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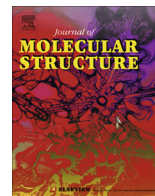


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Theoretical study of the hydrogen bonding interaction between Levodopa and a new functionalized pillared coordination polymer designed as a carrier system

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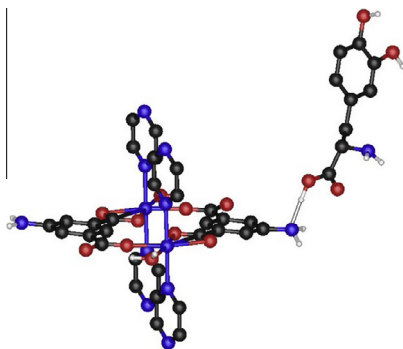
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HIGHLIGHTS

- X-ray analysis of a new coordination octahedral cobalt complex.
- Solvothermal conditions essential to obtain coordination polymers.
- Density functional calculations were used to evaluate hydrogen bonding interactions.
- The DFT calculations predict a good interaction between the amine group and Levodopa.

GRAPHICAL ABSTRACT

Functionalized pillared coordination polymer designed to interact with the carboxylic acid group present in Levodopa.



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ABSTRACT

The solvothermal reaction of $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, Pyrazine (**L1**) and 5-Aminoisophthalic acid (**L2**) led to the formation of a new functionalized pillared coordination polymer with possible application as a carrier system for drug delivery. The X-ray diffraction confirmed the structure of the material and theoretical density functional calculations using a non-empirical hybrid functional PBE0 were done to evaluate the possible hydrogen bonding interaction between the free amine group present in the pillared material and the carboxylic unit belonging to the pharmaceutical Levodopa. The stabilization energy for the model proposed resulted in 11 kcal/mol.

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Introduction

The use of carrier systems to improve the activity of known molecules for biomedical applications becomes more and more

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important because these systems usually allow a better control of the drug plasmatic levels and an increase of the efficiency in the drug stability by protection of the biodegradation is observed [1]. Recently a new class of hybrid materials called metal–organic frameworks (MOFs) have been prepared, and the number of applications in areas such as catalysis [2–6], gas storage [7–11], separations [12–14], sensing [15–17] among others are still under study. These new materials possess characteristics such as high stability and high porosity which make them ideal as carriers for a controlled drug delivery [18,19]. On the other hand, the development of nanoscale metal–organic frameworks (NMOFs) possesses several potential advantages over conventional nanomedicines such as their structural and chemical diversity, high loading capacity and their intrinsic biodegradability [20]. (NMOFs) can be synthesized using a variety of different techniques that have been developed for inorganic and organic polymeric nanoparticles [21]. Two different strategies to deliver active agents have been reported, by incorporating active agents into the frameworks or by loading active agents into the pores and channels of the NMOFs. According to this, the first strategy for drug delivery must take into account the introduction of functional groups which can be able to interact primordially by hydrogen bonding interactions with the drug to be released. Different efforts in the field of theoretical calculations have been done to understand the energies related to the hydrogen interactions between carriers systems and different drugs [22–25]. In this context, we could prepare under solvothermal synthesis a new pillared coordination polymer with free amine groups to evaluate the hydrogen bonding interaction with acid (S)-2-amine-3-(3,4-dihydroxyphenyl) propanoic (Levodopa) which is a potent pharmaceutical against Parkinson disease. In this study, theoretical density functional calculations using a non-empirical hybrid functional PBE0 [26,27] and a 6-31G basis set in all atoms have been carried in order to assess the possible interaction of Levodopa with the free amine group belonging to the pillared material **1**, the results indicate that the H-bonding interaction is favorable with a stabilization energy for this model of 11 kcal/mol which makes this material a good candidate to test for drug delivery containing carboxylic acid groups.

Experimental section

Materials

All reactants and solvents were purchased from Aldrich chemical Co., and solvents were dried previous to use [28]. Single crystals were grown using spectroscopic grade solvents.

