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

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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 was compared with 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 = 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

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 that perfectly fit to hosts. However, potential applications of β-cyclodextrins rest at the same time not only 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 that 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 smaller 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 to work with *p*-halogenophenols, naphtalen-1-ol, adamantan-1-ol, cyclohexanol, decane-1,10-diol and biphenyl-4,4′-diol (Table 1).

The inclusion ability of this dimer has been studied by means of UV–visible spectroscopy, associated with a competition method based on methyl orange (MO). In order to quantify the contribution of dimerisation, stabilities have then been compared with the capacities of β-cyclodextrin (β-CD) and RAndomly MEthylated β-cyclodextrin (RAMEB), often considered as one of the most complexing monomers (*16–19*). We also propose in this work to carry out a molecular modelling study on the conformation induced by the spacer, since it plays a significant part in the complexing ability. Indeed, if a bis-cyclodextrin is able to accommodate linear species in a cooperative way, one should check that it can direct its two cavities face-to-face.

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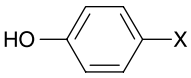
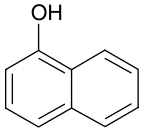
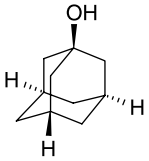
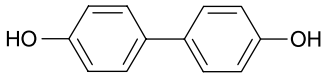
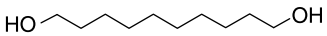
Table 1. Target substrates studied in this work for the estimation of the general inclusion ability of cyclodextrin hosts.

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

Results and discussion

$(\beta\text{-CD})_2$thiourea was prepared in one step from β-CD-NCS and β-CD-NH_2 (Figure 1). These two monomers were placed in equimolar conditions and gave, after purification on sephadex column, 74% of $(\beta\text{-CD})_2$thiourea in one hour and under heating. The structure of this bis(β-cyclodextrin) was confirmed by NMR spectroscopy, mass spectrometry and elemental analysis. This route represents one of the fastest ways to obtain a short tether dimer with an overall yield of 18% from native β-cyclodextrin.

Inclusion capacities were then investigated by UV–visible spectroscopy (^{1}H NMR titration experiments could not be performed since the host solubility was too weak to allow an accurate ^{1}H NMR observation in D_2O). Stability measurements for substrates 1–9 were realised by means of a competition method with MO. Such spectral displacement method requires, before its application to substrates 1–9, the characterisation of cyclodextrins/MO complexes. A titration is thus applied for $(\beta\text{-CD})_2$thiourea (Figure 2) and also for each monomer. The presence of isosbestic points as well as the adjustment of experimental data with the theoretical curves confirms the hypothesis of a 1:1 stoichiometry for the inclusion compounds studied. The formation constant thus determined for $(\beta\text{-CD})_2$ thiourea/MO complex is equal to $6.35 \times 10^4\,M^{-1}$, which is therefore much higher than the value of $2.82 \times 10^3\,M^{-1}$ obtained in the case of β-cyclodextrin, and of $3.01 \times 10^4\,M^{-1}$ in the case of RAMEB.

The complexation thus certainly benefits from the cooperative phenomena often described in bis-cyclodextrins' literature. The value obtained for $(\beta\text{-CD})_2$thiourea/MO inclusion compound is in an intermediate range between the

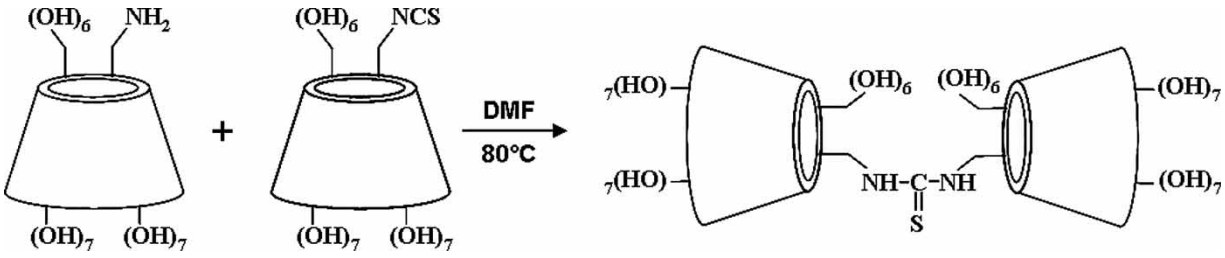


Figure 1. Synthesis of $(\beta\text{-CD})_2$thiourea from amino and isothiocyanato derivatives.

