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Models for thyroxine: Aromatic iodine-assisted self-assemblies

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Dedicated to Professors O. Yamauchi for lend us a hand in locate and give importance to these interactions and L.G. Marzilli who suggest us to work with *o*-iodohippurate ligand.

Abstract

Trying to understand the different recognition factors between thyroxine and its binding proteins, the chemistry of the ternary complexes between copper and o-iodobenzoylglycine (I-hip) [or o-iodobenzoylglycilglycine (B^IGG)] as simple thyroxine models were studied with 2,2'-bipyridyl as secondary ligand.

Two new compounds have been synthesized and structurally characterized: $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ and $[Cu(B^IGG)-(bpy)_2]^+(I^-) \cdot 4H_2O$. These compounds and other previously reported by us offer interesting recognition patterns that could have biological relevance: iodine–iodine short interactions, iodine–hydrogen(aliphatic or aromatic) interactions, iodine–metal bonds, iodine– π interactions (like C–H··· π), and aromatic self-assemblies assisted by iodine atoms. These patterns can be coupled in a synergistic manner, producing, for instance, a new C–I··· π ···I–C cluster pattern.

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1. Introduction

Thyroxine, a tetraiodinated derivative of the aminoacid tyrosine (3:5,3':5'-tetraiodothyronine, T4) (see Scheme 1), is the major thyroid hormone and the natural precursor for the most active form of this hormone, which has less iodinated (3:5,3'-triiodothyronine, T3). Normally the 99.95% of these two hormones are bounded to carrier proteins principally to thyroxine-binding globulin (TBG), to a lesser extent thyroxine-binding pre-albumin (TBPA or transthyretin (TTR)) and to albumin. The free hormone fractions are metabolically active at the tissue and cellular level.

The influence of the presence of metal ions in the interaction between thyroxine and proteins is a topic of increasing interest [1-12]. In order to understand the important role of iodine in these molecules and the binding patterns involved in their function [13–16], we present a structural study about the recognition patterns came into play by a model compound we have selected: *ortho*-iodohippuric acid (I-hipH) (Scheme 1), which presents some different kinds of interaction involving its iodine substituent.

Synthesis of the [Zn(II), Cu(II) and Ag(I) – orthoiodohippuric acid] binary complexes and several ternary complexes has been previously reported: [Zn(I-hip)₂-(OH₂)₂]₂ · 3H₂O (1) [17], [Ag(I-hip)] · 1.25H₂O (2) [18], [Cu(I-hip)₂(OH₂)₃] · 2H₂O (3) [19], [(Co, Ni or Zn)(I-hip)₂-(acv)(OH₂)₃](4) [17] and [Cu(I-hip)(phen)₂]⁺(I-hip⁻) · 7H₂O (5) [19].

On the other hand, two new ternary copper (II) complexes with 2,2'-bipyridyl (bpy) have been synthesized and structurally characterized: $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot$ $1.5H_2O$ (6) and $[Cu(B^IGG)(bpy)_2]^+(I^-) \cdot 4H_2O$ (7). We have been achieved a revision work about the influence of iodine atoms on the crystal stabilization according to

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Scheme 1. Formulae of thyroxine and two model compounds of it: o-iodohippuric acid and o-iodobenzoylglycilglycine.

the new results obtained and the previously reported by us, in three binary and four ternary complexes involving *ortho*iodohippuric acid derivatives and acyclovir (acv) or 1,10phenanthroline (phen).

2. Experimental

Elemental microanalyses were carried out using a Thermo Finnigan model Flash 1112 microanalyzer. IR spectra in the solid state (KBr pellets) were measured in the 4000–400 cm⁻¹ range on a Bruker IFS 66 spectrometer. ¹H NMR spectra were recorded at room temperature on a Bruker AMX 300 (300 MHz). Proton chemical shifts in deuterated dimethylsulfoxide ([D₆] DMSO) were referenced to [D₆] DMSO (δ [D₆] DMSO: 2.47 ppm).

