

## Article

# Inclusion Complexes between $\beta$ -Cyclodextrin and Gaseous Substances— $\text{N}_2\text{O}$ , $\text{CO}_2$ , $\text{HCN}$ , $\text{NO}_2$ , $\text{SO}_2$ , $\text{CH}_4$ and $\text{CH}_3\text{CH}_2\text{CH}_3$ : Role of the Host's Cavity Hydration

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**Abstract:** The thermodynamic aspects of the process of inclusion complex formation between  $\beta$ -cyclodextrin (acting as a host) and gaseous substances (guests;  $\text{N}_2\text{O}$ ,  $\text{CO}_2$ ,  $\text{NO}_2$ ,  $\text{SO}_2$ ,  $\text{HCN}$ ,  $\text{CH}_4$ ,  $\text{CH}_3\text{CH}_2\text{CH}_3$ ) are studied by employing well-calibrated and tested density functional theory (DFT) calculations. This study sheds new light on the intimate mechanism of the  $\beta$ -cyclodextrin/gas complex formation and answers several intriguing questions: how the polarity and size of the guest molecule influence the complexation thermodynamics; which process of encapsulation by the host macrocycle is more advantageous—insertion to the central cavity without hydration water displacement or guest binding accompanied by a displacement of water molecule(s); what the major factors governing the formation of the complex between  $\beta$ -cyclodextrin and gaseous substances are. The special role that the cluster of water molecules inside the host's internal cavity plays in the encapsulation process is emphasized.

**Keywords:** beta-cyclodextrin; gaseous substances; DFT calculations; host–guest inclusion complexes



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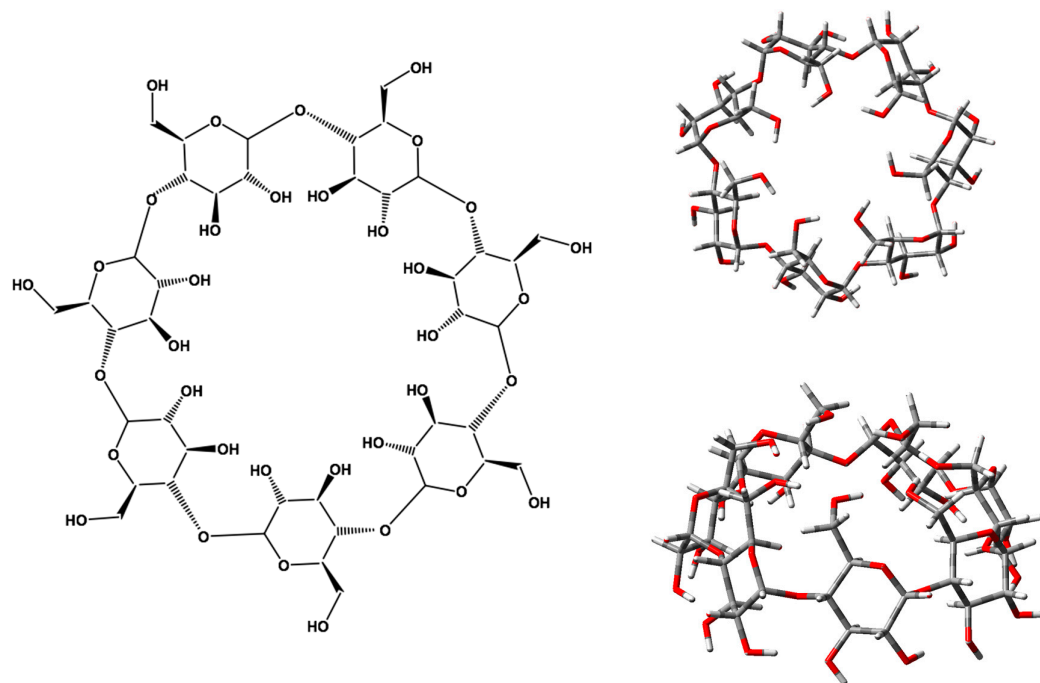
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## 1. Introduction

Encapsulating compounds of practical/scientific interest (“guests”) by specific macrocyclic cavitands (“hosts”) has proven advantageous for many fields of science/industry, such as pharmacy, food industry, cosmetics, chemical research, photochemistry, and dye tuning [1–5]. Among many host molecules, e.g., cucurbiturils [6–11], calixarenes [12,13], and crown ethers [14,15], cyclodextrins [16–19] enjoy widespread interest among both practitioners and researchers.

Cyclodextrins (CDs) are natural cyclic oligosaccharides consisting of ( $\alpha$ -1,4)-linked D-glucopyranose units produced from the biodegradation of starch by the action of bacterial enzymes. These are cone-shaped structures that possess a hydrophobic central cavity and a hydrophilic outer surface formed of primary hydroxyl groups at the narrow (upper) edge and secondary hydroxyl groups located at the wide (lower) edge. The cavities of  $\alpha$ -CD (comprising six glucopyranose subunits),  $\beta$ -CD (seven glucopyranose subunits; Figure 1), and  $\gamma$ -CD (eight glucopyranose monomers) are different diameters, and, thus, CDs are suitable for forming inclusion complexes, with a plethora of guest molecules with varying geometrical and physico-chemical characteristics [20,21]. Larger guests can be incorporated into the host's cavity through various types of non-covalent interactions [22,23]. On the other hand, hydroxyl groups from both the upper and lower rims of the cavitand may form hydrogen bonds with water molecules [24,25], other polar substances [26], and, via charge–dipole interactions, with metal cations [27,28]. Notably, the central cavity of the host, although hydrophobic, can be hydrated at ambient temperature and accommodate up to 6 and 10 water molecules for  $\alpha$ -CD [25] and  $\beta$ -CD [24], respectively. Owing to their low toxicity, a low production price, and specific structure/properties, cyclodextrins (particularly  $\beta$ -CD) or their derivatives have witnessed growing interest and application

in the food industry for the stabilization of flavors, food additives, vitamins, and protection of food components; in pharmacy, for forming inclusion complexes to increase drug solubility/stability and improve drug delivery; in cosmetics, for capturing odors, etc., [22–33].



**Figure 1.** Chemical representation and M062X/6-31G\* fully optimized structure of  $\beta$ -cyclodextrin (top and side view for the optimized structures). Color scheme: C—gray, H—white, O—red.

