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COMPLEXES OF α-, β-, AND γ-CYCLODEXTRINS WITH NITROPHENOLS: A THEORETICAL STUDY OF THE STRUCTURE AND ENERGY

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Detailed quantum mechanical calculations of the interaction of cyclodextrin (α-, β-, and γ-CD) with 4-nitrophenol (**I**), 4-nitro-2,6-dimethylphenol (**II**), 4-nitro-3,5-dimethylphenol (**III**), and their anions (**IV**-**VI**) with the formation of intercalation complexes are carried out for the first time. The calculations of the compounds are performed within the density functional theory by the hybrid Becke–Lee–Yang–Parr (B3LYP) method with LanL2DZ basis sets. For the α-CD+**III** and α-CD+**VI** complexes it is shown that a nitrophenol molecule of **III** and a nitrophenolate anion of **VI** are not contained in the α-CD torus, which agrees with the experimental equilibrium constants. It is found that the calculated equilibrium constants of the formation of guest–host complexes with phenolate anions are much larger than those of neutral molecules. The most stable CD complexes with nitrophenols and their anions should be expected for γ-CD. The β-CD complexes when the guest enters into the host cavity are formed only with compounds **I**, **V**, and **VI**.

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INTRODUCTION

In recent years the investigation of the structure and energy of complexes of the guest–host type have been of great importance in various fields of physics, chemistry, biology, and medicine. Complexes of cyclodextrins (CDs) with organic molecules are one of the most extensively studied objects in the chemistry of inclusion compounds. This is due to the appearance of completely new properties of these complexes in comparison with those of guest molecules. For instance, chromophoric properties appear. Effects of increasing solubility of organic molecules in aqueous solutions in the composition of complexes with CDs were discovered. The pharmacological activity of biologically active compounds is enhanced, the duration of therapeutic action of drugs increases. The stability of organic molecules in physiological solutions rises on storage.

In the solid state CD complexes are usually divided into three wide categories: cellular (when a guest molecule is sufficiently small for the complete inclusion into a CD cavity); channel (when a guest is not accommodated in one CD cavity and several CD molecules are required); and finally, layered complexes having a quite intricate structure. Here, we consider only cellular complexes.

Insufficient attention has been paid to the study of the bond nature in CD complexes. There are only clues to the especially significant factors of the formation of complexes in which a guest is incorporated into a CD cavity. These factors

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are as follows [1]: sterical correspondence, i.e. the guest molecule thickness should not exceed the CD cavity diameter; van der Waals type interactions; dipole-dipole interactions; charge transfer interactions and hydrogen bonds.

In general, the possible guest size increases with the CD host cavity, i.e. on passing from α- to β- and γ-CD. However, the structure of the CD host is relatively flexible, therefore the size correspondence between a guest and a host is not a strict criterion.

According to Connors [2], the free energy of complexation can be presented by the following expression:

$$\Delta G^{*}_{\text{comp}} = \Delta G_{\text{intrasolute}} + \Delta G_{\text{solvation}} + \Delta G_{\text{gen med}}. \quad (1)$$

In this expression $\Delta G_{\text{intrasolute}}$ involves hydrogen bonds, dipole-dipole interactions, and van der Waals forces; $\Delta G_{\text{solvation}}$ is the difference between the free energy of solvation of the complex and the sum of free energies of solvation of the individual guest and host. The last term is related to hydrophobic interactions and has a sophisticated nature. In three contributions, the first term in expression (1) is dominant (1), and we focus on its role in this report.