Reagents were used as received from Sigma, Merck or Aldrich. *o*-Iodohippuric acid (*o*-iodobenzoylglicine) was prepared according to the literature procedure [20,21] or supplied by Aldrich. *o*-Iodobenzoylglycilglycine (B^IGG) was also synthesized according to the general procedure for hippuric acid [20,21] (see below).

Synthesis of binary complexes, $[Zn(I-hip)_2(OH_2)_2]_2 \cdot 3H_2O$ (1) [17], $[Ag(I-hip)] \cdot 1.25H_2O$ (2) [18] and $[Cu-(I-hip)_2(OH_2)_3] \cdot 2H_2O$ (3) [19] are reported previously. Moreover, we have tried to form some ternary complexes between these compounds and others ligands: $[(Co, Ni \text{ or } Zn)(I-hip)_2(acv)(OH_2)_3]$ (4) [17], $[Cu(I-hip)(phen)_2]^+(I-hip^-) \cdot 7H_2O$ (5) [19], $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ (6) and $[Cu(B^IGG)(bpy)_2]^+(I^-) \cdot 4H_2O$ (7).

2.1. Synthesis of o-iodobenzoilglycilglycinate sodium salt $(B^{I}GG)$

Sodium bicarbonate (42 mmol) was added to a solution of glycilglycine (20 mmol) in water (35 ml). The mixture was stirred for 1 h until complete solution and *o*-iodobenzoyl chloride (20 mmol) was added together with acetone (5 ml) (in order to increase the solubility and reactivity of the *o*iodobenzoil chloride). The reaction was slightly heated at 50 °C and stirred for 4 h. Subsequently, the reaction mixture was neutralized with HCl of 1 N, stirred for 15 min, and the resulting precipitate was filtered off and washed with cold water. The neutralization-washing process was repeated three times and finally the crude *o*-iodobenzoylglycilglycinate sodium salt were washed with diethyl ether, filtered off and dry at room temperature (yield: 65%).

The isolated product, white powder, was the monohydrated sodium salt: sodium *o*-iodobenzoylglycilglycinate (B^IGG) monohydrate. *Anal.* Calc. for C₁₁H₁₂IN₂NaO₅: C, 32.86; H, 3.01; N, 6.97. Found: C, 32.73; H, 3.12; N, 6.95%. IR (cm⁻¹): 414vw, 433vw, 546m, 586m, 611m, 637m, 680m, 728w, 749m, 775w, 872w, 914vw, 943vw, 985m, 999s, 1015m, 1041w, 1093m (br), 1239s, 1263m, 1293m, 1347m, 1432s, 1443s, 1463m, 1535s, 1587m, 1620vs, 1664s, 1711s, 2043m, 3343vs. ¹H NMR ([D₆] DMSO): δ 12.03 [bs, 1H, C(2)OO(1)-H], 8.61 [t, 1H, N(7)-H, J = 5.7 Hz], 8.08 [t, 1H, N(4)-H, J = 5.4 Hz], 7.85 [d, 1H, H(14), J = 7.8 Hz], 7.42 [s(br), 2H, H(11 and 12)], 7.15 [m, 1H, H(13)], 3.85 [d, 2H, C(6)-H₂, J = 5.7 Hz], 3.76 [d, 2H, C(3)-H₂, J = 5.4 Hz].

2.2. $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O(6)$

Basic copper carbonate $[CuCO_3 \cdot Cu(OH)_2]$ (1 mmol) and I-hipH (3 mmol) in water (100 ml) were refluxed for 2 h, then the excess of insoluble reactants were filtered off, followed by the addition of solid bpy (3 mmol) and subsequently the mixture was refluxed for two more hours. Finally, sodium iodide (1.5 mmol) was added to the solution to assist the crystallization. This synthesis is similar to that previously reported to prepare acyclovir ternary compounds [17]. Green crystals of $[Cu(I-hip)(bpy)_2]^+(I^-)$. 1.5H₂O (6) suitable for X-ray diffraction studies were obtained after 4-5 days from the parental solution and has been separated one-to-one of others brown crystals corresponding to the non-desired reaction by-product $[Cu(I)(bpy)_2]^+ \cdot I^-$ [22]. The ternary complex obtained decomposes on air by lose of water molecules (yield: ca. 30%). Repetitions of this synthesis without sodium iodide addition yield a mixture of two types of crystals corresponding to $[Cu(I-hip)(bpy)_2]^+(I-hip^-) \cdot 4H_2O$ and a certain quantity of the previously described ternary complex

