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The Complexation of Water-Soluble Calix[4]Arene-Phosphine Oxides With Antiviral Drugs

Abstract

The complexation of tetrahydroxycalix[4]arene-methyldimethylphosphine oxide (**CMPO**), tetrahydroxythiacalix[4]arene-methyldimethylphosphine oxide (**TCMPO**), and tetrapropoxycalix[4]arene-methyldiethylphosphine oxide (**CEPO**) with active pharmaceutical ingredients of antiviral drugs Remdesivir, Nevirapine, Vesatolimod, Bictegravir, Emtricitabine, and Tenofovir in the water medium was studied using the RP HPLC method. By analyzing the dependence of the drug capacity values on the concentration of calixarenes in the chromatographic mobile phase, the stability constants ($K_A = 1100-12000\ M^{-1}$) of the complexes formed were determined. Quantum-chemical calculations show that the antiviral drugs form supramolecular *exo*-complexes with the calixarene-phosphine oxide molecules. These complexes can be stabilized by intermolecular hydrogen bonds between the proton acceptor P=O groups and the proton donor groups of antiviral drugs.

Keywords: calixarenes; antiviral drugs; supramolecular complexes; chromatography; molecular modeling

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Комплексоутворення водорозчинних калікс[4]арен-фосфіноксидів з антивірусними препаратами

Анотація

Методом ОФ ВЕРХ досліджено комплексоутворення тетрагідроксикалікс[4]арен-метилдиметилфосфіноксиду (**CMPO**), тетрагідрокситіакалікс[4]арен-метилдиметилфосфіноксиду (**TCMPO**) та тетрапропоксикалікс[4]арен-метилдіетилфосфіноксиду (**CEPO**) з активними фармацевтичними інгредієнтами антивірусних препаратів Ремдесивір, Невірапін, Весатолімод, Біктегравір, Емтрицитабін та Тенофовір у водному середовищі. Аналізом залежності значень хроматогофічної ємності препарату від концентрації каліксарену в рухомій фазі визначено константи стійкості утворених супрамолекулярних комплексів ($K_A = 1100-12000\ M^{-1}$). Квантово-хімічними розрахунками показано, що каліксаренфосфіноксиди утворюють з дослідженими препаратами супрамолекулярні *екзо*комплекси. Ці комплекси можуть бути стабілізовані міжмолекулярними водневими зв'язками протоноакцепторних P=O груп каліксаренів з протонодорними угрупованнями антивірусних препаратів.

Ключові слова: каліксарени; антивірусні препарати; супрамолекулярні комплекси; хроматографія; молекулярне моделювання

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■ Introduction

Antiviral drugs are widely used to prevent and treat many infectious diseases [1, 2]. However, such drugs may have low bioavailability and cause side effects [3, 4]. Therefore, in some cases, they are used as prodrugs or as supramolecular complexes with cyclodextrins. Calixarenes [5, 6] and their self-assembled supramolecular aggregates [7], which form host-guest supramolecular complexes with the active pharmaceutical ingredients (APIs) of drugs, are considered promising objects in the design of the drug delivery vectors [8–15]. Advantages of calixarene vectors include low cytotoxicity [16–20] and the absence of immune reactions [21].

Among a variety of water-soluble calixarenes, their sulfonic acid derivatives are the best-studied vectors [22]. They form supramolecular complexes with known pharmaceutical ingredients – 3-phenyl-1*H*[1]benzofuro[3,2-*c*]pyrazole (tyrosine kinase III inhibitor) [23], Carvediol (management of hypertension) [24], Paclitaxel (ovarian, breast, lung and colon cancer treatment) [25], Tramadol (analgesic) [26], Irinotecan (colon cancer treatment) [27], Nifedipine (calcium channel blocker) [28], Tenofovir (antiviral drug) [29].

Water-soluble cup-shaped calixarenes functionalized on the upper or lower rim of the macrocycle with hydrophilic organophosphorus groups are also used to create drug delivery systems.

Phosphorus-containing calixarenes are characterized by a high biological activity and low cytotoxicity [30]. The calixarene and thiacalixarene-phosphonic acids effectively and selectively inhibit ATP-hydrolase systems of smooth muscle cells [31] and therapeutically important phosphatases of various origins [32].

It has been shown that the lower-rim calixarene-diphosphoric acid, which forms supramolecular complexes with water-insoluble APIs in aqueous solutions, is appropriate for the drug formulation and delivery [33]. This acid also activates the transfer of polyarginine cell-penetrating peptides across biological membranes [34].

The upper rim modification of the calix[4]arene platform by hydrophilic phosphonic acid groups yields water-soluble derivatives that form supramolecular complexes with AFIs of antiviral drugs Tenofovir and Emtricitabine [35].

