

Original Research Article

## Inclusion Complexation of Phenol Derivatives with a $\beta$ -Cyclodextrin Based Polymer

JESSICA FLORES<sup>1</sup>, VERÓNICA JIMÉNEZ<sup>2</sup>, JULIO BELMAR<sup>1</sup>, HÉCTOR D. MANSILLA<sup>1</sup>,  
and JOEL B. ALDERETE<sup>1,2,\*</sup>

<sup>1</sup>Departamento de Química Orgánica Universidad de Concepción, Casilla, 160-C, Concepción, Chile; <sup>2</sup>Grupo de Química Teórica y Computacional, Universidad de Concepción, Casilla, 160-C, Concepción, Chile

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### Abstract

The inclusion of four phenol derivatives into a crosslinked  $\beta$ -CD polymer was studied at pH 9. Under these conditions guests are partially deprotonated and  $\beta$ -CD based polymer remains neutral. In order to rationalize the inclusion behavior of these phenolic guests, a theoretical analysis was performed based on weighted global reactivity descriptors and weighted desolvation free energies of the guests. Global reactivity descriptors, defined the frame of Density Functional Theory (DFT), were calculated at B3LYP/6-31g(d) level and desolvation free energies were obtained by using PCM solvation method at the same level of calculation. The theoretical analysis revealed that the inclusion behavior of the phenolic species can be explained in terms of the competition of hydrophobic and charge transfer interactions between the guest molecules and the  $\beta$ -CD based polymer.

### Introduction

Cyclodextrins (CD) are cyclic glucopyranose oligomers, which have a characteristic toroidal shape and well defined cavities. These compounds form host-guest complexes with a large variety of organic and inorganic compounds [1]. Due to a wide range of applications, the study of these inclusion complexes is a very important challenge in both basic and applied research [1–4]. Some important applications of CD are the removal of organic pollutants and their use as substrates for enantiomeric separations [4]. However, most of the potential uses of CD are severely limited by their solubility in water. In order to overcome this drawback, the transformation into an insoluble material is necessary [5, 6]. The synthesis of insoluble modified CD has been performed by two different methods. The first involves the preparation of polymers by cross-linking CD with proper bifunctional agents such as diisocyanates or epichlorohydrin [5–9]. The second consists in coating or grafting CD into moieties of organic polymers [10–11] or silica gel [12–14]. Recently, the synthesis of a new CD based polymer has been reported, which is very effective in the removal of organic molecules from water. This CD based polymer was prepared by cross-linking  $\beta$ -cyclodextrin ( $\beta$ -CD) with hexamethylene diisocyanate, and it has shown a very high affinity towards 4-nitrophenol and toluene [5].

In this work, we report the synthesis and inclusion properties of an insoluble  $\beta$ -CD based polymer (poly- $\beta$ -CD) obtained by cross-linking  $\beta$ -CD with adipoyl chloride.

Four phenol derivatives, whose pK<sub>a</sub> values lie between 7.15 and 10.17, were used as guest molecules in order to determine the influence of their dissociation degrees in the inclusion complexation with the  $\beta$ -CD based polymer at pH 9.

A theoretical analysis based on the calculation of global reactivity descriptors and desolvation free energies for the guests was performed in order to rationalize their inclusion complexation with poly- $\beta$ -CD. According to previous experimental reports [6], this analysis is based on the assumption that the binding sites in the polymer are essentially the  $\beta$ -CD cavities and that the global properties of these sites do not differ significantly from the properties of the isolated  $\beta$ -CD molecule. From this theoretical analysis, charge transfer and hydrophobic interactions are postulated to be the main driving forces in the inclusion complexation of the phenolic species with poly- $\beta$ -CD.

### Experimental section

#### Materials

Adipic acid, thionyl chloride, dimethylformamide and NaOH were purchased from Aldrich, whereas  $\beta$ -CD which was supplied by Calbiochemie.

\* Author for correspondence. E-mail: jalderet@udec.cl

Adipoyl chloride was synthesized from adipic acid by typical reaction with thionyl chloride and was purified by vacuum distillation (b.p = 96–98 °C at 2.5 mmHg). Adipoyl chloride was characterized by using IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy.

