UDC 547.03+547.562 DOI: 10.24959/zofh.17.910

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# The study of calixarenes complexation with phenols by RP HPLC

The Host-Guest complexation of octakis(diphenoxyphosphoryloxy)tetramethylcalix[4]resorcinarene, 5,17-bis-(N-tolyliminomethyl)-25,27-dipropoxycalix[4]arene and 5,11,17,23-tetrakis(diisopropoxyphosphonyl)-25,26,27,28-tetrapropoxycalix[4]arene with a series of 11 phenols (phenol, p-fluorophenol, p-chlorophenol, p-bromophenol, pyrogallol, p-cresol, p-aminophenol, p-nitrophenol, salicylic aldehyde, guaiacol and veratrole) has been studied by the high-performance liquid chromatography (RP HPLC) method. Chromatographic characteristics and log P of industrial phenols have been determined. Using the relationship of the phenol retention factor k' vs the calixarene concentration in the mobile phase the stability constants of the supramolecular complexes $K_A$ (29-331 $M^{-1}$) have been determined. The stability constants of the calixarene complexes show that the Host-Guest interaction strongly depends on the nature of the substituents in the Host and Guest molecules. Calixresorcinarene functionalized by diphenoxyphosphoryl groups and calixarene containing tolyliminomethyl groups formed more stable complexes with some phenols compared to calixarene functionalized by diisopropoxyphosphonyl groups. In accordance with the molecular modeling data the complexation does not change the C2v flattened-cone conformation of the calixarene skeleton. The Host-Guest complexes are stabilized by the intermolecular hydrogen bonds of phenolic OH groups with oxygen atoms of P = O groups at the upper rim, and OH groups at the lower rim of the macrocycle. Hydrophobic interactions also participate in the complexation.

***Key words:*** Calixarenes; phenols; inclusion complexes; binding constants; molecular modeling

**О. І. Кальченко, С. О. Черенок, А. В. Соловйов, С. Ю. Суйков, В. І. Кальченко**
**Дослідження комплексоутворення каліксаренів з фенолами методом ОФ ВЕРХ**

Комплексоутворення типу гість-господар октакіс-(дифеноксифосфорилокси)-тетраметилкалікс[4]резорцинарену, 5,17-біс-(N-толілімінометил)-25,27-дипропоксикалікс[4]арену та 5,11,17,23-тетракіс (діізопропоксифосфоніл)-25,26,27,28-тетрапропоксикалікс[4]арену з низкою 11 фенолів (фенол, п-фторофенол, п-хлорофенол, п-бромофенол, пірогалол, п-крезол, п-амінофенол, п-нітрофенол, саліциловий альдегід, гваякол, вератрол) було досліджено методом високоефективної рідинної хроматографії (ОФ ВЕРХ). Визначені хроматографічні характеристики фенолів та розраховано значення їх ліпофільності log P. З урахуванням залежності коефіцієнтів утримання фенолів k' від концентрації каліксаренів у рухомій фазі визначені константи стійкості їх супрамолекулярних комплексів $K_A$, які знаходяться в межах 29-331 $M^{-1}$. Значення констант стійкості комплексів вказують на те, що взаємодія типу гість-господар значною мірою зумовлена природою замісників у молекулах гостя та господаря. Каліксрезорцинарен, функціоналізований дифеноксифосфорилокси-групами, і каліксарен, що містив толіліміно-групи, утворювали стійкіші комплекси з деякими фенолами порівняно з каліксареном, що містив діізопропоксифосфонільні групи. За даними молекулярного моделювання комплексоутворення не змінює конформацію каліксаренового кістяка C2v сплощений конус. Комплекси типу гість-господар стабілізуються міжмолекулярними водневими зв'язками фенольних ОН-груп з атомами кисню P = O груп верхнього вінця і ОН-груп нижнього вінця макроциклу. Гідрофобні взаємодії також відіграють роль у комплексоутворенні.