 $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ where the origin of the iodide counter ion is not clear (an impurity or a decomposition of I-hip).

 $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ (6): Green crystals. Anal. Calc. for C₂₉H₂₃CuI₂N₅O₃ (completely dehydrated sample): C, 43.17; H, 2.87; N, 8.68; I, 31.46. Found: C, 43.19; H, 2.89; N, 7.86; I, 32.14%. IR (cm⁻¹): 417vw, 482vw, 568w, 636w, 661w, 689w, 730m, 745m, 770vs, 831vw, 870vw, 914vw, 949vw, 985vw, 999w, 1014m, 1059vw, 1101w, 1121vw, 1164m, 1254m, 1297m, 1318m, 1382s, 1430m, 1445s, 1459m, 1473s, 1497s, 1513s, 1582vs, 1601s, 1648vs, 1669s, 3059m, 3379m.

 $[Cu(I-hip)(bpy)_2]^+(I-hip^-) \cdot 4H_2O$: Blue crystals. Anal. Calc. for C₃₈H₃₈CuI₂N₆O₁₀: C, 43.22; H, 3.63; N, 7.96. Found: C, 42.50; H, 3.54; N, 7.96%. IR (cm⁻¹): 416vw, 440vw, 456vw, 532w, 579w, 624w, 636w, 652w, 663w, 672w, 715w, 732m, 762m, 772m, 867vw, 955vw, 1013m, 1031vw, 1062vw, 1086vw, 1106vw, 1158vw, 1175w, 1232w, 1253m, 1261m, 1311m, 1398vs, 1448m, 1457m, 1470m, 1506s, 1582s, 1600s, 1634s, 1652vs, 3061w, 3313m, 3394m, 3486m.

2.3. $[Cu(B^{I}GG)(bpy)_{2}]^{+}(I^{-}) \cdot 4H_{2}O(7)$

Basic copper carbonate (1 mmol) and B^IGG sodium salt (3 mmol) in water (100 ml) were refluxed for 2 h, then the

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Selected crystallographic data for compou	nds 6 and 7
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excess of insoluble reactants were filtered off, followed by the addition of solid bpy (3 mmol) and subsequently the mixture was refluxed for two more hours. An oily complex material was obtained in all attempts. Only one crystal suitable for X-ray diffraction studies could be obtained.

2.4. X-ray crystallographic study

Suitable crystals of 6 and 7 were selected for X-ray single crystal diffraction experiments and mounted at the tip of glass fibres on an Enraf-Nonius CAD4 diffractometer producing graphite-monochromated Mo K α radiation ($\lambda =$ 0.71073 Å). In each case, after the random search of 25 reflections, the indexation procedure gave rise to the cell parameters (see Table 1 for a summary of the crystal data). Data were collected in the ω -2 θ scan mode. Absorption correction for 6 was performed following the empirical DIFABS method. The structural resolution procedure was made using the WinGX package [23]. Solving for structure factor phases was performed by SHELXS-97 [24] for 6 and sir-2004 [25] for 7, and the full matrix refinement by shelxl-97 [26]. Non-H atoms were refined anisotropically and H-atoms were introduced in calculated positions and refined riding on their parents atoms. A summary of refinements parameters can also be seen in Table 1. H-atoms of water molecules could not be located in any