Phenol and 4-chlorophenol were purchased from Merck (99.98% of purity), 4-methylphenol was supplied by Sigma (99.97% of purity) and 4-nitrophenol was purchased from Calbiochem (99.98% of purity).

#### Cross-linking of $\beta$ -CD with adipoyl chloride

The synthesis of poly- $\beta$ -CD was performed in dry DMF. Three  $\beta$ -CD/adipoyl chloride molar ratios were assayed 1/6, 1/8 and 1/10. The experiment with 1/6  $\beta$ -CD/adipoyl chloride molar ratio conducted to a partially soluble gel. The 1/10  $\beta$ -CD/adipoyl chloride molar ratio gave a highly crosslinked resin, which showed a low inclusion capacity. Finally, the optimum resin was obtained by using a 1/8  $\beta$ -CD/adipoyl chloride molar ratio. Adipoyl chloride was chosen as linker because of its ease of reaction with  $\beta$ -CD and its solubility in DMF.

The synthetic experiments were carried out in a reaction flask of 250 ml equipped with a magnetic stirrer. In a typical procedure 25.8 g of adipoyl chloride in 10 ml of dry DMF were slowly added to a solution of

20 g of  $\beta$ -CD in 50 ml of dry DMF. During the addition of adipoyl chloride an ice/water bath was used. After that, the reaction mixture was stirred for 3 h. The obtained product was filtered and carefully washed with ethanol and hot water, in order to eliminate residual linker and possible synthesis by products. The synthesis of poly- $\beta$ -CD is shown in Figure 1.

The insoluble product was characterized by FT-IR spectroscopy, solid-state  $^{13}\text{C}$ -NMR spectroscopy, TGA and DSC experiments. FTIR spectrum of poly- $\beta$ CD was obtained from KBr pressed pellets (1% weight) using a NICOLET Magna 550 FTIR spectrometer. Cross-polarization magic angle spinning (CPMAS)  $^{13}\text{C}$ -NMR spectra were performed at 100.61 MHz, using 2 ms spin-lock contact time, magic angle spinning at 4.0 kHz and 5 s recycle delay. TGA and DSC experiment were performed using a STA-625 Thermal analyzer. The sample (3 mg) was heated in sealed aluminum pan under nitrogen flow with a heating rate of 5 °C  $\text{min}^{-1}$ . Figure 2 contains a schematic representation of poly- $\beta$ -CD.

#### Inclusion of phenol derivatives into poly- $\beta$ -CD

For each phenol derivative the time necessary for reaching the inclusion equilibrium was determined by measuring absorbance changes as a function of contact

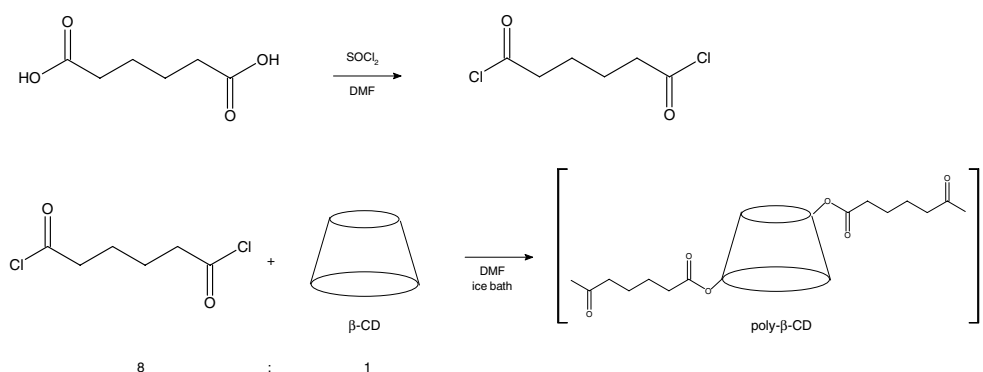


Figure 1. Synthesis of poly- $\beta$ -CD.