***Ключові слова:*** каліксарени; феноли; комплекси включення; константи зв'язування; молекулярне моделювання

**О. И. Кальченко, С. О. Черенок, А. В. Соловьев, С. Ю. Суйков, В. И. Кальченко**
**Исследование комплексообразования каликсаренов с фенолами методом ОФ ВЭЖХ**

Комплексообразование типа гость-хозяин октакис-(дифеноксифосфорилокси)-тетраметилкаликс[4]резорцинарена, 5,17-бис-(N-толилиминометил)-25,27-дипропоксикаликс[4]арена и 5,11,17,23-тетракис диизопропоксифосфонил)-25,26,27,28-тетрапропоксикаликс[4]арена с серией 11 фенолов (фенол, п-фторфенол, п-хлорфенол, п-бромфенол, пирогаллол, п-крезол, п-аминофенол, п-нитрофенол, салициловый альдегид, гваякол, вератрол) было исследовано методом высокоэффективной жидкостной хроматографии (ОФ ВЭЖХ). Определены хроматографические характеристики фенолов и рассчитаны значения их липофильности log P. С использованием зависимости коэффициентов удерживания фенолов k' от концентрации каликсаренов в подвижной фазе определены константы устойчивости их супрамолекулярных комплексов $K_A$, которые находятся в пределах 29-331 $M^{-1}$. Значения констант устойчивости показали, что взаимодействие типа гость-хозяин в значительной мере зависит от природы заместителей в молекулах Гостя и Хозяина. Каликсрезорцинарен, функционализованный дифеноксифосфорилокси-группами, и каликсарен, содержащий толилиминометильные группы, давали более устойчивые комплексы с некоторыми фенолами, чем каликсарен с диизопропоксифосфонильными группами. Согласно данным молекулярного моделирования комплексообразование не приводит к изменению конформации каликсаренового скелета уплощенный конус C2v. Комплексы типа гость-хозяин стабилизируются межмолекулярными водородными связями фенольных ОН-групп с атомами кислорода P = O групп верхнего обода макроцикла и ОН-групп его нижнего обода. Гидрофобные взаимодействия также играют роль в комплексообразовании.

***Ключевые слова:*** каликсарены; фенолы; комплексы включения; константы связывания; молекулярное моделирование

Calixarenes [1], bowl-shaped macrocyclic compounds are versatile platforms in the design of molecular receptors capable to recognize, bind and separate different organic and inorganic molecules similar in size and properties [2]. Calixarenes are able to recognize amino acids [3, 4, 5], dipeptides [6], nucleotides, nucleosides [7] and environmentally hazardous molecules [8, 9, 10]. Apparently, the outstanding receptor properties of functionalized calixarenes toward different (bio)molecules make them highly promising Hosts for sensor technologies [11, 12, 13] or for bio-medical research [14, 15, 16].

The class of phenols is important as a component of many useful industrial materials, pharmaceuticals, herbicides, disinfectants, etc. Phenols are essential raw material and additives for laboratory processes, chemical industry, chemical engineering processes, wood and plastics processing [17].

Phenolic compounds are commonly synthesized industrially; however, they are also produced by plants and microorganisms [18]. Organisms that synthesize phenolic compounds do so in response to ecological pressures, such as pathogen and insect attack, UV radiation and wounding [19]. Phenols are found in the natural world, especially in the plant kingdom, such as fruits, vegetables, herbs, spices and unfiltered olive oil [20].

In animals and humans, after ingestion, natural phenols become part of the xenobiotic metabolism. These activated metabolites are conjugated with charged species, such as glutathione, sulfate, glycine or glucuronic acid. As they are present in food consumed in human diets and in plants used in traditional medicine of several cultures, their role in human health and disease is a subject of research. Some natural phenols can be used as biopesticides [21, 22].

