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A theoretical study of atropisomerism in *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea and its inclusion in the β -cyclodextrin

A. M. Touadjine¹ · A. Mostefai¹ · A. Rahmouni¹ · S. Humbel² · A. Krallafa³ *

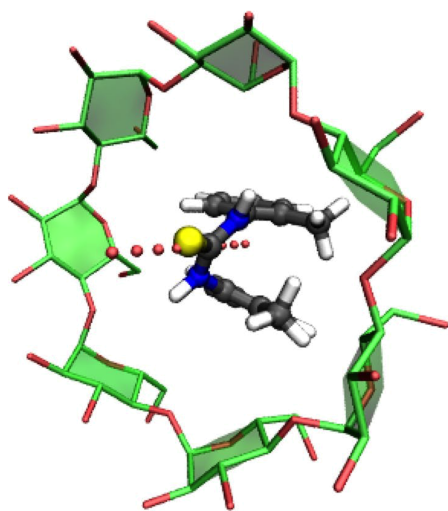
Abstract β -cyclodextrin and its derivatives form inclusion complexes with a wide variety of guest molecules, including isomers and enantiomers. The main purpose of the present theoretical investigation is to predict the enantio-discrimination of *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea and to study in details the inclusion process of the *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea with the β -cyclodextrin using static quantum calculations. The compound presents three pairs of atropisomers that can possibly be experimentally separated by inclusion within the cavity of the β -cyclodextrin. Therefore, it appears of interest to study, in the first part, the model compound, the so called *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea 1. We were interested then in the identification of the possible conformers of this compound. All conformers were fully optimized at different levels of theory. The relative energies of all possible conformers are given and discussed. Our calculations showed, as expected, that the π -stacking conformer with respect to other structures is the most stable. In the second part, we were interested then to evaluate the host-guest complex stabilization through the formation of the inclusion compounds for the 1:1 association. The inclusion process pathways are described and the most stable structures of the different complexes are sought through a global search of the potential energy surface.

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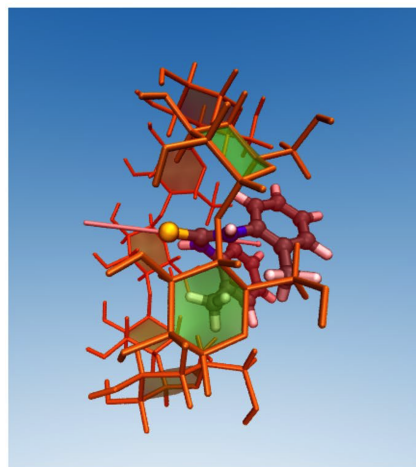


Keywords Thiourea · β -Cyclodextrin · Enantio-differentiation · Inclusion process

Introduction

Over the past 20 years, a number of theoretical studies on the chromatographic separation [1–3] of enantiomers aimed at both the rationalization and prediction of experimental results [4–8]. Recently, molecular encapsulation [9–12] has been successfully used in several technological fields [5, 6]. Pharmaceutical industry has made use of the technique to improve the bio-availabilities of drugs [13–15], to protect them from decomposition, to convert liquids to free flowing powder, and to mask unfavorable odors and tastes. Inclusion complexation [16–18] is the focus of current host–guest complexation and supramolecular chemistry [7, 8, 19–21].

Cyclodextrins (CD) [22–24] are a family of cyclic oligosaccharides containing 6(α), 7(β), 8(γ) or more glucose residues and are characterized by a truncated cone shape [25]. Cyclodextrin molecules consist of secondary hydroxyl groups extending from the wider edge while the primary groups from the narrow edge. The *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea belongs to the thiourea compounds [26] family which are active traps of heavy metals and play an important role in the field of asymmetric organo-catalysis [27]. Bifunctional chiral thioureas have emerged as a successful class of organo-catalysts for a variety of asymmetric transformations, such as the cyanosilylation of ketones [28], strecker reactions [29], Michael's additions [30] and hydro-phosphonylation of imines [31]. Their



success as bifunctional organo-catalysts is based upon their ability to function as hydrogen-bond donors and the incorporation of additional basic or acidic activating groups [32].

In the present paper we investigate the complexation of *N*-(2-methylphenyl) *N'*-(2-methylphenyl) thiourea in a typical β -cyclodextrin. The paper is organized as follow. First, we investigated the conformational space of the thiourea, with a particular focus on the π -stacking conformers. A variety of quantum chemistry methods and several different basis sets will be used, and both geometrical indicators and energy difference will be reported. Second, the inclusion processes will be modeled by moving the thiourea along the central axis of the cyclodextrin, from the one face until it goes through the macrocycle, and emerges from the other face. Two trajectories are reported: from the primary face to the secondary, and the reverse one, from the secondary to the primary face. A discussion follows.

Computational details

All calculations were performed with the Gaussian suite of program [33]. The conformational study of the thiourea was held with a variety of methods and basis sets, including DFT approach with dispersion terms. In this part we refer to MP2/6-311g(d, p) geometries and energies as the highest and most reliable data obtained. It ends up that the geometry of the π -stacking complex was equally well described with both the MP2 [34] and the DFT based calculations with a 6-311g(d) basis set and the M06-2X-D3 functional, the later has the Grimme's D3 dispersion terms included [35, 36]. An atropisomerism was hence described at the

M06-2X-D3/6-311G(d) level of calculation. In the second part of the paper, this level of calculation was used to investigate the selective atropisomer complexation process in the β -cyclodextrin.