Encapsulating gaseous substances by  $\beta$ -CD is of particular interest, as this will have implications for the food sector (foaming agents, food quality assessment), environmental pollution control, separation techniques, and fuel storage. However, research on this topic is not abundant. Pereva et al. studied the process of gas entrapment ( $N_2$ ,  $N_2O$ ,  $CO_2$ , and Ar) by  $\beta$ -CD (and  $\alpha$ -CD and  $\gamma$ -CD as well) in forming crystalline clathrates from water solutions employing pressurized gases [32]. It was found that  $\alpha$ -CD is the host of choice for encapsulating the gaseous compounds from the series [34]. A polymeric porous structure based on  $\beta$ -CD was demonstrated by Guo et al. to be efficient in capturing  $CO_2$  [35]. Mohammadi and co-workers studied the effect of  $\beta$ -CD in the dissolution of methane in water at different concentrations of the host macrocycle and variable pressure of methane [36,37]. The effect of the  $\beta$ -CD concentration, solution temperature, and additives (sodium dodecyl sulfate and multiwall carbon nanotubes) has been investigated in the past. The authors found that the simultaneous usage of  $\beta$ -CD, sodium dodecyl sulfate, and multiwall carbon nanotubes increased the amount and rate of dissolution, whereas an elevated medium temperature has the opposite effect. The mechanism of the process, however, remains enigmatic. Furthermore, the adsorption properties of  $\beta$ -CD for encapsulating six aromatic hydrocarbons from the gas phase (styrene, ethylbenzene, o-xylene, chlorobenzene, toluene, and benzene) have been investigated, and the relative affinity of each of the guest compounds toward the host macrocycle has been established [38]. Also,  $\beta$ -CD, in combination with the  $KMnO_4$ -treated filter paper, has been used as an efficient  $SO_2$  detector, with potential applications in the food and beverage industry [39]. In a recent study, Sung and Kuo shed light on the process of ozone entrapment by  $\beta$ -CD and tested the capability of the  $\beta$ -CD/ $O_3$  inclusion complexes in degrading petroleum pollutants [40].

Systematic studies on the factors governing the formation of  $\beta$ -CD/gas inclusion complexes are lacking. In this study, by employing well-calibrated and tested density functional theory (DFT) calculations, we endeavor to fill this gap and answer several

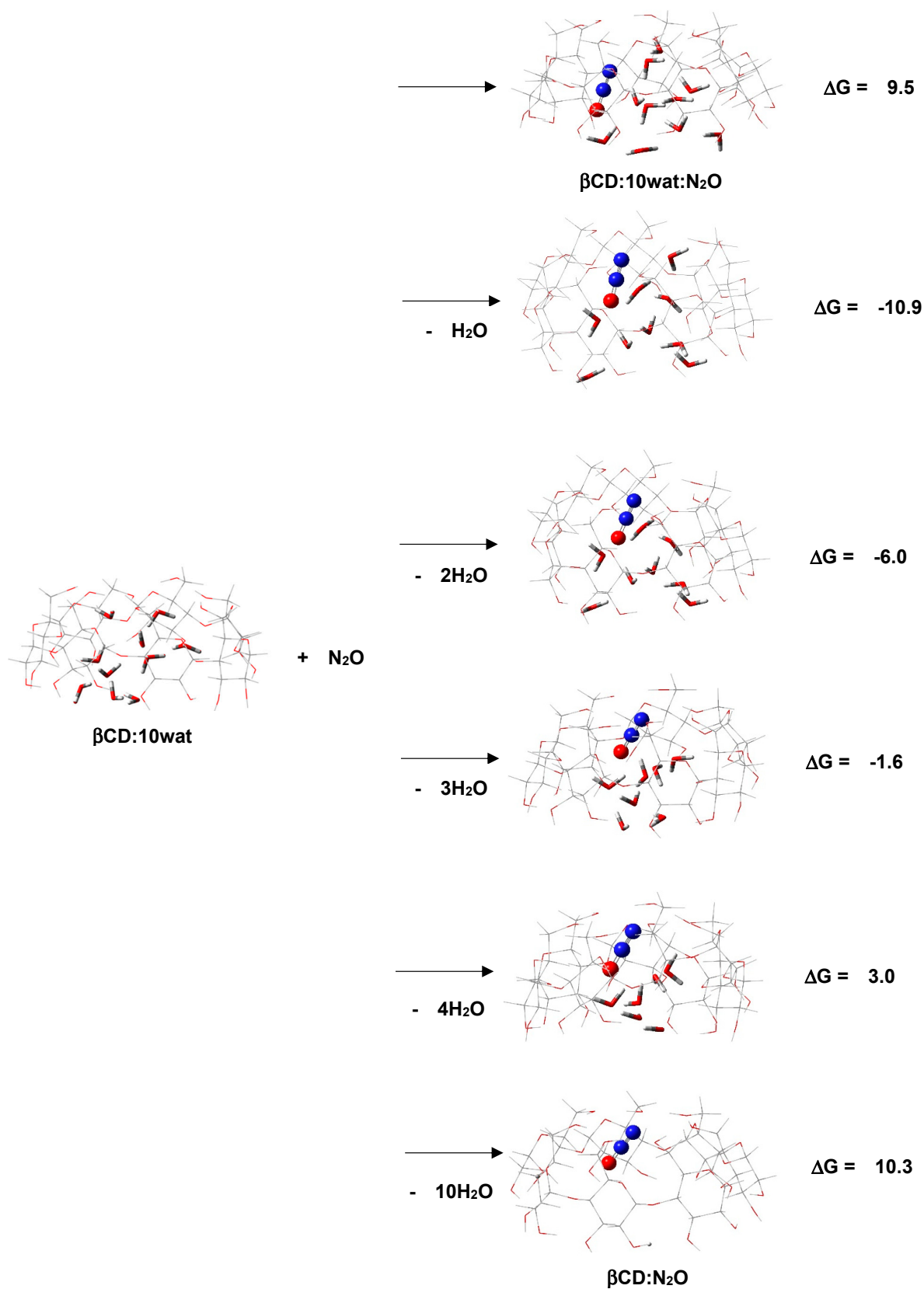
outstanding questions regarding the intimate mechanism of gas encapsulation by the host cavitand: (1) How do the polarity and size of the guest molecule affect the complexation thermodynamics? (2) Which process of gas entrapment by the host macrocycle is more favorable—addition/incorporation within the central cavity without hydration water displacement or guest binding accompanied by a substitution of water molecule(s) (how many)? (3) What is the driving force behind the formation of inclusion complexes?