Micellar alkoxycalixarene-hydroxymethylene-bisphosphonic acids form nanoscale supramolecular complexes with fluorescently labeled polylysine and HIV-1 nucleocapsid due to electrostatic interactions. Such nanocomplexes cross biological membranes and deliver the therapeutically important proteins into cells [36].

In this article, within a context of further research on the drug formulation and delivery, the host-guest complexation of the tetrahydroxycalix[4]arene-methyldimethylphosphine oxide (**CMPO**), tetrahydroxythiacalix[4]arene-methyldimethylphosphine oxide (**TCMPO**), and tetrapropoxycalix[4]arene-methyldiethylphosphine oxide (**CEPO**) hosts with active pharmaceutical ingredients of antiviral drug guests Remdesivir, Nevirapine, Vesatolimod, Bictegravir, Emtricitabine and Tenofovir (**Figure 1**) in the water medium was studied using RP HPLC and molecular modeling methods.

Due to biologically friendly properties of a phosphorus atom, a number of drugs for medicinal purposes have been created on the basis of natural and synthetic organophosphorus compounds [37]. Highly polar $Me_2P{=}O$ or $Et_2P{=}O$ groups are currently used in medicinal chemistry to improve the water solubility of API molecules, optimize their pharmacokinetic profile [38–40], and create new drugs for medicine [41–43]. It should be noted in the context of the drug design that the proton-accepting property of the oxygen atom of dimethylphosphine oxide derivatives exceeds the proton-accepting property of the oxygen atoms of phosphates, phosphonates, sulfones, and carbonyl compounds [44].

The presence of hydrophilic proton-accepting $Me_2P{=}O$ and $Et_2P{=}O$ groups on the upper rim of **CMPO**, **TCMPO**, and **CEPO** is capable of increasing the water solubility of the calixarenes. On the other hand, these groups can stabilize supramolecular host-guest complexes by forming intermolecular hydrogen bonds $P{=}O \cdots H\text{-}X$ (X = O, N) with amine, amide, hydroxyl, and other groups of the antiviral drugs.

■ Materials and methods

Reagents and Materials

Remdesivir, Nevirapine, Vesatolimod, Bictegravir, Emtricitabine, and Tenofovir were purchased from Sigma-Aldrich (St. Louis, MO, USA) or Abcam (Cambridge, UK) or obtained from UOSLAB (Kyiv, Ukraine). The cone shaped tetrapropoxycalixarene-diethylphosphine oxide **CEPO** was synthesized according to the method [45].

The solvents for the synthesis of **CMPO** and **TCMPO** were purified using standard techniques [46]. The reactions were conducted under a dry

