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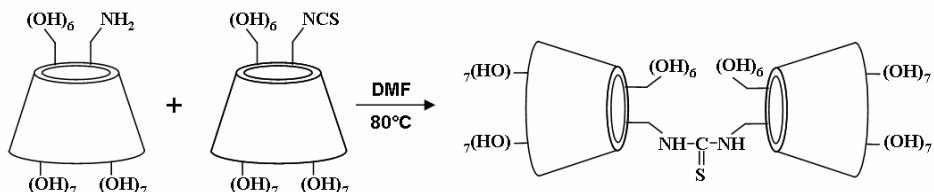
Inclusion ability of a monothiourea tethered bis(β -Cyclodextrin)

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Keywords:	cyclodextrin dimer, cooperative phenomena, formation constants, spectral displacement method



Synthesis and Inclusion Ability of a Monothiourea Tethered Bis(β -Cyclodextrin)

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Inclusion Ability of a Monothiourea Tethered Bis(β -Cyclodextrin)

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Abstract— The tail to tail monothioureido β -cyclodextrin dimer has been prepared by reacting 6-amino-6-deoxy- β -cyclodextrin with 6-isothiocyanato-6-deoxy- β -cyclodextrin. The inclusion ability of this dimer has been evaluated by UV-visible spectroscopy for substrates of moderate molecular volumes (a wide variety of hydroxylated substrates) and compared to genuine β -cyclodextrin and randomly methylated β -cyclodextrin. The definition of a complexation index allowed the treatment of these three host molecules on a hierarchical basis : the bis-cyclodextrin appears to be more efficient (average index equal to 1.17) than the methylated (1.07) or genuine (1.00) monomers. Thus, it seems that the cooperative phenomenon may lead to a general increase of the complexation ability, and not only to an enhanced recognition of specific guests. Surprisingly, this phenomenon is even really effective for the smallest substrates of our study. Such results prompted us to illustrate, on a steric point of view, the possibility of the face to face conformation, by means of molecular modelling.

Keywords: cyclodextrin dimer; cooperative phenomena; formation constants; spectral displacement method

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Introduction

The enhancement of cyclodextrins inclusion ability may be achieved by chemical modifications of genuine macrocycles. Alkylation (such as methylation or hydroxypropylation) is known to lead roughly to a general but weak increase of stabilities, whereas dimerisation, which keeps on receiving great attention (1-6), may afford a greater enhancement but apparently in a selective manner (7-9). Indeed, high stabilities, as observed in biological field, have been obtained for bis-cyclodextrins, but principally with guests which perfectly fit to hosts. However, potential applications of β -cyclodextrins rest at the same time on the intensity of host-guest recognition but also on the variety of recognised molecules. Thus, it seems convenient to determine whether a cyclodextrin dimer may be adapted to substrates of moderate molecular volume, which are usually included by monomers.

Accordingly, we chose to synthesise and characterise the monothioureido tail to tail dimer. Indeed, the choice of a bis-cyclodextrin is directed by two main structural parameters which modify the strength of cooperative phenomena: the connection sites and the spacer. Various studies showed that the tail to tail arrangement seemed more relevant than the head to head arrangement, according to its greater complexing capacities, since there is no altrose residue (10-12). Moreover, thioureido function may be easily introduced, since reactions between amino and isothiocyanato functions are generally done with high yields (13-15). In addition, a spacer also controls the relative orientation between the two cavities and their mutual spacing. Accordingly, the recognition of a substrate whose size is lower than the sum of the two cavities justifies the use of very short spacers. A C6-C6 length lower than five angstroms should allow the thioureido dimer to ensure an intimate proximity between its cavities. Finally, the stability of the thioureido function against pH limits its protonation and, as a consequence, its polarity, thus avoiding a disturbance of complexation phenomena. Since the aim of this study is to probe general inclusion capacities, a wide panel of guest molecules (representative of the units generally recognised by the monomers) was defined. In order to vary the three-dimensional coordinates of guest molecules, we chose

1
2
3 to work with p-halogenophenols, naphthalen-1-ol, adamantan-1-ol, cyclohexanol, decan-1,10-diol and
4
5 biphenyl-4,4'-diol (Table 1).
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7

8 9 **Insert Table1**

10
11 The inclusion ability of this dimer has been studied by means of UV-Visible spectroscopy, associated
12
13 with a competition method based on methyl orange (MO). In order to quantify the contribution of
14
15 dimerisation, stabilities has then been compared with the capacities of β -CD and RAMEB (RANdomly
16
17 METHylated β -cyclodextrin), often considered as one of the most complexing monomers (16-19). We also
18
19 propose in this work to carry out a molecular modeling study on the conformation induced by the spacer,
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21 since it plays a significant part in the complexing ability. Indeed, if a bis-cyclodextrin is able to
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23 accommodate linear species in a cooperative way, one should check that it can direct its two cavities face
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25 to face.
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35 36 **Results and discussion**

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38 $(\beta\text{-CD})_2$ thiourea was prepared in one step from $\beta\text{-CD-NCS}$ and $\beta\text{-CD-NH}_2$ (Figure 1). The two mentioned
39
40 monomers were placed in equimolar conditions and gave, after purification on sephadex column, 74% of
41
42 $(\beta\text{-CD})_2$ thiourea, in one hour and under heating. The structure of this bis- β -cyclodextrin was confirmed
43
44 by NMR spectroscopy, mass spectrometry and by elemental analysis. This route represents a fast way to
45
46 obtain a short tether dimer with an overall yield of 18% from native β -cyclodextrin.
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52 53 **Insert Figure1**

