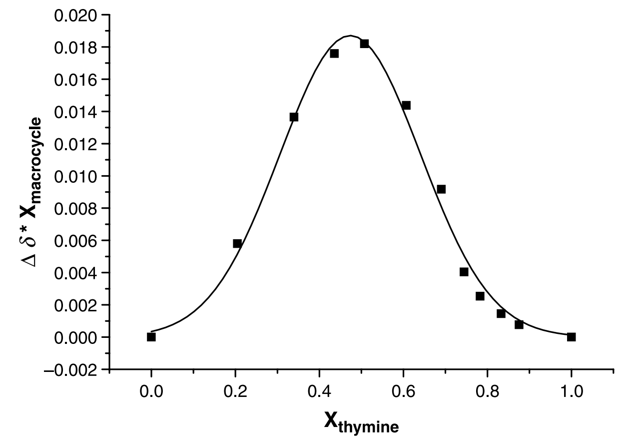

FIGURE 5 Continuous variation curve (Job's method) for the **1**-thymine complex observing the variation of the chemical shift of proton *e* in **1** (Chart 1) as function of mole ratio of thymine.

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proton *e* and the methylene protons *c* move to lower fields, indicating that protonation occurs now on the pyridine nitrogen atoms. Fitting the chemical shift of the aromatic signals vs pH, a pK_a value of 1.70 was obtained, which is significantly lower than the value reported for unsubstituted pyridine, 5.25 [31].

Electronic Spectra

The solution absorption spectra of pyridinophane **1** as a function of the pH show the following characteristics: in the pH range of 11–3 two $\pi-\pi^*$ bands are observed at 220 nm and 288 nm, and a strong absorption is found in the region $\lambda < 205$ nm. The UV-Vis spectra remain unchanged within this pH-range, however, at pH < 3 the intensities of the absorption bands are reduced and new bands appear at 250 nm and 325 nm (Fig. 3). Three isosbestic points are found at 235 nm, 261 nm and 301 nm, which indicate the coexistence of unprotonated and protonated species in equilibrium. These changes can be assigned to the protonation of the pyridine nitrogen atoms and are consistent with the changes observed in the NMR experiments. Fitting the absorption data *vs* pH gave a pK_a value of 1.53, which is in a good agreement with the value obtained from the NMR experiments.

The emission spectrum of an aqueous solution of the pyridinophane (excitation wavelength = 275 nm) showed two broad bands at 330 nm and 405 nm without any structure. The intensity of these bands is strongly pH dependent and diminishes within the 11–3 pH range. In this pH region the amine nitrogen and carboxylate oxygen atoms are protonated and the observed decrease of the emission is caused by the increase of vibrational non-radiative processes. At pH < 3 the excitation wavelength shifts from 275 nm to 325 nm and a new emission band appears at approximately 380 nm (Fig. 4). The new band becomes very intense at a pH close to 1. Fitting these data a pKa value of 1.18 was obtained for the pyridine nitrogen, which is in good agreement with the values calculated from the NMR and UV-Vis absorption spectra. The extraordinary low basicity of the pyridine nitrogen atoms in the cyclophane can be explained by the electron-withdrawing effect of the amide groups as can be deduced from the reported pK_a value for 2-acetamidopyridine [32], which is 0.8 units lower than that of unsubstituted pyridine. Moreover, the presence of protonated amine nitrogens in the $>NH^+{-}CH_2{-}CO{-}NH{-}$ moieties attached to the pyridine ring causes an additional reduction of the basicity.

Binding Constants

The binding constants between cyclophane **1** and the nucleobases thymine and uracil were determined by spectrometric and potentiometric measurements. Complex stoichiometry was determined by means of continuous variation (Job) method [33] which gave a maximum at a mole ratio of 0.5 confirming the 1:1 stoichiometry (Fig. 5). The chemical shifts of the host protons in the receptor were fitted as function of the guest concentration using Eq. (1) which considers a 1:1 stoichiometry and assumes that the total concentrations of host and guest are similar to each other [34].