The M06-Class density functionals [35, 37, 38] used in the present investigations, belong to a family of functional that have been developed by Zhao and Truhlar at the university of Minnesota (M05, M05-2x, M06, M06-2X and M06-HF). These functionals have shown accurate and great performance in the determination of the potential energy surface of non-covalent interactions and inclusion processes. Such methodology is most highly recommended [35] for the study of main-group thermo-chemistry and non-covalent interaction in super molecules, as it is the case for structure optimization and investigations of the conformational energy landscape of very large systems or for reactions involving large molecular systems.

In order to examine in details, the host–guest insertion pathways and seek for possible global minima through the inclusion complex, 25 points are selected from the capture and complexation of the guest molecule (the stable pair of atropisomers S1b, S2b) by the β -cyclodextrin up to its release from the opposite face. In order to describe the interactions of such large molecular systems with less expensive computationally CPU time, we have in a first place, frozen all atoms for the host molecule except its hydrogen atoms. Second, in order to make sure that the guest molecule is always on the axis of inclusion during the insertion process we kept frozen the sulphur and its adjacent carbon atom. Calculations of the interaction energy during the host–guest inclusion process were performed using the Pople 6-311g(d) basis set. Following these preliminary calculations along the inclusion pathway, six to eight representative points are picked up from the 25 points selected. These points are then fully optimized, with no constraint on atoms of the host–guest system.

Results and discussion

Thiourea conformations

In Table 1 are reported the relative centro-phenyl distances in the π -stacking form of the *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea calculated at different levels of theory and with different basis sets. We observe that M06-2X-D3/6-311g(d) [35] level is in good agreement with MP2 with the shortest centro-phenyl distance observed. However, the last method (MP2) is very expensive in term of memory and disk storage needed to perform the calculations. In all cases, the parallel-displaced aromatic rings are sufficiently close (3.503 Å from center to center) to give rise to a favorable interaction. This distance is in good

Table 1 Centro-phenyl distances in the closed π -stacking structure of the *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea and the energy difference ΔE between the π -stacking S2a form and the open C2 form calculated at different levels of theory

| Level of theory | Centro-phenyl distances in the π -stacking form (Å) | ΔE (kcal/mol) |
|--------------------|---|-----------------------|
| B3LYP/6-311G(d) | 4.404 | 3.73 |
| MP2/6-31G(d) | 3.865 | 6.79 |
| MP2/6-311G(d) | 3.503 | 7.83 |
| MP2/6-311+G(d) | 3.432 | 8.38 |
| MP2/6-311+G(d,p) | 3.528 | 7.89 |
| B97D/6-31G(d) | 4.047 | 7.48 |
| B97D/6-31+G(d) | 4.062 | 7.41 |
| B97D/6-311G(d) | 4.031 | 7.83 |
| B97D2/6-311G(d) | 4.027 | 7.86 |
| B97D3/6-311G(d) | 4.029 | 6.82 |
| Mo6/6-31+G(d) | 3.852 | 4.48 |
| Mo6/6-31++G(d,p) | 3.842 | 4.57 |
| WB97xd/6-311+G(d) | 3.764 | 6.64 |
| Mo6-2X/6-31++G(d) | 3.764 | 5.97 |
| Mo6-2X/6-311+G(d) | 3.73 | 6.18 |
| Mo6-2XD3/6-31G(d) | 3.765 | 6.07 |
| Mo6-2XD3/6-311G(d) | 3.597 | 7.39 |