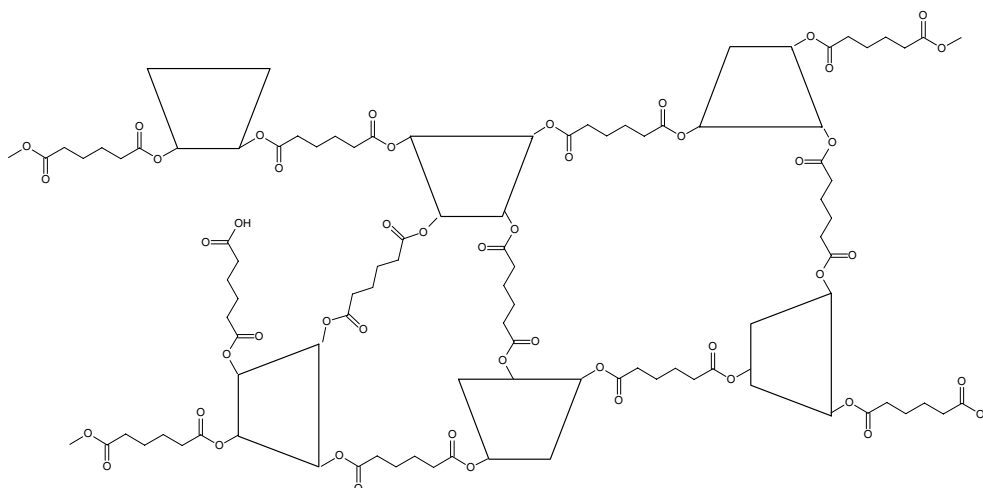


Figure 2. Schematic representation of poly- $\beta$ -CD and ester linkages between  $\beta$ -CD units and adipoyl residues.

time. The corresponding work wavelengths of the guests are reported in Table 2. After 12 hours of contact a plateau was observed for all phenol derivatives. As an example, the concentration changes of 4-chlorophenol due to its inclusion into poly- $\beta$ -CD are shown in Figure 3.

In a typical inclusion experiment, 500 ml of solution of phenol derivatives ranging from  $2.16$  to  $4.60 \times 10^{-5} \text{ M}^{-1}$  were stirred with  $0.500 \text{ g}$  of poly $\beta$ -CD at pH 9 and after the equilibria were reached (24 hours) the concentration of uncomplexed guest was determined by UV spectroscopy.

### Computational aspects

Geometry optimizations and energy calculations for neutral and anionic phenol derivatives were performed using Density Functional Theory (DFT) methods at B3LYP/6-31 g(d) level using Gaussian 94 W program [15, 16]. Electronic chemical potential and chemical hardness, both global reactivity descriptors for the isolated guests, were calculated by using approximated expressions derived in the frame of Density Functional Theory [17]. Desolvation free energies were calculated for both neutral and anionic guests by using PCM solvation method [18] at B3LYP/6-31 g(d) level.

Weighted global reactivity descriptors and weighted desolvation free energies were calculated for each phenol derivative, since under experimental conditions (pH 9) they are partially deprotonated and their neutral and anionic forms coexist in solution. The weighted properties of the guests were calculated from the individual values of their neutral and anionic forms and by calculating their percentage of dissociation at pH 9 from the corresponding dissociation constants [19].

The geometry of  $\beta$ -CD was fully optimized at HF/6-31g(d) level of calculation and the obtained structure was used in a single point calculation at B3LYP/6-31g(d). Global reactivity descriptors for the isolated  $\beta$ -CD were obtained from the latter calculation.

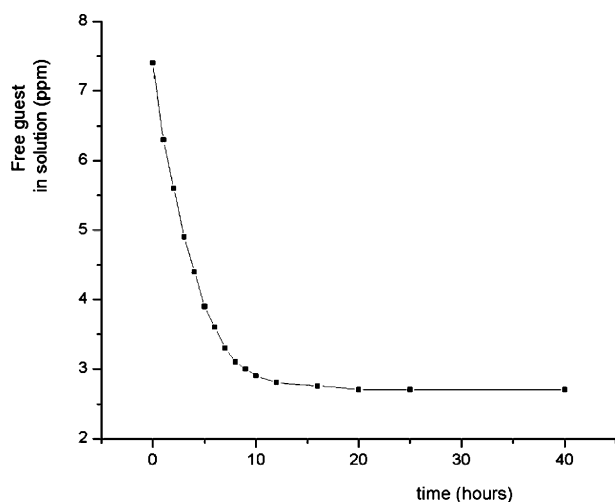


Figure 3. Concentration changes of *p*-chlorophenol due to inclusion into poly- $\beta$ -CD.