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Identification code	6	7	
Empirical formula	$C_{58}H_{52}Cu_2I_4N_{10}O_9$	$C_{31}H_{34}CuI_2N_6O_8$	
Formula weight	1667.78	935.98	
Temperature (K)	294(2)	293(2)	
Wavelength (Å)	0.71073	0.71073	
Crystal system	monoclinic	triclinic	
Space group	$P2_1/n$	$P\overline{1}$	
Unit cell dimensions			
a (Å)	15.912(3)	12.515(3)	
b (Å)	17.705(4)	12.993(3)	
c (Å)	22.472(4)	13.662(4)	
α (°)	90	66.144(16)	
β (°)	101.474(14)	65.31(2)	
γ (°)	90	71.84(2)	
Volume (Å ³)	6204(2)	1818.6(8)	
Ζ	4	2	
D_{calc} (Mg/m ³)	1.785	1.709	
Absorption coefficient (mm^{-1})	2.738	2.353	
<i>F</i> (000)	3248	922	
Crystal size (mm)	$0.46 \times 0.38 \times 0.21$	$0.46 \times 0.42 \times 0.29$	
θ Range for data collection (°)	1.44-24.98	1.73–24.98	
Index ranges	$-18 \leqslant h \leqslant 18, -21 \leqslant k \leqslant 0, 0 \leqslant l \leqslant 26$	$-14 \leq h \leq 13, -15 \leq k \leq 14, -16 \leq l \leq 0$	
Reflections collected	11182	6606	
Independent reflections (R_{int})	10888 (0.0397)	6309 (0.0295)	
Completeness to final θ (%)	99.9	98.7	
Maximum and minimum transmission	0.5971 and 0.3657		
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2	
Data/parameters	10888/748	6309/457	
Goodness-of-fit on F^2	1.024	1.299	
Final <i>R</i> indices $[I \ge 2\sigma(I)]$	$R_1 = 0.0666, wR_2 = 0.1746$	$R_1 = 0.0765, wR_2 = 0.2488$	
R indices (all data)	$R_1 = 0.1257, wR_2 = 0.2099$	$R_1 = 0.1263, wR_2 = 0.3253$	
Largest difference in peak and hole $(e \text{ Å}^{-3})$	1.767 and -1.686	2.072 and -2.050	

case. Largest diffraction peaks and holes were located close to heavy atoms in Fourier difference map. The ORTEP [27] representations of the two complexes were made at 50% probability.

The software used to generate the figures and to calculate the distances and angles values are MERCURY 1.4.1 [28], which can be obtained free of charge from CCDC, and Accelrys DS Viewer Pro 5.0 [29], which a 30-days trial version can also be obtained free of charge.

 D_{pln} , D_{Atn} and D_{lim} distances as well as θ , φ and ω angles in C–I··· π interactions are calculated as defined by Prasanna and Guru-Row [30].

In order to measure the distortions of the coordination polyhedron from the square pyramid to the trigonal bipyramid (CN = 5), the Addison parameter (τ) has been calculated according to the literature procedures [31], as an indication of the degree of trigonality. τ is defined as $(\beta - \alpha)/60$, where β and α are the two *trans*-basal angles. For a perfectly square pyramidal geometry τ is equal to zero, while it becomes unity for a perfectly trigonal-bipyramidal geometry.

3. Results and discussion

3.1. Crystal structure of $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ (6)

In X-ray crystal structure of $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ (6) (Fig. 1), we detect, in a first approach, that the coordination environment is coincident with that for compound $[Cu(I-hip)(phen)_2]^+(I-hip^-) \cdot 7H_2O$ (5). Two

complex units are present in the asymmetrical unit where the two copper(II) ions present distorted octahedral coordinations. These ions are linked to two oxygen atoms of the carboxylate anion of I-hip by means of a strong and an ancillary bonds [Cu–O distances: O(9), 2.100(8) and O(10), 2.71 Å for Cu(1); O(43), 2.217(9) and O(44), 2.47 Å for Cu(2)] and to the four nitrogen atoms from two bpy molecules [Cu–N distances: N(11), 1.972(8); N(22), 2.064(7); N(23), 2.164(8) and N(34), 1.975(7) Å for Cu(1); N(45), 2.131(8); N(56), 1.990(7); N(57), 1.982(7) and N(68), 2.089(8) Å for Cu(2)]. The positive charges of complex units are compensated by the presence of iodide atoms (one per formula unit). The structure is completed by three water molecules per asymmetrical unit.