54
55 Inclusion capacities were then investigated by UV-visible spectroscopy (^1H NMR titration experiments
56
57 could not be performed since the host solubility was too weak to allow an accurate ^1H NMR observation
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59 in D_2O). Stability measurements for substrates 1-9 was realised by means of a competition method with
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3 methyl-orange. Such spectral displacement method requires, before its application to substrates 1-9, the
4
5 characterisation of cyclodextrins/methyl-orange complexes. A titration is thus applied for (β -
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7 CD)₂thiourea (Figure 2) and for each monomer. The presence of isosbestic points as well as the
8
9 adjustment of experimental data with theoretical curves confirms the hypothesis of a 1:1 stoichiometry for
10
11 the studied inclusion compounds. The formation constant thus determined for (β -CD)₂thiourea/MO
12
13 complex is equal to $6.35 \times 10^4 \text{ M}^{-1}$, which is therefore much higher than the value of $2.82 \times 10^3 \text{ M}^{-1}$
14
15 obtained in the case of β -cyclodextrin, and of $3.01 \times 10^4 \text{ M}^{-1}$ in the case of RAMEB.
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21 **Insert Figure2**

22
23
24 The complexation thus certainly benefits from cooperative phenomena often described in bis-
25
26 cyclodextrins literature. The value obtained for (β -CD)₂thiourea/MO inclusion compound is in an
27
28 intermediate range between the lowest constants observed for β -CD dimers/MO complexes (mean value
29
30 for the 15 dimers of references (20-23) : $1.69 \times 10^4 \text{ M}^{-1}$), and the highest (mean value for the 2 dimers of
31
32 references (11,24) : $5.97 \times 10^5 \text{ M}^{-1}$). In addition, such stability is slightly lower than the corresponding urea
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34 dimer ($1.05 \times 10^5 \text{ M}^{-1}$), which suggests that sulphur atom is more destabilising than oxygen (25). This
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36 point will be discussed later, in the modeling section.
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43 Since stabilities towards methyl orange are known, the application of competition method towards
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45 substrates 1-9 may be applied. An example of spectral variations (in their first derivative form) observed
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47 with (β -CD)₂thiourea is illustrated in Figure 3. Since competition method does not afford explicit
48
49 information on stoichiometry, calculated stabilities correspond to apparent formation constants. In the
50
51 case of (β -CD)₂thiourea, existence of 1:2 complexes can not be a priori discarded, especially for small
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53 substrates. Nevertheless, each formation constant measurement has been realised for two different
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55 concentrations, and no significant differences in estimated stability have been observed. Since algorithmic
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57 treatment is based on 1:1 assumption, we may reasonably think that 1:1 inclusion compounds are
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3 predominant. In addition, if 1:2 complexes eventually existed, it has to be underlined that apparent
4 formation constants would be underestimated, since a second guest molecule does not imply any
5 expulsion of methyl orange, and thus any spectral displacement.
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10 11 **Insert Figure3**

12
13 Measured stabilities are listed in table 2 (formation constants are expressed in normal and logarithmic
14 forms). The values of log K for β -CD extend from 2.00 (for 4-fluorophenol) to 4.54 (for adamantan-1-ol),
15 and are in agreement with literature data (differences lower than 10%), at least in the case of already
16 studied complexes (26-33).
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24 25 **Insert Table2**

26
27 The range of stability is thus relatively wide, and consequently rather representative of log K observed for
28 genuine β -cyclodextrin. The variety of affinities represents indeed a crucial parameter if one tries to
29 describe the general capacities of complexation of a cyclodextrin. Consequently, the choice of our nine
30 target substrates seems suitable. The stabilities observed for $(\beta\text{-CD})_2$ thiourea extend from 2.46 to 5.04,
31 and are systematically higher than original β -cyclodextrin. In addition, it should be stressed that the
32 increase of stability is, of course, more significant in term of constant than in its logarithmic form. Such
33 an increase shows that the second cavity does not hinder the complexation process on a steric level but,
34 on the contrary, that cooperative phenomena operate for each studied substrate. This result is all the more
35 interesting as some substrates have a particularly low molecular volume: one could have thought that
36 these compounds would not benefit much from a second cavity. In fact, a strong increase of complexation
37 is even observed for p-halogenophenols, whereas their size is similar to the space offered by a simple
38 cavity. If one compares this time $(\beta\text{-CD})_2$ thiourea with RAMEB (log K ranging from 2.27 to 4.43), the
39 advantage of $(\beta\text{-CD})_2$ thiourea is less substantial, but effective for most substrates (7 out of 9). This result
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3 is rather significant, if we consider that methylated β -cyclodextrins are usually recognised as the most
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5 complexing monomers.
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9 In order to highlight the important part played by substrate size on a quantitative level, we have correlated
10
11 $\log K$ observed for 4-halogenophenols with the molar refractivity of each halogen. Obtained results are
12
13 illustrated in Figure 4. Correlation coefficients are higher than 0.994 for each cyclodextrin, thus showing
14
15 the existence of structure-affinity relationships. Accordingly, the intercept of each regression illustrates
16
17 the strength of interactions experimented by the phenolic core, whereas the slope is representative of the
18
19 sensitivity of complexation phenomena towards substituent size. Thus, $(\beta\text{-CD})_2$ thiourea leads to a better
20
21 encapsulation of aromatic nucleus with an intercept value of 2.414 against 2.216 for RAMEB, and 1.969
22
23 for β -cyclodextrin. This bis-cyclodextrin is also more sensitive to the size of halogens than genuine β -CD
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25 (slope equal to 0.088 against 0.072), but a little less than RAMEB (0.090). These results are in agreement
26
27 not only with the fact that $(\beta\text{-CD})_2$ thiourea is systematically more complexing than β -CD, but also that
28
29 biphenyl-4,4'-diol and naphthalen-1-ol are the only guests for which RAMEB is more complexing than $(\beta$ -
30
31 $\text{CD})_2$ thiourea. Indeed, on a steric point of view, these two substrates have a largely higher size than
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33 aromatic monocycles. Since RAMEB is more sensitive to this increase of volume, it leads to higher
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35 affinities for such species.
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43 44 **Insert Figure4**