## Results and discussion

### Characterization of poly- $\beta$ -CD

On the DSC thermogram of  $\beta$ -CD two endothermic peaks are observed (Figure 4a). The first one, located between  $50$  and  $150 \text{ }^\circ\text{C}$ , is associated to  $\beta$ -CD dehydration and corresponds to a loss of mass of  $\sim 13\%$  in the thermogravimetric curve which is in accordance to the loss of crystallization water from  $\beta$ -CD [20]. The second DSC peak at  $322 \text{ }^\circ\text{C}$  is associated to a  $\sim 78\%$  of weight loss which indicates  $\beta$ -CD decomposition [20].

Thermogram of poly- $\beta$ -CD shows three endothermic peaks, associated to polymer dehydration, adipoyl chains decomposition and bulk polymer decomposition, respectively. The first peak, located between  $50$  and  $200 \text{ }^\circ\text{C}$ , corresponds to a  $\sim 10\%$  of weight loss on the thermogravimetric curve. The second peak is observed between  $200$  and  $240 \text{ }^\circ\text{C}$  with an additional weight loss of  $\sim 10\%$ . The last decomposition peak is observed between  $250$  and  $450 \text{ }^\circ\text{C}$  and corresponds to  $\sim 60\%$  of weight loss. This peak of bulk decomposition has an inflection on DSC thermogram at  $307 \text{ }^\circ\text{C}$ . This decomposition temperature is lower than in native  $\beta$ -CD ( $322 \text{ }^\circ\text{C}$ ).

Pure  $\beta$ -CD FTIR spectrum displays characteristic bands for OH stretching centered at  $3380 \text{ cm}^{-1}$ , whereas pure adipoyl chloride spectrum shows a carbonyl characteristic band at  $1796 \text{ cm}^{-1}$ . Poly- $\beta$ -CD spectrum displays the following IR bands:  $3430 \text{ cm}^{-1}$  (broad, OH stretching),  $1730 \text{ cm}^{-1}$  (C=O stretching) and  $1029 \text{ cm}^{-1}$  (typical C–O vibrations). Since careful wash was performed in order to eliminate residual linker, the IR spectrum indicates the presence of an ester bond in the structure of poly- $\beta$ -CD. This result is consistent with solid state  $^{13}\text{C}$  CP/MAS NMR spectroscopy (Table 1), which shows a signal at  $180 \text{ ppm}$ , characteristic of an ester linkage between  $\beta$ -CD and adipoyl residues. Chemical shifts observed in the  $\beta$ -CD solid state  $^{13}\text{C}$  CP/MAS NMR spectrum are in agreement with previously reported data [21].

### Inclusion results

Under the experimental conditions assayed both the anionic and the neutral form of the guests coexist in solution. The dissociation degrees of the phenols were calculated from their reported dissociations constants as is shown in Table 2. At pH 9 cyclodextrin remains neutral, since the pKa of its hydroxyl groups is  $12.1$  [1].

Inclusion results are summarized in Table 2. It can be seen that the percentage of inclusion at pH 9 is directly related to the dissociation degree of each species, with the exception of 4-nitrophenol. In general, the percentage of inclusion in poly- $\beta$ -CD follows the same trend observed in native  $\beta$ -CD, in which 4-chlorophenol has the largest affinity upon complexation [22] This results suggest that the binding sites in the polymer are mainly the  $\beta$ -CD cavities, in accordance with previous experimental reports [6].