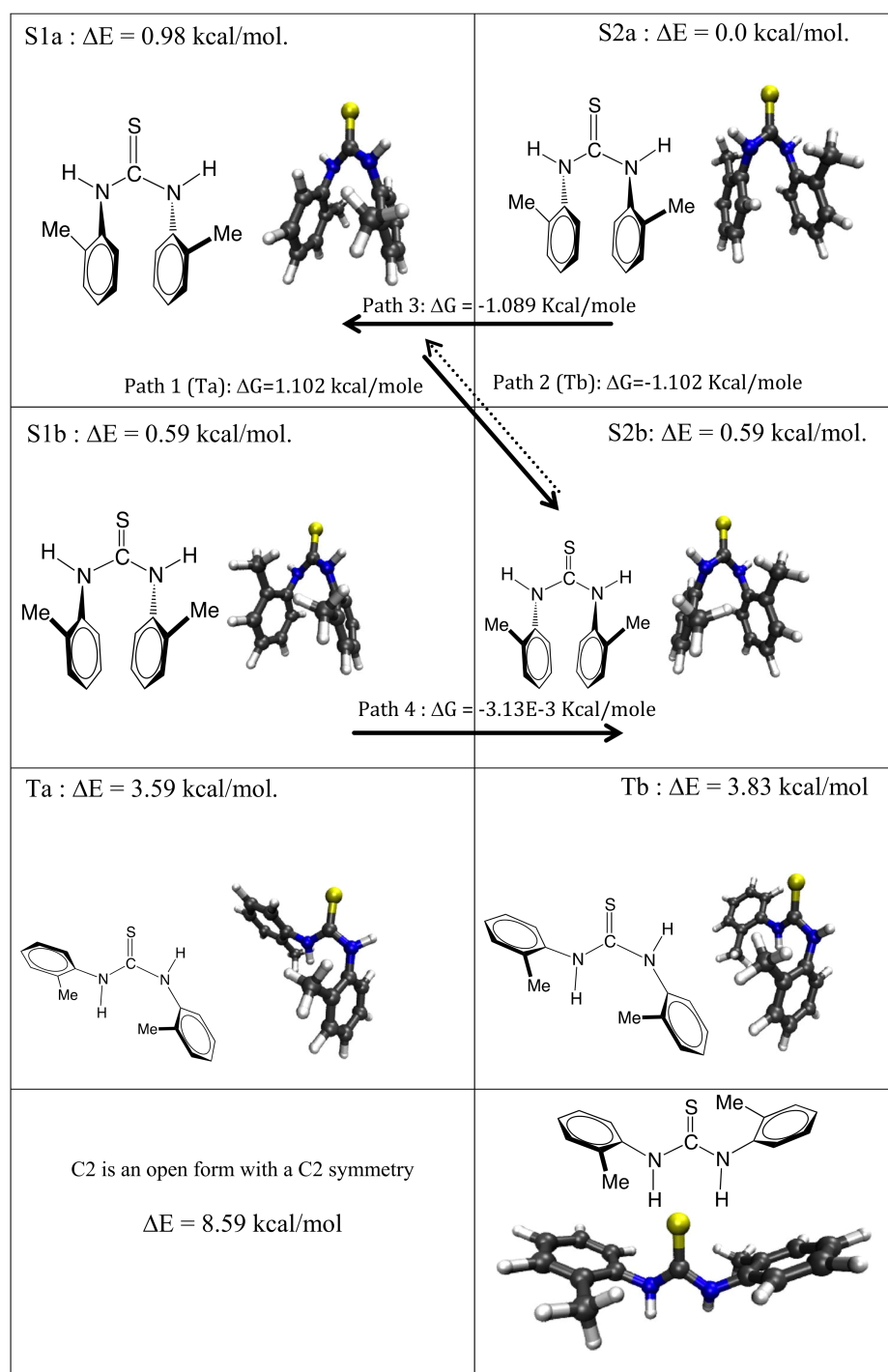
Bold characters correspond to the shortest centro-phenyl distance

agreement with typical π -stacking and parallel-displaced [39–45] geometries reported in the literature [46, 47] which ranges from 3.5 Å up to 4.0 Å.

All possible geometries which arise from the various possible isomers of *N*-(2-methylphenyl)-*N*-(2-methylphenyl) thiourea are taken into account and fully optimized. The MP2/6-311g(d,p) calculations showed that the π -stacking (S) isomers have a comparable energy (Fig. 1) with a difference of about 1 kcal. mol^{−1}. In this geometry, the π electron delocalization [47–50] explains the phenomenon of the preferential π -stacking form. This particular arrangement is linked to the aromaticity effect [49–53] between the two cycles and the decrease of the interaction energy.

The inter-conversion path between any pair of atropisomers is illustrated in Fig. 1. Such a scheme characterizes four possible paths and gives rise to four possible atropisomers (S_{1a}, S_{1b}, S_{2a} and S_{2b}) and two T atropisomers forms (Ta and Tb) [43–45]. According to their relative energy and dipole moment, these forms can be classified into three groups (S_{1a} and S_{2a}, S_{1b} and S_{2b} and Ta and Tb). The calculated free energies reported in Fig. 1, indicate that most paths are in favor of the S_{1a} π -stacking atropisomers and the low energy barriers of path 1 and path 2 as reported in Fig. 2, lead to the T forms (Ta and Tb). With the help of the calculated dipole moment (Fig. 2), the variety of atropisomers observed can be classified into pairs. We can observe the first pair S_{1b}

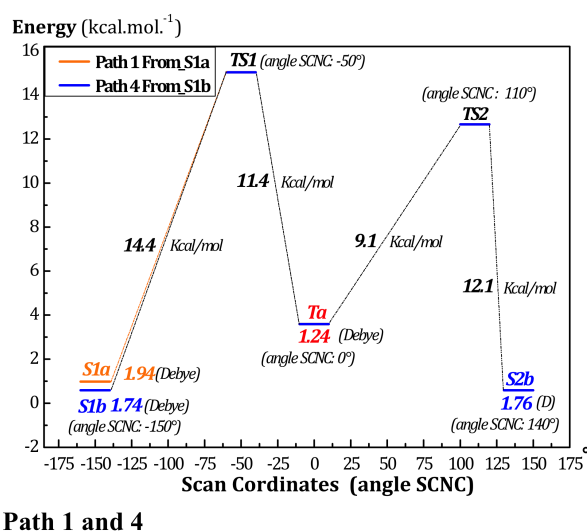
Fig. 1 Different views of the atropisomers forms of the *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea are the π -stacking forms (S) and the T forms (T). The corresponding energies calculated at MP2/6-311g(d, p) level of theory are reported for each conformer with respect to the most stable structure (S2a). (Color figure online)