Gases of interest to the food/beverage industry ( $\text{N}_2\text{O}$ ,  $\text{CO}_2$ ), environmental protection ( $\text{NO}_2$ ,  $\text{SO}_2$ ,  $\text{HCN}$ ), and fuel storage ( $\text{CH}_4$ ,  $\text{CH}_3\text{CH}_2\text{CH}_3$ ) are considered, and the respective Gibbs free energies,  $\Delta G$ , of the  $\beta$ -CD/gas complex formation are evaluated. Note that the aim of the present calculations is to yield reliable trends in the free energy changes with varying parameters, such as the polarity and size of the guest substances and the number of exchangeable water molecules from the central cavity of the host macrocycle, rather than to reproduce the absolute free energies of complex formation. Such an approach has proven reliable in studying other host/guest inclusion complexes [23,27,28] and model biological systems [41].

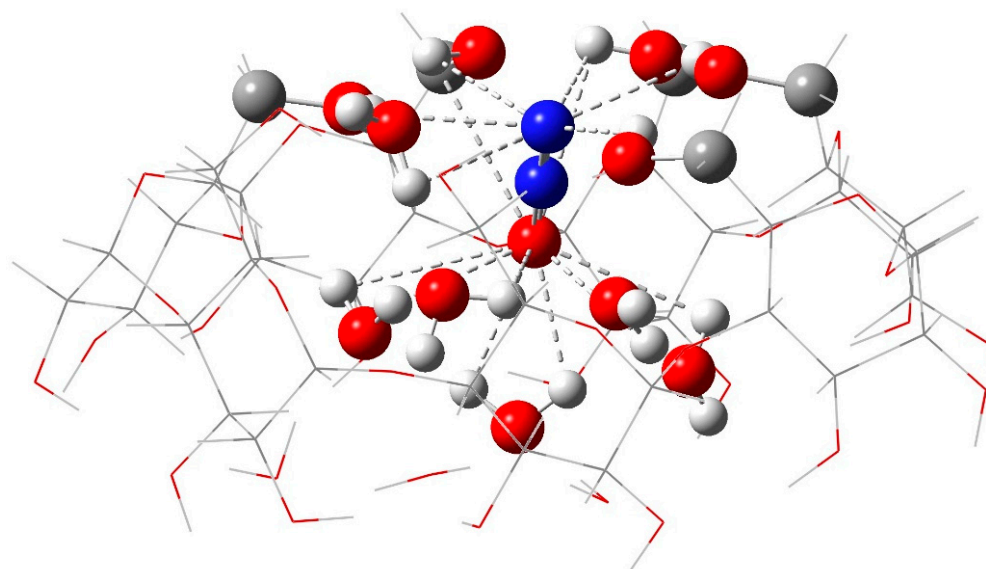
## 2. Results and Discussion

### 2.1. “Food/Beverage” Gases— $\text{N}_2\text{O}$ and $\text{CO}_2$

A DFT fully optimized structure of the hydrated  $\beta$ -cyclodextrin ( $\beta$ -CD:10wat) is shown in Figure 2, where the water cloud is stabilized by an elaborate network of hydrogen bonds between the water-cavitand upper/lower rims and water molecules themselves. The  $\text{N}_2\text{O}$ -substituted constructs,  $\beta$ -CD:Nwat: $\text{N}_2\text{O}$  (complex between  $\beta$ -cyclodextrin, N molecules of water, and gaseous  $\text{N}_2\text{O}$ ; N = 10, 9, 8, 7, 6, and 0), are also presented in Figure 2, along with the respective Gibbs free energies of complex formation. Two types of processes are considered: (i)  $\text{N}_2\text{O}$  binding to the host cavity without hydration water displacement (the uppermost reaction) and (ii)  $\text{N}_2\text{O}$  binding accompanied by the replacement of different number of water molecules (1, 2, 3, 4, and 10) from the inner space of the host cavitand (the rest of the modeled reactions). As seen, a reaction without  $\text{N}_2\text{O} \rightarrow \text{H}_2\text{O}$  exchange is thermodynamically unfavorable (first reaction in Figure 2; positive  $\Delta G$ ) due to the overcrowding of the inner cavity of the macrocycle (the number of internally coordinated particles exceeds 10), which results in increased construct strain. On the other hand, the displacement of few (1, 2, or 3) water molecules by the attacking gas is favorable, as evidenced by negative  $\Delta G$ s (reactions 2, 3, and 4 in Figure 2). Note that the size of  $\text{N}_2\text{O}$  is not very different from that of  $\text{H}_2\text{O}$ , and, therefore, substituting water molecule(s) by  $\text{N}_2\text{O}$  is not expected to impose significant additional strain on the complex. Further displacement of inner cavity waters (4 or 10) by the incoming  $\text{N}_2\text{O}$  (last two reactions in Figure 2) is no longer advantageous (positive free energies). Interestingly, the number of water molecules populating the cavern appears to be related to the efficiency of the process: the more water remains in the cavity, the more favorable the  $\text{N}_2\text{O}$  binding is. Thus, the first  $\text{N}_2\text{O} \rightarrow \text{H}_2\text{O}$  exchange is the most favorable event (second reaction in Figure 2), whereas gradually decreasing the amount of hydration water molecules lowers the efficiency of the gas encapsulation:  $\Delta G$  equals  $-10.9$  kcal/mol for the first water removal but increases to  $-6.0$ ,  $-1.6$ ,  $3.0$ , and  $10.3$  kcal/mol for the displacement of 2, 3, 4, and 10 water molecules, respectively. The balance between two opposing effects determines the stability of the  $\beta$ -CD:Nwat: $\text{N}_2\text{O}$  constructs: On one side, increased entropy of the system with a decreasing water content inside the host cavern is expected to promote the complex formation; i.e., the more water molecules displaced, the more efficient (entropically) the encapsulation process would be. On the other hand, however, the larger cloud of water molecules surrounding  $\text{N}_2\text{O}$  (i.e., fewer water molecules released) would expand the hydrogen bond network and strengthen the guest/host interactions. As an illustration, the extensive hydrogen bond network around  $\text{N}_2\text{O}$  for the  $\beta$ -CD:9wat: $\text{N}_2\text{O}$  construct is depicted in Figure 3. Thus, the richer the inner hydration shell, the more stable the inclusion construct will be. Apparently, this second effect dominates the process since, as already seen, the  $\beta$ -CD:9wat: $\text{N}_2\text{O}$  complex formation is the most thermodynamically favorable.