$$\delta_{obs} = \delta_H + 0.5\Delta\delta([H]_T + [G]_T + 1/K - (([H]_T + [G]_T + 1/K)^2 - 4[H]_T[G]_T)^{1/2}/[H]_T \qquad (1)$$

where δ_H is the chemical shift of a given proton of the macrocycle, $\Delta\delta$ is the difference between the chemical shift of the proton in the complexed and free macrocycle (complexation-induced shift at saturation, CIS), $[H]_T$ is the total concentration of the host, $[G]_T$ is the total concentration of the guest and K is the binding constant. CIS values for the protons of

TABLE I Complexation-induced ^{1}H NMR chemical shifts (CIS) of the cyclophane protons[†] in host-guest complexes with thymine and uracil (in ppm)

1	Thymine	Uracil
CH_2a	−0.079	‡
CH_2b	‡	−0.036
CH_2c	−0.061	−0.046
H*d*	‡	‡
H*e*	‡	‡

[†] Protons are labeled as shown in Chart 1; [‡] Broad signal.

the receptors used in this work are given in Table I. Typical titration plots are shown in Fig. 6 and averaged binding constants are collected in Table II.

Additional evidence for the formation of cyclophane-nucleobase 1:1 complexes was obtained from potentiometric titrations. Table III presents the stepwise equilibrium constants for the complexes formed by cyclophane with thymine and uracil. The stability constants increment from the H_3LN to H_4LN due to the increased number of protonated cyclophane groups. Comparing the binding ability of the receptor towards the nucleobases studied herein, it can be recognized that the affinity decreases in the order thymine > uracil for all the different protonated species of the cyclophane. For both guests the highest stability constant is found for the triprotonated macrocycle followed by the tetraprotonated and diprotonated ligand. With the monoprotonated species no significant interaction was detected, which is not surprising, because both NH protons are needed for the interaction with the guest (Fig. 7). Figure 8 shows the distribution of the different species present in solution in the pH range explored by our potentiometric studies (3–9). The figure shows that there are four species at pH 7.6: L, HL, H_2L and H_3LN. This demonstrates that the stability constant determined by the NMR experiment corresponds to the complex with the diprotonated ligand. The binding constants obtained by the two different methods are in good agreement.

Some reported hosts suitable for the recognition of thymine contain the 2,6-diamidopyridine moiety, which is able to form three hydrogen bonds with the imide function of the nucleobase [4]. In addition these receptors use aromatic linkers as π-stacking components. The X-ray structure of **1** described above has shown that the diamidopyridine units are organized in a parallel fashion, so that their polar groups are oriented outwards the cavity. Such an arrangement would not be favorable for a strong binding to pyrimidine nucleobases in aqueous solutions via hydrogen bonding interactions due to the competition with the water molecules.

Supramolecular complexes formed between similar cyclophanes and aromatic amines in aqueous media have been analyzed by Inoue and co-workers [35,36]. In that report was shown by ^{1}H NMR experiments that the aromatic protons of the receptor were upfield shifted upon complexation, while the aliphatic protons of the EDTA moieties were not affected, indicating that the inclusion complexes are stabilized mainly by aromatic π–π stacking interactions. However, in our experiments the addition of thymine and uracil induced upfield shifts of the methylene signals and negligible shifts of the aromatic signals, thus suggesting that a different interaction mode is operating in the complexation between the nucleobases and the explored herein pyridinophane **1**.

In order to examine if the structure of the cyclophane can rearrange to a more favorable configuration in the presence of the pyrimidine nucleobases, a computational chemistry study was carried out using the semiempirical PM3MM basis set (as provided in the Gaussian 03 package [37]),