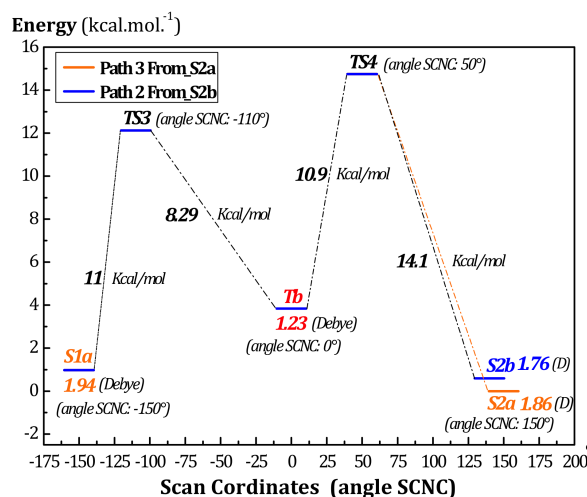
and S2_b π -stacking atropisomers with the lowest energy and a comparable dipole moment. The second pair of the π -stacking atropisomers characterized with the two forms S1_a and S2_a and the two T conformations (T_a and T_b) obtained from path 1 and path 2 respectively. All points reported in Fig. 2 are obtained from a scan over the SCNC dihedral angle.

Inclusion path

In order to study the selection of the different atropisomers forms, more likely to lead to stable complexes with the β -cyclodextrin, the potential energy profile of the inclusion process is carried out through on both sides, the primary hydroxyl group (primary face PF) and the secondary



Path 1 and 4



Path 2 and 3

Fig. 2 Inter-conversion paths between all forms of atropisomers. The π -stacking forms S1a, S1b, S2a, S2b and the T open form (Ta and Tb) are optimized at MP2/6-311g(d, p) levels of theory. The energies,

in kcal.mol⁻¹, are relative to S2a (−1086.51365 a.u) and the dipole moment for each form is in Debye. (Color figure online)

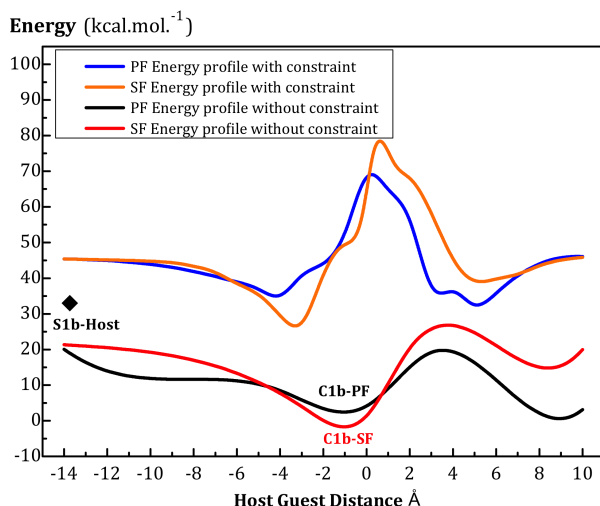


Fig. 3 Energy profile of the inclusion path of the π -stacking atropisomer form S1b (PF plot refers to the insertion through the primary face, SF plot refers to the insertion through the secondary face) with and without constraint. The black point refers to the energy of the Host+Guest without interaction at the M02-2X/6-311g(d) level of theory. (Color figure online)

hydroxyl group (secondary face SF) of the host molecule with the selected forms of atropisomers obtained.

The insertion path profiles are reported in Figs. 3 and 4. The association process is described in terms of the center of mass distance between the host and the guest molecule. Values in the x abscissa are the distances between

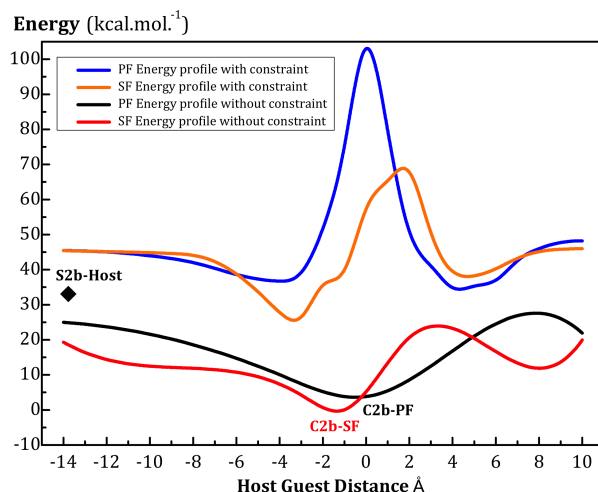


Fig. 4 Energy profile of the inclusion path of the π -stacking atropisomer form S2b (PF plot refers to the insertion through the primary face, SF plot refers to the insertion through the secondary face) with and without constraint. The black point refers to the energy of the Host+Guest without interaction at the M02-2X/6-311g(d) level of theory. (Color figure online)

the center of mass of the host and guest molecule. Several indications are reported in these figures. The isolated grey point depicts the total energy of the host and guest taken separately. This energy point may be considered as the reference of the total energy of the system in conjunction with the starting long range interactions between the molecular

components of the supramolecular complex. In Figs. 3 and 4, the insertion process is read from the left (negative host–guest distance) to the right (positive host–guest distance). For S-atropisomers, the insertion process occurs via the thiourea group either from the primary or the secondary face.