In this compound, the Addison parameter (τ) presents a value of $\tau = 0.41$. It means that, considering a coordination number CN = 5, the real coordination polyhedron is about halfway between a square pyramidal and a trigonal bipyramidal coordinations.

The 3D structure of this compound is formed by bidimensional layers coincident with the a-c-plane.

There is not present any intramolecular interaction, but the crystal unit is built by means of a lot of intermolecular interactions among complex units and also with the water molecules. The more relevant interactions should be:

(a) Stacking [32] between bipyridyl rings in the couple of complexes in the asymmetrical unit [distance C(27)···C(50) or C(29)···C(52), ca. 3.34 Å; torsion, 179°] strengthened by C_{aromatic}-H···π interactions



Fig. 1. ORTEP representation (50% probability) of the asymmetrical unit in $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ (6). Numeration of several atoms has been omitted for clarity.



Fig. 2. ORTEP representation (50% probability) of the complex $[Cu(B^{I}GG)(bpy)_{2}]^{+}(I^{-}) \cdot 4H_{2}O(7)$.

for each bipyridyl [distance $H(2)\cdots C(28)$, $H(36)\cdots C(50)$ and $H(36)\cdots C(51)$; 2.79, 2.70 and 2.87 Å], which yields a more extended and complex $C-H\cdots \pi\cdots \pi\cdots H-C$ interaction.

- (b) An extended stacking, normal to the described $C-H\cdots\pi\cdots\pi\cdots H-C$ units, between four aromatic rings, two o-iodobenzovl rings, which are part of the C-H··· π contact, at the inside [distance $C(2) \cdots C(38)$ or $C(4) \cdots C(36)$, ca. 3.36 Å; torsion, 175°], and two bipyridyl ligands which do not participate in that interaction at the outside of the group [distance $C(2) \cdots C(21)$ or $C(3) \cdots C(21)$, ca. 3.25 Å and torsion, 158°; distance $C(67) \cdots C(36)$, ca. 3.31 Å and torsion, 157°]. This π -cluster unit, is extended along the *a* direction, like a wire, assisted by the formation of another stacking between the winger bipyridyl rings [distance $C(16) \cdots C(64)$, ca. 3.49 Å and torsion 173°] and strengthened by contacts between $O(44) \cdots H(18)$ and $O(10) \cdots H(64)$ (see below). These infinite stacking chains are intertwined by orthogonal C-H··· π ··· π ···H-C clusters which grow from the two central *o*-iodobenzoyl rings to right and left sides. These crisscrossed strings form 2D networks which are piled in the *b* direction related, for instance, by the iodine anions and water molecules (for more information see Section 3.3.1.5).
- (c) An interesting C_{aromatic}−H···O hydrogen bonds¹ between carboxylate or carboxamide from I-hip ligand and bipyridyl [distance and angle: C(27)− H(27)···O(43), 3.34 Å and 153°; C(52)−H(52)···O(9),

3.41 Å and 144°; C(47)–H(47)····O(7), 3.22 Å and 127°;C(32)–H(32)···O(41), 3.39 Å and 146°; C(18)–H(18)···O(44), 3.33 and 143°; and C(64)–H(64)···O(10), 3.46 Å and 158°].