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47 In order to quantify the stability enhancement (independently of absolute values of $\log K$), we chose to
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49 express affinities in indexes form (complexation indexes I_{comp}), by dividing each $\log K$ by corresponding
50
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52 $\log K$ for genuine cyclodextrin :
$$I_{\text{comp}} = \frac{\log k_{\text{host } j / \text{substrate } i}}{\log k_{\beta\text{-CD} / \text{substrate } i}}$$

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3 Results are illustrated in Figure 5. One can notice that enhancement is relatively homogeneous from one
4 substrate to another, in spite of important differences in their structures. The enhancement of host volume
5 (through cavity extension for RAMEB, and through cooperativity for $(\beta\text{-CD})_2$ thiourea) thus leads to a
6 rather systematic improvement of stability. Consequently, it does represent an improvement of general
7 inclusion ability, and not a particularly selective phenomenon. Since these values are homogeneous, it is
8 possible to treat on a hierarchical basis the complexation capacities of each cyclodextrin, by averaging
9 individual indexes. The positive influence of methylation on monomeric species results here in an
10 increase of 10% for RAMEB (mean index of 1.07 against 1.00 for $\beta\text{-CD}$). Dimerisation is even more
11 favorable with an average value of 1.17. If such an advantage has already been shown in the case of
12 substrates with important sizes, improvement of recognition for small molecules is an absolutely new and
13 notable property.
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30 **Insert Figure5**

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33 In addition, since substrates 1-9 present relatively linear conformations, cooperative phenomena may take
34 place only if this dimer aligns its two cavities. We thus sought to illustrate the steric possibility of such
35 conformation, by modeling the bis-cyclodextrin host alone. The potential surface of $(\beta\text{-CD})_2$ thiourea was
36 investigated by associating molecular mechanics (OPLS) and stochastic methods. Assuming the planar
37 character of thioureido function, we thus carried out a conformational search by applying a Monte Carlo
38 simulation on the four dihedrals controlling the spacer structure (Figure 6), and this for each rotamer.
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49 **Insert Figure6**

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52 After 100000 deformations, two types of conformations are obtained. Cooperative conformations
53 correspond to an alignment of the cavities, whereas the non cooperative conformations correspond
54 roughly to a perpendicular arrangement. These structures are illustrated by their most stable conformation
55 in Figure 7.
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Insert Figure7

The cavities of cooperative conformations face each other without any steric hindrance between them. Defining the distance from a cavity to another between the average plans of O(6) oxygens, a value of 2.4 Å is obtained for cooperative conformation. Such proximity, associated to the face to face conformation, is probably the major parameter which favors cooperative phenomena, especially for small substrates as halogenophenols. Moreover, the short distance existing between the two macrocycles allows the formation of hydrogen bonds. Indeed, a minimisation realised on the orientation of protons located on primary hydroxyls groups leads to systematic interactions for each pair of glucose, from a cavity to another. Short distances between each pair of hydroxyl proton and facing hydroxyl oxygen are recorded (2.45 Å on average). One could think that this crown of hydrogen bonds should stabilise cooperative forms. It could also explain the decrease of $(\beta\text{-CD})_2$ thiourea solubility (if compared to genuine $\beta\text{-CD}$), by decreasing the solvation of primary face. It should also be noticed that face to face structures imply that thioureido spacer directs its sulphur atom inside the cavity. Since sulphur atoms are bulkier than oxygen atoms, this information may explain the lower stability of the methyl orange/ $(\beta\text{-CD})_2$ thiourea complex compared to the methyl orange/ $(\beta\text{-CD})_2$ urea complex: inclusion happens in a more hindered cavity for thioureido dimer than for urea analogue. If cooperative conformations correspond to the energetic minima predicted by simulations, non cooperative conformations also appear in our calculations, but with a slightly lower stability (within the limit of one kcal/mol). In this case, the orientations of the cavities are characterised by a lack of potential cooperativity for linear molecules. Since the two types of conformation seem probable, the dynamic behavior of the spacer should lead to a succession of cooperative and non cooperative conformations. Consequently, cooperative complexation of substrates is possible, but the conversion between the two kinds of conformations probably should lead to a destabilisation. Our simulations cannot release on a quantitative level the proportion between cooperative and non cooperative forms in solution, but they clearly show the steric possibility of the face to face conformations.