Phenols (aspirin and paracetamol, first of all) are widely used as inflammatory drugs [23]. Crofelemer is applied for the treatment of diarrhea. Phenolic compound Combretastatin is active as an anticancer drug [24].

In this paper the results of studying the Host-Guest complexation of octakis(diphenoxyphosphoryloxy)-tetramethylcalix[4]resorcinarene (**CA-1)**, 5,17-bis-(N-tolyliminomethyl)-25,27-dipropoxycalix[4]arene (**CA-2**) and 5,11,17,23-tetrakis(diisopropoxyphosphonyl)-25,26,27,28-tetrapropoxycalix[4]arene (**CA-3**) with a series of phenols (phenol **1**, *p*-fluorophenol **2**, *p*-chlorophenol **3**, *p*-bromophenol **4**, pyrogallol **5**, *p*-cresol **6**, *p*-aminophenol **7**, *p*-nitrophenol **8**, salicylic aldehyde **9**, guaiacol **10**, veratrole **11**) (Fig. 1) in the acetonitrile-water solution by the RP HPLC methods are presented. The stability constants of the complexes were determined. The mechanism of the Host-Guest complexation was studied by the molecular modeling method. The information on the supramolecular Host-Guest interaction of calixarenes with phenol derivatives can be useful for design of chemosensors and drug carriers.

## Experimental Part

**CA-1, CA-2, CA-3** were synthesized by the methods [25, 26, 27], respectively. Acetonitrile was obtained from Acros Organics (Thermo Fisher Scientific, New Jersey – USA), and phenols were purchased from Sigma-Aldrich (St. Louis, MO, USA).

**RP HPLC analysis**

RP HPLC analysis was performed using the liquid chromatographic system (Hitachi, Ltd., Tokyo, Japan). The column (250 × 4.6 mm i.d.) was packed with LiChrosorb RP-18 (Merck, Darmstadt, Germany). The UV detector was operated at 254 nm. The flow rate was 0.8 ml/min. Experiments were performed with isocratic conditions. All chromatograms were obtained at 26 °C. The mixture of acetonitrile–water (80 : 20, v/v) was used as a mobile phase. The mobile phases contained calixarene additives in the concentrations of 0.05-0.6 mM. The samples of analytes for injections were dissolved in the same mixture (C = 0.01 mM) of acetonitrile–water (80 : 20, v/v). The volume of the samples injected was 20 μL. For equilibration of the chromatographic column the mobile phase with the calixarene additive was fluxed for 3 h before analysis. Under these conditions the column was saturated with calixarene.

The stability constants $K_A$ of the calixarene complexes with phenols were determined by the RP HPLC method described in [28]. The method is based on changing the phenols retention factor *k'* induced by the complexation with calixarenes in the mobile phase.

**Determination of the *log P* values of phenols**

The values of *log P* of phenols **1-11** (Tab. 1) were calculated from equation 1:

$$log\ P = 2.11 \cdot (\log k'), \qquad (1)$$

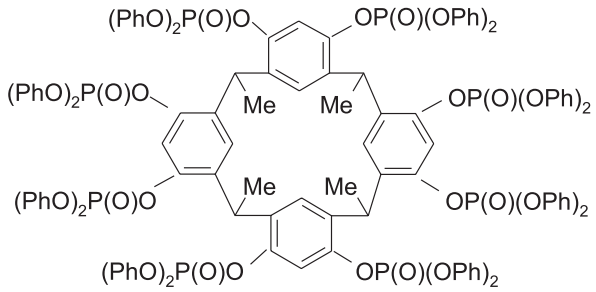
where the coefficient 2.11 is the ratio of the experimental value of *log P* of phenol 1.46 [29] to *log k'* of the phenol value of 0.69 determined by the RP HPLC method in this work. The reason of the experimental determination of lipophilicity was a mismatch of the literature data of the *log P* values of the phenols studied. For example, *log P* of *p*-nitrophenol **9** is 1.96 according to [30] and 1.68 according to [31].