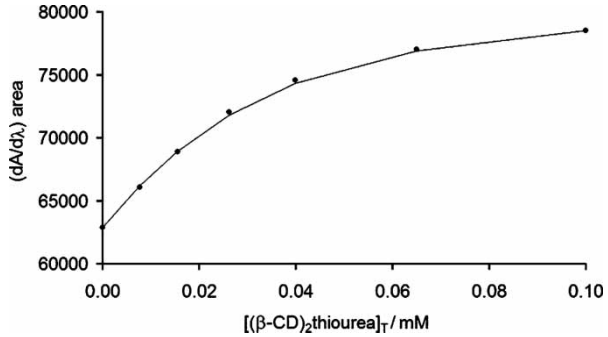


Figure 2. Fit between experimental titration (dots) and theoretical titration (line) for MO/(β-CD)$_2$thiourea inclusion compound.

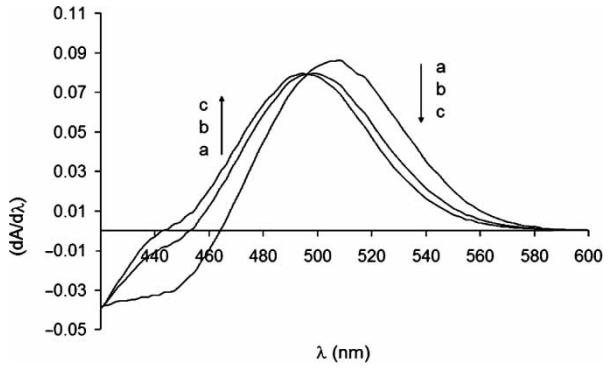


Figure 3. Derivatives of the molecular absorption spectra for solutions with: a, 0.02 mM MO; b, 0.02 mM MO + 0.05 mM (β-CD)$_2$thiourea + 5 mM *p*-fluorophenol and c, 0.02 mM MO + 0.0 5 mM (β-CD)$_2$thiourea.

lowest constants observed for β-CD dimers/MO complexes (mean value for the 15 dimers of references (*20–23*): $1.69 \times 10^4\,M^{-1}$), and the highest (mean value for the two dimers of references (*11*, *24*): $5.97 \times 10^5\,M^{-1}$). In addition, such stability is slightly lower than the corresponding urea dimer ($1.05 \times 10^5\,M^{-1}$), which suggests that sulphur atom is more destabilising than oxygen atom (*25*). This point will be discussed in the modelling section.

Since stabilities towards MO are known, the application of competition method towards substrates 1–9 may be used. An example of spectral variations (in their first derivative form) observed with (β-CD)$_2$thiourea is illustrated in Figure 3. Since competition method does not afford explicit information on stoichiometry, calculated stabilities correspond to apparent formation constants. In the case of (β-CD)$_2$thiourea, existence of 1:2 complexes cannot be *a priori* discarded, especially for small substrates. Nevertheless, each formation constant measurement has been realised for two different concentrations, and no significant differences in the estimated stability have been observed. Since algorithmic treatment is based on 1:1 assumption, we may reasonably think that 1:1 inclusion compounds are predominant. In addition, if 1:2 complexes eventually existed, it has to be underlined that apparent formation constants would be underestimated, since a second guest molecule does not imply any expulsion of MO, and thus any spectral displacement.

Measured stabilities are listed in Table 2 (formation constants are expressed in normal and logarithmic forms). The values of log *K* for β-CD extend from 2.00 (for 4-fluorophenol) to 4.54 (for adamantan-1-ol), and are in agreement with literature data (differences $< 10\%$), at least in the case of already studied complexes (*26–33*).

The range of stability is thus relatively wide, and consequently rather representative of log *K* observed for genuine β-cyclodextrin. The variety of affinities represents indeed a crucial parameter if one tries to describe the general capacities of complexation of a cyclodextrin. Consequently, the choice of our nine target substrates seems suitable. The stabilities observed for (β-CD)$_2$ thiourea extend from 2.46 to 5.04, and are systematically higher than original β-cyclodextrin. In addition, it should be stressed that the increase of stability is, of course, more significant in terms of constant than in its logarithmic form. Such an increase shows that the second cavity does not hinder the complexation process on a steric level but, on the contrary, that cooperative phenomena operate for each substrate studied. This result is all the more

Table 2. Formation constants (K/M^{-1}) and logarithmic form of formation constants for the inclusion compounds formed between substrates 1–9 and each host (β-CD, RAMEB and (β-CD)$_2$thiourea; SDs $< 10\%$ for *K* values).