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3 In order to illustrate the expected cooperative phenomena that should be induced by such conformations,
4 we have realised the docking of p-fluorophenol, the smallest substrate of our study, into (β -CD)₂thiourea,
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6 in its face to face form. After 100000 conformations generated by monte carlo docking, the most stable
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8 structures (within one kcal/mol) are all located at the interface between the two cavities (Figure 8).
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12 13 **Insert Figure8**

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17 The energetic difference between free and complexed forms is equal to -16.01 kcal/mol in favor of the
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19 inclusion compound, against -13.12 kcal/mol if the substrate is located in only one cavity. The simulation
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21 thus predicts that a substrate experiences more stabilising van der Waals interactions if this one occupies
22
23 partially both cavities than if it fully occupies one single cavity. This behavior explains not only the
24
25 increase of inclusion ability for (β -CD)₂thiourea, but also the predominance of 1:1 complexes. Indeed, if
26
27 the first substrate is strongly bound at the interface, there is not enough space available for a second
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29 substrate to be fully encapsulated.
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35 The molecular modeling results thus emphasised that cooperative phenomena should be responsible of the
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37 enhancement of inclusion compounds stability. Accordingly, the strong inter-cavity proximity underlined
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39 in our simulations probably plays a determining part.
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43 44 45 **Conclusion**

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49 The study of a representative panel of substrates usually recognised by monomeric cyclodextrins enabled
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51 us to treat on a hierarchical basis the inclusion capacities of the tail to tail monothioureido β -cyclodextrin
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53 dimer, as compared to the monomeric species β -CD and RAMEB. We demonstrated by this way that a
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55 bis-cyclodextrin with a short spacer may lead to a general improvement of inclusion ability and not only
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57 to a selective increase for specific guests. Moreover, we have shown that molecules with low molecular
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59 volume particularly benefit from cooperative mechanisms. The inter-cavity proximity seems to be an
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3 essential factor for this phenomenon, which is also controlled by the conformation induced by the spacer.
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5 So, in order to explore this last point, a similar study on the corresponding disulfide dimer is under
6
7 investigation. Indeed, the two spacers lead to similar inter-cavity distance, but induced conformations
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9 could be appreciably different from one another.
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12 13 14 15 16 17 **Experimental Section**

18 19 20 *General comments*

21
22
23 All chemicals were purchased from Aldrich. RAMEB was synthesised from β -CD according to literature
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25 (34), with a mean ring substitution of 14. DMF was distilled from barium oxide. β -cyclodextrin
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27 derivatives and the other reactants were dried under diminished pressure (5×10^{-2} mbar) at 120°C for 24h
28
29 before use.
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31

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34 Mass spectrometry spectra were obtained using a Platform II Micromass spectrometer, in positive
35
36 electrospray ionisation mode and with MeOH:H₂O (50:50) as solvent (cone voltages 110 and 200). ¹H
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38 and ¹³C NMR spectra were recorded with a Brüker ASPECT 3000 spectrometer ; chemical shifts are
39
40 reported in parts per million (δ). UV-Visible spectrometry was performed with a UV-Visible Perkin
41
42 Elmer Lambda 2S spectrometer. The temperature of the 10 mm cell was kept constant at 298K by means
43
44 of a thermostated bath. Elemental analysis were obtained using a Thermoquest CE Instrument CHNS EA
45
46 1110. As a result of the low proportion of nitrogen and sulphur atoms in comparison with the limit of
47
48 detection of the instrumentation, only the percentages of carbon and hydrogen are specified.
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52 53 54 *(β -CD)₂thiourea synthesis*

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57 β -CD-NCS (35) (1.17 g ; 1 mmol) was added to a stirred solution of β -CD-NH₂ (36) (1.13 g ; 1 mmol) in
58
59 dry DMF (25 ml). The mixture was heated under N₂ at 80°C for 1 h, then concentrated under reduced
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3 pressure (half of the volume) and poured into acetone. The precipitate was isolated by filtration. The
4
5 crude product (in aqueous solution) is then purified by two successive Sephadex G25 chromatography
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7 columns (1.71 g, 74%); δ_{H} (DMSO-d₆, 250 MHz): 3.05-4.16 (m, 84H, H-2, H-3, H-4, H-5, H-6); 4.16-
8
9 4.64 (m, 12H, 6-OH); 4.64-5.03 (m, 14H, 12H-1, 2H-1A); 5.41-6.12 (m, 28H, 2-OH, 3-OH), 7.08-7.37 (s,
10
11 2H, NH); δ_{C} (DMSO-d₆, 62.9 MHz): 31.5 (C-6A); 60.7 (C-6); 72.9 (C-5); 73.2 (C-3); 73.9 (C-2); 82.4
12
13 (C-4); 102.8 (C-1); 186.9 (CS); ESI⁺ MS : m/z 2333 [100%, M+Na⁺], 2349 [21%, M+K⁺]. Anal. Calcd
14
15 for C₈₅H₁₄₀O₆₈N₂S.2H₂O : C, 43.52; H, 6.14; O, 47.78; N, 1.19; S, 1.37. Found : C, 43.49; H, 6.59; O,
16
17 47.46; N, 1.31; S, 1.15.
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23 *Formation constants determination*

