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# Correlation Models for the Inclusion Complexation of Aliphatic Compounds with α- and β-Cyclodextrins

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# Correlation Models for the Inclusion Complexation of Aliphatic Compounds with α- and β-Cyclodextrins

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**Complexation free energies of aliphatic compounds with α- and β-cyclodextrins were analyzed in terms of theoretical and empirical parameters that account for the role of van der Waals, hydrophobic, electrostatic, charge transfer interactions and steric effects. Two multivariate correlations were obtained to describe the inclusion behavior of 73 aliphatic guests in α-cyclodextrin and 37 species in β-cyclodextrin. For the first time, these models have dealt with the inclusion complexation of neutral, anionic and cationic aliphatic species. Results indicate that the most important factor involved in the inclusion of aliphatic guests is van der Waals interaction, whereas charge transfer appears as a key factor that differentiates the inclusion complexation between neutral and ionic species. Additionally, steric effects affect the inclusion complexation with α-cyclodextrin, whose smaller cavity is subjected to steric hindrance when there are voluminous guests.**



*Keywords*: Aliphatic compounds; Correlation model; Cyclodextrins; van der Waals interactions

## INTRODUCTION

Cyclodextrins are cyclic oligomers of α-D-glucose formed by the action of certain enzymes on starch [1]. The most important cyclodextrins are those composed by six, seven and eight glucose monomeric units and are named α-, β- and γ-cyclodextrins, respectively. Among them, α-cyclodextrin and β-cyclodextrin are the most known and widely employed (Fig. 1). The three-dimensional shape of cyclodextrins is similar to a truncated cone, where all hydroxyl groups point outside the molecule, conferring a highly polar character to the molecular exterior. On the other hand, glycosidic linkages delimit the molecular cavity and are responsible for its hydrophobic character. One of the most important features about cyclodextrins is their ability to form inclusion complexes with a large variety of organic and inorganic compounds, referred to as "guests". Inclusion complexes are stabilized by guest penetration into cyclodextrin's well-defined molecular cavity [1]. Due to their ability to form inclusion complexes, cyclodextrins have been the subject of extensive experimental and theoretical research and have been employed in a wide range of applications [1–4].

Both the determination of inclusion association constants and the identification of the forces involved in complexation phenomena are central issues in the field of cyclodextrin research. Usually, molecular inclusion is not possible with a single interaction, but rather occurs through the simultaneous cooperation of several weak forces [5–7]. Although, the nature and the specific role of each interaction have yet to be well stated, it is customarily accepted that cyclodextrin's high affinity to organic non-polar guests arises due to the hydrophobic character of their molecular cavity [1–4]. In this sense, the most important contributions to complex stabilization should be originated from the penetration of the guest's hydrophobic fragment into the cyclodextrin cavity and the organic guest's dehydration.

Even though this general idea applies in most cases, it cannot explain all energetic trends and orientation features found in several inclusion complexes, such as the case of aliphatic alcohols, amines and carboxylic acids, whose association constants are larger than those corresponding to alkanes, violating the general rule of hydrophobicity as the key factor governing the

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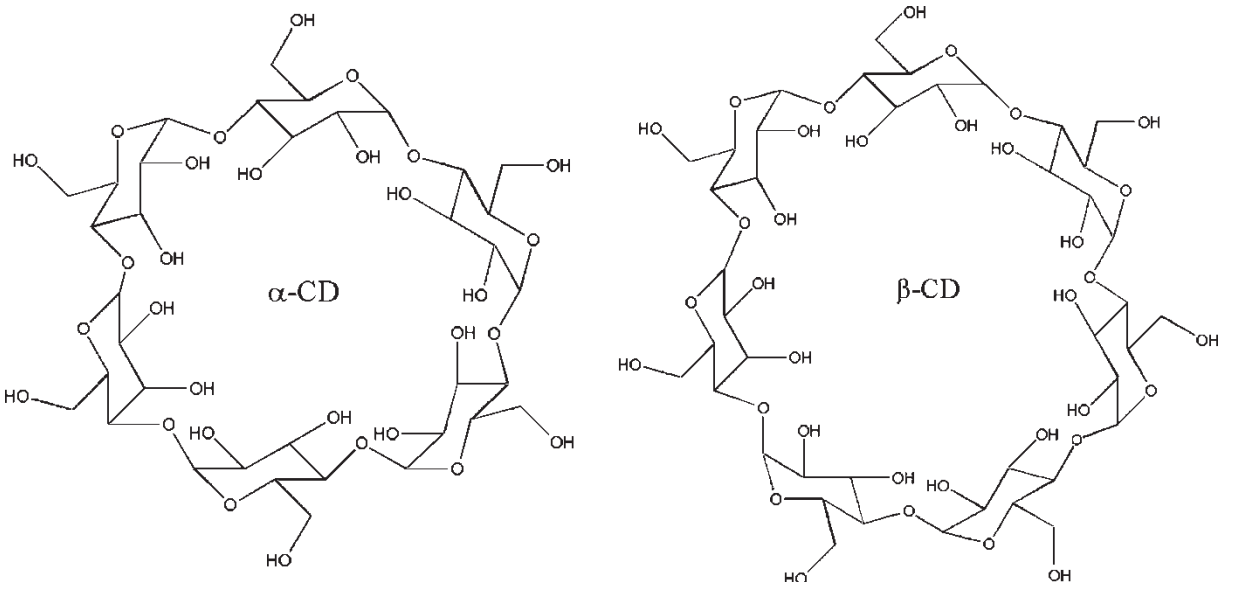


FIGURE 1 Structure of α-cyclodextrin and β-cyclodextrin.



inclusion complexation with cyclodextrins. In addition, it has been observed that aliphatic carboxylates and chlorhydrates result in association constants similar to those observed for their corresponding neutral species [8]. This behavior is not expected considering the hydrophilic character of ionic guests. Up to now, those unusual cases have been customarily considered as exceptions to general cyclodextrin performance.