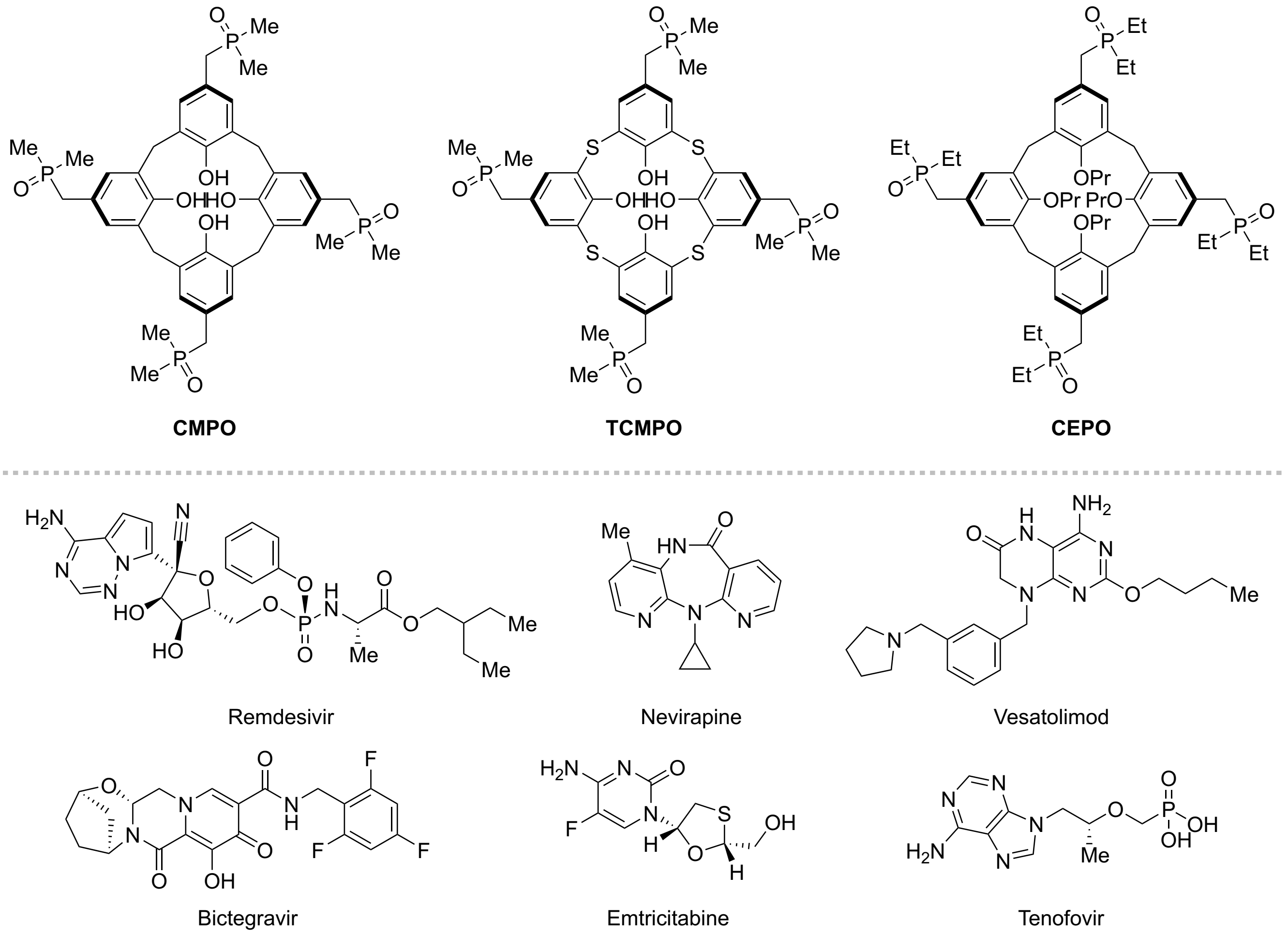


Figure 1. The water soluble calixarene-phosphine oxide hosts **CMPO, TCMPO, CEPO**, and antiviral drug guests Remdesivir, Nevirapine, Vesatolimod, Bictegravir Emtricitabine and Tenofovir

argon atmosphere, using anhydrous solvents. Chemical glassware was dried at 150 °C under vacuum. Melting points were determined using a Boetius apparatus. NMR spectra ^{1}H (300 MHz), ^{31}P (81 MHz) were recorded using a Varian VXR-300 spectrometer. Chemical shifts are reported relative to tetramethylsilane (^{1}H) used as an internal standard, or relative to H_3PO_4 (85%) (^{31}P) as an external standard.

CMPO and **TCMPO** were synthesized by the Arbuzov reaction of the corresponding tetrachloromethyltetrahydroxy(thia)calixarenes **1,2** with the trimethylsilyl ester of dimethylphosphinic acid in CH_2Cl_2 solution at 25 ^{o}C for 24 hours (**Scheme 1**).

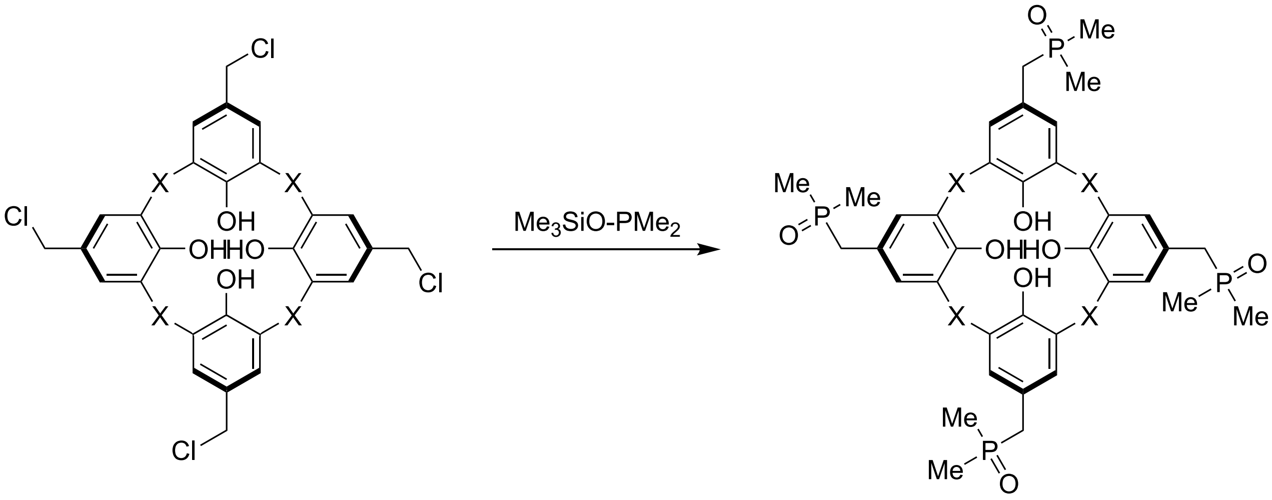
CMPO and **TCMPO** are solid compounds that are readily soluble in water, DMSO and DMF and insoluble in nonpolar solvents. The structure of the calixarenes was confirmed by the ^{1}H, ^{31}P NMR spectra (*SI File*, **Figures S1**, **S2**, **S3**, **S4**).