Among the three pairs of atropisomers, S_{1b} and S_{2b} have a comparable dipole moment, and are therefore the most appropriate candidate for possible complexation with the β -CD. The energy profile illustrated in Fig. 5 does not reveal any selective process as neither for the

S_{1b} and S_{2b} forms nor for the faces involved in the complex formation with the β -cyclodextrin. Stable structures are obtained with atropisomers (S_{1b} , S_{2b}) when the thiourea group is included into the hydrophobic cavity of the β -cyclodextrin. These results lead to the conclusion that all forms of complexes are present (Fig. 5). The stabilization energy of each form is in favor of the host–guest association (Table 2), however, the deformation energy of the host and guest molecules, illustrates the large structural changes that undergoes the host molecule. In all cases the calculated GM/HM charge transfer [49–53] is

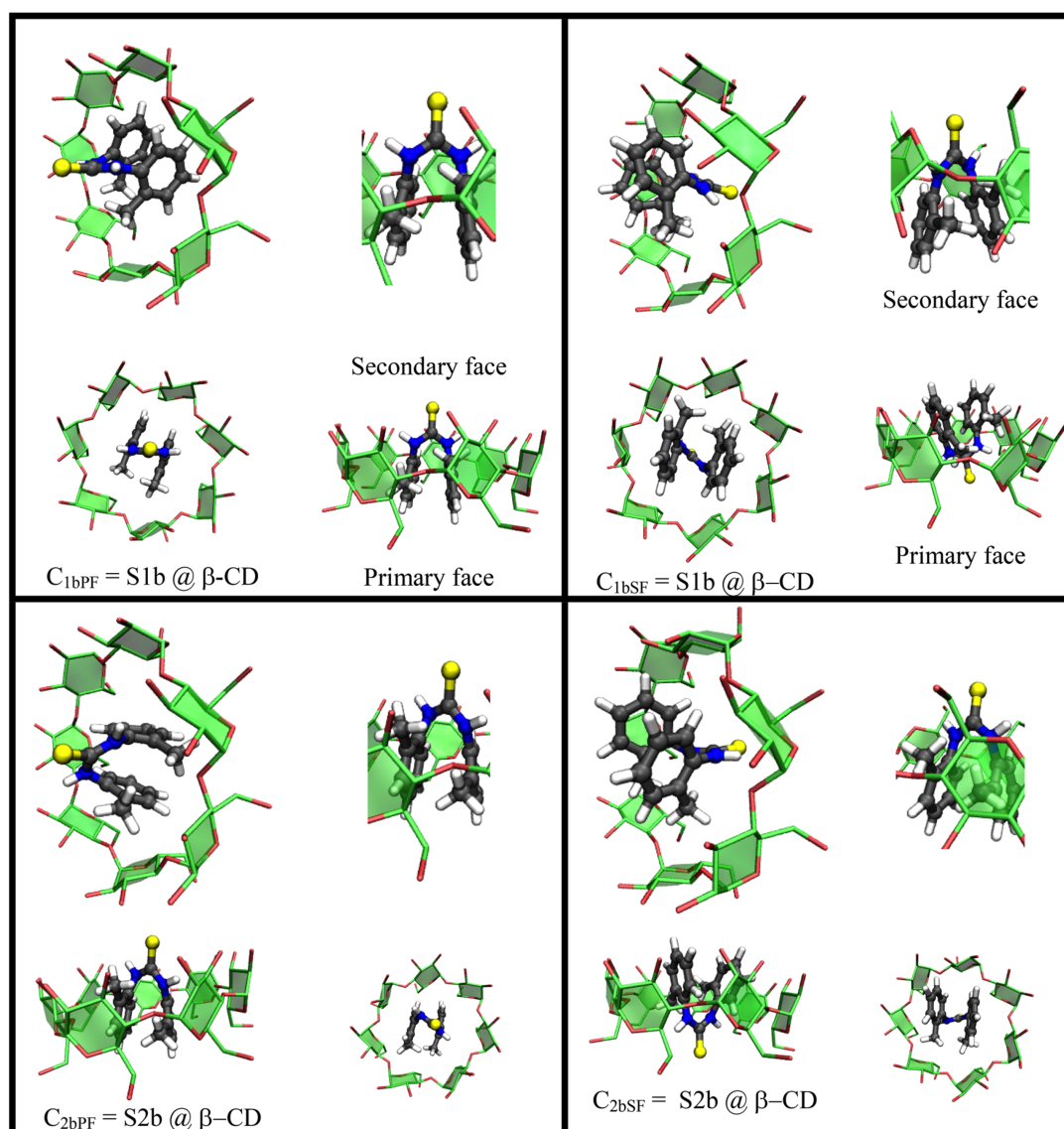


Fig. 5 The four possible host–guest complex’s as a result of the insertion process, process path (PF) refers to the insertion through the primary face (points C1bPF and C2bPF) and path (SF) refers to

the insertion through the secondary face (Points C1bSF and C2bSF). (Color figure online)

Table 2 Stabilization energy (SE), deformation Energy (ΔE_{def}) and charge transfer (CT) in the complex of the *N*-(2-methylphenyl)-*N'*-(2-methylphenyl) thiourea (S1b and S2b) and β -CD calculated at M02-2X/6-311g(d) levels of theory (in kcal/mol)

| | Complex S1b— β -CD | | Complex S2b— β -CD | |
|--|--------------------------|----------------------|--------------------------|----------------------|
| | Primary face C1bPF | Secondary face C1bSF | Primary face C2bPF | Secondary face C2bSF |
| SE (kcal/mol) | −46.0 | −45.0 | −45.8 | −45.0 |
| ΔE_{def} (Guest) (kcal / mol) | 1.7 | 3.8 | 2.3 | 1.0 |
| ΔE_{def} (Host) (kcal / mol.) | 11.4 | 5.5 | 10.3 | 6.9 |
| CT (a.u) | 0.20 | 0.30 | 0.18 | 0.30 |

