Design and Synthesis of Crown Ether Thiosemicarbazones

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Abstract

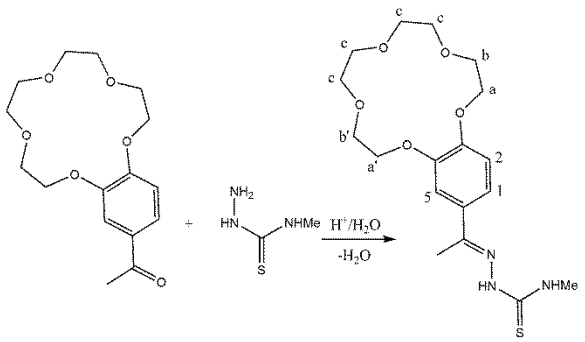
Herein we report on the synthesis of a molecule that combines thiosemicarbazone and crown ether functions. The main feature is that the study has being performed beginning with the design of the compound using DFT calculations, with the package of programs g09[1], after which follows the final synthesis and characterization using ^{1}H NMR, IR and crystallographic analysis.

Introduction

Thiosemicarbazones are well known compounds that show antitumoral and antibacterial proprieties;[2] the crown ether moiety may act as an ion sensor for entrapping cations by size selectively from the environment, and it is also implied in the production of sensors, membrane ion transport or potential anti-cancerous species, among others[3]. The combination of both functions into the same molecule should increase their unique applications

Experimental

4'-acetylbenzo-15-crown-5-ether was added to a solution of 4-methyl-thiosemicarbazide in water with acid catalysis. The mixture was stirred for 4h at room temperature, after which the white precipitate was filtered off, washed with water and dried.



Scheme 1: Synthesis of the crown ether thiosemicarbazone compound.

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[1] M. J. Frisch *et al*. *Gaussian 09*, Revision D.01; Gaussian, Inc., Wallingford CT, 2013.

[2] (a) A. I. Matesanz, J. M. Pérez, P. Navarro, J. M. Moreno, E. Colacio, P. Souza, *J. Inorg. Biochem.* **1999,** *76.* (b) G. Domagk, *Quimioteraia de la tuberculosis por las tiosemicarbazonas.* Científico Médica, **1951.** (c) M. T. Cocco, C. Congiu, V. Onnis, M. L. Pellerano , A. De Logu *Bioorganic and Medicinal Chemistry,* **2002,** *10* 501.

[3] (2) (a) C Preihs, D. Magda, J. Sessler *J. Porphyrins and Phthalocyanines*, **2011**, *15*, 539. (b) Z. Sun, M. Barboiu, Y-M Legrand, E. Petit, A. Rotaru, *Angew. Chem. Int. Ed*. **2015**, *54*, 14473

The NMR spectra (*vide infra*) shows that the *Me*=CN signal appears at higher field than in the case of the free ketone, confirming the condensation. Suitable crystals for X-ray analysis were grown for compound **1**; their structural analysis confirmed the synthesis.

DFT studies

In order to determine the best conformation of compound **1**, DFT studies using the package of programs g09[1] (B3LYP/6-31G(d)) in a solution of acetone were carried out. Moreover, frequency calculations were also performed finding no imaginary frequencies and, thus, confirming the stationary points. The starting structure was the experimental one. The conformers were generated by rotating three points in the molecule (MeCPh, S=CNHMe and NHMe). All the conformers are represented in Figure 1. In addition, a comparison between the experimental results and the theoretical calculations was done to confirm the wellness of the model, as is shown in Figure 2.