**Molecular modeling**

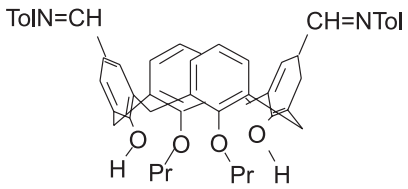
Molecular modeling of calixarenes and their Host-Guest complexes were carried out using the Hyper Chem 8.0 program in the force field (PM3) [32]. The structures were calculated by the semi-empirical method. The RMS (the standard deviation of the word root mean square) gradient was equal to 0.01 kcal/A mol.

## Results and Discussion

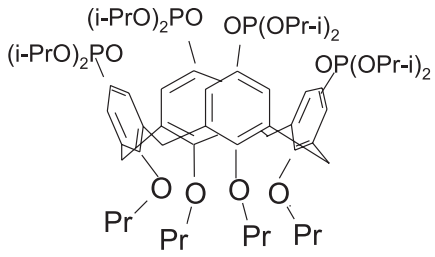
Calixarenes were registered on the chromatograms by sharp peaks with retention factors 8.65 (**CA-1**), 0.89 (**CA-2**) and 2.38 (**CA-3**). As shown, addition of




**CA-1**

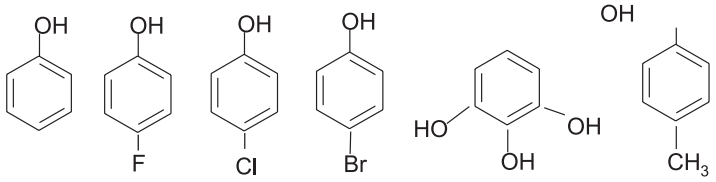



**CA-2**

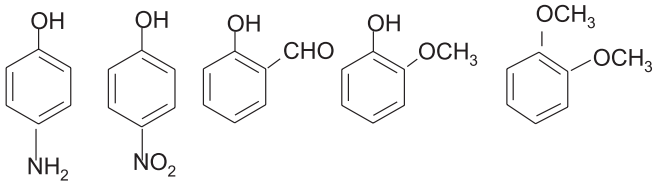



**3**

**CA-3**




**1** **2** **3** **4** **5** **6**




**7** **8** **9** **10** **11**

Fig. 1. Calix[4]arenes **CA-1, CA-2** and **CA-3** (Hosts) and phenols **1-11** (Guests)

**Table 1**

The values of *log P* of phenols **1-11,** the stability constants $K_A$ ($M^{-1}$) (RSD = 9-15 %) and free Gibbs energies *ΔG* (kDj/mol) of their Host-Guest complexes with **CA-1**, **CA-2**, **CA-3**

| No. | Guest | CA-1 | | CA-2 | | CA-3 | | log P |
|---|---|---|---|---|---|---|---|---|
| | | $K_A$ | ΔG | $K_A$ | ΔG | $K_A$ | ΔG | |
| **1** | Phenol | 123 | -11.9 | 211 | -13.24 | 33 | -8.65 | 1.46 |
| **2** | *p*-Fluorophenol | 102 | -11.44 | 141 | -12.24 | 140 | -12.22 | 1.27 |
| **3** | *p*-Chlorophenol | 92 | -11.18 | 240 | -13.56 | 36 | -8.86 | 1.53 |
| **4** | *p*-Bromophenol | 119 | -11.82 | 235 | -13.50 | 29 | -8.33 | 1.49 |
| **5** | Pyrogallol | 116 | -11.76 | 160 | -12.55 | nd | nd | 1.40 |
| **6** | *p*-Cresol | 94 | -11.24 | 216 | -13.29 | nd | nd | 1.49 |
| **7** | *p*-Aminophenol | 306 | -14.16 | 230 | -13.45 | 331 | -14.30 | 1.47 |
| **8** | *p*-Nitrophenol | 166 | -12.64 | 220 | -13.34 | 34 | -8.72 | 1.47 |
| **9** | Salicylic aldehyde | 40 | -9.12 | 141 | -12.24 | 94 | -11.24 | 1.04 |
| **10** | Guaiacol | 209 | -13.21 | 324 | -14.3 | 130 | -12.04 | 2.22 |
| **11** | Veratrole | 80 | -10.84 | 246 | -13.62 | 263 | -13.78 | 1.53 |