Instrumentation

Elemental analyses were performed on a PerkinElmer Series II CHNS/O model 2400 analyzer and the sample was measured after stirring the material with CHCl_3 during 2 h and dried in an oven at 120 °C during 24 h. IR spectra were recorded on a PerkinElmer FTIR/FTFIR Spectrum 400 spectrometer with a reflectance ATR accessory. Single crystal X-ray diffraction analyses of compounds (**1–3**) were performed on an Enraf–Nonius Kappa-CCD (λ Mo $K\alpha = 0.71073$ Å, graphite monochromator, $T = 298$ K, CCD rotating images scan mode). All reflection data set were corrected for Lorentz and polarization effects. The crystals were mounted on conventional MicroLoops™. The structure was solved using direct methods with SHELX-S-97 [29,30] or SIR2004 [31]. The refinement of the structure (based on F^2 of all data) was performed by full matrix least-squares techniques with SHELX-L-97 [30,31]. All software manipulations were done under the WinGX [32] environment program set. The hydrogen atoms of the coordination polymer were

positioned geometrically and refined using a riding model approximation with distances $\text{N–H} = 0.86$ and $\text{C–H} = 0.93$ Å. Single crystal structure validation was done with PLATON [33]. Molecular perspectives were drawn under ORTEP-3 [34].

Synthesis

[Co (L1)(L2)]_n (1). A mixture containing $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (242 mg, 0.8323 mmol), **L1** (100 mg, 1.2485 mmol), **L2** (302 mg, 1.6647 mmol) H_2O (5 mL) and MeOH (5 mL) was heated at 120 °C for 24 h. After the mixture was allowed to cool slowly to room temperature, purple rectangular shaped crystals were obtained with a yield around 70%. mp > 350 °C. IR ν_{max} : 3311 and 3272 (NH_2), 1540 (C=O), 1475 (C–N), 1391, 1309, 1255, 1162, 1036, 960, 897, 808, 767, 675 cm^{-1} . Anal. Calc. for $\text{C}_{12}\text{H}_9\text{CoN}_3\text{O}_4$: C, 45.30; H, 2.85; N, 13.21%. Found C, 45.27; H, 2.92; N, 13.29%.

Computational details

The calculations were performed using the PBE0 hybrid exchange–correlation functional in combination with the 6-311++G** or the 6-31G basis set using the TeraChem software package [35]. The structure visualization and molecule overlap was performed using Molden software [36].

Results and discussion

Solvothermal reaction of $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, Pyrazine (**L1**) and 5-Aminoisophthalic acid (**L2**) in a mixture of solvents DMF:MeOH: H_2O yielded the pillared metal–organic framework with free amine groups in the structure. The reaction was done in two steps, $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and (**L1**) in MeOH/ H_2O were refluxed for 1 h, followed by slow cooling at room temperature and posterior addition of (**L2**) in DMF to finally heat at 120 °C for 24 h.

X-ray diffraction

Pillared material **1** crystallized and the X-ray structure is shown in Fig. 1. The crystallographic data are summarized in Table 1. The structure of the functionalized pillared material **1** showed that two Pyrazine moieties are coordinated to the cobalt atom occupying the apical positions while three 5-Aminoisophthalic acid moieties are coordinated to the cobalt atom occupying the equatorial positions. The Pyrazine moieties in material **1** seems to be in a face π – π stacking interaction, but the distance of 4.12 Å is far enough to be considered according to several studies previously reported [37,38]. The cobalt (II) atom displays a distorted octahedral geometry being surrounded by four oxygen and two nitrogen atoms Fig. 2. Coordination bond distances are in the range from 2.181 to 1.994 Å, similar to those observed in cobalt complexes Table 2. The bond angles around the hexacoordinated cobalt atom are in the range from 59.93° to 178.74°. Finally, a view along a axis of the extended structure of pillared material **1** shows the free amine groups essential to interact by hydrogen bonding Fig. 3.

Theoretical DFT calculations

In order to predict a possible interaction between the pharmaceutical drug Levodopa and the new synthesized functionalized pillared material **1**, an interaction complex model that includes both molecules was tested. Theoretical calculations were performed on a portion of the functionalized pillared material **1** and were taken directly from the crystal structure. The selected portion is presented in Fig. 4 and it consists of two cobalt atoms, four Pyrazine molecules, two 5-Aminoisophthalic acid molecules and two