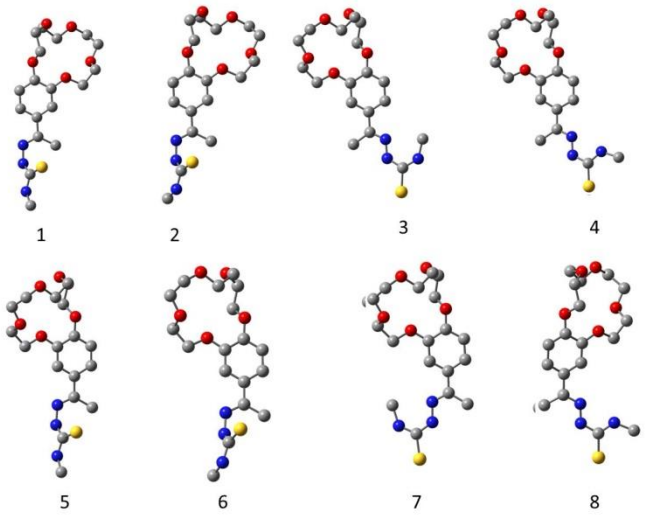


Figure 1: Conformers for 1 to 8 .

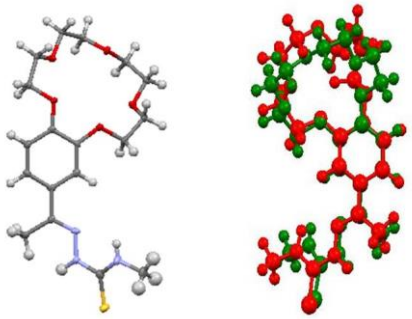
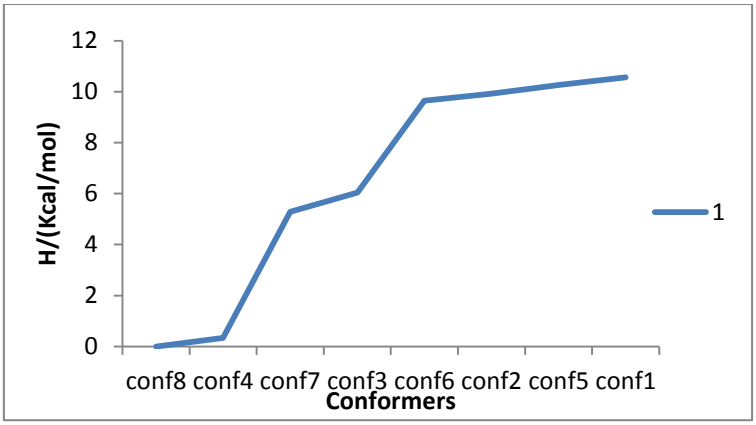


Figure 2: Experimental structure on the left and comparison between the experimental (red) and the theoretical (green) on the right.

As shown in the graphic, the most stable conformer is **8**, while the less stable is **1.** The differences between the position of the crown ether with respect to the thiosemicarbazone arrangement are those that less affect the whole stability of the molecule (all below 1Kcal/mol). On the other hand, the rotation around the S=CN system is the one with a higher

contribution to the energetic gap (*ca.* 10Kcal/mol). This can be due to the rigidity of the S=CN system versus the mobility of the phenyl ring.



Conclusions

We have shown that the synthesis of this type of compounds is feasible mild conditions in water, so it can also be called green synthesis. DFT calculations show that there are not significant differences in the energy of the conformers. However, the conformations of the thiosemicarbazone component are the determining part of the energetic differences.

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Experimental

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.58 (s, 1H, N*H*), 7.57 (m, 1H, N*H*Me), 7.28–7.24 (m, 1H, H1), 7.21 (d, ^{4}J(H1H5) = 2.2 Hz, 1H, H5), 6.85 (d, ^{3}J(H1H2) = 8.4 Hz, 1H, H2), 4.21–4.14 (m, 4H, Ha, Ha'), 3.96–3.90 (m, 4H, Hb, Hb'), 3.79–3.71 (m, 8H, Hc), 3.27 (d, ^{3}J(NH*Me*) = 4.9 Hz, 3H, NH*Me*), 2.23 (s, 3H, *Me*C=N).