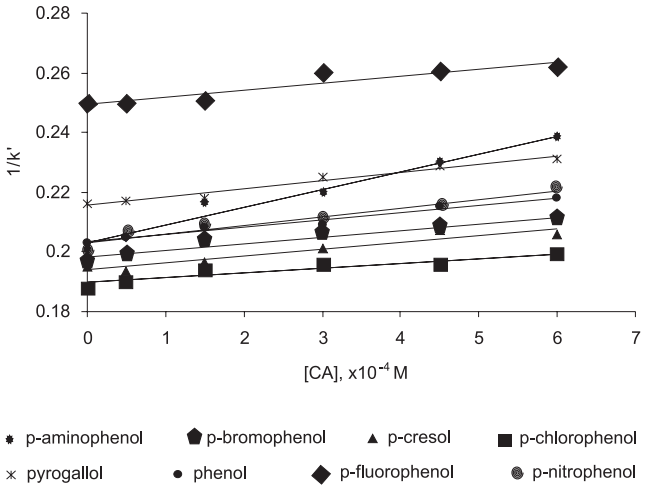



Fig. 2. Plots of 1/*k'* for phenols *vs* the **CA-1** concentration in the mobile phase (r = 0.89-0.98)

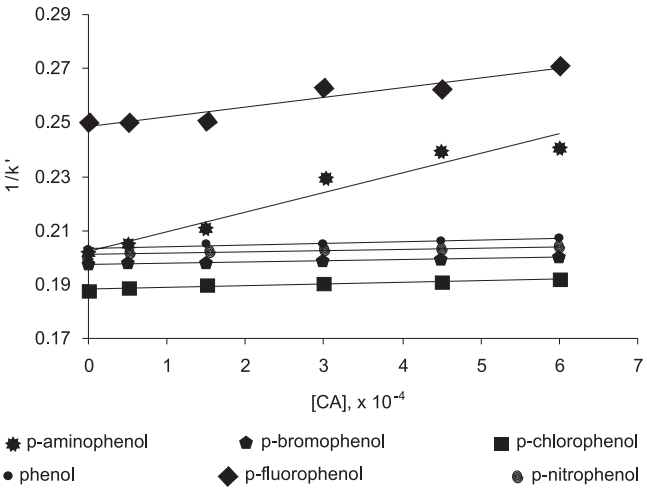



Fig. 4. Plots of 1/*k'* for phenols *vs* the **CA-3** concentration in the mobile phase (r = 0.93-0.96)

calixarene to the mobile phase decreases the retention factors *k'* of phenols **1-11** due to formation of the Host-Guest inclusion complexes. The linear character of plots of 1/*k'* ns the calixarene concentration (Fig. 2-4) indicates 1 : 1 stoichiometry of the Host-Guest supramolecular complexes formed. It allows using equation (2) correctly for calculation of the stability constants $K_A$:

$$1/k' = 1/k_0' + K_A \times [CA]/k_0', \qquad (2)$$

where $k_0'$ і $k'$ – are capacity factors of the Guest molecule determined in the absence and the presence of the calixarene Host in the mobile phase.