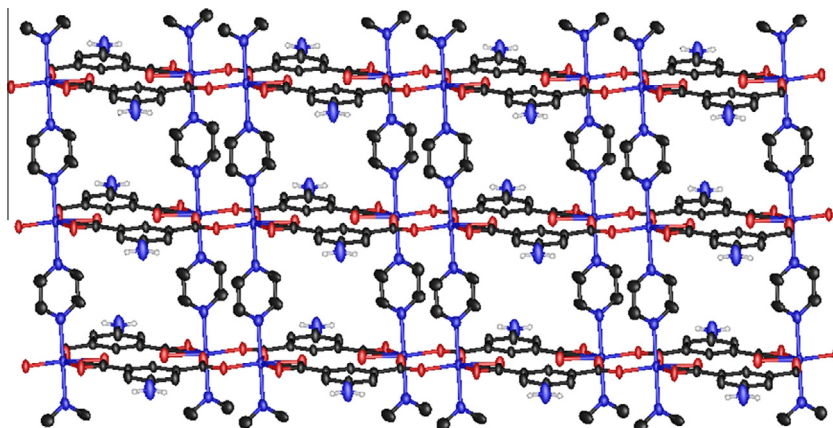


Fig. 1. View along *c* axis of the extended structure of pillared material **1** showing the two organic ligands presents in the structure, some hydrogen atoms were omitted for clarity.

Table 1
Crystallographic data for pillared material **1**.

Compound	1
Chemical formula	C ₁₂ H ₉ CoN ₃ O ₄
Formula weight	318.15
Space group	Triclinic
Crystal system	P-1
Crystal size (mm ³)	0.125 × 0.075 × 0.025
Crystal color and shape	Brown rectangular
<i>a</i> (Å)	7.1438(5)
<i>b</i> (Å)	10.0442(6)
<i>c</i> (Å)	11.8077(9)
α (°)	78.662(4)
β (°)	84.857(4)
γ (°)	88.157(4)
Volume (Å ³)	827.28(10)
Formula units per cell, <i>Z</i>	2
δ_{calc} (g cm ⁻³)	1.277
μ (mm ⁻¹)	1.050
<i>R</i> (int)	0.1058
<i>R</i> _w = [$\sum w(F_o - F_c)^2 / \sum w F_o^2$] ^{1/2} , <i>w</i> = 1/ σ^2 (all data)	0.1513
Goodness of fit, <i>S</i>	1.019
No. of parameters	181
$\Delta\rho_{\text{min}}$ (e Å ⁻³)	0.427
$\Delta\rho_{\text{max}}$ (e Å ⁻³)	-0.422

water molecules which were added to account for the octahedral geometry of cobalt atoms and to mimic the oxygen-cobalt repetition of the polymer. Most of the atoms in the selected portion of the pillared material **1** were held fixed except the two water molecules and the free amine groups. The closed shell configuration was tested to be stable and the amine group of the optimized portion was used to test the interaction with the carboxylic group of the Levodopa molecule.

Structural optimization was performed using the unrestricted PBE0 [39] hybrid exchange–correlation functional in combination with the 6-311G** basis for non-metal atoms and the 6-31G basis for cobalt atoms using the TeraChem software package [35]. Calculations were performed with a spin multiplicity of one and for this fixed frame of pillared material spin contamination was absent. The optimized complex model is presented in Fig. 5. The hydrogen bonding interaction between the donor amine group and the acceptor carboxylic group gave a value of 1.74 Å with an angle

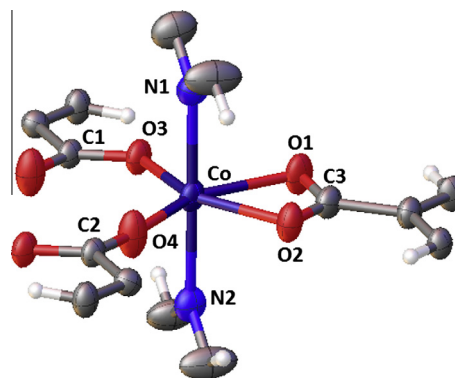


Fig. 2. Distorted octahedral geometry around cobalt (II) atom. The apical positions are occupied by two nitrogen atoms corresponding to two the Pyrazine moieties while the equatorial position are occupied by four oxygen atoms corresponding to three 5-Aminoisophthalic acid moieties, two oxygen chelating and two oxygen bridging to other cobalt atom.

Table 2
Selected bond distances (Å) and bond angles (°) for pillared material **1**.