To develop a better understanding of inclusion complexation phenomena, several authors have developed quantitative correlation models that account for inclusion complexation constants or free energies in terms of molecular descriptors related to the guests' structural and molecular properties [9–12]. The main achievements of these models have been to find appropriate relationships between the employed molecular descriptors and the nature of host–guest interactions. Most reported correlation models deal with the inclusion of neutral aromatic guests in both α- and β-cyclodextrin [8–9]. On the other hand, the inclusion complexation with aliphatic species has only been attained by Suzuki [11] and Katritzky [12], who incorporated nearly 20 aliphatic molecules into their calibration sets, composed by 102 and 218 organic guests for α- and β-cyclodextrin, respectively. In spite of these achievements, the reported models have neglected the inclusion complexation of a large variety of aliphatic guests, including neutral and ionic species. Therefore, the search for a quantitative model that can account for the complexation of these species still needs to be developed.

In the present work, we propose the building of correlation models for the inclusion complexation of a large set of neutral and ionic aliphatic compounds in terms of easily interpretable molecular descriptors, which provide insights into physicochemical phenomena involved in the inclusion complexation of aliphatic species.

## DATA SETS AND COMPUTATIONAL ASPECTS

The inclusion association constants of 73 aliphatic compounds with α-cyclodextrin and 37 aliphatic compounds with β-cyclodextrin in aqueous solution were selected from experimental reports compiled by Connors [8]. In the case of ionic species, special care was taken in order to select association constant determined under pH conditions where cyclodextrins remain essentially neutral. A set of empirical and theoretical descriptors was chosen in order to build multi-linear correlation models that account for hydrophobic, electrostatic, Van der Waals, charge transfer and steric effects.

Theoretical descriptors were obtained from *ab initio* calculations at HF/6-31G(d) level, with Gaussian 98W package of programs [13]. Isolated guests were optimized in gas phase and these structures were employed to calculate the molecular polarizability ($\alpha_H$), the maximum absolute charge located on a guest atom ($Q_{\max}$), and the molecular dipole moment ($\mu_H$), where $\alpha_G$ was computed as the average of the diagonal elements of the polarizability tensor, $Q_{\max}$ was obtained from Mulliken population analysis, and the magnitude of $\mu_H$ as reported in Debye.

In addition, a modified zero-order connectivity index ($\chi^*$) was employed to account for the role

of steric effects on the inclusion complexation with branched aliphatic species. This index was calculated according to the definition provided in the Results and Discussion section.

A charge transfer parameter (ΔN) defined in the frame of Density Functional Theory (DFT) [14,15] was employed to describe the role of charge transfer interactions on the inclusion complexation with aliphatic guests. ΔN was calculated from the isolated structures of hosts and guests, employing gas phase calculations at HF/6-31g(d) level, assuming that errors due to the neglect of solvation effects can be overcome by performing studies over structurally related compounds [16]. The following operational definitions were employed in the calculation of ΔN.

$$\Delta N = -\frac{(\mu_H - \mu_G)}{(\eta_H + \eta_G)} \quad (1)$$

$$\mu = \frac{(e_{HOMO} + e_{LUMO})}{2} \quad (2)$$

$$\eta = \frac{(e_{LUMO} - e_{HOMO})}{2} \quad (3)$$

where H and G represent host and guest molecules, respectively.

Finally, the octanol–water partition free energy ($\Delta G_{OW}$) was selected as an empirical descriptor for the hydrophobic character of the aliphatic guests under study. The value of $\Delta G_{OW}$ was calculated from experimental reports of octanol–water partition constants [17,18].

Subsequently, calculated and empirical molecular descriptors were employed to build multi-linear correlation models that account for the inclusion complexation free energies of 73 and 37 aliphatic compounds with α- and β-cyclodextrin, respectively. Correlation models were built using the classical least-squares method [19]. Before constructing models, any significant statistical correlation among the employed molecular descriptors was discarded in order to ensure the statistical relevance of the obtained results.

The most relevant regression parameters were selected using a sequential procedure based on the calculation of the squared linear correlation coefficient and the F-test. The strategy starts by building a single variable model with the molecular descriptor that provides the largest correlation coefficient $r^2$. Then, $r^2$ and F are evaluated for all the possible combinations of two regression parameters, maintaining the first selected molecular descriptor. The second regression parameter is the one that maximizes the values of $r^2$ and F. If F is less than the critical value ($p = 0.05$), the procedure stops and the single variable model is chosen as the best correlation. If F is larger than the critical value, the second parameter is added to the correlation. Then, $r^2$ and F are successively calculated for the incorporation of each one of the remaining variables and so on until no other variable can be considered. According to this procedure, significance of the regression parameters can be directly inferred from the order of the molecular descriptors' incorporation in the correlation. Once the model has been built, the squared correlation coefficient ($r^2$) and the cross-validation regression coefficient ($r^2_{cv}$) were employed to evaluate its statistical quality.

The cross-validation regression parameter ($r^2_{cv}$) reflects the stability of the obtained regression model by focusing on the sensitivity of the model to the elimination of any single data point. Briefly, for each data point, the regression coefficients are recalculated with the same descriptors but for the data set without this point. The obtained regression is used to predict the value of the eliminated point, and the set of estimated values calculated in this way is correlated with the experimental values.

## RESULTS AND DISCUSSION

### Descriptive Analysis on the Inclusion Complexation of Aliphatic Species with Cyclodextrins

Before building correlation models, we analyzed the role of several factors that should be involved in the inclusion complexation of aliphatic species. Based in this analysis, we identified a suitable set of molecular descriptors that account for the inclusion complexation free energies of a large group of aliphatic species.

