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Experimental and theoretical study of thymine and cytosine derivatives: the crucial role of weak noncovalent interactions[†]

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In this paper we report the synthesis of N¹-hexylthymine (1), N¹-hexylcytosine (2), N¹-hexylcytosine hydrobromide (3) and $[(N^1-hexylcytosinium) \cdot (N^1-hexylcytosine)]_2 \cdot [Cl_2Hg(\mu-Cl)_2HgCl_2]$ (4) (the hemiprotonated form of the N¹-hexylcytosine forming a CHC⁺ pair with carbonyl-amino symmetric and N³–N³ recognitions) and X-ray characterization of compounds 1, 3 and 4. In the solid state, N¹-hexylthymine 1 follows exactly the same behaviour as N¹-hexyluracil. In addition to strong hydrogen bonding interactions, various weak forces, *i.e.* C–H/ π , carbonyl–carbonyl (C=O···C=O) and anion– π interactions (between the bromide and N¹ of cytosine in 3), play a key role in stabilizing the 3D architectures of the compounds. The theoretical calculations allow estimation of the strength of these contacts and how they influence each other.

Introduction

The field of crystal engineering is nowadays viewed as a comprehensive discipline, which is developed by scientists with different interests. One of those is the construction of fascinating topological architectures, and another one deals with modeling, synthesis, evaluation and utilization of crystalline solids having desired functions.^{1,2} Unfortunately, the principle of designed synthesis of functional materials has not been achieved, mainly because the delicate nature of competing weak forces makes it difficult to succeed in a previously designed crystal engineering experiment.³ Crystal structure prediction, which is an arduous task, needs a precise understanding and complete control over the complicated interplay of weak noncovalent interactions responsible for crystal packing, since they are operating simultaneously.^{3–5}

Several noncovalent interactions are very commonly used by chemists to construct supramolecular assemblies, such as hydrogen-bonding,^{6,7} π – π stacking,⁸ cation– π ⁹ and C–H··· π ¹⁰ contacts. Moreover, lone pair (l.p.)– π ¹¹ and anion– π interactions¹² have been increasingly reported in the literature. For instance, Egli and co-workers have reported two important cases of l.p.– π interactions in biomacromolecules,¹³ *i.e.*, the stabilization of the structure of Z-DNA¹⁴ and the induction of the

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ribosomal frame-shifting RNA pseudoknot.¹⁵ In addition, the anion $-\pi$ interaction has been observed in several biological systems. For instance, it participates in the inhibition of the enzyme urate oxidase by cyanide¹⁶ or the enzymatic chlorination of tryptophan by PrnA flavin-dependent halogenase.¹⁷ There are several excellent reviews¹⁸ that describe different aspects of the anion $-\pi$ interaction.

Moreover, finding new models for the study of nucleic acids which mimic both the reactivity and the solubility conditions of the biological models is of great importance. The use of simple acyclic nucleosides as the methyl derivatives of the nucleobases permits an enormous increase in the solubility of the molecules in water, but maybe they are not the best examples to understand the behaviour of the real bases. In this context, we have recently communicated that the combination of a uracil ring with a long aliphatic chain leads to a very interesting solid state architecture that resembles a lipid bilayer.¹⁹ The hydrogen bond donor/ acceptor capability of the nucleobase is responsible for the formation of the 2D-hydrogen bonding network that nicely stacks with another 2D layer by means of π - π interactions. Hydrophobic interactions between the aliphatic chains are responsible for the final architecture (see Fig. 1). Interestingly, the prepared compounds, although insoluble in water, present increased solubility in methanol and methanolic solutions, which could perhaps model the cytoplasm dielectric constant.