A conical conformation of **CMPO** was confirmed by the presence of two wide signals of the AB spin system of axial (3.77 ppm) and equatorial (5.01 ppm) protons of methylene linkers broadened due to slow in NMR time scale rotation of benzene fragments around Ar-CH_2-Ar bonds in ^{1}H NMR spectrum recorded in DMSO-d_6 solution [47]. The ^{1}H NMR spectrum of **CMPO** also contains signals of CH_3 groups (1.32 ppm, d, $^2J_{HP}$ = 15 Hz), CH_2P groups (2.88 ppm, d, $^2J_{HP}$ = 15 Hz), ArH groups (6.94 ppm, s) and a wide signal of OH groups (9.61 ppm) (*SI File*, **Figure S1**).

The ^{1}H NMR spectrum of **TCMPO** contains signals of CH_3 groups (1.25 ppm, d, $^2J_{HP}$ = 15 Hz), CH_2P groups (2.98 ppm, d, $^2J_{HP}$ = 15 Hz), a wide signal of OH groups (4.10 ppm), and a signal of ArH groups (8.00 ppm, s) (*SI File*, **Figure S3**). The ^{31}P NMR spectra of the calixarenes contain signals 43.16 ppm (**CMPO**) and 45.7 ppm (**TCMPO**) (*SI File*, **Figures S2**, **S4**, respectively).

Tetrahydroxycalix[4]arene-methyldimethylphosphine oxide (CMPO)

A solution of 2.46 g (16.4 mmol) of dimethyltrimethylsilylphosphinite in 20 mL of a dry CH_2Cl_2 was added dropwise to a stirred solution of 1.24 g (2 mmol) tetrachloromethyltetrahydroxycalix[4]arene **1** in 40 mL of a dry CH_2Cl_2 at room temperature. The reaction mixture was stirred for 24 hours. The solvent was evaporated under



1: X=CH$_2$

2: X=S

CMPO: X=CH$_2$

TCMPO: X=S

Scheme 1. The synthesis of **CMPO** and **TCMPO**

reduced pressure, and the viscous oil was dried under vacuum (8–10 Torr). The residue was dissolved in 25 mL of methanol and stirred for 6 hours, then the solution was evaporated to dryness under vacuum (8–10 Torr). The residue was triturated with hexane, filtered, and air-dried. The resulting product was obtained by crystallization from absolute isopropanol.

A white hygroscopic crystalline powder. Yield – 1.07 g (68%). M. p. 188–190 °C. Anal. Calcd. for $C_{40}H_{52}O_8P_4$, %: C 61.22, H 6.68, P 15.79. Found, %: C 61.00, H 6.50, P 15.43. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.32 (24H, d, $^2J_{HP}$ = 15 Hz, P-CH$_3$), 2.88 (8H, d, $^2J_{HP}$ = 15 Hz, Ar-CH$_2$-P), 3.77 (4H, bs, Ar-CH$_{2(ax.)}$-Ar), 5.01 (4H, bs, Ar-CH$_{2(eq.)}$-Ar), 6.94 (8H, s, ArH), 9.61 (4H, bs, OH). ^{31}P NMR (80.95 MHz, DMSO-d_6), δ, ppm: 43.16.

Tetrahydroxythiacalix[4]arene-methyldimethylphosphine oxide (TCMPO)

A solution of 2.46 g (16.4 mmol) of dimethyltrimethylsilylphosphinite in 20 mL of a dry CH$_2$Cl$_2$ was added dropwise to a stirred solution of 1.38 g (2 mmol) tetrachloromethyltetrahydroxythiacalix[4]arene **2** in 40 mL of a dry CH$_2$Cl$_2$ at room temperature. The reaction mixture was stirred for 24 hours. The solvent was evaporated under reduced pressure, and the viscous oil was dried under the vacuum (8–10 Torr). The residue was dissolved in 25 mL of methanol and stirred for 6 hours, then the solution was filtered, evaporated to dryness under vacuum (8–10 Torr). The residue was triturated with hexane, collected by filtration, and air-dried. The resulting product was obtained by crystallization from absolute isopropanol.