The stability constants $K_A$ of the calixarene complexes are within 29-331 $M^{-1}$ (Tab. 1). This is close to the stability constant of the *β*-cyclodextrin – pyrogallol complex determined by the UV-visible ($K_A$ = 78 $M^{-1}$) and fluorescence ($K_A$ = 227 $M^{-1}$) spectroscopy in the water solution [33]. Free Gibbs energies *DG* of the calixarene complexes calculated by equation (3) are from -8.33 to -14.30 kJ/mol (Tab. 1).

$$DG = -RT \cdot \ln K_A \qquad (3)$$

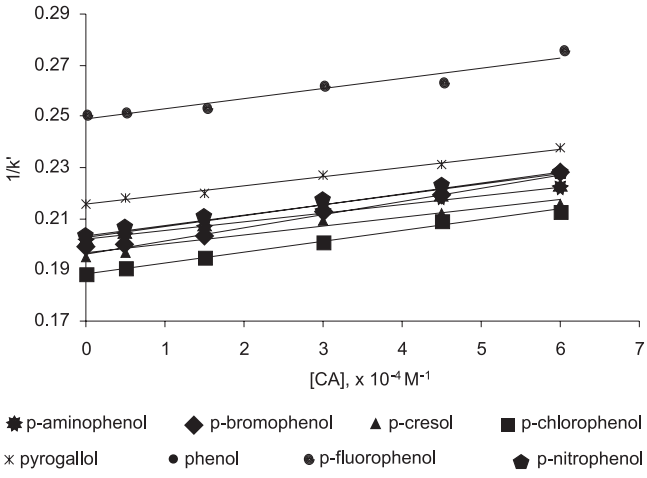



Fig. 3. Plots of 1/*k'* for phenols *vs* the **CA-2** concentration in the mobile phase (r = 0.97-0.99)

To clarify the nature of the Host-Guest interaction the molecular modeling of the calixarene Hosts **CA-1, CA-2 CA-3** and their complexes with *p*-aminophenol and phenol was carried out (Fig. 5).

In accordance with the molecular modeling data the calixarene macrocyclic skeleton of **CA-1**, **CA-2** and **CA-3** and their Host-Guest complexes exist in the *flattened-cone* conformation with C2*v* symmetry. Two aromatic rings in the distal position are "coplanar" oriented, but two other ones are "perpendicular" oriented to the main plane of the macrocycle. The dihedral angles characterized inclination of benzene rings A, B, C, D relatively to the main macrocycle plane formed by $CH_2$ links are presented in Tab. 2. As shown from Tab. 2, the complexation with phenols does not practically change dihedral angles in the calixarene macrocyclic skeleton.

In all complexes formation of the intermolecular hydrogen bonds between OH groups of phenols and oxygen atoms of calixarenes are observed (H···O distances are within 2.91-3.19 Å). In complex (**a**) OH and $NH_2$ groups of *p*-aminophenol form the hydrogen bonds with oxygen atoms of distal P = O groups of **CA-1**. In complex (**b**) phenol forms the hydrogen bond with the oxygen atom of the OH group at the lower rim of calixarene **CA-2**. In complex (**c**) phenol forms the hydrogen bond with the P = O group at the upper rim of the macrocycle **CA-3**.

Short contacts between calixarenes and phenol molecules (Fig. 5) indicate that the Host-Guest complexes can be additionally stabilized by various nonvalence Van der Waals, π-π, and hydrophobic interactions. Fig. 6 presents the linear dependences of the