#### *Guest's Hydrophobicity*

As pointed out by Rekharsky *et al.*, the inclusion free energies of aliphatic compounds increase in absolute value with the number of carbon atoms in the hydrocarbon chain. This behavior has been considered as a consequence of the hydrophobic character of aliphatic species since hydrophobicity is expected to increase with the number of carbon atoms [20,21].

The hydrophobic character of aliphatic molecules has been customarily related to the octanol–water partition free energy ($\Delta G_{OW}$). In aliphatic species, $\Delta G_{OW}$ linearly decreases with the number of methylene groups in the hydrocarbon chain, with slopes near to $\approx -3$ kJ/mol in most cases [20,21]. When comparing different families of aliphatic species, alkanes seem to be the most hydrophobic compounds, followed by carboxylic acids, alcohols, amines, carboxylates, chlorhydrates and sulfonates (Fig. 2). According to their hydrophobic character, alkanes are expected to show the largest affinity upon cyclodextrins; however the experimental

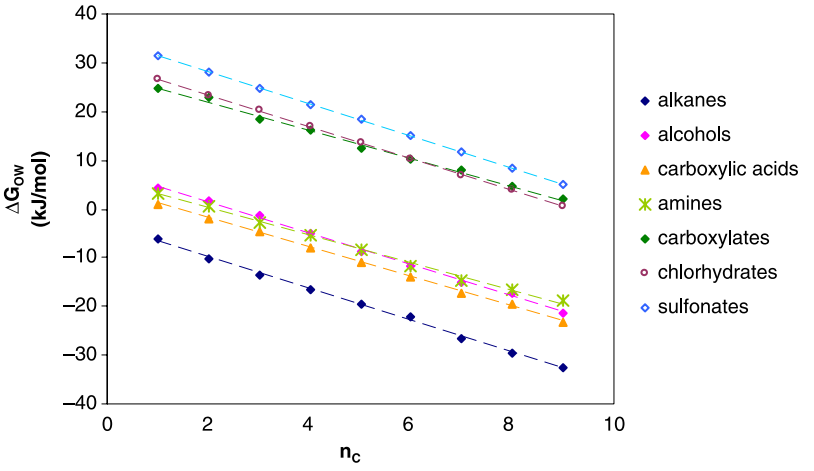


FIGURE 2 Octanol–water partition free energies for aliphatic species $\Delta G_{OW}$ in kJ/mol.

trends for complex stabilities indicate that alkanes posses smaller association constants than functionalized aliphatic species, both neutral and ionic (Fig. 3). These results suggest that hydrophobic interactions are important, but that they are not the only interactions that govern the aliphatic species' inclusion behavior with cyclodextrins.

### *Electrostatic Interactions*

Electrostatic interactions are expected to be of importance in the inclusion complexation with cyclodextrins, especially in the case in which guests possess polar groups, such as aliphatic alcohols, amines and carboxylic acids.

To describe the role of electrostatic interactions in the inclusion complexation of aliphatic species, we calculated the maximum charge located on a guest atom ($Q_{max}$), and the guest's molecular dipole moment ($\mu_G$) for alkanes, alcohols, amines, carboxylic acids, carboxylates, chlorhydrates and sulfonates (Table I). As expected, functionalized aliphatic molecules have larger values of $Q_{max}$ and $\mu_H$ than alkanes, suggesting that electrostatic interactions should be of importance in determining inclusion complex stability.

### *Van der Waals Interactions*

Van der Waals interactions, composed by induction and dispersion forces, are expected to be important in the inclusion complexation of polarizable guests.

Since both induction and dispersion forces depend on the polarizability of the interacting species, the role of van der Waals interactions on inclusion complexation can be analyzed by relating the aliphatic guests' binding strength to their molecular polarizability, $\alpha_G$. Figure 4 shows the calculated values of $\alpha_G$ for a series of aliphatic compounds as a function of the number of carbon atoms in their hydrocarbon chains. It can be seen that $\alpha_G$ linearly increases with the number of methylene units in the aliphatic chains. Additionally, for neutral species, it can be seen that the larger the guest's polarizability, the more stable is the inclusion complex. This result indicates that van der Waals interactions are relevant to determine the energetic trends of neutral inclusion complexes. In the case of anionic species, the polarizability trend does not agree with the inclusion preferences of different families of guests. Therefore, other factors should contribute to the cyclodextrin complexation with ionic aliphatic species.

### *Charge Transfer Interactions*

In a recent attempt to rationalize the inclusion complexation of some organic anions, Liu and Guo suggested that charge transfer plays a relevant role in inclusion complex stabilization [22]. In our previous work, we employed a DFT-derived parameter ΔN as a molecular descriptor to account for the role of charge transfer in the inclusion complexation of aromatic anions with α-cyclodextrin [23].

According to DFT, the charge transfer between two reacting species can be described as a function of global reactivity descriptors, such as electronic chemical potential ($\mu$) and molecular hardness ($\eta$). Both $\mu$ and $\eta$ are reactivity descriptors that determine the global response of the energy of a system to the change in the number of electrons at fixed external potential. Electronic chemical potential measures the escaping tendency of the electron cloud of atoms or molecules. On the other hand, $\eta$ can be seen as the resistance of an atom or molecule to undergo charge transfer processes. The charge transfer process between two reacting species proceeds at constant external potential through the equalization of the chemical potentials between them. In addition, charge transfer is expected to