		β-CD		RAMEB		(β-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	34,354	4.54	10,880	4.04	109,648	5.04
8	Biphenyl-4,4′-diol	4694	3.67	27,126	4.43	14,125	4.15
9	Decane-1,10-diol	1413	3.15	813	2.91	4467	3.65

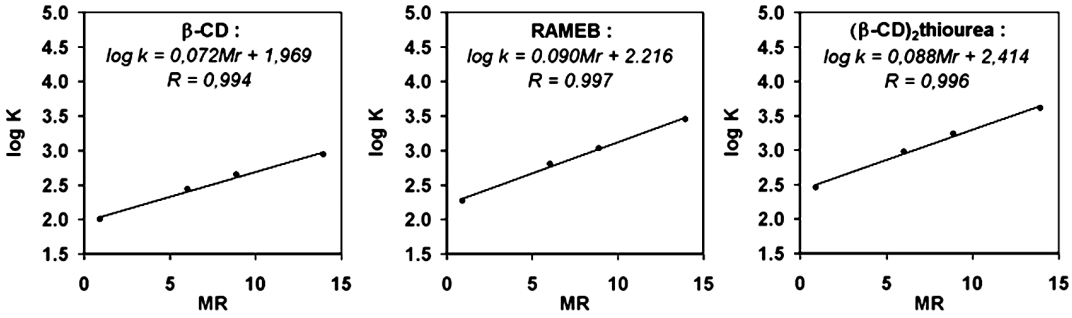


Figure 4. Correlation between the molar refractivity of halogens and the formation constants observed for *p*-halogenophenols and β-CD, RAMEB and $(\beta\text{-CD})_2$thiourea.

interesting as some substrates have a particularly low molecular volume: one could have thought that these compounds would not benefit much from a second cavity. In fact, a strong increase of complexation is even observed for *p*-halogenophenols, whereas their size is similar to the space offered by a simple cavity. If one compares this time $(\beta\text{-CD})_2$thiourea with RAMEB ($\log K$ ranging from 2.27 to 4.43), the advantage of $(\beta\text{-CD})_2$thiourea is less substantial, but effective for most substrates (seven out of nine). This result is rather significant if we consider that methylated β-cyclodextrins are usually recognised as the most complexing monomers.

In order to highlight the important part played by substrate size on a quantitative level, we have correlated $\log K$ observed for 4-halogenophenols with the molar refractivity of each halogen. Obtained results are illustrated in Figure 4. Correlation coefficients are higher than 0.994 for each cyclodextrin, thus showing the existence of structure–affinity relationships. Accordingly, the intercept of each regression illustrates the strength of interactions experimented by the phenolic core, whereas the slope is representative of the sensitivity of complexation phenomena towards substituent size. Thus, $(\beta\text{-CD})_2$thiourea leads to a better encapsulation of aromatic nucleus with an intercept value of 2.414 against 2.216 for RAMEB, and 1.969 for β-cyclodextrin. This bis-cyclodextrin is also more sensitive to the size of halogens than genuine β-CD (slope equal to 0.088 against 0.072), but a little less than RAMEB (0.090). These results are in agreement not only with the fact that $(\beta\text{-CD})_2$thiourea is systematically more complexing than β-CD, but also that biphenyl-4,4′-diol and naphtalen-1-ol are the only guests for which RAMEB is more complexing than $(\beta\text{-CD})_2$thiourea. Indeed, on a steric point of view, these two substrates have a larger size than aromatic monocycles. Since RAMEB is more sensitive to this increase in volume, it leads to higher affinities for such species.