A white hygroscopic powder. Yield – 1.06 g (62%). M. p. 220–222 °C. Anal. Calcd. for $C_{36}H_{44}O_8P_4S_4$, %: C 50.46, H 5.18, P 14.46, S 14.07. Found, %: C 50.81, H 5.03, P 14.20, S 13.75. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.25 (24H, d, $^2J_{HP}$ = 15 Hz, P-CH$_3$), 2.98 (8H, d, $^2J_{HP}$ = 15 Hz, Ar-CH$_2$-P), 7.43 (8H, s, Ar*H*). ^{31}P NMR (80.95 MHz, DMSO-d_6), δ, ppm: 45.70.

HPLC analysis

The RP HPLC analysis of **CMPO**, **TCPO**, **CEPO**, and antiviral drugs was performed on a Hitachi high-pressure liquid chromatography equipment (Hitachi, Ltd., Tokyo, Japan) under isocratic conditions using a Zorbax CN chromatographic column (250×4.6 mm) (supplier Agilent) and a mobile phase of H$_2$O/MeCN (80/20, *v*/*v*). The choice of such a two-component mobile phase was due to the need for simultaneous solubility of calixarenes and antiviral drugs of different natures during chromatographic analyses. The concentration of **CMPO**, **TCPO**, and **CEPO** in the mobile phase varied within the range of 0.1×10^{-4}–1.4×10^{-4} M. Samples of the antiviral drugs for analysis were prepared in a solvent identical to the mobile phase (C = 1×10^{-5} M) and injected in amounts of 20 µL. All chromatograms were obtained at 28 °C. The wavelength of the UV detector was 254 nm. Each sample was analyzed in triplicate.

Molecular modeling

CMPO, **TCPO**, **CEPO**, and their complexes were simulated in vacuum (PM3, HyperChem software, evaluation version 8.0.10 [48]). The RMS gradient was 0.01 kcal mol^{-1}.

Results and discussion

The main criterion for assessing the complexing properties of host molecules is the value of the stability constant of the supramolecular complex with guest molecules. To determine the stability constants of the calixarene complexes, various physical methods are used: microcalorimetry [49], nuclear magnetic resonance [50], UV and fluorescence spectroscopy [51, 52], selective transport through liquid membranes [53], mass spectrometry [54], surface plasmon resonance [55], etc. However, the application of these methods may be limited by the unsatisfactory solubility of calixarene receptors and substrate molecules, or by the high cost of the methods.

A convenient and rapid method for determining the stability constants of complexes is reversed-phase high-performance liquid chromatography [56, 57]. This method has been used to determine the stability constants of calixarene complexes with organic substrates of various natures in aqueous or aqueous-organic solutions [58, 59]. According to this method, stability constants are determined from the dependence of the retention time or capacity factor of the substrate on the concentration of calixarene in the mobile phase. The addition of calixarenes to the mobile phase reduces the retention time of analytes due to the formation of supramolecular host-guest complexes and the increasing polarity of the chromatographic column surface upon the calixarene sorption. The inverse sorption of calixarenes by the column surface and the linear dependence of the capacity value $1/k'$ of the analyte on the calixarene concentration indicate 1:1 stoichiometry complexes in the mobile phase flow. This allows us to use equation (1) [56, 57] to calculate the stability constants of the host-guest complexes:

$$1/k' = 1/k'_0 + K_A \times [CA]/k'_0 \qquad (1)$$

where: k_0' and k' are the capacity factors of the analyte determined before and after the addition of calixarene to the mobile phase, $[CA]$ is the concentration of calixarene in the mobile phase.

Under the analysis conditions, the antiviral drugs and the calixarenes have retention times t_R: 6.735 min (Remdesivir), 6.915 min (Nevirapine), 7.327 min (Vesatolimod), 5.873 min (Bictegravir), 12.825 min (Emtricitabine), 3.573 min (Tenofovir), 6.040 min (**CMPO**), 3.943 min **(TCMPO)**, 3.543 min (**CEPO**) (*SI File*, **Figures S5**, **S6**).

Calixarenes **CMPO**, **TCPO**, and **CEPO** were characterized by linear adsorption isotherms (**Figures S7**, **S8**, **S9**), which indicated their reverse adsorption on the surface of the Zorbax CN column. The addition of the calixarenes to the mobile phase reduces the retention time t_R of the antiviral drugs. The linear dependence of the drug parameter $1/k'$ on the concentration of calixarenes in the mobile phase (**Figures 2**, **3**, **4**) indicates the formation of supramolecular host-guest complexes with the stoichiometry of 1:1.

The stability constants of the complexes K_A (1100–12000 M^{-1}) calculated by formula (1), and the values of the Gibbs free energies $-\Delta G$ (4.20–5.30 kcal×mol^{-1}) calculated by the equation $\Delta G = -\mathrm{RT} \times \ln K_A$ are given in **Table 1**. The stability constants K_A are rather close to the stability constant of the 1:1 complex of the calix[4]arenesulfonic acid with an antiretroviral drug Tenofovir disoproxil fumarate determined by the UV-Vis spectroscopy in the DMSO solution [29].