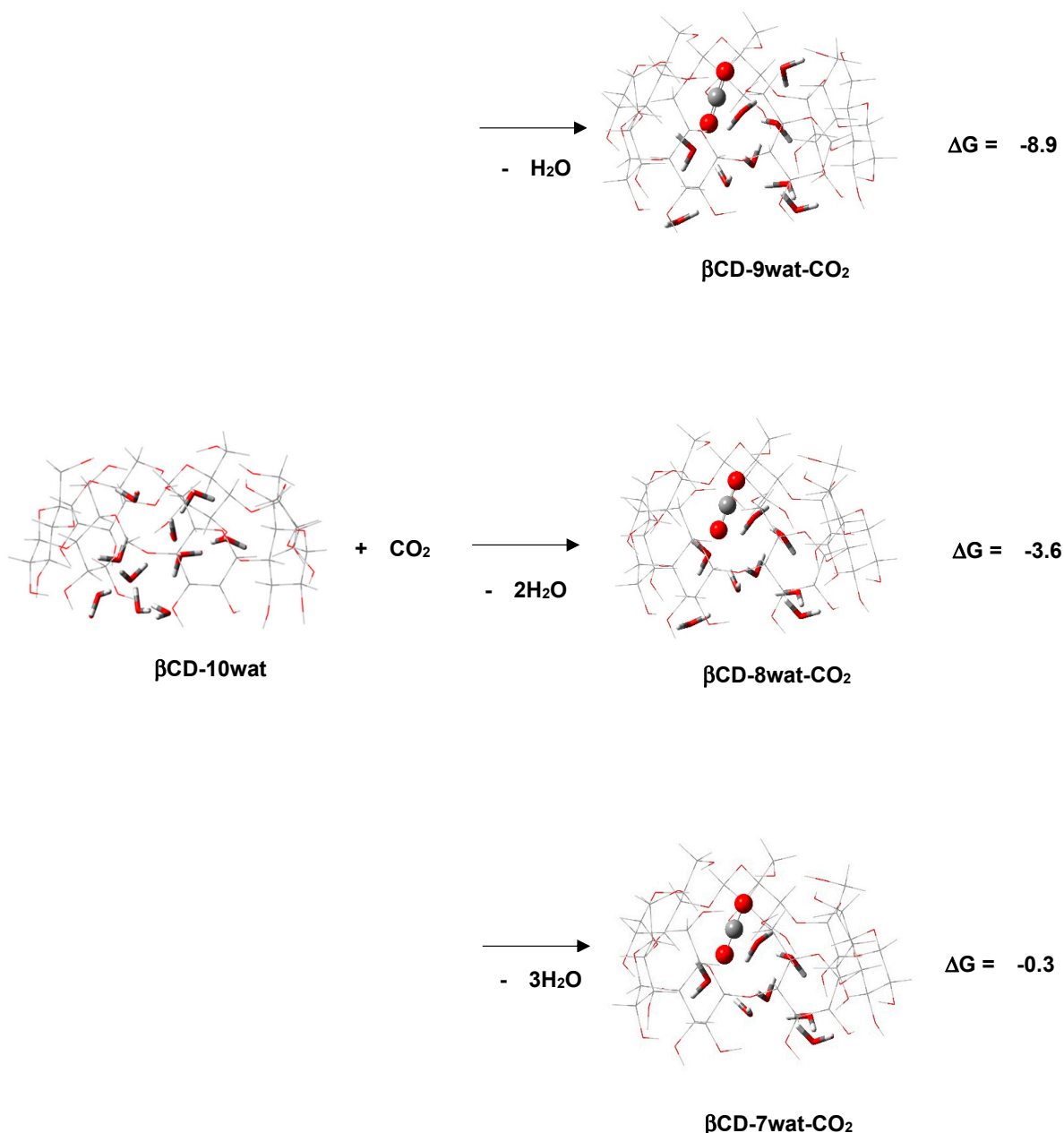
**Figure 2.** M062X/6-31G\* fully optimized structures of  $\beta$ -CD inclusion complexes with water and  $\text{N}_2\text{O}$  ( $\beta$ -CD:Nwat: $\text{N}_2\text{O}$  signifies a complex between  $\beta$ -cyclodextrin, N molecules of water and gaseous  $\text{N}_2\text{O}$ ; N = 10, 9, 8, 7, 6 and 0), and the respective Gibbs free energies of complex formation (in kcal/mol; 1 kcal/mol = 4.184 kJ/mol). Color scheme: C—gray, H—white, O—red, N—blue.



**Figure 3.** Hydrogen bond network in  $\beta$ -CD:9wat:N<sub>2</sub>O complex (complex between  $\beta$ -cyclodextrin, 9 molecules of water and gaseous N<sub>2</sub>O). Hydrogen bonds are formed between water molecules from the internal cavity and -OH groups from the narrow rim of  $\beta$ -CD, on one side, and the end oxygen and nitrogen atoms of N<sub>2</sub>O, on the other. The latter bear negative charges of  $-0.365$  electrons and  $-0.317$  electrons, respectively.

The process of CO<sub>2</sub> encapsulation by  $\beta$ -CD was also studied. Optimized structures of inclusion complexes comprising nine, eight, and seven water molecules and the respective free energies of complex formation are given in Figure 4. As seen, the  $\beta$ -CD:Nwat:CO<sub>2</sub> structures are similar to those of the respective  $\beta$ -CD:Nwat:N<sub>2</sub>O counterparts containing the same number of hydration water molecules. Trends in the free energy changes are also similar. Reactions with the displacement of one, two, or three water molecules are thermodynamically favorable (negative free energies), but the efficiency of the process gradually decreases with the shrinking water cloud inside the macrocycle cavern:  $\Delta G$  is  $-8.9$  kcal/mol for the first water displacement and increases to  $-3.6$  and  $-0.3$  kcal/mol for the next two reactions. These are comparable with the free energies of the respective reactions involving H<sub>2</sub>O  $\rightarrow$  N<sub>2</sub>O exchange,  $-10.9$ ,  $-6.0$ , and  $-1.6$  kcal/mol for the displacement of one, two, and three water molecules, respectively (Figure 2). Since the trends in changing the inclusion complex structures and respective thermodynamic parameters for the first three cavity water dislocations of the  $\beta$ -CD:Nwat:CO<sub>2</sub> complexes (Figure 4) are unambiguous and closely follow those of their  $\beta$ -CD:Nwat:N<sub>2</sub>O counterparts (Figure 2), we did not find it necessary to expand the series of reactions for the former constructs with a dislodgment of more than three water molecules. Similar considerations apply for the next gases from the series as well (see next paragraphs). Although the CO<sub>2</sub> molecule is not polar (total dipole moment of 0 Debye), the local C=O dipoles and negative charge on oxygen atoms ( $\xi = -0.451$  electrons) secure favorable interactions with the hydrated host cavity, thus stabilizing the inclusion complex. Note, however, that N<sub>2</sub>O, which possesses a dipole moment  $\mu = 0.166$  Debye [42], has an advantage over CO<sub>2</sub> for binding to  $\beta$ -CD since dipole–dipole interactions additionally stabilize the structure of the former, as compared to that of the latter (compare  $\Delta G$ s of complex formation in Figures 2 and 4).