In order to quantify the stability enhancement (independently of absolute values of $\log K$), we chose to express affinities in indexes form (complexation indexes I_{comp}), by dividing each $\log K$ by the corresponding $\log K$ for genuine cyclodextrin:

$$I_{comp} = \frac{\log K_{\text{host}\,j\,/\,\text{substrate}\,i}}{\log K_{\beta\text{–CD/substrate}\,i}}$$

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

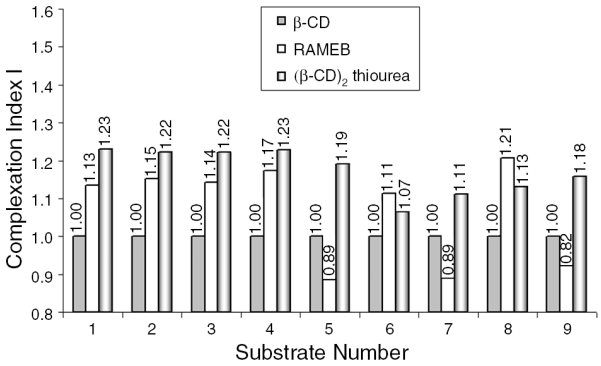


Figure 5. Values of the complexation indexes for the inclusion compounds formed between substrates 1–9 and each host (β-CD, RAMEB and $(\beta\text{-CD})_2$thiourea).

In addition, since substrates 1–9 present relatively linear conformations, cooperative phenomena may take place only if this dimer aligns its two cavities. We thus sought to illustrate the steric possibility of such conformation by modelling the bis-cyclodextrin host alone. The potential surface of (β-CD)$_2$thiourea was investigated by associating molecular mechanics optimised potentials for liquid simulations (OPLS) with stochastic methods. Assuming the planar character of thioureido function, we thus carried out a conformational search by applying a Monte Carlo simulation on the four dihedrals controlling the spacer structure (Figure 6), and this was done for each rotamer.

After 100,000 deformations, two types of conformations are obtained. Cooperative conformations correspond to an alignment of the cavities, whereas the non-cooperative conformations correspond roughly to a perpendicular arrangement. These structures are illustrated by their most stable conformation in Figure 7.

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 with the face-to-face conformation, is probably the major parameter which favours cooperative phenomena, especially for small substrates like 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 an average). One could think that this crown of hydrogen bonds should stabilise cooperative forms. It could also explain the decrease of (β-CD)$_2$thiourea solubility (if compared with genuine β-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 MO/(β-CD)$_2$thiourea complex compared with the MO/(β-CD)$_2$urea

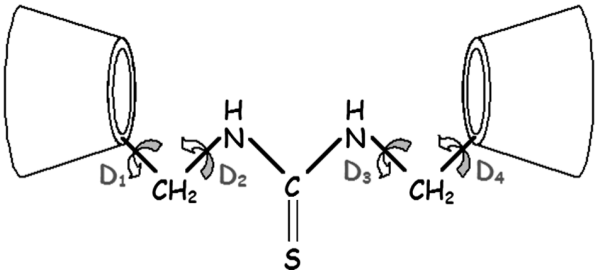


Figure 6. Schematic drawing of the four dihedrals controlling (β-CD)$_2$thiourea conformation.

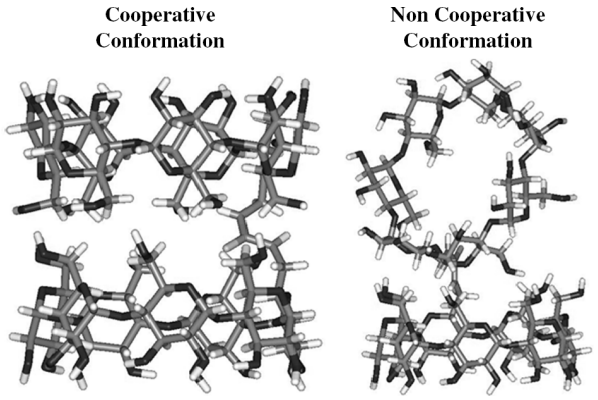


Figure 7. Most stable structures obtained after conformational search for (β-CD)$_2$thiourea.

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, then non-cooperative conformations also appear in our calculations, but with a slightly lower stability (within the limit of 1 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 behaviour 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.

In order to illustrate the expected cooperative phenomena that should be induced by such conformations, we have realised the docking of *p*-fluorophenol, the smallest substrate of our study, into (β-CD)$_2$thiourea, in its face-to-face form. After 100,000 conformations are generated by Monte Carlo docking, the most stable structures (within 1 kcal/mol) are all located at the interface between the two cavities (Figure 8).