In [3] α-CD and *p*-nitrophenol complexes were studied using the DFT method (3-21g, 3-21+g** basis set) and crystallography; the optimized structures of the complexes are compared with the experimental results. In the review [4] theoretical studies of the structure and physicochemical properties of CDs and their complexes performed in 1998-2003 are discussed. As a rule, the calculations of inclusion complexes of organic molecules with CDs are based on either molecular mechanics methods or semi-empirical quantum chemical methods. Sometimes, after the performance of these calculations the only higher level calculation, e.g. by the Hartree–Fock or DFT method, is carried out for the obtained geometry of the complex. For instance, in [5] inclusion complexes of β-CD with bisphenol A, biphenol, and isopropylphenol were analyzed by NMR; the experimental results were compared with the calculated ones obtained by AM1 (geometry optimization) and DFT (SP, energy in one point) methods. In [6] by means of the AM1 method complexes of α-CD and β-CD with benzoic acid and phenol were studied. It is shown that out of two possible orientations of a guest in α-CD the head-first structure is more favorable, and for β-CD, on the contrary, the tail-first structure is more favorable. In [7] the detailed calculations of inclusion complexes of optical isomers of histidine in γ-CD were carried out by the DFT method and it is shown that the L-isomer is more strongly bonded to CD.

EXPERIMENTAL

The calculations of the compounds and their complexes were performed at the DFT level [8]. The hybrid Becke–Lee–Yang–Parra (B3LYP) method with LanL2DZ basis sets was applied [9, 10]. All calculations with the full optimization of molecular geometries and the calculation of normal vibrational frequencies were carried our using the GAUSSIAN-09 program [11] in the LINUX kernel.

RESULTS AND DISCUSSION

In this work, detailed quantum mechanical calculations of the interaction of 4-nitrophenol (**I**), 4-nitro-2,6-dimethylphenol (**II**), 4-nitro-3,5-dimethylphenol (**III**) and their anions (**IV-VI**) with α-, β-, and γ-CD with the formation of inclusion complexes were performed for the first time. Table 1 lists the calculation results of the total energies of the compounds and inclusion complexes under study. Here E_t is the total energy of a molecular system.

$$E_{\text{ZPC}} = E_t + \text{ZPC};$$

$$E_H = E_t + \text{ZPC} + E_{\text{vib}} + E_{\text{rot}} + E_{\text{trans}},$$

$$E_G = E_H - TS,$$

where ZPC is the zero point correction; E_{vib} is the energy of the vibrational motion; E_{rot} is the energy of the rotational motion; E_{trans} is the energy of the translational motion; S is the entropy; is the Kelvin temperature.

Based on the energy and entropy values given in Table 1, it is possible to calculate changes in the energies and entropies caused by complexation. These data are summarized in Table 2.

TABLE 1. Calculation Results of Energies and Entropies of α-, β-, and γ-CD, Nitrophenols and Their Anions **I-VI** and Complexes of the Guest–Host Type

System	E_t, au	E_{ZPC}, au	E_G*, au	S, kcal/mol·deg
α-CD	–3664.0253	–3662.9909	–3663.0906	350.4
4-Nitrophenol (**I**)	–511.8999	–511.7933	–511.8265	88.6
4-Nitro-2,6-dimethylphenol (**II**)	–590.5263	–590.3639	–590.4012	104.5
4-Nitro-3,5-dimethylphenol (**III**)	–590.5169	–590.3543	–590.3909	102.6
4-Nitrophenolate anion (**IV**)	–511.3780	–511.2842	–511.3171	87.2
4-Nitro-2,6-dimethylphenolate anion (**V**)	–590.0034	–589.8539	–589.8910	103.3
4-Nitro-3,5-dimethylphenolate anion (**VI**)	–589.9878	–589.8377	–589.8741	100.7
α-CD+**I**	–4175.9439	–4174.7994	–4174.9094	390.5
α-CD+**II**	–4254.5646	–4253.3644	–4253.4780	405.4
α-CD+**III**	–4254.5647	–4253.3650	–4253.4793	407.1
α-CD+**IV**	–4175.4514	–4174.3175	–4174.4213	374.0
α-CD+**V**	–4254.0584	–4252.8696	–4252.9794	395.1
α-CD+**VI**	–4254.0786	–4252.8910	–4253.0045	402.3
β-CD	–4274.8313	–4273.6189	–4273.7282	388.8
β-CD+**I**	–4786.7709	–4785.4485	–4785.5666	424.6
β-CD+**II**	–4865.3937	–4864.0157	–4864.1377	440.0
β-CD+**III**	–4865.3661	–4863.9891	–4864.1152	450.5
β-CD+**IV**	–4786.2691	–4784.9603	–4785.0796	427.2
β-CD+**V**	–4864.8963	–4863.5318	–4863.6519	436.0
β-CD+**VI**	–4864.8875	–4863.5216	–4863.6399	429.7
γ-CD	–4885.4789	–4884.0961	–4884.2206	447.8
γ-CD+**I**	–5397.4330	–5395.9389	–5396.0742	486.8
γ-CD+**II**	–5476.0579	–5474.5084	–5474.6479	503.0
γ-CD+**III**	–5476.0497	–5474.4998	–5474.6373	498.4
γ-CD+**IV**	–5396.9433	–5395.4631	–5395.5987	486.9
γ-CD+**V**	–5475.5639	–5474.0282	–5474.1655	497.9
γ-CD+**VI**	–5475.5688	–5474.0313	–5474.1673	493.0