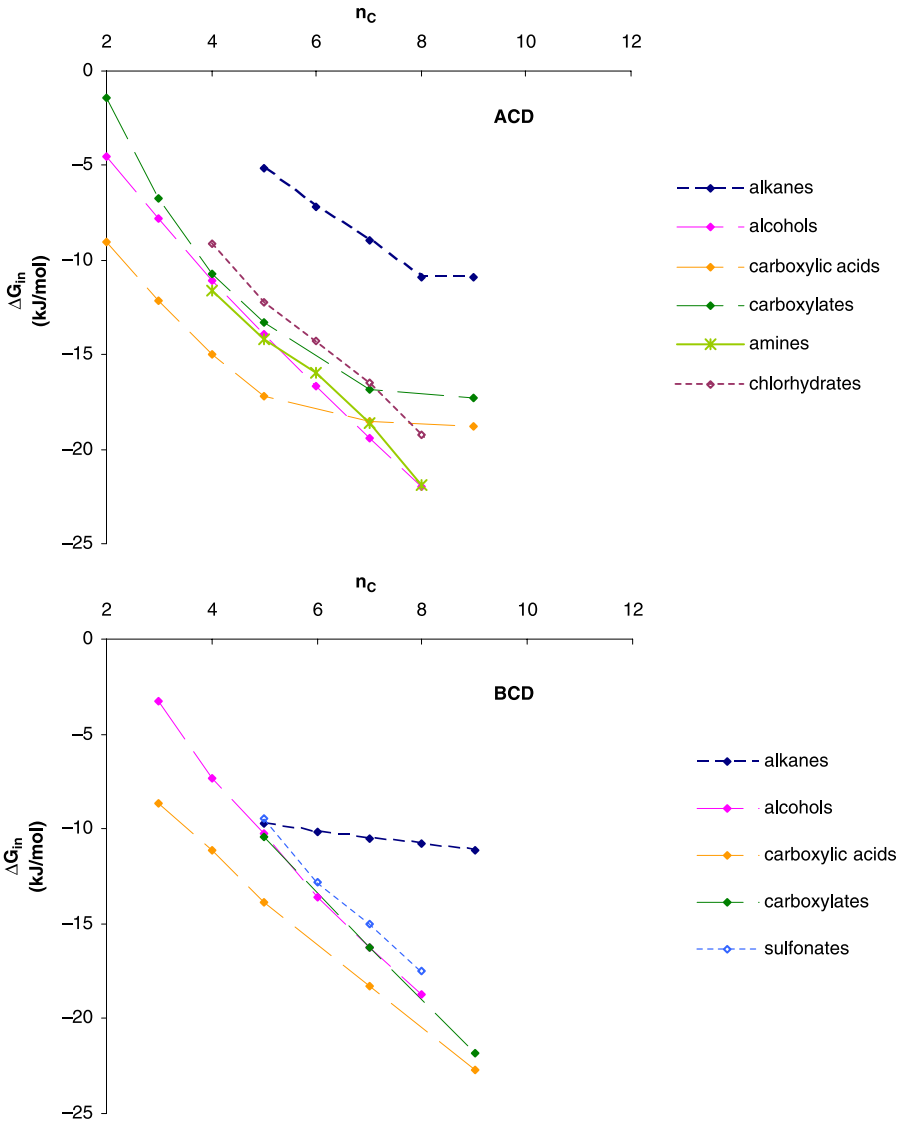


FIGURE 3 Inclusion free energies for aliphatic species $\Delta G_{in}$ in kJ/mol as a function of the number of carbon atoms in the hydrocarbon chains ($n_C$). Experimental $\Delta G_{in}$ values were taken from ref. [8].

occur from the species with the highest $\mu$ to the one that has the least. From $\mu$ and $\eta$, a useful expression for the maximum amount of charge transferred between two reacting species can be obtained (Eq. (1)).

ΔN is a very useful parameter whose magnitude reflects the extension of the charge transfer between two species [14,15]. Hence, we now propose the use of ΔN as a suitable descriptor to account for the role of charge transfer on the inclusion complexation of aliphatic guests with α- and β-cyclodextrin. We calculated ΔN values for the interaction between neutral and ionic aliphatic species with both α- and β-cyclodextrin. As can be seen in Table I, ΔN has non-zero values only for carboxylates, chlorhydrates and sulfonates, suggesting that charge transfer should be of importance in their inclusion complexation.

### *Steric Effects*

Steric effects are expected to be important in the inclusion complexation of branched aliphatic species. As pointed out by Rekharsky *et al.* [20,21], branching induces a destabilization of inclusion complexes of aliphatic alcohols with α-cyclodextrin. Herein, we propose the use of a modified connectivity index $\chi^*$ to quantify the effect of molecular branching on inclusion complex stability based on the zero-order Randic's connectivity index [24] (Eq. (4)).

$$\chi^0 = \sum (\delta_i \delta_j)^{1/2} \tag{4}$$

The modified connectivity index $\chi^*$ is defined as:

$$\chi^* = \chi^0 - \chi^0_{\text{linear}} \tag{5}$$

TABLE I Molecular descriptors and complexation free energies of aliphatic compounds with α- and β-cyclodextrins