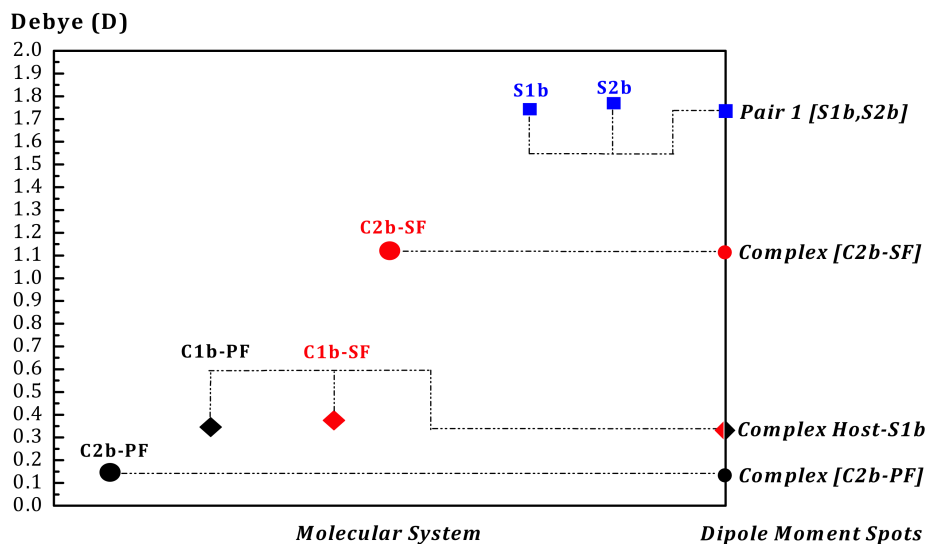
observed in the insertion process, however, the GM/HM charge transfer through the PF is twice that of the calculated one observed through the SF. This suggest that electronic properties are playing an essential role in the differences between all types of host–guest molecular complexes. These interactions would be reinforced in a solvent as water. Indeed, the calculation of the dipole moment of the molecular complexes and the atropisomers S1b and S2b in Fig. 6 are illustrative of possible separations between all components. We can observe four possible host–guest complex's as a result of the insertion process, the insertion process through the path PF of atropisomers

S1b and S2b leading to complex C1bPF and C2bPF and the insertion process through the path SF of atropisomers S1b and S2b leading to complex C1bSF and C2bSF. If the atropisomers S1b and S2b are similar, out of the four complexes only C2bPF and C2bSF are well separated at the difference with the C1bPF and C1bSF.

Conclusion

The atropisomerism is well described at the M06-2X-D3/6-311G(d) level of calculation. Couples of atropisomer forms with comparable dipole moments are observed with an energy difference less than 1 kcal/mol. This work has shown that the conformational study of the thiourea and the accurate search of enantio-differentiation between *N*-(2 methylphenyl)-*N'*-(2 methyl phenyl) thiourea atropisomers using the β -CD as a complexing agent can be performed theoretically at different levels of theory. The search for global minima through the inclusion process pathway lead to a complete mechanism and illustrates in more details all possible orientations and regio-selective insertions involved in host–guest interactions. The combination of the energy profile, with thermodynamics data such as the stabilization, deformation energies and electronic properties can complete our knowledge of the host–guest associative process. The S1b and S2b pair of atropisomers can

Fig. 6 Dipole moments of the host–guest molecular complex's and the corresponding atropisomers S1b and S2b



possibly be separated by inclusion within the cavity of the β -cyclodextrin.