* Calculation of E_G was performed at 298.15 K.

In [12] equilibrium constants of the formation of guest–host complexes were found experimentally for α-CD and nitrophenols **I-VI**. For α-CD+**III** and α-CD+**VI** complexes the experimental data indicate the zero equilibrium constant. Our calculations of α-CD+**III** and α-CD+**VI** complexes show that the nitrophenol molecule of **III** and the nitrophenolate anion of **VI** does not enter into the α-CD torus and makes bonds with external hydroxyl groups. The equilibrium constant is related to the Gibbs free energy by the following expression: $\Delta G = -RT \ln K$. Based on the data on the Gibbs free energy of the complexes, which were obtained in our calculations and the experimental equilibrium constants [12] it is possible to formulate the linear relationship. In the determination of regression parameters we must exclude from the consideration complexes with nitrophenols **III** and **VI**, for which zero experimental constants were obtained. The formulated linear equation has the following parameters: $\lg K_{11} = 2.75 - 0.088\Delta E_G$; $R = 0.91$; $F(1,2) = 9.51$; $P = 0.09$, where $K_{11} = [LS]/[L][S]$, see [2, 12], R is the correlation coefficient; F is the Fisher criterion; P is the confidence probability. The equilibrium constants calculated by this equation are given in Table 3.

Comparing the equilibrium constants of the formation of guest–host complexes for α-CD and γ-CD, it is possible to note that phenolate anions have much larger K_{11} than the neutral molecules. This is especially evident for γ-CD complexes.

TABLE 2. Calculation Results of Changes in the Energies and Entropies during the Formation of Guest–Host Complexes

System	ΔE_t, kcal/mol	ΔE_{ZPC}, kcal/mol	ΔE_G, kcal/mol	ΔS, kcal/mol	Guest coordination in the host
α-CD+**I**	–11.72	–9.50	+4.83	–48.6	Inside the torus
α-CD+**II**	–8.13	–6.01	+8.68	–49.5	»
α-CD+**III**	–15.87	–12.46	+1.38	–45.6	Outside the torus
α-CD+**IV**	–30.18	–26.56	–8.51	–63.6	Inside the torus
α-CD+**V**	–18.61	–15.54	+1.35	–58.6	»
α-CD+**VI**	–41.11	–39.13	–24.99	–48.8	Outside the torus
β-CD+**I**	–24.85	–22.67	–7.42	–52.8	Inside the torus
β-CD+**II**	–22.63	–20.68	–5.24	–53.2	Outside the torus
β-CD+**III**	–11.19	–10.02	+2.47	–40.8	»
β-CD+**IV**	–37.47	–35.88	–21.50	–48.8	»
β-CD+**V**	–38.65	–37.02	–20.55	–56.1	Inside the torus
β-CD+**VI**	–42.93	–40.78	–23.62	–59.8	»
γ-CD+**I**	–33.95	–31.05	–17.02	–49.6	»
γ-CD+**II**	–33.02	–30.37	–16.41	–49.2	»
γ-CD+**III**	–33.79	–31.06	–16.21	–51.9	»
γ-CD+**IV**	–54.19	–51.91	–38.28	–48.1	»
γ-CD+**V**	–51.18	–49.04	–33.87	–53.2	»
γ-CD+**VI**	–64.11	–61.16	–45.63	–55.5	»