(d) And finally, iodine atoms interact with their environment: thus, iodine from o-iodobenzoyl rings, shows an intramolecular contact between this halogen and the oxygen atom from amide bond [distances $I(1) \cdots O(7)$ and $I(2) \cdots O(41)$, 3.42 and 3.26 Å]. Although the contact angle is not very adequate [angle C=O···I, 80°], we observe a decrease in the torsion between the aryl ring and the peptidic bond of the I-hip ligand, with regard to the binary I-hip complexes, which could be explained by the presence of this interaction. And finally, the iodide anions interact with I-Caromatic [distance I(4)...I(1), 3.89 Å] and H-C_{aromatic} moieties [distance I(4) \cdots H(41), 2.83; $I(4) \cdots H(58)$, 3.08; $I(3) \cdots H(14)$, 3.07; and $I(3) \cdots H(48)$, 3.10 Å]. All these contacts are shorter than the corresponding van der Waals values $[I \cdots I]$, 3.96; $I \cdots O$, 3.50; and $I \cdots H$, 3.18 Å] calculated by Bondi [33].

3.2. Crystal structure of $[Cu(B^{I}GG)(bpy)_{2}]^{+}(I^{-}) \cdot 4H_{2}O$ (7)

In this X-ray structure, the copper(II) ion present a distorted octahedral coordination (see Fig. 2), being linked to the two O atoms of the carboxylate in I-hip [Cu(1)-O distances: O(1), 2.012(7) and O(2), 2.74 Å] and to the four N atoms from two bpy molecules [Cu(1)-N distances: N(1A), 2.041(8); N(12A), 1.993(9); N(1B), 2.175(10) and N(12B), 2.016(9) Å]. The coordination environment is again coincident with the

¹ All hydrogen bond distances are given between the donor and the acceptor atoms; angles of interaction correspond to $D-H\cdots A$.

corresponding to compounds **5** and **6** and the complex unit is positively charged and compensated by the presence of one iodide atom. The presence of seven water molecules completes the structure (water molecules O1W and O2W have complete occupancy (100%); but O3W, O4W and O5W have only 40%; O6W, 30%; and O7W, 50% occupancy). The 3D structure of this compound is also formed by bi-dimensional layers in the a-b-plane.

The Addison parameter (τ) relating to this compound presents a value of $\tau = 0.33$. In this compound, the geometry is a little nearer to a square pyramid than those for compound **6**, but anyway it is also faraway from any of the two perfect geometries.



Fig. 3. Iodine–iodine interaction in compound $[Cu(I-hip)_2(OH_2)_3] \cdot 2H_2O$ (3). In order to centre this short contact with a value of 3.78 Å, only the nearness of iodine atoms has been represented (more structural information in Ref. [19]).



With regard to iodine interactions, one short contact between iodine moiety and iodide anion are present [distance $I(10)\cdots I(15)$, 3.81 Å], shorter than the corresponding van der Waals distance must be mentioned and the iodide anion also interacts with H–C_{aromatic}, as in compound **6** [distance $I(15)\cdots H(9B)$, 3.09 Å].

Finally, two C_{aromatic}–H···O hydrogen bonds are also present between O atoms from carboxylato/peptide and bipyridyl (type A) moieties [distance and angle: C(4A)– H(4A)···O(5), 2.98 Å and 119.9°; C(5A)–H(5A)···O(2), 3.52 Å and 166.1°; and C(8A)–H(8A)···O(2), 3.46 Å and 163.5°].



Fig. 4. Iodine-hydrogen interaction (depicted with black lines) and iodine-metal bond (depicted as a standard bond) in compound 2 [18]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Fig. 5. C–I··· π interaction in compound [Zn(I-hip)₂(OH₂)₂]₂ · 3H₂O (1) [17]. The I···C_{aromatic} distance values are 3.56 and 3.74 Å alternatively.

3.3. Iodine interactions present in these compounds

Different levels of interactions and self-assemblies involving iodine atoms have been detected in the seven compounds previously described.

3.3.1. A simple type of recognition patterns

3.3.1.1. Iodine-iodine interaction $(I \cdots I)$. [Cu(I-hip)₂-(OH₂)₃] · 2H₂O (3) presents a short contact between two iodine atoms in I-hip rings (Fig. 3). The bond distance is about 0.2 Å shorter than de van der Waals value and the final 3D structure is generated by means those reported iodine contacts which yields different planes in the *c* direction.