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References

- Armstrong, D.W., DeMond, W.: Cyclodextrin Bonded Phases For the Liquid Chromatographic Separation of Optical, Geometrical, and Structural Isomers. *J. Chromatogr. Sci.* **22**, 411–416 (1984)
- Berthod, A., Jin, H.L., Beesley, T.E., Duncan, J.D., Armstrong, D.W.: Cyclodextrin chiral stationary phases for liquid chromatographic separations of drug stereoisomers. *J. Pharm Biomed Anal.* **8**(2), 123–130 (1990)
- Hinze H.L.: Applications of cyclodextrins in chromatographic separations and purification methods. *Sep. Purif. Methods* **10** (2), 159–237 (1981)
- Allouch A., El Hassan I., Abou Dalle A., El-Nakat H., El Omar F.: Inclusion complex of thiourea substrate with hydroxypropyl- β -cyclodextrin. *Chem. Sci. Trans.* **2**(2), 663–669 (2013)
- Pais, L.S., Loureiro, J.M., Rodrigues, A.E.: Modeling strategies for enantiomers separation by SMB chromatography. *AIChE J.* **44**(3), 561–569 (1998)
- Loftsson, T., Brewster, M.E.: Pharmaceutical applications of cyclodextrins. I. drug solubilization and stabilization. *J. Pharm. Sci.* **85**(10), 1017–1025 (1996)
- Gellman, S.H.: Molecular recognition. *Chem. Rev.* **97**, 1231–1232 (1997)
- Hamilton, J.A., Sabesan, M.N.: Structure of inclusion complexes of cyclomaltoheptaose (cycloheptaamylose): crystal structure of the benzocaine adduct. *Carbohydr. Res.* **102**, 31 (1982)
- Klingert, B., Rihs, G.: Molecular encapsulation of transition-metal complexes in cyclodextrins. I. Synthesis and X-ray crystal structure of $[(\eta^3\text{-C}_3\text{H}_5)\text{Fe}(\eta^6\text{-C}_6\text{H}_6)]\text{PF}_6 \cdot 2\alpha\text{-CD} \cdot 8\text{H}_2\text{O}$. *Organometallics* **9**(4), 1135–1141 (1990)
- Dick, D.L., Rao T.V.S., Sukumaran, D., Lawrence, D.S.: Molecular encapsulation: cyclodextrin-based analogues of heme-containing proteins. *J. Am. Chem. Soc.* **114**(7), 2664–2669 (1992)
- Hof, H., Craig, S.L., Nuckolls, C., Rebek, J. Jr.: Molecular Encapsulation. *Angew. Chem. Int. Ed.* **41**(9), 1488–1508 (2002)
- Palmer L.C., Rebek J. Jr.: The ins and outs of molecular encapsulation. *Org. Biomol Chem.* **2**(21), 3051–3059 (2004).
- Veber, D.F., Johnson, S.R., Cheng, H.Y., Smith, B.R., Ward, K.W., Kopple, K.D.: Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **45**(12), 2615–2623 (2002)
- Leeson, P.D., Springthorpe, B.: The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discov.* **6**(11), 881–890 (2007)
- Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R.: A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res.* **12**(3), 413–420 (1995)
- Chen, G., Jiang, M.: Cyclodextrin-based inclusion complexation *bridgingsupramolecular chemistry and macromolecular self-assembly*. *Chem. Soc. Rev.* **40**(5), 2254–2266 (2011)
- Baboota, S., Agarwal, S.P.: Inclusion complexation of meloxicam with β -cyclodextrin. *Indian J. Pharm. Sci.* **64**(4), 408–411 (2002)
- Marques, H.C., Hadgraft, J., Kellaway, I.W.: Studies of cyclodextrin inclusion complexes. I. the salbutamol-cyclodextrin complex as studied by phase solubility and DSC. *Int. J. Pharm.* **63**(3), 259–266 (1990)
- Bliidi Boukamel N., Krallafa A., Bormann D., Caron L., Canipelle M., Tilloy S., Monflier E.: Theoretical Investigations of the Inclusion Processes of (4-tert-butylphenyl) (3-sulfonatophenyl) (phenyl) Phosphine in β -Cyclodextrin. *J. Incl. Phen. and Macrocycl. Chem.* **42**, 269–274 (2002)
- Chekirou, N.L., Krallafa A., Bormann D.: Theoretical Investigations and Mechanisms of the Inclusion Processes of bi(3-sulfonatophenyl) (4-tert-butylphenyl) phosphine in the β -cyclodextrin. *J. Incl. Phenom. Macrocycl. Chem.* **53**, 89–95 (2005)
- Chekirou, N.L., Benomrane, I., Lebsir, F., Krallafa, A.M.: Theoretical and experimental study of the tetracain/ β -cyclodextrin inclusion complex. *J. Incl. Phenom. Macrocycl. Chem.* **74**, 211–221 (2012)
- Szejtli, J.: Cyclodextrins and Their Inclusion Complexes (Cyclodextrine und ihre Einschlußkomplexe). Verlag der Ungarischen Akademie der Wissenschaften. Akadémiai Kiadó, Budapest. *Starch-Stärke* **34**, 395–395 (1982)
- Rekharsky, M.V., Inoue, Y.: Complexation thermodynamics of cyclodextrins. *Chem Rev.* **98**(5), 1875–1918 (1998)
- Del Valle, E.M.: Cyclodextrins and their uses: a review. *Process Biochem.* **39**(9), 1033–1046 (2004)
- Szejtli, J.: Introduction and general overview of cyclodextrin chemistry. *Chem. Rev.* **98**, 1743–1753 (1998)
- Venkatachalam, T.K., Mao, C., Uckun, F.M.: Effect of stereochemistry on the anti-HIV activity of chiral thiourea compounds. *Bioorg. Med. Chem.* **12**(15), 4275–4284 (2004)
- Dalko P.I., Moisan L.: In the golden age of organocatalysis. *Angew. Chem. Int.* **43**, 5138–5175 (2004)
- Fuerst, D.E., Jacobsen, E.N.: Thiourea-catalyzed enantioselective cyanosilylation of ketones. *J. Am. Chem. Soc.* **127**(25), 8964–8965 (2005)
- Tsogoeva, S.B., Hatley, M.J., Yalalov, D.A., Meindl, K., Weckbecker, C., Huthmacher, K.: Thiourea-based non-nucleoside inhibitors of HIV reverse transcriptase as bifunctional organocatalysts in the asymmetric Strecker synthesis. *Bioorg. Med. Chem.* **13**, 5680–5685 (2005)
- Hoashi, Y., Yabuta, T., Yuan, P., Miyabe, H., Takemoto, Y.: Enantioselective tandem Michael reaction to nitroalkene catalyzed by bifunctional thiourea: total synthesis of (–)-epibatidine. *Tetrahedron* **62**(2–3), 365–374 (2006)
- Joly, G.D., Jacobsen, E.N.: Thiourea-catalyzed enantioselective hydrophosphonylation of imines: practical access to enantiomerically enriched α -amino phosphonic acids. *J. Am. Chem. Soc.* **126**, 4102–4103 (2004)
- Steele, R.M., Monti, C., Gennari, C., Piarulli, U., Andreoli, F., Vanthuyne, N., Roussel, C.: Enantioselective cyanosilylation of aldehydes catalysed by a diastereomeric mixture of atropisomeric thioureas. *Tetrahedron Asymmetr.* **17**, 999–1006 (2006)
- Frisch M.J., Trucks G.W., Schlegel H.B. et al.: Gaussian 09. Gaussian Inc, Wallingford (2009)
- Moller C., Plesset M.S.: Note on an approximation treatment for many-electron systems. *Phy. Rev.* **46**, 618 (1934)
- Zhao, Y., Truhlar, D.G.: The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **120**(1–3), 215–241 (2008)
- Grimme, S., Ehrlich, S., Goerigk, L.: Effect of the damping function in dispersion corrected density functional theory. *J. Comp. Chem.* **32**, 1456–1465 (2011)
- Hohenstein, E.G., Chill, S.T., Sherrill, C.D.: Assessment of the performance of the M05–2X and M06–2X exchange-correlation