We have recently shown that these uracil derivatives form very interesting quartets, with the same geometric parameters as those found in RNA strands, stabilized by the presence of a silver atom.²⁰

Our recent findings bring us to study the effect of the long aliphatic chains on the structure of cytosine and thymine. Therefore, in this paper we report the synthesis and X-ray

Universitat Autònoma, E-08193 Cerdanyola del Vallés, Barcelona, Spain † Electronic supplementary information (ESI) available: Experimental procedures for the preparation of 1–4, X-ray crystal data and computational details. CCDC reference numbers 864483–864485 for compounds 1, 3 and 4. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ce25580d



Fig. 1 Crystal packing of N¹-hexyluracil.

geometry of characterization of the related N¹-hexylthymine (1), finding a similar structure as is described below. Furthermore, we report the synthesis and solid state structures of the protonated (hydrobromide, 3) and hemiprotonated (4) forms of N¹-hexylcytosine (2). In the former compound, an interesting anion- π interaction is observed. In the latter compound, one protonated N¹-hexylcytosine and one neutral N¹-hexylcytosine moiety form an asymmetric base pair (CHC⁺) comprising three hydrogen bonds.

The pKa reported for cytosine in water is 4.4,²¹ therefore the apparently easy protonation in N³ may induce the formation of different pairing patterns. While neutral cytosine only forms one kind of cytosine–cytosine pair, three possibilities are envisaged in protonated cytosine that are drawn in Scheme 1. The results presented herein will help to shed light to this topic, which is still an object of study and discussion in the literature.²²

Finally, the different noncovalent interactions observed in the solid state have been studied using high level *ab initio* calculations (RI-MP2/auc-cc-pVDZ), focusing our attention on the energy associated with each interaction. In compound 1, where the interactions are dominated by dispersion, the standard MP2 method overestimates the interaction. Therefore, we have used the spin-component scaled SCS-RI-MP2 method, which dramatically improves the accuracy, and provides energies similar to the ones computed using the CCSD(T) method.²³

Crystal data collection and refinement

Suitable crystals of **1** and **4** were selected for X-ray single crystal diffraction experiments, covered with oil (Infineum V8512, formerly known as Paratone N) and mounted at the tip of a nylon CryoLoop on an Oxford Diffraction Xcalibur system with a Ruby detector, using graphite monochromated Mo-K α radiation ($\lambda = 0.7107$ Å). Crystallographic data were collected at 183(2) K. The program suite CRYSALISPro²⁴ was used for data collection, semi-empirical absorption correction and data reduction.

X-ray single-crystal data for 3 were measured on an Enraf-Nonius CAD4 diffractometer with a Mo-K α sealed tube (λ =



Scheme 1 The four possible cytosine–cytosine base pairs. Among the two hemiprotonated forms, the *carbonyl-amino symmetric*, $N^3 - N^3$ will be preferred if the whole molecule does not restrict the geometry, due to the presence of a third hydrogen bond interaction, mimicking a guanine–cytosine interaction.

0.71073 Å) and graphite monochromator. Cell parameters were determined from a set of 25 reflections in the range $4.6^{\circ} < \theta < 16.6^{\circ}$. Data collection was performed at room temperature with $\omega/2\theta$ scans. Measured intensities were corrected for Lorentz and polarization with XCAD4.²⁵ Numerical absorption correction by Gaussian quadrature was applied.

Solving for structure factor phases was performed by direct methods using SHELXS97²⁶ for compounds **3** and **4** and SIR97²⁷ for compound **1** and the full-matrix least-squares refinement on F^2 , by SHELXL97.²⁶ The structures were checked for higher symmetry with the aid of the program PLATON.²⁸ Non-H atoms were refined anisotropically and H-atoms were introduced in calculated positions and refined riding on their parent atoms.

The hexyl aliphatic chains in all the compounds are disordered over several different positions:

In compound 4, the occupancy for atoms from C9 to C12 and C69 to C72, as well as their corresponding relatives C9' to C12' and C69' to C72', is 50%. Atoms from C29 to C32 present a partial occupancy of 70% while their corresponding relatives from C29' to C32' present 30% occupancy.