| Guests | $Q_{màx}$ (au) | $\mu_G$ (D) | $\Delta G_{OW}$ (kJ/mol) | $\alpha_G$ (bohr$^3$) | ΔN (au) | $\chi^*$ | $\Delta G_{in}^{ACD}$ (kJ/mol) | $\Delta G_{in}^{BCD}$ (kJ/mol) |
|---|---|---|---|---|---|---|---|---|
| Neutral | | | | | | | | |
| *alkanes* | | | | | | | | |
| n-pentane | 0.156 | 0.00 | −19.35 | 52.41 | 0.007 | 0.000 | −5.15 | −9.70 |
| n-hexane | 0.156 | 0.00 | −22.26 | 62.60 | 0.001 | 0.000 | −7.16 | −10.15 |
| n-heptane | 0.156 | 0.00 | −26.60 | 72.84 | 0.003 | 0.000 | −8.95 | −10.50 |
| n-octane | 0.156 | 0.00 | −29.57 | 83.12 | 0.006 | 0.000 | −10.86 | −10.74 |
| *alcohols* | | | | | | | | |
| ethanol | 0.735 | 1.74 | 1.77 | 25.19 | 0.000 | 0.00 | −3.98 | −0.45 |
| 1-propanol | 0.741 | 1.65 | −1.43 | 38.92 | 0.000 | 0.00 | −7.79 | −3.62 |
| 1-butanol | 0.743 | 1.69 | −5.02 | 51.51 | 0.000 | 0.00 | −11.05 | −7.50 |
| 1-pentanol | 0.743 | 1.62 | −8.62 | 64.42 | 0.000 | 0.00 | −13.94 | −10.50 |
| 1-hexanol | 0.743 | 1.68 | −11.59 | 77.75 | 0.000 | 0.00 | −16.71 | −13.93 |
| 1-heptanol | 0.744 | 1.62 | −14.95 | 91.25 | 0.000 | 0.00 | −19.38 | −16.20 |
| 1-octanol | 0.744 | 1.68 | −17.12 | 104.96 | 0.001 | 0.00 | −21.95 | −18.75 |
| 1,3-propanodiol | 0.739 | 3.35 | 5.94 | 37.32 | 0.006 | 0.00 | −3.62 | |
| 1,4-butanodiol | 0.744 | 0.00 | 4.74 | 47.35 | 0.002 | 0.00 | −5.12 | |
| 1,5-pentanodiol | 0.743 | 3.31 | −0.64 | 57.50 | 0.003 | 0.00 | −8.40 | |
| 1,6-hexanodiol | 0.744 | 0.00 | −3.92 | 67.70 | 0.002 | 0.00 | −11.36 | |
| 1,7-heptanodiol | 0.743 | 3.30 | −7.25 | 77.98 | 0.003 | 0.00 | −14.28 | |
| 1,8-octanodiol | 0.744 | 0.00 | −10.53 | 88.29 | 0.002 | 0.00 | −17.56 | |
| 1,9-nonanodiol | 0.743 | 3.29 | −13.80 | 98.63 | 0.001 | 0.00 | −20.28 | |
| 1,10-decanodiol | 0.744 | 0.00 | −17.07 | 108.99 | 0.004 | 0.00 | −21.99 | |
| 2-propanol | 0.749 | 1.77 | −0.29 | 34.65 | 0.006 | 0.37 | −5.15 | −3.31 |
| 2-butanol | 0.747 | 1.65 | −3.48 | 44.65 | 0.005 | 0.50 | −8.10 | −7.23 |
| 2-pentanol | 0.748 | 1.65 | −6.79 | 54.79 | 0.002 | 0.50 | −11.71 | −10.11 |
| 2-hexanol | 0.748 | 1.64 | −10.05 | 65.00 | 0.001 | 0.50 | −14.28 | |
| 2-octanol | 0.748 | 1.65 | −16.55 | 85.56 | 0.002 | 0.50 | −17.98 | −17.87 |
| 1,2-propanodiol | 0.750 | 2.21 | 5.25 | 37.08 | 0.004 | 0.50 | −2.72 | |
| 2-methyl-1-propanol | 0.745 | 1.60 | −4.34 | 44.48 | 0.002 | 0.50 | −8.10 | −9.37 |
| 2-methyl-2-propanol | 0.751 | 1.65 | −2.00 | 44.34 | 0.010 | 1.17 | −3.72 | −9.74 |
| 1,2-butanodiol | 0.745 | 2.16 | 3.10 | 47.04 | 0.003 | 0.63 | −6.32 | |
| 3-methyl-1-butanol | 0.739 | 1.62 | −6.62 | 54.40 | 0.003 | 0.50 | −10.80 | −12.61 |
| 2-methyl-1-butanol | 0.745 | 1.60 | −7.36 | 54.35 | 0.003 | 0.63 | −11.65 | −11.87 |
| 2,2-dimethyl-1-propanol | 0.747 | 1.60 | −7.48 | 54.00 | 0.009 | 1.41 | −8.39 | |
| 3-methyl-2-butanol | 0.756 | 1.64 | −7.31 | 54.04 | 0.002 | 1.10 | −7.25 | −10.96 |
| 2-methyl-2-butanol | 0.756 | 1.59 | −5.08 | 54.11 | 0.008 | 1.41 | −8.74 | −12.03 |
| 3-pentanol | 0.754 | 1.64 | −6.91 | 54.52 | 0.001 | 0.63 | −10.72 | −9.89 |
| 1,2-pentanediol | 0.765 | 2.49 | 0.29 | 57.19 | 0.000 | 0.63 | −10.80 | |
| 4-methyl-2-pentanol | 0.749 | 1.60 | −10.06 | 64.41 | 0.003 | 1.00 | −9.82 | −11.65 |
| 3-hexanol | 0.754 | 1.64 | −9.42 | 64.74 | 0.002 | 0.63 | −12.52 | |
| 3,3-dimethyl-2-butanol | 0.757 | 1.60 | −8.45 | 63.35 | 0.000 | 2.10 | −7.43 | |
| 1,2-hexanediol | 0.765 | 2.53 | −3.45 | 67.42 | 0.000 | 0.63 | −12.86 | |
| 1,5-hexanediol | 0.748 | 2.39 | −3.45 | 67.56 | 0.004 | 0.50 | −8.81 | |
| 2,5-hexanediol | 0.750 | 0.00 | −2.98 | 67.40 | 0.004 | 1.00 | −8.08 | |
| 4-heptanol | 0.755 | 1.66 | −12.67 | 74.99 | 0.006 | 0.63 | −12.98 | |
| 2-methyl-2-pentanol | 0.757 | 1.59 | −10.26 | 64.30 | 0.012 | 1.41 | | −11.86 |
| 3-methyl-3-pentanol | 0.764 | 1.60 | −10.26 | 63.83 | 0.015 | 1.66 | | −12.27 |
| 3-ethyl-3-pentanol | 0.763 | 1.58 | −13.53 | 73.62 | 0.018 | 1.90 | | −13.02 |
| 2-methyl-2-hexanol | 0.756 | 1.59 | −13.53 | 74.54 | 0.012 | 1.41 | | −13.30 |
| *Carboxylic acids* | | | | | | | | |
| Formic | 0.661 | 1.60 | 3.08 | 14.61 | 0.059 | 0.00 | −3.51 | |
| Acetic | 0.688 | 1.79 | 0.97 | 23.34 | 0.041 | 0.00 | −5.49 | |
| Propionic | 0.700 | 1.68 | −1.88 | 33.65 | 0.037 | 0.00 | −9.03 | |
| Butyric | 0.702 | 1.61 | −4.51 | 44.04 | 0.035 | 0.00 | −12.16 | −8.62 |
| Pentanoic | 0.702 | 1.65 | −7.93 | 54.15 | 0.034 | 0.00 | −15.56 | −11.16 |
| Hexanoic | 0.703 | 1.59 | −10.96 | 64.35 | 0.033 | 0.00 | −16.60 | −14.08 |
| Octanoic | 0.703 | 1.58 | −17.41 | 84.90 | 0.028 | 0.00 | −18.57 | −18.32 |
| Decanoic | 0.703 | 1.58 | −23.34 | 105.59 | 0.021 | 0.00 | | −22.69 |
| 1,4-butanodioic | 0.699 | 0.00 | 3.37 | 45.80 | 0.055 | 0.00 | −11.45 | |
| 1,6-hexanodioic | 0.701 | 0.00 | −0.46 | 66.12 | 0.041 | 0.00 | −14.31 | |
| 1,7-heptanodioic | 0.702 | 3.19 | −3.48 | 76.39 | 0.036 | 0.00 | −16.37 | |
| 1,8-octanodioic | 0.702 | 0.00 | −5.39 | 86.68 | 0.034 | 0.00 | −17.99 | |
| *Amines* | | | | | | | | |
| n-butylamine | 0.835 | 1.51 | −5.54 | 48.11 | 0.044 | 0.00 | −11.64 | |
| n-pentylamine | 0.835 | 1.56 | −8.50 | 58.26 | 0.045 | 0.00 | −14.16 | |
| n-hexylamine | 0.835 | 1.53 | −11.76 | 68.48 | 0.045 | 0.00 | −15.98 | |
| n-heptylamine | 0.835 | 1.57 | −14.67 | 78.75 | 0.045 | 0.00 | −18.61 | |
| n-octylamine | 0.835 | 1.53 | −16.55 | 89.06 | 0.045 | 0.00 | −21.86 | |
| n-nonylamine | 0.835 | 1.58 | −19.86 | 99.40 | 0.045 | 0.00 | | |