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26 Evaluation of (β-CD)₂thiourea, β-CD and RAMEB inclusion capacities towards nine target substrates has
27
28 been carried out in water by the use of UV- Visible spectroscopy associated to a competition method,
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30 since this method was well suited to the substrates solubility. First of all, the cyclodextrin / competing dye
31
32 system is characterised by means of the well known titration method. Then, the absorption variations of
33
34 the Cyclodextrin/MO system upon addition of a third molecule (each substrate) constitutes a spectral
35
36 displacement method and allows the determination of formations constants, independently from the
37
38 spectral characteristics of substrates 1-9. For both titration and competition methods, spectra are used in
39
40 their derivative form, in order to avoid any spectral influence of diffraction phenomena (37).
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46
47 Titration method : Experimental conditions were different for each cyclodextrin in order to optimise the
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49 spectral differences between free and complexed forms of MO. For (β-CD)₂thiourea experiments, MO
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51 concentration is fixed to 0.02 mM and (β-CD)₂thiourea concentration is varied from 0 to 0.1mM. Spectra
52
53 were recorded between 430 and 610 nm. For β-CD and RAMEB experiments, MO concentration is fixed
54
55 to 0.1 mM, β-CD concentration is varied from 0 to 0.5mM, RAMEB concentration is varied from 0 to
56
57 0.1mM. Spectra were recorded between 430 and 610 nm. Formation constants are calculated by means of
58
59 an algorithmic treatment described elsewhere (37), assuming a 1:1 stoichiometry.
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3 Competition method : For $(\beta\text{-CD})_2$ thiourea experiments, MO and $(\beta\text{-CD})_2$ thiourea concentrations are
4
5 fixed respectively to 0.02 mM and 0.1mM. Spectra were recorded between 430 and 610 nm. For $\beta\text{-CD}$
6
7 and RAMEB experiments, MO, $\beta\text{-CD}$ and RAMEB concentrations are fixed respectively to 0.1mM,
8
9 0.5mM and 0.1mM. For each cyclodextrin, substrate concentrations were adjusted to give the same
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11 spectral displacement. Formation constants are calculated by means of an algorithmic treatment described
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13 elsewhere (37), assuming a 1:1 stoichiometry. The determination was repeated three times for each
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15 inclusion compounds, and the standard deviation was inferior to 10%.
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21 *Molecular modeling*

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23
24 In order to check if the face to face conformation is possible, the behavior of $(\beta\text{-CD})_2$ thiourea in the
25
26 absence of any substrate was studied by the use of the BOSS 4.2. software (38-39). The z matrix of $(\beta\text{-}$
27
28 $\text{CD})_2$ thiourea was written on the basis of non distorted monomeric $\beta\text{-cyclodextrin}$ with C7 symmetry.
29
30 Such a conformation has been chosen since the C7 symmetry corresponds to the average structure of $\beta\text{-}$
31
32 CD , even if this average is consecutive to successive structures which are more or less distorted. In order
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34 to take into account electrostatic interactions between each cavity, atomic charges have been estimated on
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36 the basis of the electrostatic potentials at the ab initio 6.31G* (Spartan software (40)), by simulating
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38 various fragments of $(\beta\text{-CD})_2$ thiourea.
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45 The relative orientation between the cavities of $(\beta\text{-CD})_2$ thiourea is controlled by four dihedrals (assuming
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47 the planar character of thioureido function). The corresponding potential surface has been investigated by
48
49 a conformational search based on a Monte Carlo method and OPLS force field (41-42), on each rotamer.
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51 The internal structure of each cyclodextrin moiety is kept constant during the conformational search, in
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53 order to concentrate on the relative orientation which will control cooperative phenomena. Thus, only the
54
55 four dihedrals of the spacer are submitted for a conformational search of 100000 successive generated
56
57 structures. Simulations were realised with Powell as minimisation algorithm (convergence : 0.01
58
59 kcal/mol) and with a dielectric constant fixed to 78.3. The conformer identification was done with the
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3 following parameters : RMS criteria, 10.0 Å; internuclear distance criteria 40.0 Å²; energetic criteria, 1
4 kcal/mol.
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7
8 Docking of p-fluorophenol was then realised with the cooperative conformation of (β-CD)₂thiourea. The
9 relative orientation between host and guest was defined by the use of 4 dummy atoms. The cooperative
10 dimer conformation was kept rigid and substrate inclusion was simulated by means of 2 distances, 1 angle
11 and 3 dihedrals, thus covering the six intermolecular degrees of freedom. In each study, 100000
12 successive generated structures were considered. The simulation was realised with conjugated gradient as
13 minimisation algorithm (convergence : 0.01 kcal/mol), with a dielectric constant fixed to 78.3. The
14 stabilisation energy (ΔE, kcal/mol) is expressed as the energetic difference between complexed form and
15 free species.
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28 *Acknowledgement*

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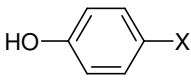

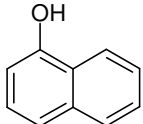
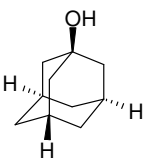
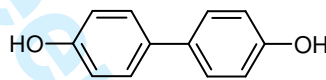
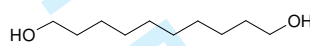
N°	Substrate	Molecular volume (Å ³)
1 : X = F		1 : 123.1
2 : X = Cl		2 : 134.8
3 : X = Br		3 : 141.1
4 : X = I		4 : 150.1
5		135.5
6		169.3
7		187.2
8		215.3
9		244.5

Table 1. Target substrates studied in this work for the estimation of the general inclusion ability of cyclodextrin hosts.

		β -CD		RAMEB		$(\beta$ -CD) ₂ thiourea	
		K	log K	K	log K	K	log K
1	4-fluorophenol	100	2.00	186	2.27	288	2.46
2	4-chlorophenol	275	2.44	646	2.81	955	2.98
3	4-bromophenol	447	2.65	1072	3.03	1738	3.24
4	4-iodophenol	871	2.94	2818	3.45	4074	3.61
5	cyclohexanol	977	2.99	447	2.65	3631	3.56
6	naphtalen-1-ol	1585	3.20	3631	3.56	2570	3.41
7	adamantan-1-ol	34354	4.54	10880	4.04	109648	5.04
8	biphenyl-4,4'-diol	4694	3.67	27126	4.43	14125	4.15
9	decane-1,10-diol	1413	3.15	813	2.91	4467	3.65

Table 2. Formation constants (K/M^{-1}) and logarithmic form of formation constants, for the inclusion compounds formed between substrate 1 to 9 and each host (β -CD, RAMEB and $(\beta$ -CD)₂thiourea). (Standard deviations < 10% for K values).