In compound **3**, the aliphatic chain (from C7 to C12) is disordered over three positions (C7–C12, 50% occupancy; C7'–C12' and C7''–C12'', 25% occupancy for each).

In compound 1, the aliphatic chains on the N¹-thymine moieties are disordered over two positions. Occupancy for atoms from C10 to C12 is 70% while their corresponding relatives (C10' to C12') present 30% occupancy. Atoms from C30 to C32 present a partial occupancy of 75% while their corresponding relatives form C30' to C32' present 25% occupancy.

Table 1 Crystal data and structure refinement parameters for compounds 1, 3 and 4

	1	3	4
Empirical formula	$C_{11}H_{18}N_2O_2$	C ₁₀ H ₁₈ BrN ₃ O	C40H70Cl6Hg2N12O4
Formula weight	210.27	276.18	1396.96
Crystal system	Orthorhombic	Triclinic	Monoclinic
Space group	Pbca	$P\overline{1}$	$P2_1/c$
aĺÅ	11.6964(8)	6.685(1)	7.4416(2)
b/Å	17.7522(4)	8.004(3)	28.1838(11)
c/Å	22.7940(12)	12.907(6)	25.9487(6)
α/°	90	89.62(5)	90
β/°	90	84.50(3)	91.616(3)
γl°	90	81.14(3)	90
Volume/Å ³	4732.9(4)	679.2(4)	5440.1(3)
Ζ	16	2	4
Density calc./Mg m ⁻³	1.180	1.350	1.706
Absorption coefficient/mm ⁻¹	0.082	3.009	5.981
F(000)	1824	284	2752
Crystal size/mm	$0.42 \times 0.19 \times 0.12$	$0.50 \times 0.12 \times 0.06$	$0.41 \times 0.10 \times 0.06$
Theta range for data collection/°	2.46 to 25.68	1.59 to 26.00	2.68 to 26.37
Index ranges	$-14 \leqslant h \leqslant 14$	$-8 \leqslant h \leqslant 8$	$-7 \leq h \leq 9$
	$-21 \leq k \leq 21$	$-9 \leq k \leq 9$	$-35 \leq k \leq 32$
	$-26 \leqslant l \leqslant 27$	$0 \leq l \leq 15$	$-32 \leqslant l \leqslant 24$
Reflections collected	16777	2785	32624
Independent reflections	4483 [R(int) = 0.0234]	2661 [R(int) = 0.0332]	11114 [R(int) = 0.0319]
Completeness to θ max (%)	99.9	99.8	99.9
Max. and min. transmission	0.9903 and 0.9665	0.8375 and 0.3444	0.7155 and 0.1930
Data/restraints/parameters	4483/138/313	2661/417/229	11114/289/671
Goodness-of-fit on F^2	1.050	1.016	0.972
$R_1, wR_2 [I > 2\sigma(I)]$	0.0599/0.1795	0.0547/0.1126	0.0520/0.1555
R_1 , wR_2 (all data)	0.1085/0.1982	0.1309/0.1344	0.0896/0.1652
Largest diff. peak and hole/e $Å^{-3}$	0.337 and -0.218	0.401 and -0.404	2.399 and -1.164



Scheme 2 Synthetic route to compounds 1–4.

Publication material was generated with WinGX,²⁹ ORTEP-3 for windows³⁰ and Mercury.³¹

Crystal data collection and refinement parameters are shown in Table 1.

Results and discussion

Synthesis of the compounds.

We have synthesized compounds 1-4 by means of the general procedure shown in Scheme 2. Compounds 1 and 3 were easily obtained from either thymine or cytosine in two steps. The first step consists of the synthesis of the O,O'-bistrimethylsilyloxy (or N,O-bistrimethylsilyloxy) derivative using hexamethyldisilazane

(HMDS) for silylation. The second step is the alkylation of N¹ using 1-bromohexane and the subsequent desilylation in refluxing methanol. Curiously, the reaction on thymine yields the neutral compound 1 and the reaction on cytosine yields the hydrobromide salt 3. Compound 2 and 4 were obtained from 3 by reaction with K₂CO₃ and mercuric chloride, respectively. See supplementary material for details regarding the synthesis, and methods.[†]

Crystal Structure Description of 1.