The energetic difference between the free and the complexed forms is equal to − 16.01 kcal/mol in favour of the inclusion compound, against − 13.12 kcal/mol if the substrate is located in only one cavity. The simulation thus predicts that a substrate experiences more stabilising van der Waals interactions if it occupies partially both cavities than when it fully occupies one single cavity. This behaviour explains not only the increase of inclusion ability for (β-CD)$_2$thiourea, but also the predominance of 1:1 complexes. Indeed, if the first substrate is strongly bound at the interface, there is not enough space available for a second substrate to be fully encapsulated.

The molecular modelling results thus emphasised that cooperative phenomena should be responsible for the

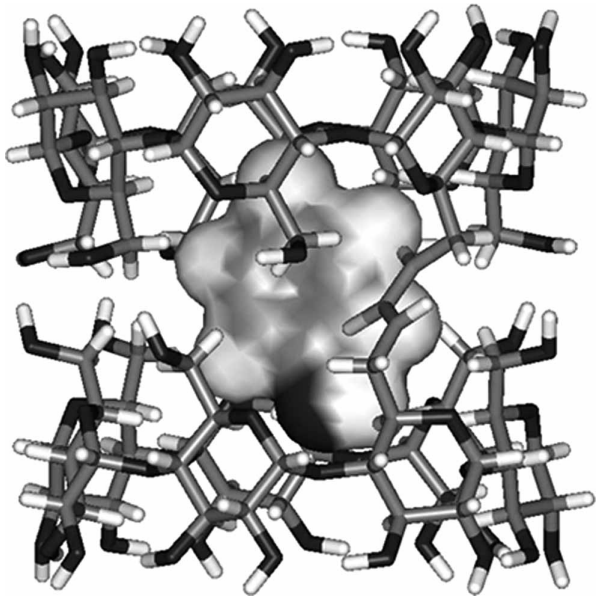


Figure 8. Most stable structure obtained after conformational search for the docking of *p*-fluorophenol inside (β-CD)$_2$thiourea (stick representation for the host and van der Waals surface for the guest).

enhancement of inclusion compounds stability. Accordingly, the strong inter-cavity proximity underlined in our simulations probably plays a determining part.

Conclusion

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

Experimental section

General comments

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

Mass spectrometry spectra were obtained using a Platform II Micromass spectrometer, in positive electrospray ionisation mode and with MeOH:H_2O (50:50) as solvent (cone voltages 110 and 200 V). ^{1}H and ^{13}C NMR spectra were recorded with a Brüker ASPECT 3000 spectrometer; chemical shifts were reported in parts per million (δ). UV–visible spectrometry was performed with a UV–visible Perkin-Elmer Lambda 2S spectrometer. The temperature of the 10 mm cell was kept constant at 298 K by means of a thermostated bath. Elemental analysis was obtained using a Thermoquest CE Instrument CHNS EA 1110. As a result of the low proportion of nitrogen and sulphur atoms in comparison with the limit of detection of the instrumentation, only the percentages of carbon and hydrogen are specified.

(β-CD)$_2$thiourea synthesis

β-CD-NCS (*35*) (1.17 g, 1 mmol) was added to a stirred solution of β-CD-NH_2 (*36*) (1.13 g, 1 mmol) in dry DMF (25 ml). The mixture was heated under N_2 at 80°C for 1 h, then concentrated under reduced pressure (half of the volume) and poured into acetone. The precipitate was isolated by filtration. The crude product (in aqueous solution) was then purified by using two successive Sephadex G25 chromatography columns (1.71 g, 74%). δ_H (dimethyl sulfoxide (DMSO)-d_6, 250 MHz): 3.05–4.16 (m, 84H, H-2, H-3, H-4, H-5, H-6), 4.16–4.64 (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, 2H, NH); δ_C (DMSO-d_6, 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 (C-4), 102.8 (C-1), 186.9 (CS); ESI^+ MS: *m/z* 2333 [100%, M + Na +], 2349 [21%, M + K +]. Anal. calcd for $C_{85}H_{140}O_{68}N_2S.2H_2O$: C, 43.52; H, 6.14; O, 47.78; N, 1.19; S, 1.37. Found: C, 43.49; H, 6.59; O, 47.46; N, 1.31; S, 1.15.