From the obtained results it follows that the most stable complexes with nitrophenols should be expected for γ-CD. The β-CD complexes with nitrophenols and their phenolate anions when a guest enters into the host cavity are the least and form only with compounds **I**, **V**, and **VI**. This is quite surprising because for β-CD the torus radius is, as mentioned above, intermediate as compared to other CDs. We additionally calculated complexes in which a guest did not enter into the host and confirmed this fact. Effects of the electronic character, which are still difficult for identification, seem to be important here.

Fig. 1 shows the structure of α-CD+**I** and α-CD+**II** inclusion complexes; Fig. 2 shows the structures of α-CD+**IV** and α-CD+**V**. The given structures as well as the other studied complexes are characterized by that a guest enters into the host cavity from the side of the nitro group. Fig. 3 depicts the calculated vibrational and rotational-vibrational spectra of the α-CD+**I** inclusion complex.

TABLE 3. Calculated Logarithms of Equilibrium Constants of the Formation of Guest–Host Complexes. Experimental Values [2, 12] are Given in Parentheses

System	ΔE_G, kcal/mol	$\lg K_{11}$	Guest coordination in the host	System	ΔE_G, kcal/mol	$\lg K_{11}$	Guest coordination in the host
α-CD+**I**	+4.83	2.32 (2.28)	Inside the torus	β-CD+**IV**	–21.50		Outside the torus
α-CD+**II**	+8.68	1.98 (1.78)	»	β-CD+**V**	–20.55	4.64	Inside the torus
α-CD+**III**	+1.38	(0)	Outside the torus	β-CD+**VI**	–23.62	4.83	»
α-CD+**IV**	–8.51	3.49 (3.33)	Inside the torus	γ-CD+**I**	–17.02	4.24	»
α-CD+**V**	+1.35	2.63 (3.07)	»	γ-CD+**II**	–16.41	4.19	»
α-CD+**VI**	–24.99	(0)	Outside the torus	γ-CD+**III**	–16.21	4.18	»
β-CD+**I**	–7.42	3.40	Inside the torus	γ-CD+**IV**	–38.28	6.11	»
β-CD+**II**	–5.24		Outside the torus	γ-CD+**V**	–33.87	5.73	»
β-CD+**III**	+2.47		»	γ-CD+**VI**	–45.63	6.75	»