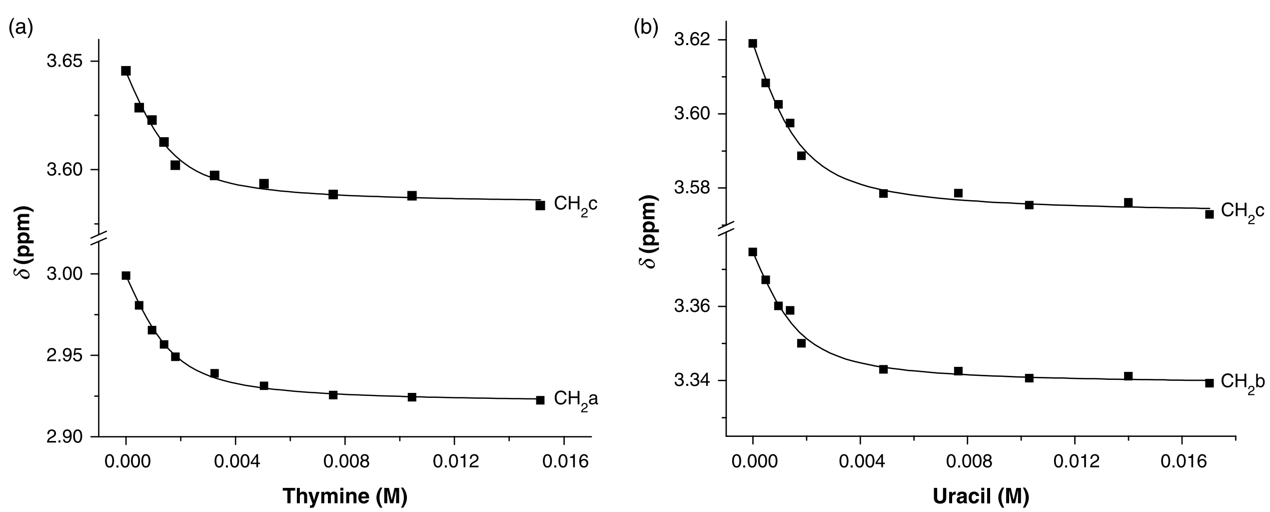

FIGURE 6 Typical titration plots for the (a) **1**-thymine and (b) **1**-uracil complexes. The methylene groups are numbered as shown in Chart 1.

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TABLE II Binding constants for the **1**-thymine and **1**-uracil complexes in water determined by ^1H NMR (20°C, pH 7.6)

	Guest, K (M^{-1})	
Host	Thymine	Uracil
1	2000 ± 313	1738 ± 338
EDTA	†	†

† No interaction detected.

TABLE III Binding constants of cyclophane with thymine and uracil determined by potentiometry (298.1 K in 0.1 M KCl)

	log K	
Reaction†	Thymine	Uracil
$H_2L + HN = H_3LN$	2.86 ± 0.04	2.23 ± 0.03
$H_3L + HN = H_4LN$	3.56 ± 0.05	3.04 ± 0.02
$H_4L + HN = H_5LN$	3.52 ± 0.04	2.54 ± 0.03

† N = Nucleobase. Charges are omitted for clarity.

which corrects for PM3 deficiencies in the description of amide linkages. For the optimization process, the atom coordinates determined by the X-ray analysis of **1** were used to define the initial structure and one guest molecule was positioned within the macrocyclic cavity. After energy minimization the resulting structures of **1**-thymine and **1**-uracil were analyzed and it was found that these molecular arrangements represents a reasonable mode of interaction in accordance with the binding constants and the calculated CIS values (Fig. 7). Different starting positions were also tested, and in all cases the final structures were very similar.

The optimized structures of complexes of the nucleobases complexes **1**-thymine and **1**-uracil show 2,6-diamidopyridine units that are almost coplanar with their polar groups directed to the center of the macrocyclic ring. All carboxyl and carboxylate groups are located at the same side of the macrocyclic ring plane resulting in a U-shaped arrangement of the functional groups. In both complexes, the orientation of the guest is almost perpendicular to the mean plane of the host and is orientated along the axis formed by the two protonated amine atoms of the zwitterionic $> NH^{+-}$ CH_2COO^- groups (Fig. 7). Three hydrogen bonds were detected: two between the nucleobase carbonyl groups and the $-NH^+-$ amine groups of the host and another between the nucleobase $-N(1)H$ group and one of the carboxylate groups of the host. Already mentioned, these structures are consistent with the CIS-values observed for by ^1H-NMR spectroscopy. The upfield shift of the host methylene protons is due to the electron density increase of the amine nitrogens atoms upon hydrogen bonds formation with the nucleobases. As can be seen from Fig. 7, the thymine methyl group is located at the periphery of the complex and is not involved in intermolecular contacts as supported by the binding constants calculated for **1**-thymine and for **1**-uracil.

Although the methylene groups belonging to the EDTA moieties in macrocycle **1** suffer the most important shifts by the guest presence there is an important cooperative effect, a fact that is shown by the observation that no significant interaction between thymine or uracil and unsubstituted EDTA could be measured in water. Thus the macrocyclic framework imparts rigidity and pre-organizes the host functional groups for a better geometrical arrangement which establishes multiple sites of contact allowing for an effective binding with the guest.