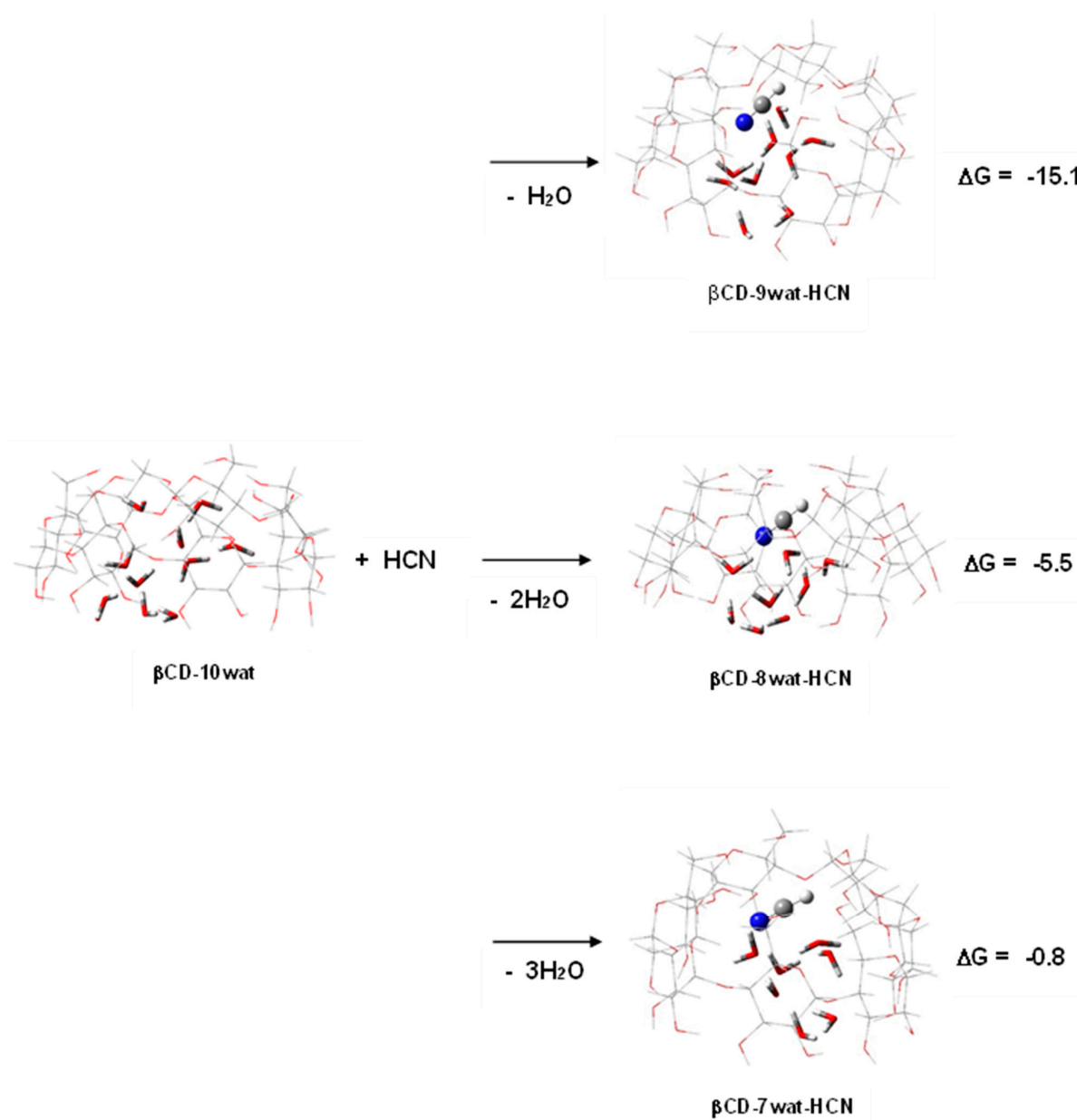


**Figure 4.** M062X/6-31G\* fully optimized structures of  $\beta$ -CD complexes with water and  $\text{CO}_2$  ( $\beta$ -CD:Nwat: $\text{CO}_2$  signifies a complex between  $\beta$ -cyclodextrin, N molecules of water and gaseous  $\text{CO}_2$ ; N = 9, 8, 7), and the respective Gibbs free energies of complex formation (in kcal/mol; 1 kcal/mol = 4.184 kJ/mol). Color scheme: C—gray, H—white, O—red.