TABLE I – *continued*

| Guests | $Q_{màx}$ (au) | $\mu_G$ (D) | $\Delta G_{OW}$ (kJ/mol) | $\alpha_G$ (bohr$^3$) | $\Delta N$ (au) | $\chi^*$ | $\Delta G_{in}^{ACD}$ (kJ/mol) | $\Delta G_{in}^{BCD}$ (kJ/mol) |
|---|---|---|---|---|---|---|---|---|
| Anions | | | | | | | | |
| *Carboxylates* | | | | | | | | |
| Propionate | 0.767 | 5.50 | 22.73 | 32.29 | 0.381 | 0.00 | | |
| Butyrate | 0.767 | 7.92 | 18.26 | 42.32 | 0.359 | 0.00 | −6.78 | |
| Pentanoate | 0.767 | 10.31 | 16.19 | 52.41 | 0.347 | 0.00 | −10.73 | |
| Hexanoate | 0.767 | 13.08 | 12.39 | 62.60 | 0.336 | 0.00 | −13.27 | −10.44 |
| Octanoate | 0.767 | 18.64 | 9.64 | 86.59 | 0.320 | 0.00 | −16.81 | −16.29 |
| Decanoate | 0.767 | 24.40 | 6.37 | 107.28 | 0.310 | 0.00 | | −21.85 |
| Oxalate | 0.714 | 5.52 | 34.29 | 27.89 | 0.306 | 0.00 | −2.17 | |
| 1,4-butanodioic monocarboxylate | 0.759 | 10.68 | 27.74 | 47.23 | 0.315 | 0.00 | −7.11 | |
| 1,6-hexanodioic monocarboxylate | 0.764 | 16.48 | 21.20 | 67.76 | 0.299 | 0.00 | −12.45 | |
| 1,7-heptanodioic monocarboxylate | 0.766 | 19.77 | 17.92 | 78.07 | 0.292 | 0.00 | −14.82 | |
| 1,8-octanodioic monocarboxylate | 0.766 | 22.42 | 14.58 | 88.37 | 0.287 | 0.00 | −17.09 | |
| *Sulphonates* | | | | | | | | |
| n-octilsulphonate | 0.777 | 19.53 | 8.44 | 103.76 | 0.272 | 0.00 | | −17.36 |
| n-nonilsulphonate | 0.777 | 22.25 | 5.17 | 114.13 | 0.268 | 0.00 | | −19.04 |
| n-decilsulphonate | 0.777 | 24.99 | 1.89 | 124.51 | 0.264 | 0.00 | | −20.61 |
| Cations | | | | | | | | |
| *Chlorhydrates* | | | | | | | | |
| Butylamonium | 0.469 | 9.10 | 16.85 | 46.61 | 0.363 | 0.00 | −9.15 | |
| Pentylamonium | 0.469 | 11.89 | 13.58 | 56.84 | 0.346 | 0.00 | −12.21 | |
| Hexylamonium | 0.469 | 14.68 | 10.31 | 67.11 | 0.332 | 0.00 | −14.29 | |
| Heptylamonium | 0.469 | 17.59 | 7.04 | 77.42 | 0.320 | 0.00 | −16.48 | |
| Octylamonium | 0.469 | 20.49 | 3.76 | 87.76 | 0.309 | 0.00 | −19.23 | |
| Nonylamonium | 0.469 | 23.46 | 0.43 | 98.01 | 0.300 | 0.00 | −20.72 | |

where $\chi^0$ represents the Randic's connectivity index for a branched molecule and $\chi^0_{linear}$ corresponds to the Randic's connectivity index associated to a linear isomer with the same number of carbon atoms than the branched species.