Pillared material 1			
Bond distances (Å)		Bond angles (°)	
Co—O1	2.245(3)	O1—Co—O2	59.93(10)
Co—O2	2.098(3)	O1—Co—O3	90.28(11)
Co—O3	2.030(3)	O1—Co—O4	152.19(11)
Co—O4	1.994(3)	O1—Co—N1	89.91(13)
Co—N1	2.181(4)	O1—Co—N2	91.27(13)
Co—N2	2.173(4)	O2—Co—O3	150.20(12)
C1—O3	1.270(4)	O2—Co—O4	92.27(12)
C2—O4	1.232(5)	O2—Co—N1	89.60(12)
C3—O1	1.258(5)	O2—Co—N2	90.61(12)
C3—O2	1.260(5)	O3—Co—O4	117.49(12)
		O3—Co—N1	89.46(12)
		O3—Co—N2	90.97(12)
		N1—Co—N2	178.74(15)
		N1—Co—O4	88.89(14)
		N2—Co—O4	89.86(14)

between the atoms N1—H1—O1 of 174.0°. As showed Koukaras et al., this values are in full agreement with what would be expected for a typical hydrogen bond (~1.6–2.0 Å), which is also verified by the O1—N1 distance of 2.74 Å. Fig. 6 presents an interaction energy profile as a function of distance between the N1—H1 atoms, the complex model was further optimized with this

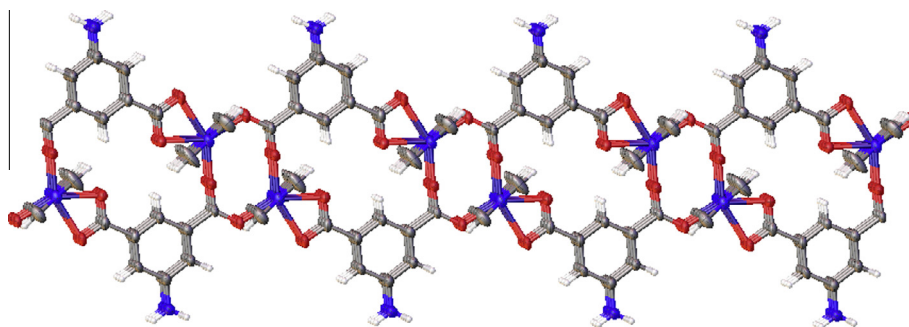


Fig. 3. View along *a* axis of the extended structure of pillared material **1**, showing the free amine groups presents in the structure.

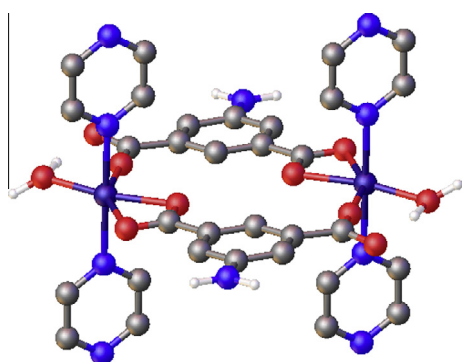


Fig. 4. Selected portion of the functionalized pillared material **1**. Two water molecules were added to account for the octahedral symmetry of the Co atoms. Some hydrogen were omitted for clarity.

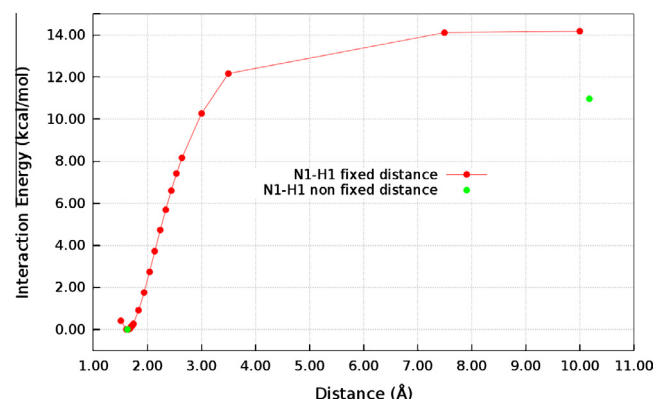


Fig. 6. Interaction energy profile as a function of distance between the N1—H1 atoms, the complex model was further optimized with this distance constraint. Scan was performed with a 6-31G basis in all atoms.