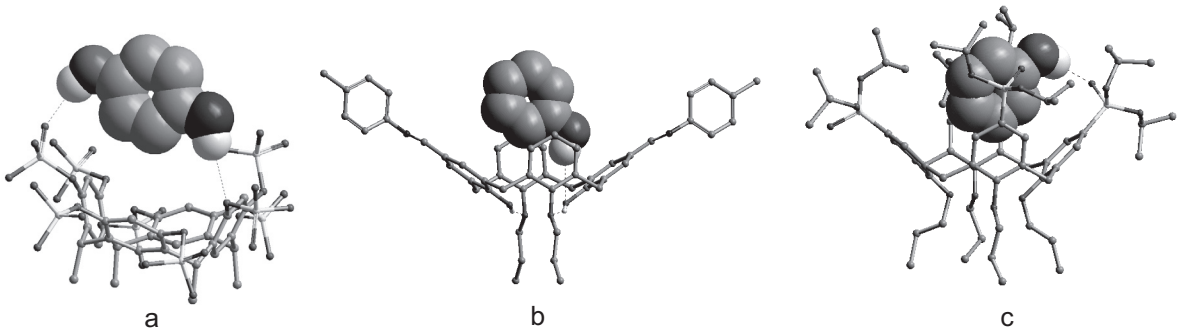



Fig. 5. Energy minimized structures of the Host-Guest complexes: **CA-1** with *p*-aminophenol (a), **CA-2** and **CA-3** with phenol (b, c). Phenyl substituents at the upper rim of **CA-1** are omitted for clarity. Hydrogen bonds are shown as dotted lines

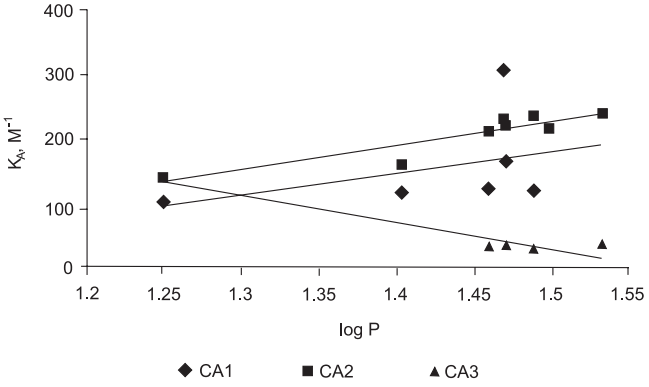



Fig. 6. Plots *log* $K_A$ of **CA-1** (r = 0.60), **CA-2** (r = 0.92) and **CA-3** (r = 0.96) of the complexes on *log P* of phenols **1-8**

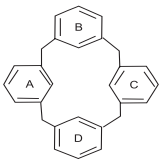
stability constants $K_A$ of **CA-1, CA-2** and **CA-3** from *log P* of the phenol derivatives confirming the role of the hydrophobic interaction in the process of the Host-Guest complexation.

## Conclusions

Calix[4]arenes form stable supramolecular Host-Guest complexes with phenols in acetonitrile-water solutions. The stability constants of the complexes determined by the RP HPLC method show that the complex stability is strongly dependent on the nature of the substituents in the Host and Guest molecules. In accordance with the molecular modeling the complexation does not change the C2*v flattened-cone* conformation of the calixarene skeleton. The Host-Guest complexes are stabilized by the intermolecular hydrogen bonds of phenolic OH groups with oxygen atoms of P = O groups at the upper rim of the macrocycle and OH groups at the lower rim of the macrocycle. Hydrophobic interactions also participate in the Host-Guest complexation processes.

**Table 2**

The inclination (dihedral angles) of benzene rings A, B, C, D in calixarenes **CA-1, CA-2, CA-3** and their complexes with *p*-aminophenol and phenol




| Calixarenes or their Host-Guest complexes | Dihedral angles, (°) | | | |
|---|---|---|---|---|
| | A | B | C | D |
| **CA-1** | 149 | 103 | 148 | 107 |
| **CA-1** – *p*-aminophenol | 148 | 115 | 147 | 104 |
| **CA-2** | 148 | 91 | 148 | 91 |
| **CA-2** – phenol | 147 | 101 | 146 | 101 |
| **CA-3** | 140 | 88 | 128 | 94 |
| **CA-3** – phenol | 137 | 99 | 130 | 102 |

**Conflicts of Interest**: authors have no conflict of interest to declare.

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*Надійшла до редакції 10.01.2017 р.*

**Acknowledgement**
This work is supported by the State Fund for Fundamental Research of Ukraine.