- functionals for noncovalent interactions in biomolecules. *J. Chem. Theory Comput.* **4**(12), 1996–2000 (2008)
38. Bryantsev V.S., Diallo M.S., van Duin A.C., Goddard III W.A.: Evaluation of B3LYP, X3LYP, and M06-Class Density functionals for predicting the binding energies of neutral, protonated, and deprotonated water clusters. *J. Chemical Theory Comput.*, **5**(4), 1016–1026 (2009)
 39. Hunter, C.A., Sanders, J.K.: The nature of π – π interactions. *J. Am. Chem. Soc.* **112**(14), 5525–5534 (1990)
 40. Hobza, P., Selzle, H.L., Schlag, E.W.: Potential energy surface for the benzene dimer. Results of *ab Initio* CCSD(T) calculations show two nearly isoenergetic structures: t-shaped and parallel-displaced. *J. Phys. Chem.* **100**(48), 18790–18794 (1996)
 41. Sinnokrot M.O., Sherrill C.D.J: Highly accurate coupled cluster potential energy curves for the benzene dimer: sandwich, t-shaped, and parallel-displaced configurations. *Phys. Chem. A* **108**, 10200–10207 (2004)
 42. Pavlov, A., Mitrasinovic, P.M.: Theoretical insights into dispersion and hydrogen-bonding interactions in biomolecular systems. *Curr. Org. Chem.* **14**(2), 129–137 (2010)
 43. Cozzi F., Ponzini F., Annunziata R., Cinquini M., Siegel J.S.: Polar interactions between stacked π systems in fluorinated 1,8-diarylnaphthalenes: importance of quadrupole moments in molecular recognition. *Angew. Chem. Int Ed. Engl.* **34**(9), 1019–1020 (1995)
 44. Podeszwa R., Bukowski R. and Szalewicz K.J: Potential Energy Surface for the Benzene Dimer and Perturbational Analysis of π – π Interactions. *Phys. Chem. A* **110**, 10345–10354 (2006)
 45. Cyranski, M.K.: Energetic Aspects of Cyclic π -Electron Delocalization: Evaluation of the Methods of Estimating Aromatic Stabilization Energies. *Chem Rev.* **105**(10), 3773–3811 (2005)
 46. Schleyer P.V.R: Introduction: Delocalization- π and σ . *Chem. Rev.* **105**(10), 3433–3435 (2005)
 47. Jug, K., Koester, A.M.: Influence of σ and π electrons on aromaticity. *J. Am. Chem. Soc.* **112**(19), 6772–6777 (1990)
 48. Glukhovtsev M.: Aromaticity today: energetic and structural criteria. *J. Chem. Educ.* **74**(1), 132 (1997)
 49. Katritzky, A. R., Karelson, M., Sild, S., Krygowski, T.M., Jug, K.: Aromaticity as a quantitative concept. 7. aromaticity reaffirmed as a multidimensional characteristic. *J. Org. Chem.* **63**(15), 5228–5231 (1998)
 50. Hunter, C.A., Lawson, K.R., Perkins, J., Urch, C.J.: Aromatic interactions. *J. Chem. Soc.* **2**(5), 651–669 (2001)
 51. Brédas, J.L., Beljonne, D., Coropceanu, V., Cornil, J.: Charge-transfer and energy-transfer processes in π -conjugated oligomers and polymers: a molecular picture. *Chem. Rev.* **104**(11), 4971–5004 (2004)
 52. Hazra, P., Chakrabarty, D., Chakraborty, A., Sarkar, N.: Intramolecular charge transfer and solvation dynamics of Nile Red in the nanocavity of cyclodextrins. *Chem. Phys. Lett.* **388**(1), 150–157 (2004)
 53. Kim, H. J., Heo, J., Jeon, W.S., Lee, E., Kim, J., Sakamoto, S., Kim, K.: Selective inclusion of a hetero-guest pair in a molecular host: formation of stable charge-transfer complexes in cucurbituril. *Angew. Chem. Int. Ed.* **40**(8), 1526–1529 (2001)