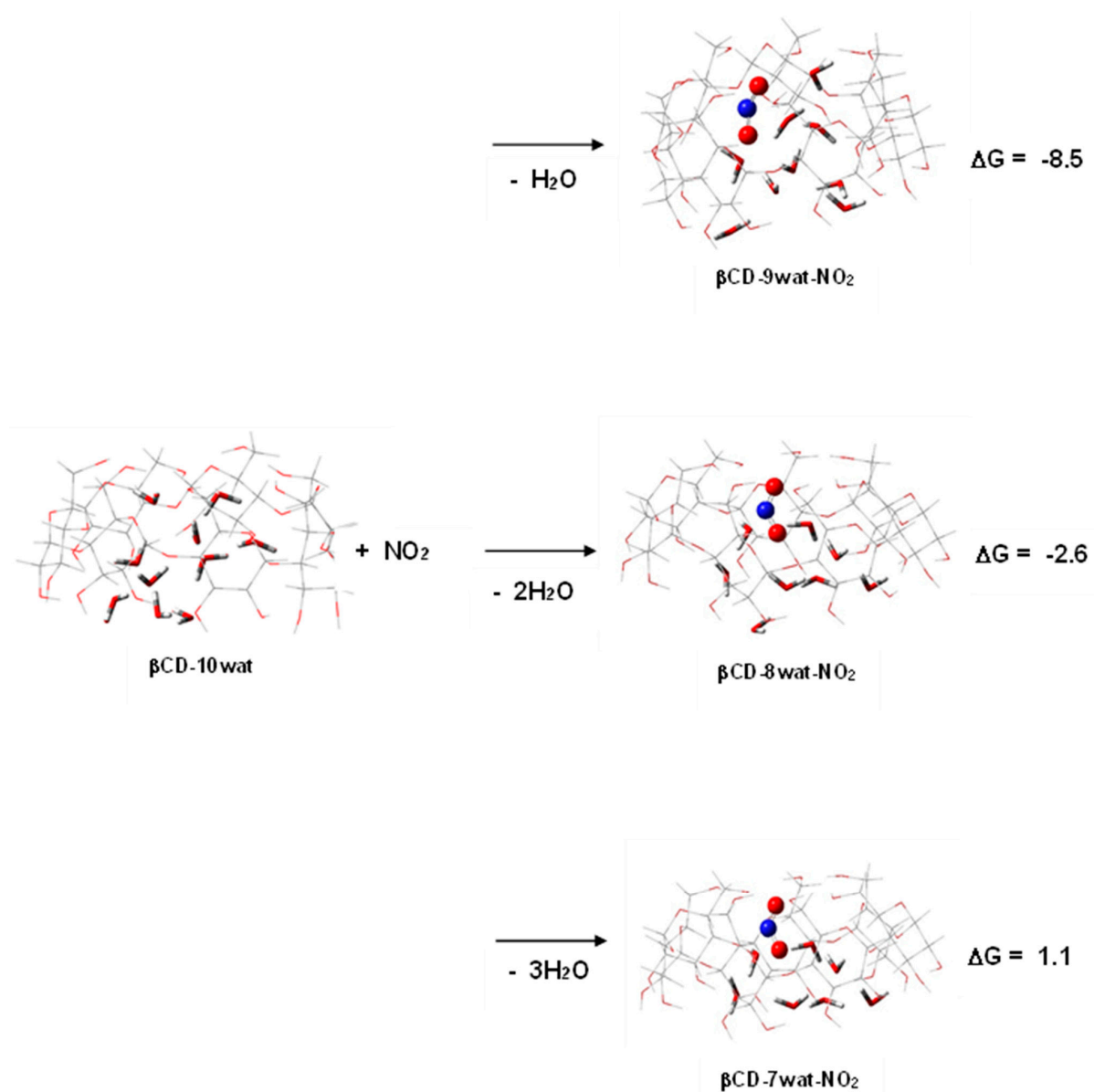
## 2.2. Poisonous Gases—HCN, $\text{NO}_2$ , and $\text{SO}_2$

The affinity of  $\beta$ -CD towards a series of poisonous gases—HCN,  $\text{NO}_2$ , and  $\text{SO}_2$ —was probed. The results are presented in Figure 5, Figure 6, and Figure 7, respectively. The obtained data reveal that the host macrocycle is quite efficient in entrapping these gases, evidenced by formation  $\Delta G$ s ranging between  $-15$  and  $-1$  kcal/mol for the HCN complexes (Figure 5),  $-9$  and  $-3$  kcal/mol for the  $\text{NO}_2$  constructs (Figure 6), and  $-15$  and  $-6$  kcal/mol for the  $\text{SO}_2$  counterparts (Figure 7). The lowest (most favorable)  $\Delta G$ s are evaluated for the  $\beta$ -CD:Nwat:HCN and  $\beta$ -CD:Nwat: $\text{SO}_2$  structures. This is not surprising in view of the high dipole moments of the guest entities ( $\mu = 2.98$  Debye for HCN and 1.62 Debye for  $\text{SO}_2$ ) [42] and strong negative charge on the respective hydrogen bond donors, such as N (from HCN;  $\xi = -0.353$  electrons) and O (from  $\text{SO}_2$ ;  $\xi = -0.321$  electrons).

On the other hand, the inclusion complexes of  $\text{NO}_2$  appear less stable due to the weaker physicochemical parameters of the attacking gas: dipole moment of 0.303 Debye [43] and charge on the oxygen atoms of  $-0.151$  electrons.