Compound 1 crystallizes in the orthorhombic *Pbca* space group with the asymmetric unit formed by a 4-carbonil-N³ symmetric thymine–thymine base pair,²² as can be seen in Fig. 2. The base



Fig. 2 50% probability ORTEP representation for compound 1 (the lower occupancy positions for the aliphatic chains have been omitted for clarity). The two molecules are related by hydrogen bonds [distances: $N_3 \cdots O24$, 2.8123(6) Å and $N_{23} \cdots O4$, 2.8350(6) Å; angles: $N_3 - H_3 - O24$, 176.7° and $N_{23} - H_3 - O_4$, 173.8°] forming a thymine-thymine pair.



Fig. 3 Symmetry equivalence coloring for compound **1** forming a plane normal to the *c* direction (aliphatic chains have been reduced for clarity). The central base pair is forming hydrogen bonds with four other base pairs all around [distances and angles: O22…C6, 3.2511(8) Å and 162.14(4)° (light blue); O2…C26, 3.2103(8) Å and 161.96(4)° (pink); O2…C27, 3.4947(9) Å and 142.80(5)° (pink); O4…C8, 3.5501(8) Å and 145.44(5)° (orange)].

pair is surrounded by four additional pairs, forming a recognition plane (normal to the c axis of the crystal) with all the aliphatic chains placed at the same side.

The non-standard hydrogen bonding interactions that extend the H-bond network to form the 2D layer are depicted in Fig. 3. First, the O2 of one molecule forms an intermolecular bifurcated H-bond, one hydrogen atom belongs to the thymine ring and the other one to the aliphatic chain (pink lines). Second, the O22 is linked by a H-bond to C6 (blue line) and, finally, the O4 forms an $O \cdots H-C$ bond with the aliphatic chain (orange line).

An important aspect of this structure is that the 3D architecture, which resembles a lipid bi-layer (see Fig. 4), is very similar to that previously reported for 1-hexyluracil (see Fig. 1). This result confirms that the combination of a pyrimidine base and a long aliphatic chain leads to a well-defined 3D arrangement combining hydrophobic and hydrophilic layers. It would be nice to confirm the robustness of this arrangement using

1-hexylcytosine. Unfortunately, all attempts to obtain suitable crystals for X-ray crystallography of 1-hexylcytosine have been unsuccessful. The noncovalent interactions that are responsible for the formation of the stacked 2D H-bonded layers in compound **1** will be further studied in more detail below.

Crystal Structure Description of 3

Compound 3 crystallizes in the triclinic space group $P\overline{1}$ with the asymmetric unit consisting of one molecule of N¹-hexylcytosine hydrobromide (the ORTEP representation can be seen in Fig. 5).

The cytosinium moiety is surrounded by three different bromide atoms lying approximately in the same plane and interacts with them by means of several N-H...Br hydrogen bonds. Each bromide also interacts with three different cytosinium moieties, forming a planar ribbon (Fig. 6) reinforced by C-H···O hydrogen bonds between adjacent cytosinium rings. This ribbon is placed in a whole stepped 2D layer thanks to hydrophobic interactions between the aliphatic chains. The presence of the bromide in the structure avoids the formation of cytosine-cytosine pair interactions as described in Scheme 1. The bromide is to some extend out of the plane caused by hydrogen bonding interactions with two adjacent aliphatic chains [d(C(7)H…Br), 3.262 Å; d(C(10)H…Br), 3.060 Å]. In addition, an interesting anion- π interactions are observed between the bromide and a cytosinium ring (directed to the N¹ atom). A more detailed description of the solid state architecture of 3 is included in the supplementary material.⁺

Crystal Structure Description of 4.