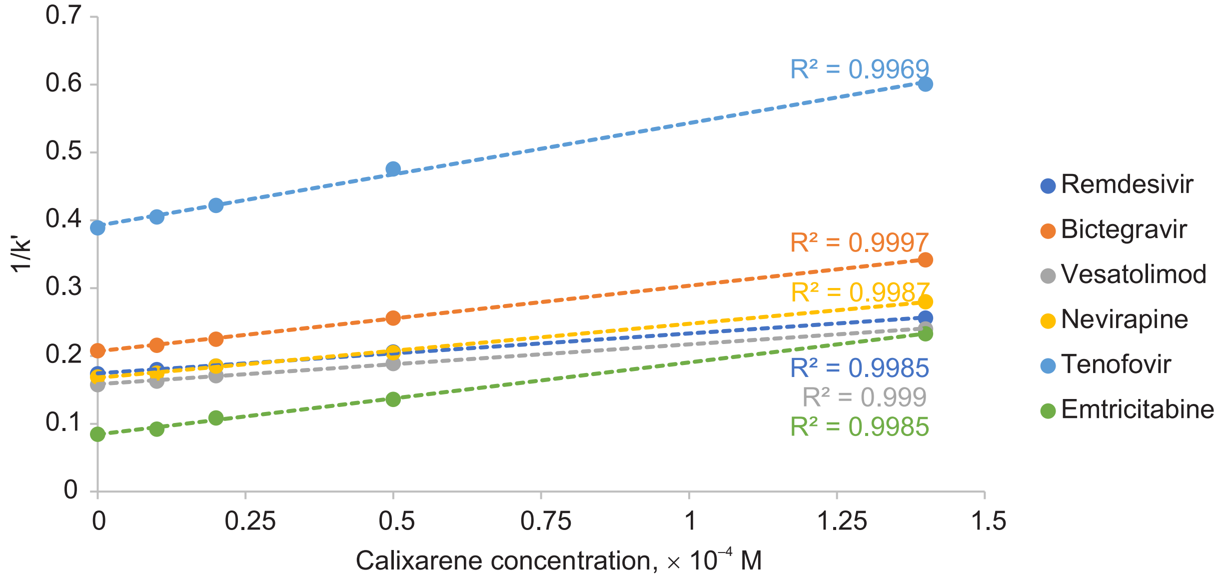


Figure 2. The dependence of $1/k'$ values of the antiviral drugs on the concentration of **CMPO** in the mobile phase

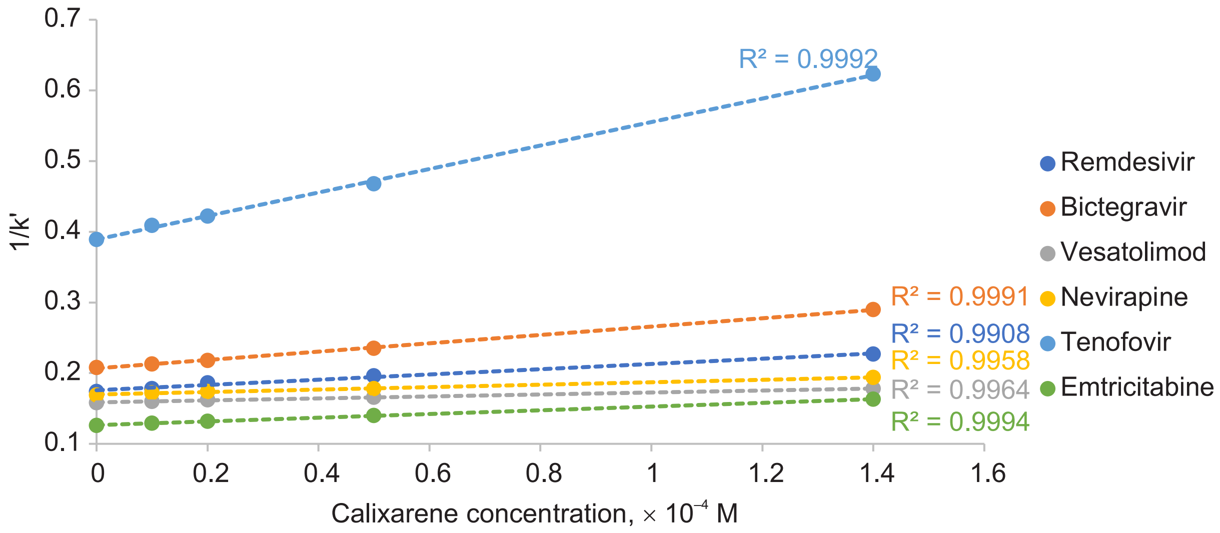


Figure 3. The dependence of 1/*k′* values of the antiviral drugs on the concentration of **TCMPO** in the mobile phase