Formation constants determination

Evaluation of (β-CD)$_2$thiourea, β-CD and RAMEB inclusion capacities towards nine target substrates has been carried out in water by the use of UV–visible spectroscopy associated with a competition method, since this method was well suited to the substrates' solubility. First of all, the cyclodextrin/competing dye system was characterised by means of the well-known titration method. Then, the absorption variations of the cyclodextrin/MO system upon the addition of a third molecule (each substrate) constitute a spectral displacement method and allow the determination of formations constants,

independently of the spectral characteristics of substrates 1–9. For both titration and competition methods, spectra are used in their derivative form, in order to avoid any spectral influence of diffraction phenomena (*37*).

Titration method

Experimental conditions were different for each cyclodextrin in order to optimise the spectral differences between the free and the complexed forms of MO. For $(\beta\text{-CD})_2$ thiourea experiments, MO concentration was fixed to 0.02 mM and $(\beta\text{-CD})_2$thiourea concentration was varied from 0 to 0.1 mM. Spectra were recorded between 430 and 610 nm. For β-CD and RAMEB experiments, MO concentration was fixed to 0.1 mM, β-CD concentration was varied from 0 to 0.5 mM and RAMEB concentration was varied from 0 to 0.1 mM. Spectra were recorded between 430 and 610 nm. Formation constants were calculated by means of an algorithmic treatment described elsewhere (*37*), assuming a 1:1 stoichiometry.

Competition method

For $(\beta\text{-CD})_2$thiourea experiments, MO and $(\beta\text{-CD})_2$ thiourea concentrations were fixed to 0.02 and 0.1 mM, respectively. Spectra were recorded between 430 and 610 nm. For β-CD and RAMEB experiments, MO, β-CD and RAMEB concentrations were fixed to 0.1, 0.5 and 0.1 mM, respectively. For each cyclodextrin, substrate concentrations were adjusted to give the same spectral displacement. Formation constants were calculated by means of an algorithmic treatment described elsewhere (*37*), assuming a 1:1 stoichiometry. The determination was repeated three times for each inclusion compounds, and the SD was inferior to 10%.

Molecular modelling

In order to check if the face-to-face conformation is possible, the behaviour of $(\beta\text{-CD})_2$thiourea in the absence of any substrate was studied by the use of the BOSS 4.2. software (*38*, *39*). The *z* matrix of $(\beta\text{-CD})_2$thiourea was written on the basis of non-distorted monomeric β-cyclodextrin with *C*7 symmetry. Such a conformation has been chosen since the *C*7 symmetry corresponds to the average structure of β-CD, even if this average is consecutive to successive structures that are more or less distorted. In order to take into account electrostatic interactions between each cavity, atomic charges have been estimated on the basis of the electrostatic potentials at the *ab initio* 6.31G* (Spartan software (*40*)), by simulating various fragments of $(\beta\text{-CD})_2$thiourea.

The relative orientation between the cavities of $(\beta\text{-CD})_2$ thiourea is controlled by four dihedrals (assuming the planar character of thioureido function). The corresponding potential surface has been investigated by a conformational search based on a Monte Carlo method and OPLS force field (*41*, *42*), on each rotamer. The internal structure of each cyclodextrin moiety is kept constant during the conformational search, in order to concentrate on the relative orientation which will control cooperative phenomena. Thus, only the four dihedrals of the spacer are submitted for a conformational search of 100,000 successive generated structures. Simulations were realised with Powell's as minimisation algorithm (convergence: 0.01 kcal/mol) and with a dielectric constant fixed to 78.3. The conformer identification was done with the following parameters: RMS criteria, 10.0 Å; internuclear distance criteria 40.0 $Å^2$; energetic criteria, 1 kcal/mol.

The docking of *p*-fluorophenol was then realised with the cooperative conformation of $(\beta\text{-CD})_2$thiourea. The relative orientation between the host and the guest was defined by the use of four dummy atoms. The cooperative dimer conformation was kept rigid and the substrate inclusion was simulated by means of two distances, one angle and three dihedrals, thus covering the six intermolecular degrees of freedom. In each study, 100,000 successive generated structures were considered. The simulation was realised with conjugated gradient as minimisation algorithm (convergence: 0.01 kcal/mol), with a dielectric constant fixed to 78.3. The stabilisation energy (ΔE, kcal/mol) is expressed as the energetic difference between complexed form and free species.

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