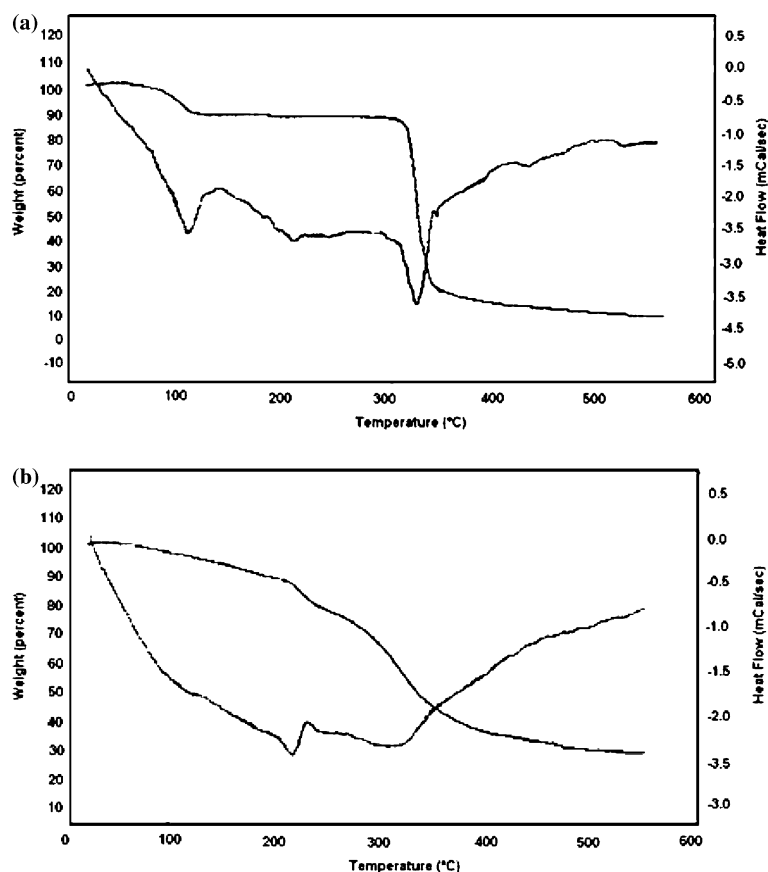


Figure 4. TGA and DSC curves for (a)  $\beta$ -CD and (b) poly- $\beta$ -CD.

In order to rationalize the inclusion behavior in poly- $\beta$ -CD it can be assumed that the properties of the binding sites in the polymer do not differ significantly from the properties of the native  $\beta$ -CD. Therefore an approximate model for the inclusion complexation in poly- $\beta$ -CD can be obtained by considering the interaction

Table 1.  $^{13}\text{C}$  CP/MAS NMR spectra of poly- $\beta$ -CD and  $\beta$ -CD. Carbons in  $\beta$ -CD units are labeled according to the usual numbering of glucose units

	C <sub>1</sub>	C <sub>4</sub>	C <sub>2,3,5</sub>	C <sub>6</sub>	-CH <sub>2</sub> - (adipoyl chains)	-CH <sub>2</sub> - (adipoyl chains)	C=O (adipoyl chains)
$\beta$ -CD	105	85	76	61			
Poly- $\beta$ -CD	105	85	74	65	35	25	180

between the isolated  $\beta$ -CD and guests. This simplified model should provide some useful information for the understanding of the complexation phenomena between poly- $\beta$ -CD and the phenolic guests under study.

Before analyzing the specific aspects of these complexation equilibria it is necessary to consider that inclusion phenomena are composite processes, where several interactions can take place. It has been customary considered that the main interactions involved in complexation processes are electrostatic, van der waals, hydrophobic and charge transfer interactions. Among these intrinsic forces, hydrophobic interactions have been commonly recognized as the main factors involved in the inclusion complexation with CD [23]. On the other hand, charge transfer interactions have been mentioned as driving forces in the inclusion complexation of some anionic guests that show higher affinities

Table 2. Inclusion properties of phenol derivatives into poly $\beta$ -CD in aqueous solution at pH 9. C<sub>ini</sub> and C<sub>eq</sub> correspond respectively to the initial and equilibrium concentrations of the guests

Species	$\lambda$ (nm)	C <sub>ini</sub> $\times 10^5$ (M)	C <sub>eq</sub> $\times 10^5$ (M)	Loading (mmol g <sup>-1</sup> )	% Phenol included	pK <sub>a</sub>	% anion at pH 9
4-methyl phenol	213	3.19	1.87	0.0274	43	10.17	6
Phenol	235	4.40	1.61	0.0558	63	9.89	11
4-chlorophenol	245	4.60	0.48	0.0815	90	9.18	40
4-nitrophenol	401	2.16	0.66	0.0149	69	7.15	99

with the CD cavity than their neutral species [24]. According to the experimental findings of the present study it can be proposed a competition between charge transfer and hydrophobic interactions in the complexation processes between the phenolic guests and poly- $\beta$ -CD.