Figure Captions

Figure 1. Synthesis of $(\beta\text{-CD})_2$ thiourea from amino and isothiocyanato derivatives.

Figure 2. Fit between experimental titration (dots) and theoretical titration (line) for MO/ $(\beta\text{-CD})_2$ thiourea inclusion compound.

Figure 3. Derivatives of the molecular absorption spectra for solutions with 0.02mM MO (a), 0.02mM MO + 0.05mM $(\beta\text{-CD})_2$ thiourea + 5mM p-fluorophenol (b), 0.02mM MO + 0.05mM $(\beta\text{-CD})_2$ thiourea (c).

Figure 4. Correlation between the molar refractivity of halogens and the formation constants observed for p-halogenophenols and $\beta\text{-CD}$, RAMEB and $(\beta\text{-CD})_2$ thiourea.

Figure 5. Values of the complexation indexes for the inclusion compounds formed between substrates 1 to 9 and each host ($\beta\text{-CD}$, RAMEB and $(\beta\text{-CD})_2$ thiourea).

Figure 6. Schematic drawing of the four dihedrals controlling $(\beta\text{-CD})_2$ thiourea conformation.

Figure 7. Most stable structures obtained after conformational search for $(\beta\text{-CD})_2$ thiourea.

Figure 8. Most stable structure obtained after conformational search for the docking of p-fluorophenol inside $(\beta\text{-CD})_2$ thiourea (stick representation for the host, van der Waals surface for the guest).

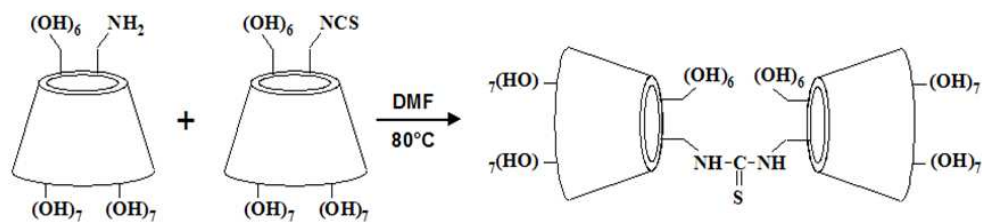


Figure 1. Synthesis of (β-CD)₂thiourea from amino and isothiocyanato derivatives.
215x47mm (104 x 111 DPI)

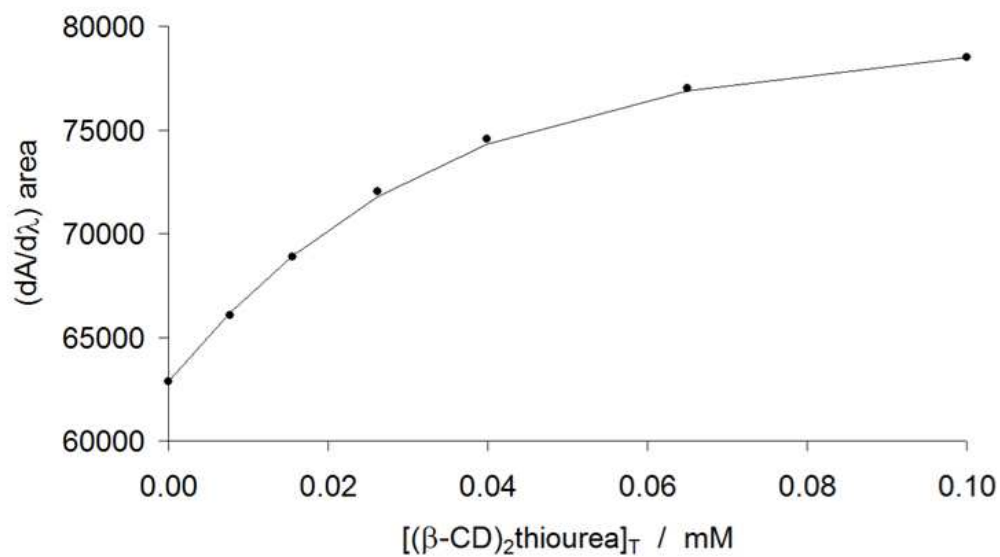


Figure 2. Fit between experimental titration (dots) and theoretical titration (line) for the inclusion compound MO/ $(\beta\text{-CD})_2$ thiourea.
123x70mm (150 x 150 DPI)