Although **1** has a relatively simple structure, it is important to remark that the magnitude of the binding constants determined for **1**-thymine and **1**-uracil are 1000 times higher than those reported data for other more complex receptors [19].

In conclusion, we have prepared and structurally characterized a new macrocycle capable of binding free thymine and uracil nucleobases in water via hydrogen bonds. The extension of this study to the

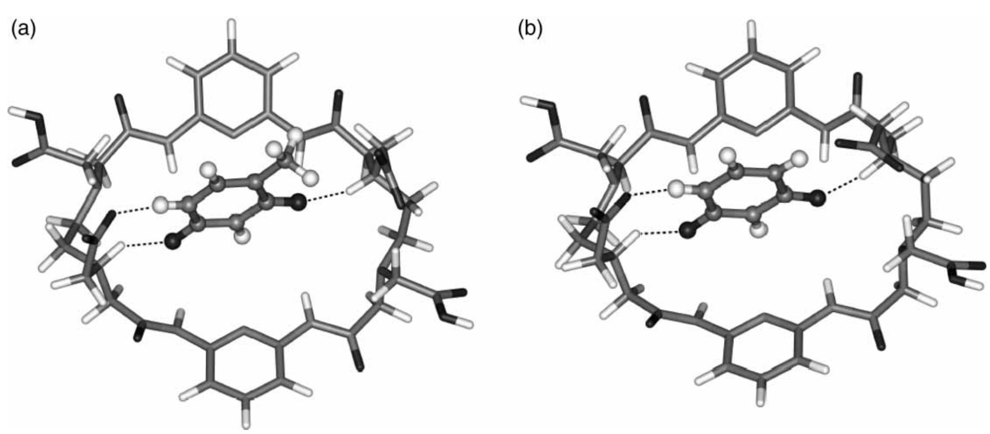

FIGURE 7 Energy minimized structure of the (a) **1**-thymine and (b) **1**-uracil complexes using PM3MM. Dotted lines represent hydrogen bonds.

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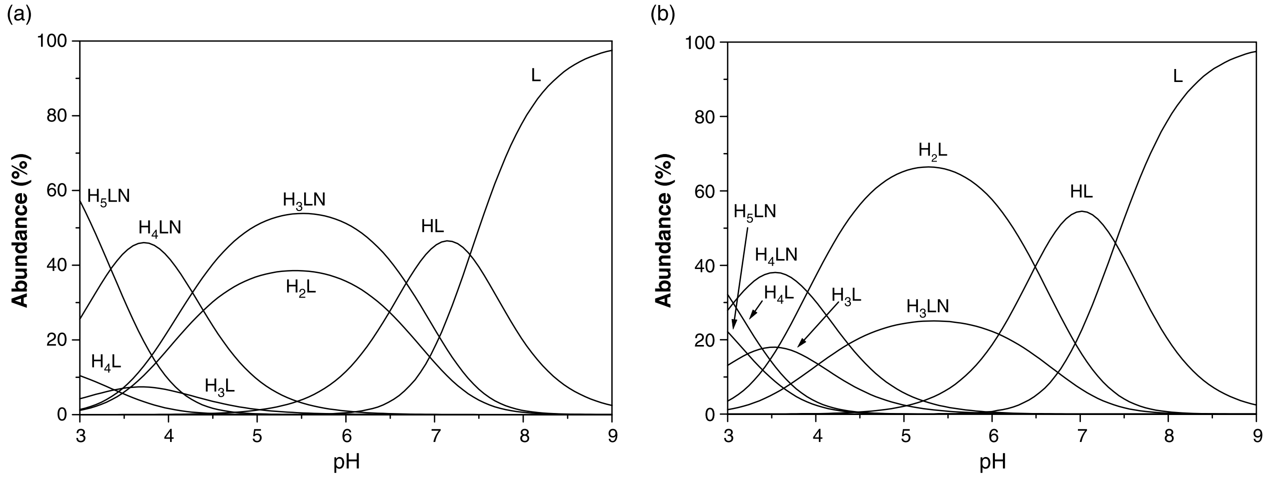

FIGURE 8 Distribution diagrams of (a) **1**-thymine and (b) **1**-uracil complexes.

recognition of other free nucleobases and nucleotides in water is currently under way.

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