Crystallographic analysis indicates that the reaction between N¹-hexylcytosine and mercuric chloride yields an outer sphere complex salt with formula $[(N^1-hexylcytosinium)\cdot(N^1-hexylcytosine)]_2$. [Cl₂Hg(µ-Cl)₂HgCl₂]. The asymmetric unit contains two hemi-protonated cytosine pairs (CHC⁺) and the anionic Hg₂Cl₆²⁻ moiety (see Fig. 7).

In the bimetallic mercury moiety each Hg²⁺ is bounded to two bridging and two terminal chlorine atoms that form a distorted tetrahedron around each metallic centre. This is quite a common anionic moiety and even longer polymeric chains have been described.

Concerning the hemiprotonated cytosine pairs (CHC⁺), very few examples of this recognition pattern have been previously



Fig. 4 Crystal packing of N¹-hexylthymine.



Fig. 5 ORTEP representation (50% probability) for compound **3** (the lower occupancy positions for the aliphatic chain have been omitted for clarity).



Fig. 6 In compound **3**, a planar ribbon is formed thanks to hydrogen bonds between the cytosinium rings and bromides [distances and angles: Br1'…N4, 3.385(4) Å and 165.7(3)° (black); Br1…N3, 3.239(3) Å and 161.1(2)° (black); Br1…N4, 3.529(4) Å and 144.2(3)° (green); Br1''…N4, 3.434(5) Å and 114.0(3)° (green); O2…C5, 3.123(5) Å and 125.9(3)° (violet); O2…C6, 3.191(5) Å and 122.2(3)° (violet)].



Fig. 7 ORTEP representation (50% probability) for compound **4** (the lower occupancy positions for the aliphatic chains have been omitted for clarity).

reported in the literature. Among them, just in JETHAS³² and ODICOU01³³ the authors define and describe a related cytosine–cytosinium pair.

Two CHC⁺ units are stacked in the crystal structure as will be discussed further on. This stacking is reinforced due to the presence of hydrogen bonds established between the exocyclic amino groups from cytosine rings and the monodentate chlorines belonging to the Hg₂Cl₆²⁻ anions at both sides of each stacking couple [distances and angles: Cl1…N4, 3.343(4) Å and 169.4(3)°; Cl3…N24, 3.350(5) Å and 170.4(3)°; Cl2…N44, 3.266(5) Å and 176.5(3)°; Cl4…N64, 3.426(4) Å and 159.8(3)°]. The presence of two H-bonds at each side of the Hg₂Cl₆²⁻ anions is responsible for the formation of a planar ribbon (intercalation of anions and cations), which is extended in the *b* direction of the crystal by



Fig. 8 Symmetry equivalence coloring for compound 4 showing the ribbon formed by alternation of $Hg_2Cl_6^{2-}$ anions (depicted in green) and stacked $CHC^+\cdots CHC^+$ cations (frontal and zenithal views).

hydrophobic interactions between aliphatic chains forming a 2D layer (Fig. 8). To pile the subsequent layers, chlorine atoms are in close contact with upper and lower rings.

Theoretical analysis of the noncovalent interactions

In this part of the manuscript we study the energetic features of some complexes observed in the solid state. In compound 1 we have focused our attention in the noncovalent interactions that govern the formation of the stacked 2D-layers. At first sight it seems that this assembly should be governed by π - π stacking interactions. However a closer look reveals that the thymine rings of one 2D-layer are not located over the thymine rings of the adjacent layer. In contrast, an absolute lack of overlapping is observed, see Fig. 9.

We have computationally analyzed a fragment of compound 1 where two crucial interactions are established. They are responsible for the aggregation of the 2D layers to generate the final 3D architecture. These interactions are C-H/ π and carbonyl…carbonyl interactions, which are indicated in the theoretical model used to study this assembly (see Fig. 10). Both



Fig. 9 Zenithal view of the 2D stacked layers in **1**. The hexyl chains and hydrogen atoms have been omitted for clarity. The lower layer rings are colored.