In order to determine the role of charge transfer interactions in the complexation of phenol derivatives with poly- $\beta$ -CD some DFT global reactivity descriptors were obtained with the aid of computational calculations at B3LYP/6-31g(d) level. On the other hand desolvation free energies were also calculated as a measure of hydrophobic interactions.

Global reactivity descriptors provide useful information about the chemical behavior of atoms and molecules. Among them, the electronic chemical potential and chemical hardness are the most frequently employed, since they can be directly related to chemically interpretable phenomena [25]. The electronic chemical potential  $\mu$  can be seen as the tendency of an atom or molecule to donate electron density to another system. The larger the electronic chemical potential, the easier the charge transfer will be. On the other hand, chemical hardness  $\eta$  can be seen as the resistance of an atom or molecule to distort its electron cloud. Hence, while a high electronic chemical potential favors charge transfer interactions, a large chemical hardness acts against these processes.

We have employed the following approximate expressions [17] to evaluate the electronic chemical potential and chemical hardness:

$$\mu \cong -\frac{e_{\text{HOMO}} + e_{\text{LUMO}}}{2} \quad (1)$$

$$\eta \cong \frac{e_{\text{LUMO}} - e_{\text{HOMO}}}{2} \quad (2)$$

where,  $e_{\text{HOMO}}$  and  $e_{\text{LUMO}}$  represent the energy of the frontier molecular orbitals. Due to the inconsistency of Equation (2) for anions [26] the chemical hardness of these species was calculated using the following relationship introduced by Komorowski [26]:

$$\eta_b = \frac{e_{\text{LUMO}} - e_{\text{HOMO}-1}}{2} \quad (3)$$

Finally, chemical softness  $S$  is defined as the inverse of chemical hardness according to the following expression:

$$S = \frac{1}{\eta} \quad (4)$$

According to the previous arguments global reactivity descriptors were calculated for the isolated neutral and anionic guests and for the isolated  $\beta$ -CD molecule, since it has been assumed that the nature of the inclusion sites in the polymer do not differ significantly from native  $\beta$ -CD.

In the case of phenolic guests it is necessary to notice that they are partially dissociated under experimental conditions, therefore weighted global reactivity descriptors must be obtained by taking into account the corresponding dissociation degrees of each species.

Table 3 shows the calculated global reactivity descriptors for isolated  $\beta$ -CD and isolated phenols and the weighted calculated values for the guests at experimental conditions.

According to their weighted electronic chemical potentials guests can be arranged as follows:

$$\begin{array}{lcl} 4\text{-nitrophenol} & > & 4\text{-chlorophenol} \\ & > & \text{phenol} & > & 4\text{-methylphenol} \\ \mu = 1.91 \text{ eV} & & & & \mu = -1.12 \text{ eV} \\ \mu = -2.28 \text{ eV} & & & & \mu = -2.48 \text{ eV} \end{array}$$

This order is consistent with the percentage of inclusion experimentally determined

$$\begin{array}{lcl} 4\text{-chlorophenol} & > & 4\text{-nitrophenol} \\ & > & \text{phenol} & > & 4\text{-methylphenol} \\ 90\% & & & & 69\% \\ 63\% & & & & 43\% \end{array}$$

with the exception of 4-nitrophenol. Therefore, this should imply that charge transfer interactions are participating in the inclusion complexation of the phenolic guests with poly- $\beta$ -CD. The weighted electronic chemical potentials obtained for the guests are lesser that the corresponding value of the isolated  $\beta$ -CD, showing their stronger electron acceptor ability compared to it. Therefore charge transfer between species should occur from  $\beta$ -CD to the phenolic guests.

On the other hand, according to their weighted chemical softness, phenol derivatives can be arranged in the following order:

$$\begin{array}{lcl} 4\text{-nitrophenol} & > & 4\text{-chlorophenol} \\ & > & 4\text{-methylphenol} & > & \text{phenol} \\ S = 0.48 \text{ eV}^{-1} & & & & S = 0.36 \text{ eV}^{-1} \\ S = 0.35 \text{ eV}^{-1} & & & & S = 0.34 \text{ eV}^{-1} \end{array}$$

From Table 3 it can be seen that 4-chlorophenol, 4-methylphenol and phenol have similar values of