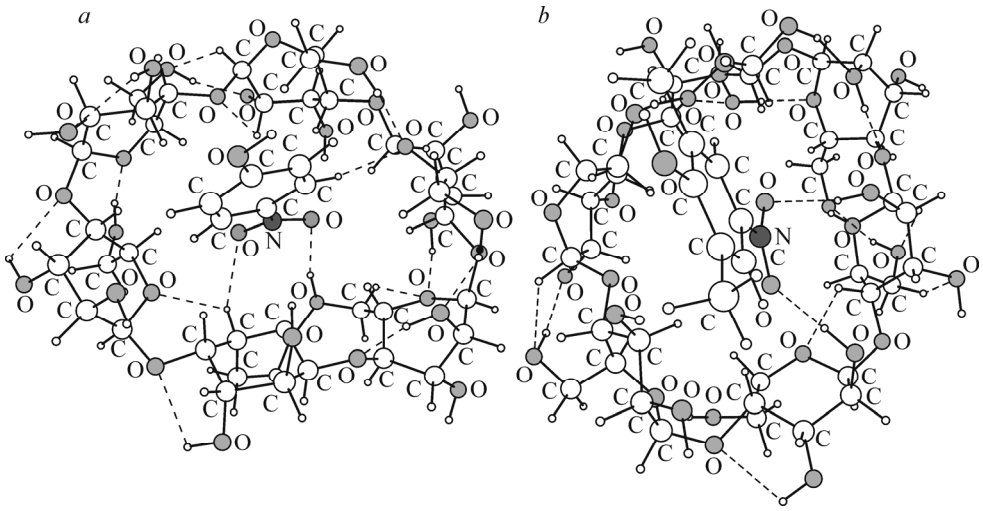

Fig. 1. Structures of α-CD+**I** (*a*) and α-CD+**II** (*b*) inclusion complexes.

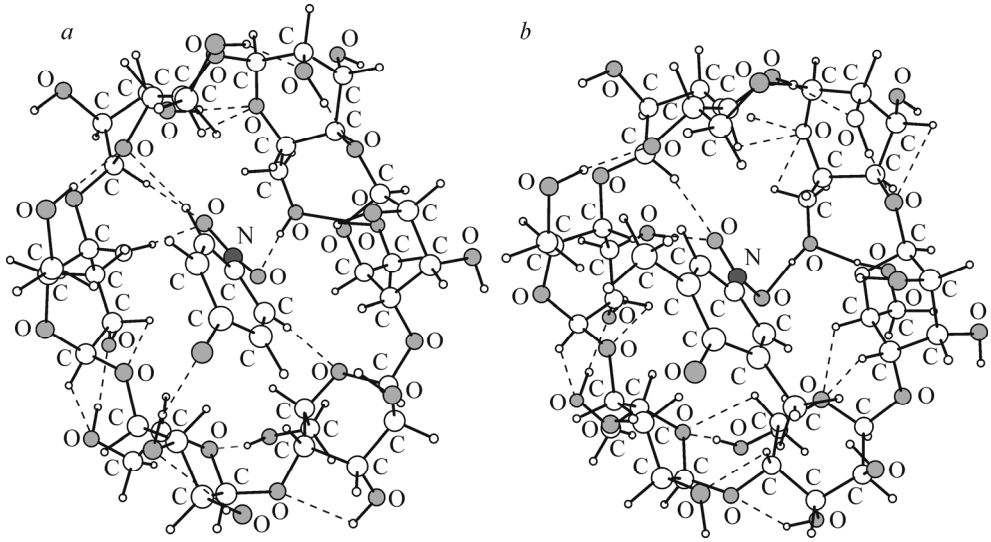

Fig. 2. Structures of negatively charged α-CD+**IV** (*a*) and α-CD+**V** (*b*) inclusion complexes.

The spectra of this complex and also of all the other studied complexes contain well discernable low-intensity bands in the range 1610-1670 cm^{-1}, which are typical of benzene ring vibrations and can be used to identify nitrophenol CD inclusion complexes.

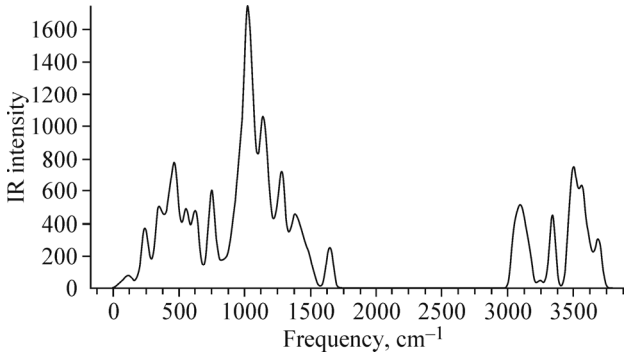

Fig. 3. Calculated vibrational and rotational-vibrational spectra of the α-CD+**I** inclusion complex.

CONCLUSIONS

Thus, in this work it is shown that for α-CD and γ-CD the formation of inclusion complexes with nitrophenolate anions is more favorable than with the neutral molecules. At the same time, the most stable complexes with all nitrophenols studied should be expected for γ-CD.

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