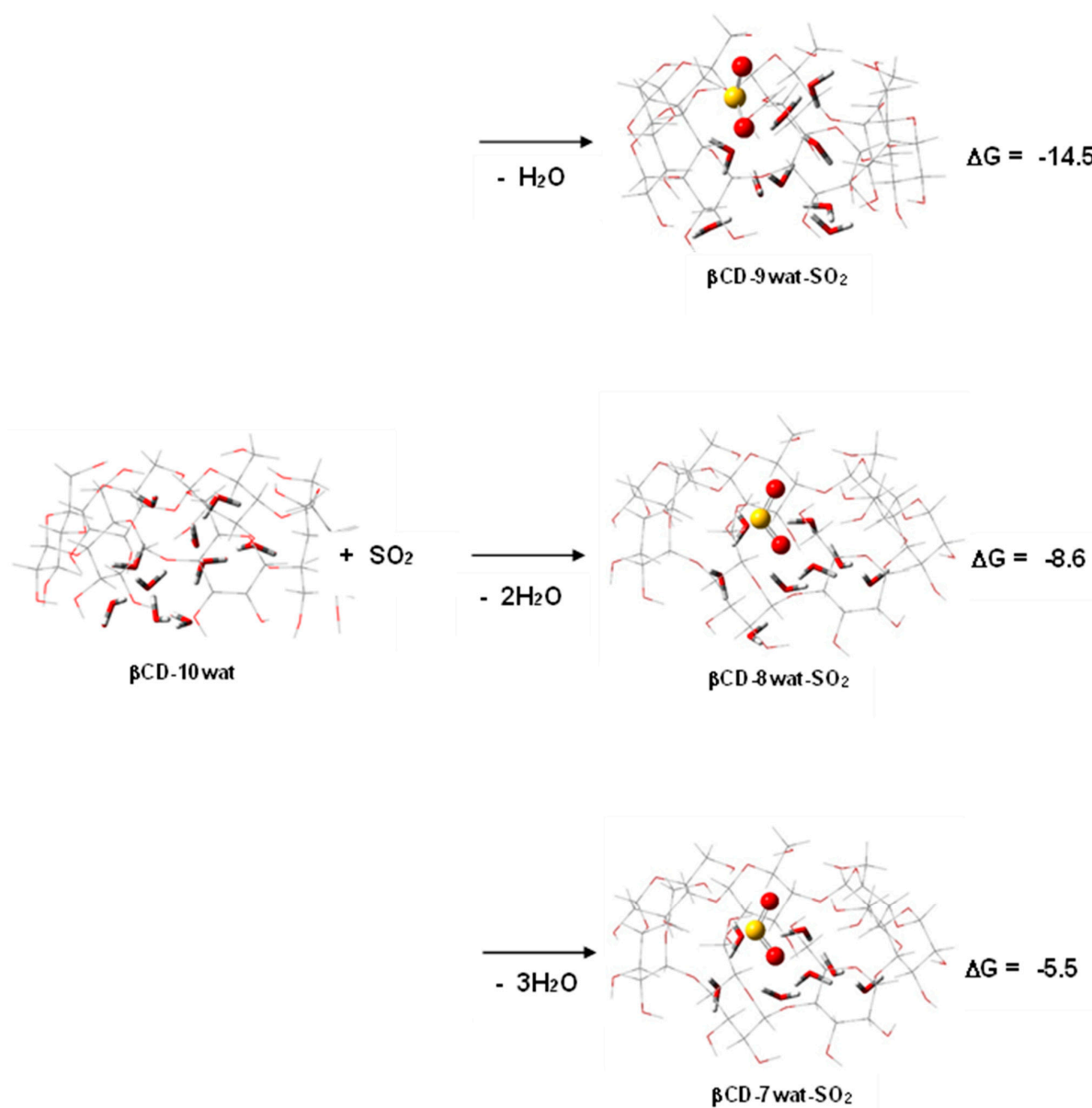


**Figure 5.** M062X/6-31G\* fully optimized structures of  $\beta$ -CD complexes with water and HCN ( $\beta$ -CD:Nwat:HCN signifies a complex between  $\beta$ -cyclodextrin, N molecules of water and gaseous HCN; N = 9, 8, 7), and the respective Gibbs free energies of complex formation (in kcal/mol; 1 kcal/mol = 4.184 kJ/mol). Color scheme: C—gray, H—white, O—red, N—blue.



**Figure 6.** M062X/6-31G\* fully optimized structures of  $\beta$ -CD complexes with water and  $\text{NO}_2$  ( $\beta$ -CD:Nwat: $\text{NO}_2$  signifies a complex between  $\beta$ -cyclodextrin, N molecules of water and gaseous  $\text{NO}_2$ ; N = 9, 8, 7), and the respective Gibbs free energies of complex formation (in kcal/mol; 1 kcal/mol = 4.184 kJ/mol). Color scheme: C—gray, H—white, O—red, N—blue.