Table 3. Global reactivity descriptors for isolated guests and  $\beta$ -CD and weighted global reactivity descriptors for the guests under experimental conditions (pH 9). The electronic chemical potential,  $\mu$  (eV), chemical hardness,  $\eta$  (eV), softness,  $S$  ( $\text{eV}^{-1}$ ) were calculated at B3LYP/6-31G\* level

	4-methylphenol			Phenol			4-chlorophenol			4-nitrophenol			$\beta$ -CD
	Neutral	Anion	Weighted	Neutral	Anion	Weighted	Neutral	Anion	Weighted	Neutral	Anion	Weighted	
$\mu$	-2.84	2.84	-2.48	-2.96	2.99	-2.28	-3.24	2.10	-1.12	-4.57	2.00	1.91	2.83
$\eta$	2.91	2.71	2.90	2.99	2.74	2.96	2.84	2.69	2.78	2.35	2.09	2.09	4.17
$S$	0.34	0.37	0.35	0.33	0.36	0.34	0.35	0.37	0.36	0.42	0.48	0.48	0.24

weighted chemical softness, hence they should oppose to charge transfer in the same extension. On the other hand, according to the large weighted softness of 4-nitrophenol one should expect that this species has the largest tendency to favor charge transfer interactions and therefore it should be expected that 4-nitrophenol has a larger inclusion percentage than the other guests. Since experimental observations show that 4-chlorophenol is the guest with the largest inclusion percentage, then one can infer that another interaction different from charge transfer is taking place in the inclusion complexation of phenol derivatives with poly- $\beta$ -CD.

Table 4 shows the calculated desolvation free energies of anionic and neutral phenol guests and their corresponding weighted values at pH 9. Desolvation free energies of anionic species are higher than for neutral ones, in accordance with the expected increasing hydrophobicity going from anionic to neutral species. The ordered weighted desolvation free energies show that 4-nitrophenol is the least hydrophobic species, since it has the highest desolvation free energy among the phenolic guests under study

$$\begin{array}{rcl}
 4 - \text{nitrophenol} & > & 4 - \text{chlorophenol} \\
 > \text{phenol} & > & 4 - \text{methylphenol} \\
 \Delta G = 52.24 \text{ kcal mol}^{-1} & & \Delta G = 28.69 \text{ kcal mol}^{-1} \\
 \Delta G = 15.43 \text{ kcal mol}^{-1} & & \Delta G = 10.60 \text{ kcal mol}^{-1}
 \end{array}$$

If only hydrophobic interactions are taken into account it can be expected that the higher the hydrophobicity of guests, the higher the affinity with poly- $\beta$ -CD. Therefore, 4-nitrophenol should be the guest with the lowest inclusion percentage. However, the included amount of 4-nitrophenol is not the lowest, but lies between 4-chlorophenol and phenol.

This result suggest that the trend observed in the inclusion complexation of phenolic guest with poly- $\beta$ -CD can not be explained in terms of a single interaction, but by the competition of both charge transfer and hydrophobic interactions between host and guests. Global reactivity descriptors analysis showed that charge transfer interaction participate in the inclusion of phenolic species with poly- $\beta$ -CD. However, to get a better description of these inclusion processes it is necessary to consider the influence of hydrophobic interactions, specially in the case of totally dissociated species, where desolvation free energies become larger.

Table 4. Desolvation free energies for neutral and anionic species calculated at b3lyp/-31 g(d) level and weighted desolvation free energies calculated from reported dissociation constants for each phenol derivative at pH 9. All values are given in kcal mol<sup>-1</sup>

Guest	Neutral	Anion	Weighted
4-methylphenol	6.91	65.12	10.60
Phenol	8.87	66.36	15.43
4-chlorophenol	7.96	60.06	28.69
4-nitrophenol	8.93	52.85	52.24

## Concluding remarks

The synthesis of poly- $\beta$ -CD was performed by crosslinking of  $\beta$ -CD and adipoyl chloride. The obtained product is a resin that retains the inclusion properties of native  $\beta$ -CD. The inclusion behavior of several phenol derivatives in poly- $\beta$ -CD at pH 9 was studied. A theoretical analysis based on weighted global reactivity descriptors and weighted desolvation free energies showed that the inclusion complexation of the phenolic guest with poly- $\beta$ -CD can be rationalized in terms of the simultaneous cooperation of charge transfer and hydrophobic interactions between host and guests.

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