Similar type of interaction is also present in compound $[(Co, Ni \text{ or } Zn)(I-hip)_2(acv)(OH_2)_3](4)$. Likewise, an equivalent contact Ph-I···I⁻ appears in compounds $[Cu(I-hip)-(bpy)_2]^+(I^-) \cdot 1.5H_2O$ (6) and $[Cu(B^IGG)(bpy)_2]^+(I^-) \cdot 4H_2O$ (7). In all cases, these iodide interactions are very important to maintain the 3D crystal structure.

3.3.1.2. Iodine-hydrogen interaction $(I \cdots H-C)$. Another type of interaction is present between iodine and hydrogen(-C) atoms as, for instance, in complex [Ag(I-hip)]· 1.25H₂O (**2**), where iodine moiety is closed to two hydrogen atoms from glycine moieties (Fig. 4). These distances are approximately 3.10 Å whereas the calculated van der Waals distance is 3.18 Å.

In the other compounds, as in [(Co, Ni or Zn)(I-hip)₂-(acv)(OH₂)₃] (4), [Cu(I-hip)(bpy)₂]⁺(I⁻) \cdot 1.5H₂O (6) and [Cu(B^IGG)(bpy)₂]⁺(I⁻) \cdot 4H₂O (7), is also detected this kind of interaction, where the hydrogen atoms belong to aromatic rings instead of aliphatic chains.

3.3.1.3. Iodine-metal bond (I-Ag). Complex [Ag(I-hip)]· 1.25H₂O (**2**) also presents direct bonds between iodine (I-hip) and two silver atoms at 3.15 and 3.36 Å (Fig. 4). These contacts are in the levels described in the literature for Ag–I short contact or large bond. Iodine bonded to metals is only present in silver complexes.



Fig. 6. Two types of connected interactions which direct the formation of a planar structure in compound $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ (6). The stacking piled along the *a* direction extended to all the crystal is depicted with green lines (vertical in the center of the figure) and the C–H··· π ···H–C patterns which are observed in horizontal and indicated with black lines (one on the left side and another one on the right side). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3.1.4. Iodine– π system interaction $(C-I\cdots\pi)$. Binary derivative $[\text{Zn}(\text{I-hip})_2(\text{OH}_2)_2]_2 \cdot 3\text{H}_2\text{O}(1)$ holds, in its crystal structure, a close contact between iodine atoms and aromatic rings which remember us a $C-H\cdots\pi$ interaction. In these complex an extended $C-I\cdots\pi$ interaction (Fig. 5) where one iodine moiety of I-hip contacts closely with the aromatic ring of another I-hip molecule is present. The interaction occurs in the neighbourhood of the iodine moieties (see Fig. 5). This fact tells us than the iodine atom is important in the interaction not only to bond another ring, but also to active the aromatic ring in order to be bonded.

A recent publication [30] has been defined various parameters (three distances and three angles) in order to explore and compare this interaction type. In compound 1, the six parameter values are (for shorter/longer interactions): D_{pln} , 3.577/3.778 Å; D_{Atn} , 3.559/3.739 Å; D_{lim} , 3.493/3.709 Å; θ , 78.13–78.02°/80.70–77.93°; φ , 79.70–79.40°/78.33–81.16° and ω , 84.10°/84.22°. In the cited paper, is also defined de maximum distance at which a iodine–aromatic ring contact can be considered as interaction: D_{max} , identified as sum of the van der Waals radii of iodine and half-thickness of aromatic ring with an added tolerance of 5% of this sum in order to address electrostatic contributions to the interaction, has a value of 3.86 Å. Our results, confirm the directional preference of the C–I··· π interactions.

3.3.1.5. Interactions promoted by iodine atoms which do not directly participate in them. Iodine substitution in aromatic rings improves the capability of interaction between these

aromatic rings. Thus, in $[Cu(I-hip)(bpy)_2]^+(I^-) \cdot 1.5H_2O$ (6) is not possible to detect any important iodine interaction, but there are very important stacking self-assemblies. In Fig. 6 are depicted the 2D plane formed by these interactions. In green colour represent the stacking along the *a* direction, which crosses all the crystal, whereas in black colour two C-H···π···H-C cluster patterns are shown. Detailed distances of these interactions have been reported in Section 3.1.