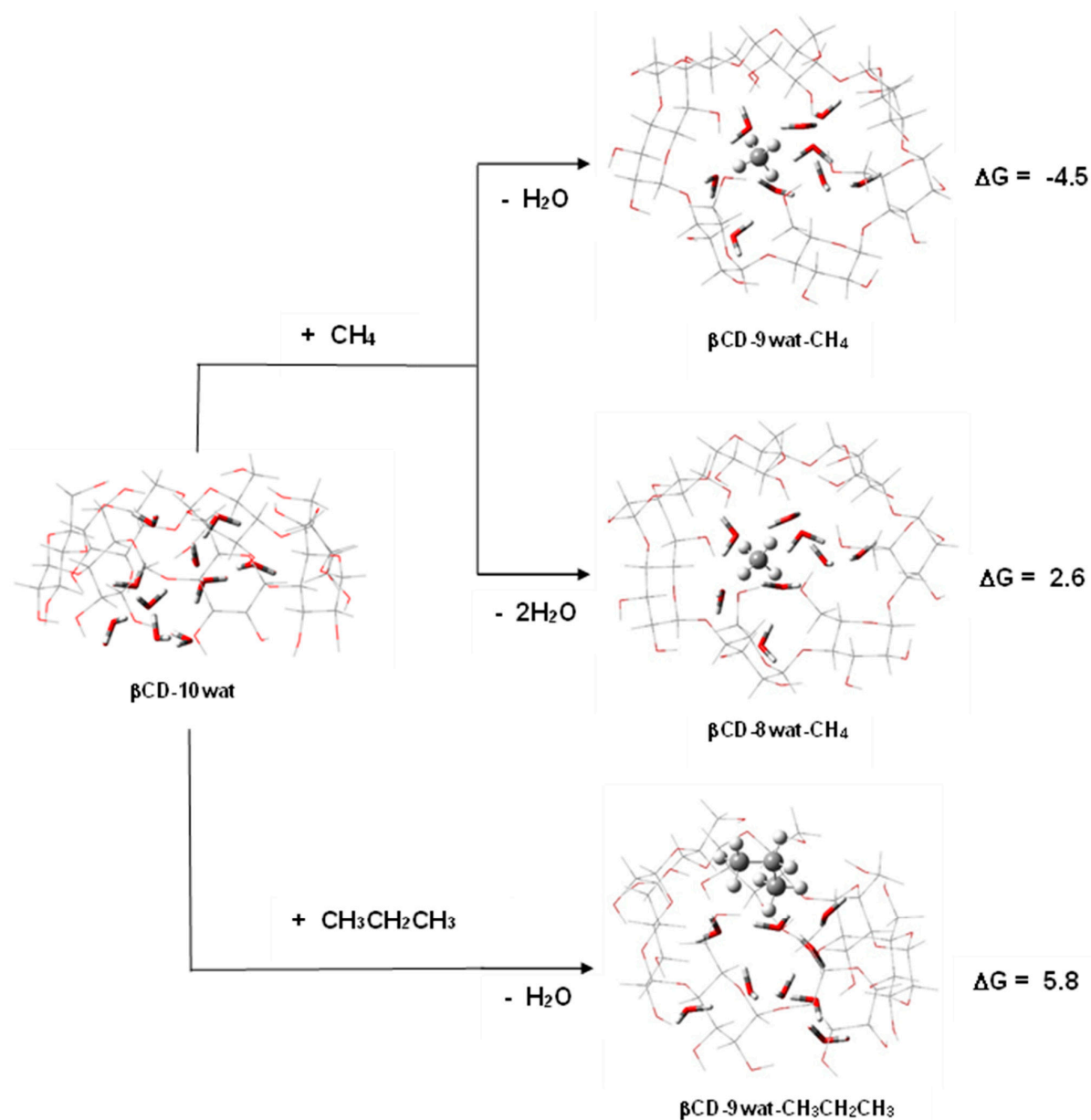




**Figure 7.** M062X/6-31G\* fully optimized structures of  $\beta$ -CD complexes with water and  $\text{SO}_2$  ( $\beta\text{-CD:Nwat:SO}_2$  signifies a complex between  $\beta$ -cyclodextrin, N molecules of water and gaseous  $\text{SO}_2$ ; N = 9, 8, 7), and the respective Gibbs free energies of complex formation (in kcal/mol; 1 kcal/mol = 4.184 kJ/mol). Color scheme: C—gray, H—white, O—red, S—yellow.

### 2.3. Saturated Hydrocarbons—Methane and Propane

Complexes of some representatives of the group of natural fuel gases (methane and propane) were also modeled, and the respective thermodynamic parameters were evaluated (Figure 8). These molecules, unlike the previous ones (see above), do not possess highly negatively charged atoms, and their dipole moments are either non-existent (methane) or very tiny (propane with  $\mu = 0.083$  Debye [44]). Expectedly, the interactions with the host cavitand are rather weak, and, as seen (Figure 8), the encapsulation of the bulkier propane seems impossible (large positive  $\Delta G$ ), whereas the methane binding to  $\beta$ -CD seems (slightly) favorable for the first  $\text{CH}_4 \rightarrow \text{water}$  exchange only. The calculations imply that, as a whole, the affinity of  $\beta$ -CD toward light-saturated hydrocarbons is quite low.



**Figure 8.** M062X/6-31G\* fully optimized structures of  $\beta$ -CD complexes with water, methane and propane, and the respective Gibbs free energies of complex formation (in kcal/mol; 1 kcal/mol = 4.184 kJ/mol). Color scheme: C—gray, H—white, O—red.

### 3. Methods

The water, gas molecules, and  $\beta$ -CD and its respective inclusion complexes were modeled explicitly. Note that  $\text{NO}_2$  is a radical in the ground state with multiplicity of 2, while the multiplicity of the other reagents is 1. The most energetically favorable structure of the  $\beta$ -CD macrocycle was considered, i.e., “closed” configuration, characterized by internal hydrogen bonds arranged in a “tail-head” fashion of the constituent -OH groups from both narrow and wide rims of the molecule [24,45] (Figure 1). The host  $\beta$ -CD, in line with earlier estimates [24], was modeled in its fully hydrated form, comprising 10 water molecules populating the internal cavity. The following complex formation reaction was considered:



where  $N = 10, 9, 8, 7, 6$ , or  $0$ .

The geometries of all interacting entities as well as those of the resultant inclusion complexes were optimized at the M062X/6-31G\* level of theory using the Gaussian 09 package of programs [46]. Minnesota M062X functional in combination with split-valence double- $\zeta$  basis set was employed in the computations as it has been proven to be reliable in reproducing geometrical parameters of a number of macrocyclic compounds and their inclusion complexes [23,24,43]. Vibrational frequencies (none of them imaginary), thermal energies,  $E_{th}$ , and entropies,  $S$ , at  $T = 25\text{ }^{\circ}\text{C}$  and 1 atm pressure were evaluated at the same level of theory. The electronic energies,  $E_{el}$ , were corrected at a higher level of theory (M062X/6-31+G\*\*) via single-point calculations on the M062X/6-31G\* optimized structures. Taking into account the differences in the respective quantities between the products and reactants in Equation (1), the Gibbs free energy for the process was evaluated as

$$\Delta G = \Delta E_{el} + \Delta E_{th} + \Delta pV - T\Delta S \quad (2)$$

where  $\Delta pV$  is a work term accounting for the difference in the number of moles in the two sides of Equation (1).

The ChelpG population analysis scheme [47], based on reproduction of the molecular electrostatic potential by fitting the atomic charges, was used in evaluating the atomic charges of the guest molecules.

#### 4. Conclusions

The complexation of a series of gas molecules by  $\beta$ -CD was studied. Notably, the interactions in these systems are electrostatic in nature (dipole-dipole interactions), and, therefore, the present analysis based on the electric charge distribution and polarity of the participating entities, in combination with the characteristic thermodynamic properties, is able to capture the major factors determining the encapsulation process. The results from the present calculations reveal that the host macrocycle is quite efficient in trapping polar substances, such as  $\text{N}_2\text{O}$ , HCN,  $\text{NO}_2$ , and  $\text{SO}_2$ , or non-polar entities, which possess strong electronegative centers ( $\text{CO}_2$ ). Generally, the effectiveness of the gas encapsulation increases with the increasing polarity of the guest molecule. On the other side,  $\beta$ -CD does not appear to be an appropriate host for binding saturated non-polar hydrocarbons (methane and propane in this case).

Our finding that  $\beta$ -CD favors the complexation of polar gas molecules seems, at first glance, at odds with the notion that the inner cavity of the host is mostly hydrophobic and, thus, is expected to tolerate the encapsulation of predominantly non-polar species. Things, however, fall into place when the role of water in the process is considered. At ambient temperature,  $\beta$ -CD can accommodate up to ten water molecules in its internal cavity, which form strong hydrogen bonds among themselves and with the -OH groups from the upper and lower rims of the cavitand [24]. When a polar gas molecule inserts itself into the  $\beta$ -CD central cavity, it, in fact, hardly interacts with the hydrophobic walls of the host but is immersed into a pool of  $\text{H}_2\text{O}$  molecules (and -OH dipoles), which provides a “friendly” hydrophilic medium for the incoming substance (Figure 3). As the calculations suggest, the richer the water cloud around the guest entity and the more elaborate the resultant hydrogen-bond network in the cavity, the more efficient the encapsulation process is.

**Author Contributions:** Conceptualization, T.D. and T.S.; Validation, T.D.; Formal analysis, T.S.; Investigation, T.D. and T.S.; Writing—original draft, T.D. and T.S. All authors have read and agreed to the published version of the manuscript.

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