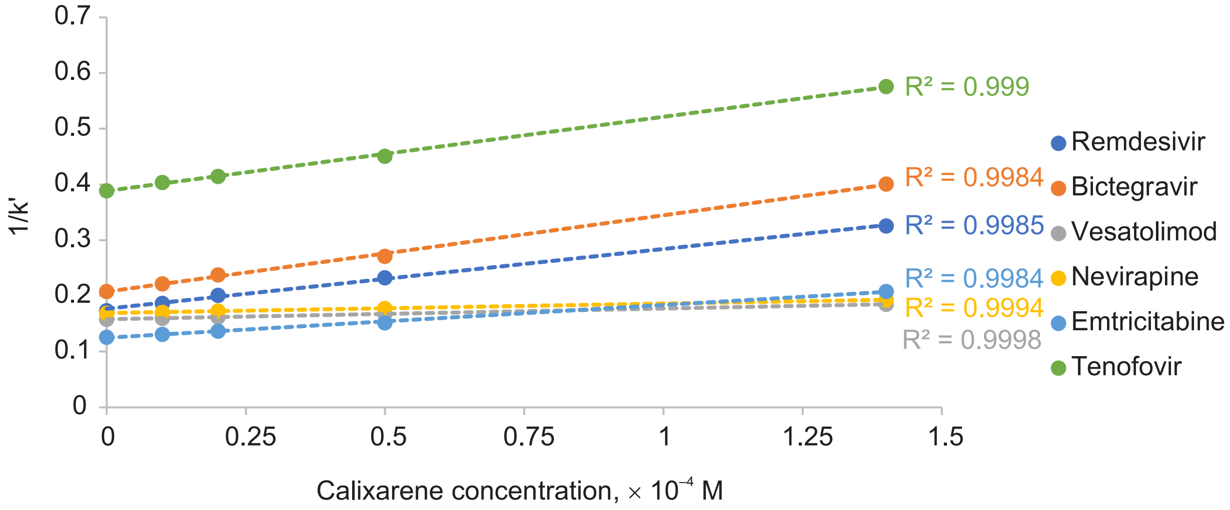


Figure 4. The dependence of 1/*k′* values of the antiviral drugs on the concentration of **CEPO** in the mobile phase

The values of the stability constants K_A and Gibbs free energies ΔG depend on the structure of the calixarene host and the antiviral drug guest and decrease in the order:

Emtricitabine > Nevirapine > Bictegravir >
Tenofovir > Vesatolimod > Remdesivir

for complexes with **CMPO**;

Emtricitabine > Tenofovir > Remdesivir >
Bictegravir > Nevirapine > Vesatolimod

for complexes with **TCPO**; and

Emtricitabine > Remdesivir > Tenofovir >
Bictegravir > Vesatolimod > Nevirapine

for complexes with **CEPO**.

Table 1. Stability constants K_A M^{-1}, (RSD %), and Gibbs free energies ΔG kcal×mol^{-1} of the complexes of **CMPO, TCMPO** and **CEPO** with antiviral drugs

Antiviral drug	CMPO		TCMPO		CEPO	
	K_A	ΔG	K_A	ΔG	K_A	ΔG
Remdesivir	3400 (27)	4.81	2600 (28)	4.65	7050 (32)	5.24
Nevirapine	4300 (14)	4.95	1340 (11)	4.26	1100 (28)	4.15
Vesatolimod	3980 (17)	4.90	1200 (24)	4.20	1250 (23)	4.20
Bictegravir	4300 (18)	4.95	2230 (19)	4.56	2560 (17)	4.64
Emtricitabine	12000 (16)	5.55	7530 (22)	5.30	7800 (18)	5.30
Tenofovir	4200 (21)	4.93	4440 (18)	4.97	3450 (16)	4.82