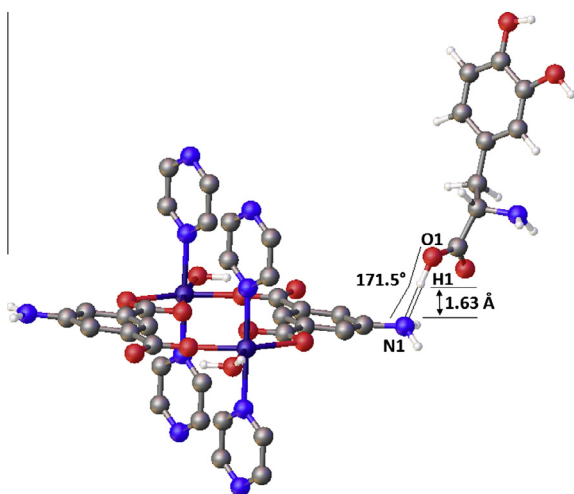


Fig. 5. Optimized interaction complex consisting of the selected portion of functionalized pillared material **1** and the Levodopa molecule. Some hydrogen atoms were omitted for clarity.

distance constraint. As can be seen from Fig. 6, the interaction between the two fragments is not an artifact, namely, that a minimum in the energy profile exists. The potential energy scan was performed with a 6-31G basis in all atoms. Red curve was obtained holding fixed the N1—H1 distance and the green points were obtained by releasing the N1—H1 constraint of the minimum and higher energy points on the red curve profile. The interaction energy resulted in 10.98 (green points on the plot) kcal/mol which predicts a favorable interaction for this level of theory.

Finally, in Fig. 7 we observe the structural overlap between the residue **L2** + Levodopa of the optimized interaction complex

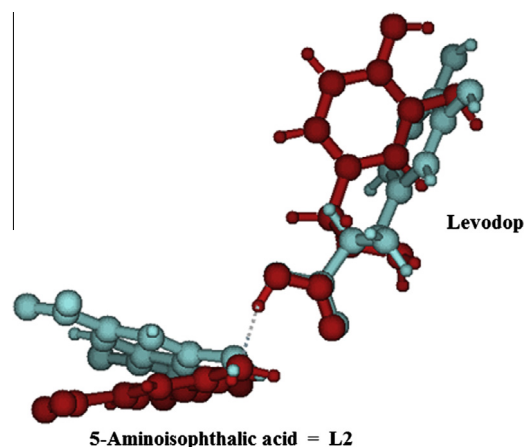


Fig. 7. Overlap between **L2** + Levodopa representing the interaction between the amine group and the carboxylic acid of the optimized interaction complex obtained with PBE0/6-31G (red color) and an isolated model of **L2** + Levodopa obtained at the PBE0/6-311++G** level of theory (green color). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

obtained with PBE0/6-31G (red color) and an isolated model of **L2** + Levodopa obtained at the PBE0/6-311++G** level of theory (green color). The overlap was performed by setting to maximum coincidence the carboxylic group of Levodopa. From this picture it is possible to observe that the optimized complex presents a rotational difference regarding the HC(NH₂)CH₂Ph(OH)₂ fragment in Levodopa, nevertheless, the principal **L2** fragment and Levodopa interaction is very similar, in fact, the hydrogen bonding distance

for this smaller model in green color is predicted to be 1.82 Å with an angle between the atoms N–H–O of 164.4°. The predicted interaction energy for this smaller model was evaluated to be of 9.42 kcal/mol. From this analysis is expected that the moiety **L2** in the pillared material **1** is conserving its main character and indeed the interaction with Levodopa remains favorable.

Conclusions

In conclusion we synthesize strategically a new functionalized pillared coordination polymer by solvothermal synthesis and theoretical calculations were done to examine the interaction of the amine group present in the polymer with the pharmaceutical drug Levodopa, using a properly selected cluster model. The DFT calculations for the complex presented in this work confirms that a possible H-bonding interaction between the MOF and the potent pharmaceutical against Parkinson disease, acid (S)-2-amine-3-(3,4-dihydroxyphenyl) propanoic (Levodopa), remains favorable. This opens the experimental study to assess the Levodopa-MOF coordination ratio.

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Appendix A. Supplementary material

The XYZ coordinates of the optimized model at PBE0/6-31G level of theory is included. CIF files containing tables of crystallographic parameters, atomic coordinates, anisotropic thermal parameters, bond distances, bond angles, as well as a list of structure factors have been deposited in the Cambridge Crystallographic Data Centre (CCDC no. 934217 for **1**). Copies of this information may be obtained free of charge from the director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/data_request/cif).

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.molstruc.2014.11.042>. These data include MOL files and InChIKeys of the most important compounds described in this article.

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