Fig. 10 Carbonyl–carbonyl and C–H/ π interactions observed in the formation of the 2D layer stacking and some energetic features of the assembly (BSSE corrected) at the SCS-RI-MP2/aug-cc-pVDZ level. Distances are in Å.

interactions are also complemented by attractive dispersion interactions between the thymine rings. The distance of the antiparallel carbonyl…carbonyl interaction is 3.049 Å and the computed energy (BSSE corrected) is -4.4 kcal mol⁻¹, in agreement with previous theoretical studies.³⁴ This interaction energy has been computed using the two thymine rings (A and A') that establish the C= $O \cdots C=O$ interaction of the assembly shown in Fig. 10. In addition, two equivalent C–H/ π interactions are established in the assembly shown in Fig. 10. They are formed between one hydrogen atom of the methyl group of the thymine of one layer and the thymine ring of the other layer. The energy associated with the C–H/ π and thymine–thymine dispersion attraction interaction is -3.8 kcal mol⁻¹ (computed using A and B). Finally, the hydrogen bonding interaction represented in Fig. 10 is part of the extended hydrogen bonding network that governs the formation of the 2D layers (see Fig. 3) and its interaction energy is -3.9 kcal mol⁻¹ (computed using A and B'). It should be mentioned that the interaction energies shown in Fig. 10 are probably overestimated because in the solid state other neighbouring interactions are also present. We have also optimized the model system shown in Fig. 10 and we have compared the total formation of the assembly using the X-ray coordinates and the optimized geometry (shown in Fig. S2, see supporting information[†]). The formation energy using the X-ray coordinates is -18.7 kcal mol⁻¹ (BSSE corrected) at the SCS-RI-MP2/aug-cc-pVDZ level of theory, which strongly agrees with the formation energy using the optimized assembly, which is $-16.4 \text{ kcal mol}^{-1}$.

For compound 3 the theoretical study is focused on the analysis of the anion- π interaction observed between the Br⁻



Fig. 11 Top (right) and perpective views of the anion- π interaction observed in the solid state of compound 3. The binding energy (BSSE corrected) of the anion- π interaction is also indicated. Distances are in Å.

and the protonated cytosine (see Fig. 11). This protonated cytosine also establishes numerous interactions coplanar to the molecular plane, as has been described above. An interesting and rare feature of this anion– π interaction is that the bromide is located over one nitrogen atom of the cytosine ring. Therefore, we have analyzed two aspects of this interaction: first the location of the anion and second the binding energy associated with the interaction. It should be mentioned that some of us have recently demonstrated in Cl⁻…triazine complexes that the anion can be located at any point over the triazine ring without losing much in the way of interaction energy with respect to the minimum.³⁵

In an effort to rationalize if the anion- π interaction is in part responsible for the unexpected location of the bromide, we have computed the electrostatic potential energy surface of a theoretical model (see Fig. 12). In this model a methyl group has been used instead of the hexyl chain and, in order to use a neutral system, we have included the bromide ion that is coplanar to the ring and forms two strong N-H...Br bonds. Blue contours indicate regions where the interaction with anions is favourable. As expected, the most favourable region is coplanar to the ring; however it is not available since it is occupied by neighbouring molecules or anions in the crystal structure. Over the ring, there is a very small region where the potential is 55 kcal mol^{-1} and a more extended region (lighter blue) where the potential is 40 kcal mol^{-1} . Interestingly, this region also includes the nitrogen atom that interacts with the bromide in the crystal. Obviously, the final location of the anion is determined by the rest of intermolecular interactions also present in the crystal. The computed anion- π interaction energy at the RI-MP2/aug-ccpVDZ level of theory is -21.7 kcal mol⁻¹ (see Fig. 11 and S3[†]).