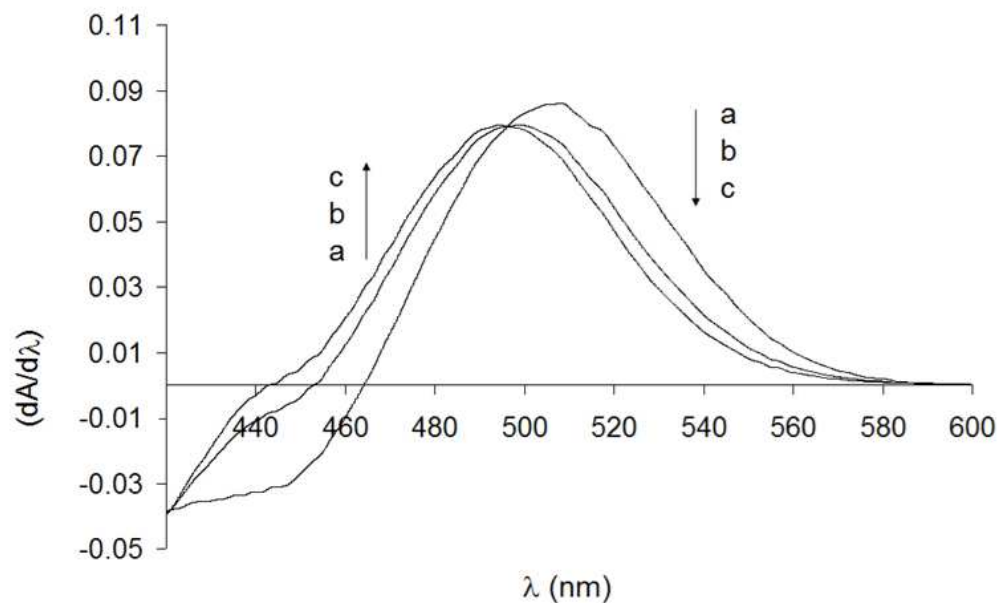


Figure 3. Derivatives of the molecular absorption spectra for solutions with 0.02mM MO (a), 0.02mM MO + 0.05mM (β-CD)2thiourea + 5mM p-fluorophenol (b), 0.02mM MO + 0.05mM (β-CD)2thiourea (c).

127x79mm (150 x 150 DPI)

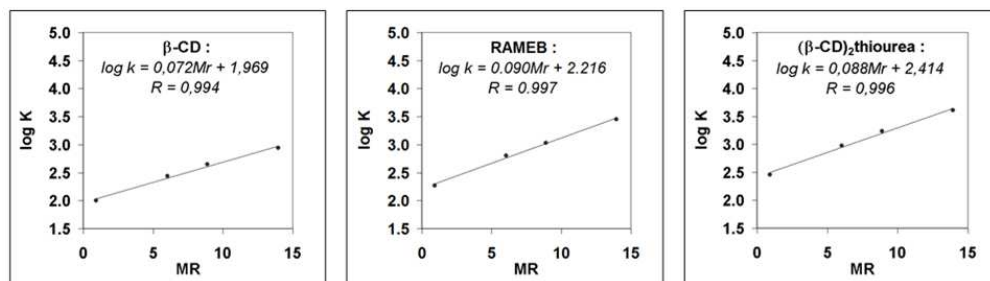


Figure 4. Correlation between the molar refractivity of halogens and the formation constants observed for p-halogenophenols and β -CD, RAMEB and $(\beta\text{-CD})_2$ thiourea.
162x45mm (150 x 150 DPI)

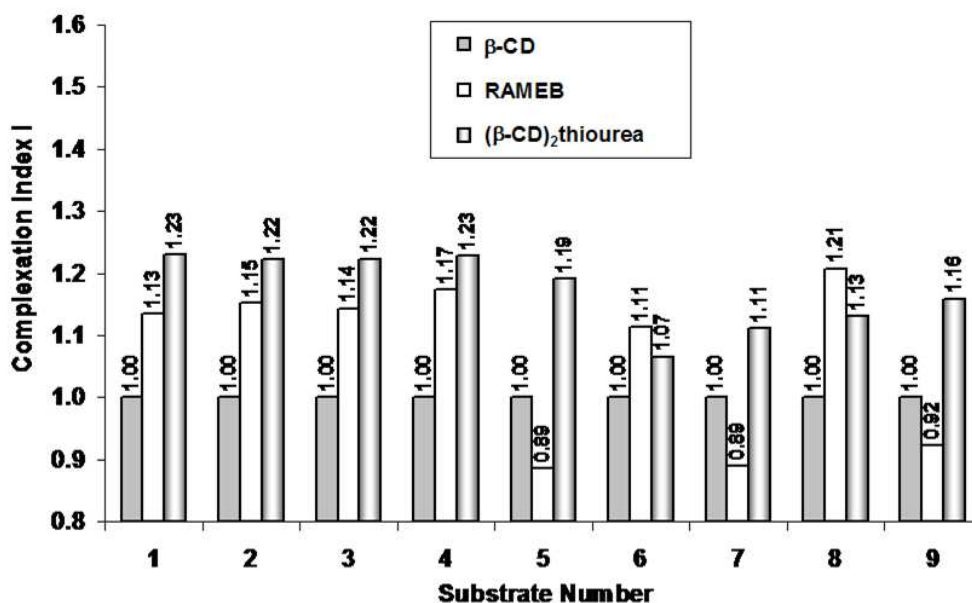


Figure 5. Values of the complexation indexes for the inclusion compounds formed between substrates 1 to 9 and each host (β -CD, RAMEB and $(\beta\text{-CD})_2$ thiourea).
140x85mm (150 x 150 DPI)