Table I contains the calculated values of $\chi^*$ for the branched aliphatic molecules under study. In the case of α-cyclodextrin, branching decreases the complex stability in comparison with the corresponding linear isomers. On the other hand, branching does not seem to significantly change inclusion complex stability in the case of β-cyclodextrin. The difference between α- and β-cyclodextrin in their inclusion behavior with branched aliphatic species arises from the size of their

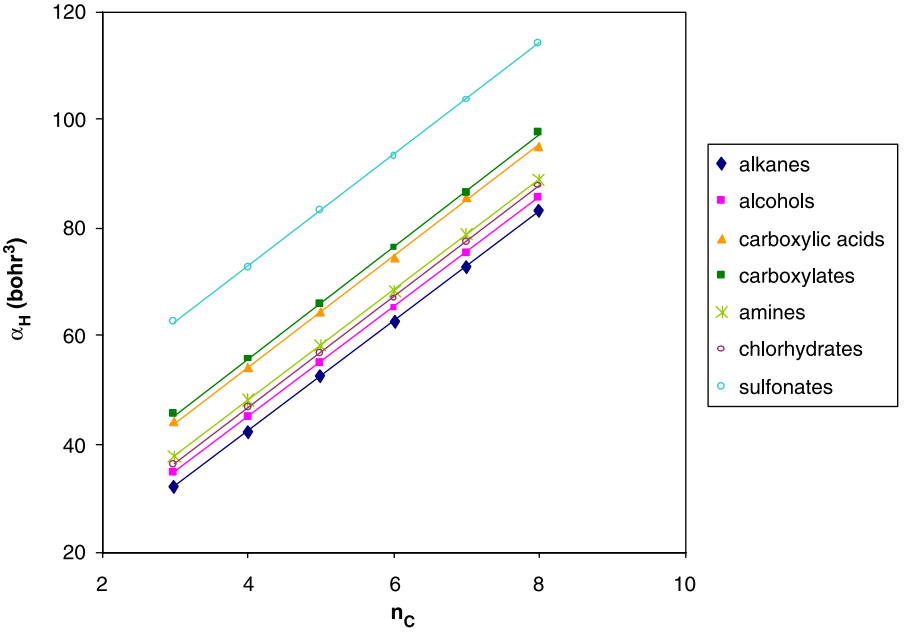


FIGURE 4 Molecular polarizability of aliphatic species $\alpha_H$ (bohr$^3$).

molecular cavities. In contrast with β-cyclodextrin, α-cyclodextrin has a smaller cavity and consequently is subjected to steric hindrance, being unable to include highly voluminous molecules.

### Correlation Models

We have employed $\Delta G_{OW}$, $\alpha_G$, $Q_{max}$, $\mu_G$, ΔN and $\chi^*$ descriptors to build two multi-linear correlation models that account for the inclusion complexation free energies of aliphatic compounds with α- and β-cyclodextrin.

In the case of α-cyclodextrin, the obtained multi-linear correlation is shown in Eq. (6). Table II contains the statistical parameters associated to this equation and the order of statistical relevance of the employed molecular descriptors. Figure 5 displays the performance of the built correlation to account for inclusion free energies of aliphatic species with α-cyclodextrin.

$$\Delta G^{\alpha}_{in} = 7.67 - 0.15\ \alpha_G - 12.23\ Q_{max} + 3.00\ \chi^* + 0.26\Delta G_{OW} - 20.38\ \Delta N$$
$$N = 73 r^2 = 0.9080\ r^2_{CV} = 0.8985\ \text{RMSD} = 1.55 \quad (6)$$

The most important statistical factor in the correlation is $\alpha_G$, showing that van der Waals interactions play a crucial role in determining the stability of aliphatic complexes. The coefficient for $\alpha_G$ shows that an increase in the molecular polarizability is related to increased inclusion complex stability, in agreement with the attractive nature of van der Waals interactions.

The second parameter of importance is the maximum charge located on a guest atom. The model shows that the higher the guest's charge, the more stable are the inclusion complexes with α-cyclodextrin. This result indicates that electrostatic interactions are of importance in the inclusion complexation with highly polar or charged guests.

The next regression parameter in the correlation is $\chi^*$, which shows that branching decreases the stability of aliphatic inclusion complexes, in accordance with experimental observations [20,21].

The following parameter is the octanol-water partition free energy. The coefficient associated to $\Delta G_{OW}$ in Eq. (6) shows that an increase in the guest's hydrophobicity (i.e. a decrease in the value of $\Delta G_{OW}$) is related to an increase in inclusion complex stability, in agreement with the role of hydrophobic interactions on inclusion complexation phenomena.

TABLE II Statistical parameters for the inclusion correlation model for aliphatic species with α-cyclodextrin (Eq. (6))

| Variable | Number of variables | Partial F-test | Cumulated $r^2$ | RMSD |
|---|---|---|---|---|
| $\alpha_H$ | 1 | 226.69 | 0.7590 | 2.49 |
| $Q_{max}$ | 2 | 137.27 | 0.7945 | 2.29 |
| $\chi^*$ | 3 | 136.93 | 0.8544 | 1.93 |
| $\Delta G_{OW}$ | 4 | 135.84 | 0.8639 | 1.87 |
| ΔN | 5 | 134.30 | 0.9080 | 1.54 |