There are other examples in which the presence of a iodine substitution in the aromatic rings helps to stabilize the formation or reinforcement of stacking interactions. For instance, in compound [(Co, Ni or Zn)(I-hip)₂-(acv)(OH₂)₃] (4), it is possible to detect a stacking interaction between acyclovir and I-hip which enforce the formation of two enantiomeric structures.

3.3.2. A complex pattern of recognition factors

3.3.2.1. Iodine–iodine $(I \cdots I)$ plus iodine–hydrogen $(I \cdots H-C)$ interactions. [(Co, Ni or Zn)(I-hip)₂(acv)(OH₂)₃] (4) show two types of described single recognition patterns involving iodine atoms (Fig. 7). Thus, the resulting iodine network is formed by iodine–hydrogen(aromatic) contacts at 3.15 Å [van der Waals value, 3.18 Å] and iodine–iodine bonds at 3.80 Å [van der Waals value, 3.96 Å]. In the picture, the first ones are indicated in green thin lines, and the second ones are indicated in black thin lines.

3.3.2.2. $C-I\cdots\pi\cdots\pi\cdots I-C$. Another interesting way of interaction between iodine atoms is by means a long



Fig. 7. Network of interactions in complex [(Co, Ni or Zn)(I-hip)₂(acv)(OH₂)₃] (4) [17]. There are hydrogen-iodine interactions depicted with green lines and iodine-iodine contacts indicated with black lines. These two types of recognitions form to chains of iodine atoms which are related to each other by means of tandems of C-H···I interactions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Fig. 8. New C–I··· π ·· π ·· π ··I–C cluster pattern presents in complex [Cu-(I-hip)(phen)₂]⁺(I-hip⁻) · 7H₂O (**5**) [19]. As it is the most complex iodine interactions observed in the family of compounds presented in this work, we have represented the implied atoms as boundary surfaces in order to well understand the composition of recognition patterns.

distance $C-I\cdots\pi\cdots\pi\cdots\pi-I-C$ as can be observed in [Cu(I-hip)-(phen)₂]⁺(I-hip⁻) · 7H₂O (5). Fig. 8 illustrates these ideas and show this new pattern of molecular recognition: an stacking interaction between two aryl rings from I-hip [distance, 3.39 Å; torsion, 180°] reinforced by two interesting C-I···C(ring) interactions [distance, 3.60 and 3.55 Å], similar to a C-H··· π one, on each stacked ring. We can also understand this cluster as two C-I··· π interactions locked by a stacking between two other *o*-iodobenzoyl rings (four iodophenyl moieties are implied in these kind of interaction).

The six distance parameters for compound **5** are: D_{pln} , 4.158 Å; D_{Atn} , 3.551–3.602 Å; D_{lim} , 3.509 Å; θ , 54.90–57.26°; φ , 106.64–103.88° and ω , 115.04°. These results are also in agreement with the discussion about this type of interaction, made for compound **1**.

4. Conclusion

Different and interesting patterns of molecular recognition involving iodine atoms are shown in this paper. Among these interactions it is possible to include: $I \cdots I$, $I \cdots H-C$ (aromatic or aliphatic), $I \cdots M$ (metal ion), $I \cdots \pi$ (like C–H··· π) and aromatic self-assemblies assisted by iodine atoms. These interactions could be similar to their formed between thyroxine and its binding molecules because of the similarity between thyroxine and the different iodohippurate compounds studied in the present work.

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Appendix A. Supplementary material

CCDC 237826, 269073, 285764, 237828, 237827, 285763, 624402 and 624403 contain the supplementary crystallographic data for 1, 2, 3, 4 (Co complex), 4 (Zn complex), 6 and 7. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving. html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.poly. 2006.11.024.

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