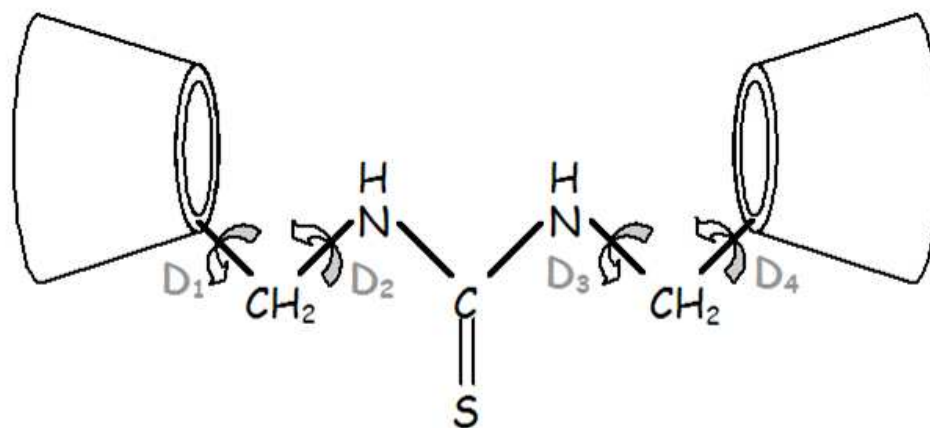
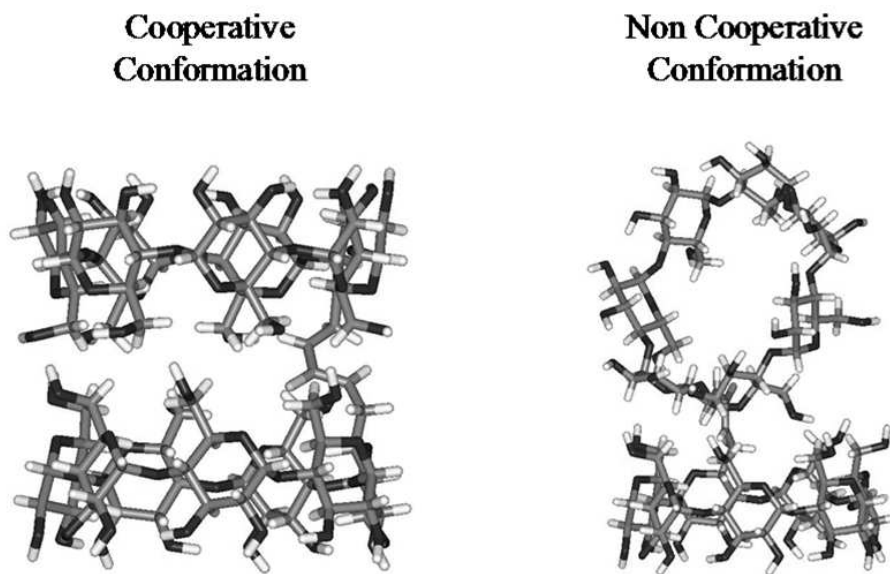


Figure 6. Schematic drawing of the four dihedrals controlling (β-CD)₂thiourea conformation.
108x48mm (150 x 150 DPI)



28 Figure 7. Most stable structures obtained after conformational search for (β-CD)₂thiourea.
29 207x118mm (106 x 108 DPI)

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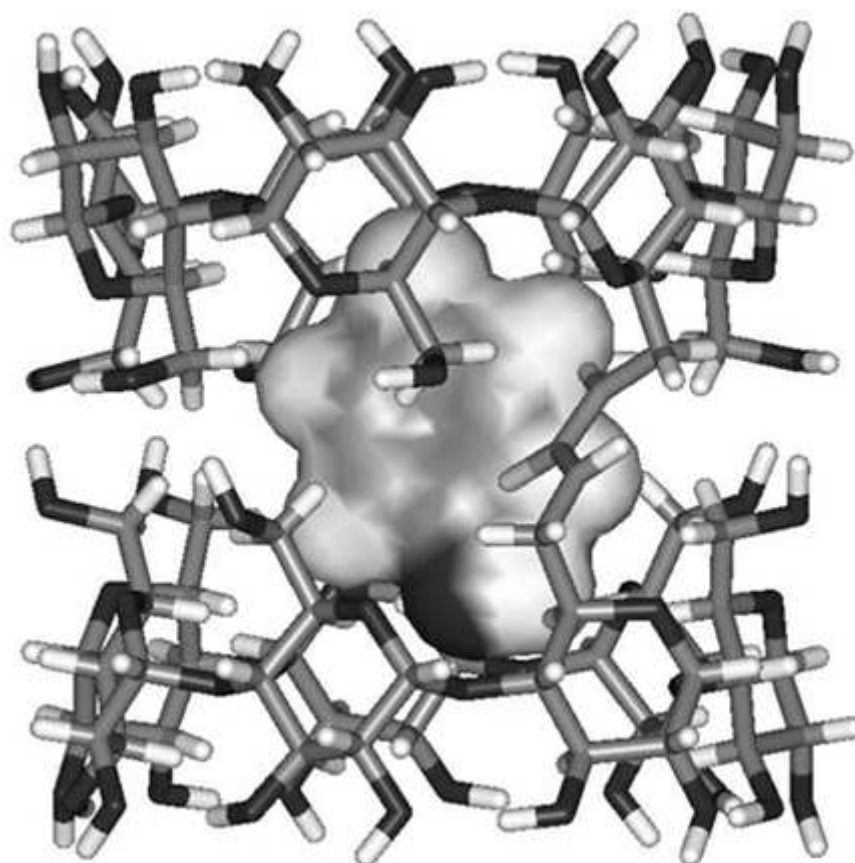


Figure 8. Most stable structure obtained after conformational search for the docking of p-fluorophenol inside (β-CD)2thiourea (stick representation for the host, van der Waals surface for the guest).
168x164mm (67 x 67 DPI)

Only