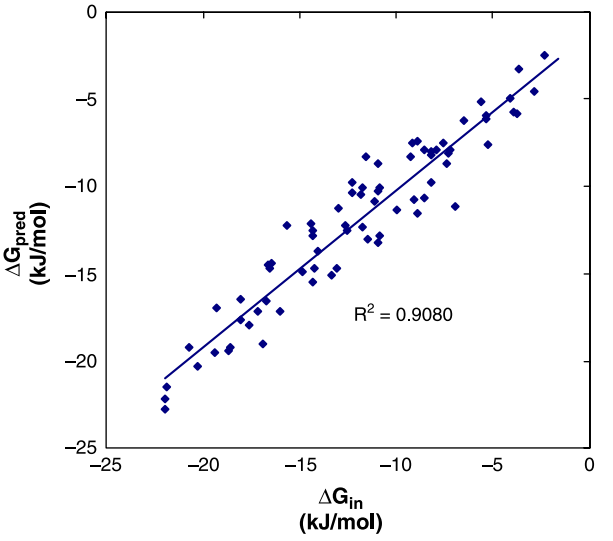


FIGURE 5 Experimental $\Delta G_{in}$ (kJ/mol) and predicted $\Delta G_{pred}$ (kJ/mol) inclusion free energies for aliphatic species in α-cyclodextrin. Experimental $\Delta G_{in}$ values were taken from ref. [8].

The last parameter involved in Eq. (6) is the charge transfer between host and guest, ΔN. The corresponding coefficient indicates that an increase in ΔN induces a larger stability of the inclusion complexes. Since ΔN has non-zero values only for ionic species, the correlation shows that charge transfer should be of importance only in the inclusion complexation of this kind of guests.

In the case of β-cyclodextrin, the correlation model that describes the inclusion complexation of aliphatic species is shown in Eq. (7). Table III contains the statistical parameters for this correlation and the order of the employed molecular descriptors' statistical significance. Figure 6 displays the performance of the built correlation to account for inclusion free energies of aliphatic species with β-cyclodextrin.

$$\Delta G^{\beta}_{in} = 0.05 - 0.14\ \alpha_G + 0.32\ \Delta G_{OW} - 20.67\ \Delta N$$
$$N = 37\ r^2 = 0.9125\ r^2_{CV} = 0.91\ \text{RMSD} = 1.54 \quad (7)$$

Like α-cyclodextrin, the most important factor involved in the inclusion complexation of aliphatic species with β-cyclodextrin is the guest's molecular polarizability, indicating the importance of van der Waals's effect on inclusion phenomena.

The second parameter in Eq. (7) is the octanol–water partition free energy, $\Delta G_{OW}$. This molecular descriptor is related to the hydrophobic character of the guests and shows that the larger the guest's hydrophobicity, the more stable is the inclusion complex, in accordance

TABLE III Statistical parameters for the inclusion correlation model for aliphatic species with β-cyclodextrin (Eq. (7))

| Variable | Number of variables | Partial F-test | Cumulated $r^2$ | RMSD |
|---|---|---|---|---|
| $\alpha_H$ | 1 | 204.31 | 0.8502 | 1.90 |
| $\Delta G_{OW}$ | 2 | 149.80 | 0.8954 | 1.52 |
| ΔN | 3 | 118.32 | 0.9125 | 1.47 |

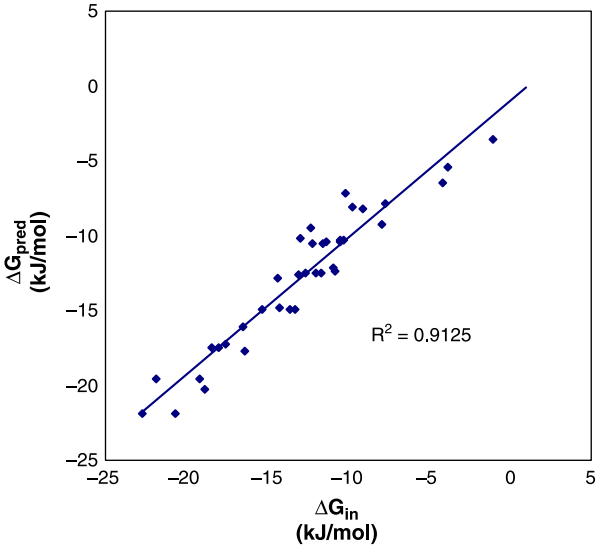


FIGURE 6 Experimental $\Delta G_{in}$ (kJ/mol) and predicted $\Delta G_{pred}$ (kJ/mol) inclusion free energies for aliphatic species in β-cyclodextrin. Experimental $\Delta G_{in}$ values were taken from ref. [8].

with the role of hydrophobic interactions on inclusion complexation with cyclodextrins.

The last factor involved in Eq. (7) is ΔN, suggesting that charge transfer interactions are relevant in the determining the inclusion complex stabilities with ionic aliphatic species and β-cyclodextrins, as was observed in the case of α-cyclodextrin.

According to Eqs. (6) and (7), the inclusion complexation with cyclodextrins arises from the cooperation of several weak forces instead of the predominance of a unique interaction. For both α- and β-cyclodextrin the most relevant driving force for the inclusion complexation with aliphatic species is van der Waals interaction.

Even though Eq. (7) does not include electrostatic descriptors as regression parameters, electrostatic interactions should be of importance in the inclusion complexation with β-cyclodextrin. The absence of electrostatic parameters in this correlation model arises from the nature of the calibration set, composed only by functionalized guests whose charges are quite similar.

## CONCLUDING REMARKS

The inclusion complexation of aliphatic compounds with α- and β-cyclodextrin was closely examined in order to identify the most important factors that govern their inclusion behavior. For the first time, the obtained correlation models have described the inclusion complexation of ionic aliphatic species. In this sense, charge transfer interactions can be helpful to explain the unusual stabilization of ionic aliphatic inclusion complexes. It is important to note that the present analysis ignores both the contributions of solvation and the influence of different buffers on complexation thermodynamics. Nevertheless, a reasonably consistent picture of complexation's energetic trends has been presented in terms of easily interpretable molecular descriptors.

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