Finally, we have studied several aspects of the base stacking found in compound **4**. As aforementioned, one protonated 1-hexylcytosine and one neutral hexylcytosine moiety form an asymmetric base pair comprising three hydrogen bonds. The computed interaction energy for this basis pair is -55.5 kcal mol⁻¹. The formation of this complex is very preferred mainly because the central hydrogen bond is strong due to the cationic nature of the N–H group. In addition, this supramolecular complex (Cyt···Cyt⁺) forms a π -stacking interaction with itself (see Fig. 13, left) forming a multicomponent assembly. The surprising feature of this stacking is that each supramolecular Cyt···Cyt⁺ complex is positively charged (+1) and therefore a repulsive electrostatic interaction in the



Fig. 12 EPS of compound 2. Energies in kcal mol^{-1} . Each 3D contour is plotted every 15 kcal mol^{-1} .





Fig. 13 Partial views of the crystal structure of compound **4**. Distances are in Å. Some energetic features of the assemblies (BSSE corrected) are indicated.

assembly can be anticipated. We have analyzed this issue and also the particular binding mode of the stacking between individual bases where the amino groups interact with the π -systems (see Fig. 13, right). This type of stacking between aromatic ringcontaining nitrogen atoms has been described before,³⁶ and it is energetically favourable.

We have examined, using the theoretical model shown in Fig. 13, the energetic characteristics of the different stacking interactions observed in compound 4, paying special attention to the stacking of the two sets of Cyt...Cyt⁺ complexes [the $(Cyt \cdots Cyt^{+})_{2}$ assembly] and the individual $Cyt \cdots Cyt^{+}$ stacking interaction. In the theoretical model the hexyl chain has been replaced by a methyl group. We have first computed the formation energy of the $(Cyt \cdots Cyt^{+})_{2}$ assembly from the previously formed base pair $(Cyt \cdots Cyt^+)$ complex. As expected, the interaction energy is positive (see Fig. 13) due to the electrostatic repulsion. However, this repulsive energy is not large considering the short distance between the two charged N-H groups. This is due to the formation of two $\pi - \pi^+$ stacking interactions between one neutral and one charged cytosine. It is very favourable $(-8.6 \text{ kcal mol}^{-1})$ indicating that this binding mode is energetically preferred. This favourable interaction explains the modest repulsive energy of the $(Cyt \cdots Cyt^{+})_{2}$ assembly.

Once the π - π^+ stacking interaction was examined, we focused our attention on the effect of the counterion. As shown above, the (Cyt...Cyt⁺)₂ assembly is energetically unfavourable, however it is formed in the crystal structure because of the decisive role of the [Hg₂Cl₆]²⁻ anion that staples two π - π^+ moieties by means of four strong hydrogen bonds (see Fig. 14). The double ion-pair complex presents an interaction energy computed from the previously formed π - π^+ stacking complexes and the anion that is -251.6 kcal mol⁻¹, which compensates the repulsive electrostatic interaction of the (Cyt...Cyt⁺)₂ assembly.



Fig. 14 Equation used to compute the interaction energy in this fragment of compound 4.

Concluding remarks

In conclusion, we have synthesized and X-ray characterized some thymine and cytosine compounds. Obviously, hydrogen bond and ion-pair interactions govern the primary structural motifs that constitute the backbone of the supramolecular network arrangement. For instance, they control the selfassociation of the nucleobases to form 2D layers in 1-hexylthymine (1) and the formation of the asymmetric base pair comprising three hydrogen bonds in 4. However, less conventional and predictable noncovalent interactions, *i.e.* anion– π , C– H/ π and carbonyl–carbonyl (or dispersion π – π) contacts, are found to have a pivotal role in the final solid-state architecture of the molecules.

The investigation herein reported also reflects that the comprehensive understanding of weak intermolecular forces that govern crystal packing should potentially allow a rational design of solids with tailored physical and chemical properties. The results described above are certainly of importance in this regard, especially the combined experimental and theoretical results obtained in the analysis of dispersion-dominated C=O···C=O and C-H/ π interactions in compound 1, anion- π interactions in compound 4.

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