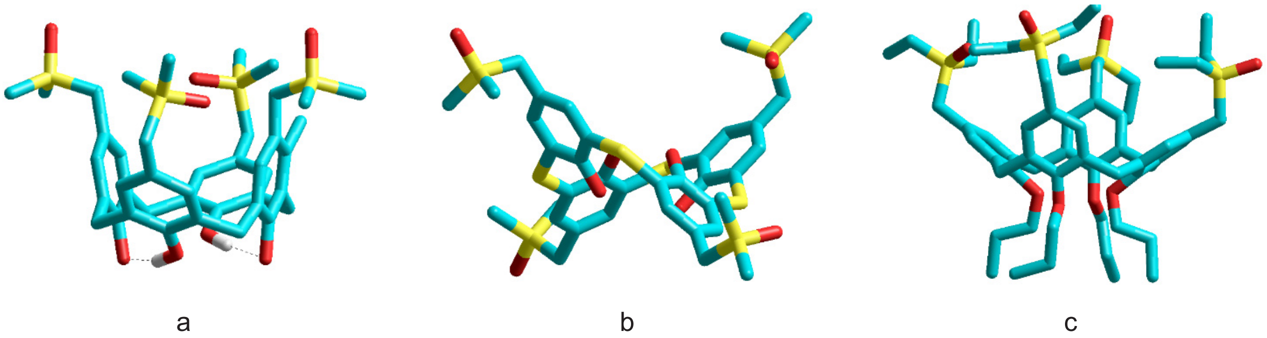


Figure 5. Energy-minimized molecular structures of **CMPA** (a), **TCMPO** (b), and **CEPO** (c)

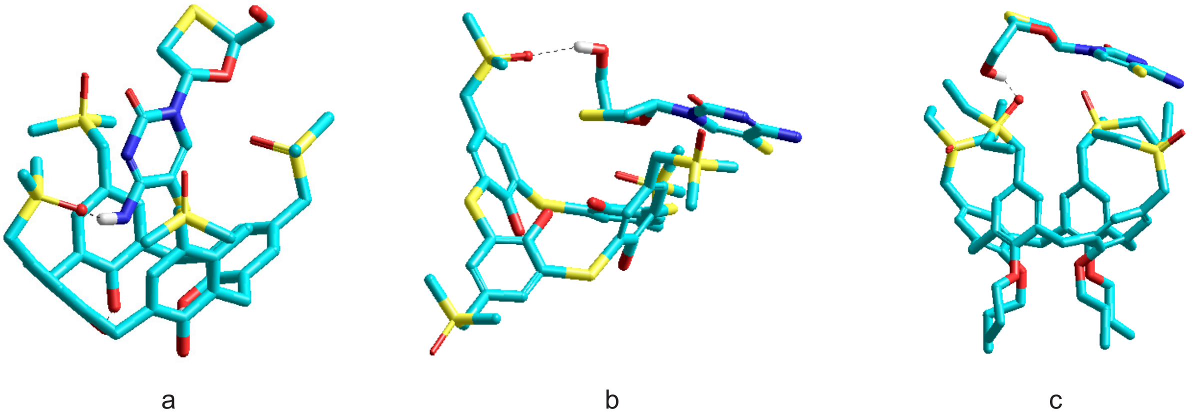


Figure 6. Energy-minimized molecular structures of supramolecular complexes **CMPA**×Emtricitabine (**a**), **TCMPO**×Emtricitabine (**b**) and **CEPO**×Emtricitabine (**c**)

The dependence of the stability constants on the structure of the calixarene and the antiviral agent is complex and can be determined by hydrogen bonds, van der Waals forces, solvatophobic, and other non-covalent interactions. To understand the nature of the complex formation, the structures of the calixarenes and their complexes with molecules of antiviral agents were energetically minimized. According to energy minimization data, **CMPO** and **CEPO** molecules exist in the *cone*-shaped conformations stabilized by strong intramolecular hydrogen bonds (δ_{OH} = 9.61 ppm) or voluminous propyl groups, respectively, which restrict rotation of the benzene ring through the macrocyclic annulus. The **TCMPO** molecule with rather weak intramolecular hydrogen bonds O-H···O-H (δ_{OH} = 4.10 ppm) is unable to stabilize the *cone* conformation and exists in the symmetrical conformation *1,3-alternate* (**Figure 5**).

Energy-minimized structures of the most stable complexes **CMPA** × Emtricitabine (a), **TCMPO** × Emtricitabine (b) and **CEPO** × Emtricitabine (c) (**Table 1**) are presented in **Figure 6**. According to the calculation, the calixarenes form the exo-complexes with the large and branched molecule Emtricitabine hanging over the upper rim of the macrocycle. The complexes are stabilized by intermolecular hydrogen bonds of the proton acceptor groups $Me_2P{=}O$ of the calixarenes with the amino group (**Figure 6a**) or the methylol group (**Figures 6b** and **6c**) of Emtricitabine.

■ Conclusions

The stability constants K_A (1100–12000 M^{-1}) of the supramolecular host-guest complexes between tetrahydroxycalix[4]arene-methyldimethylphosphine oxide (**CMPO**), tetrahydroxythiacalix[4]arene-methyldimethylphosphine oxide (**TCMPO**), and tetrapropoxycalix[4]arene-methyldiethylphosphine oxide (**CEPO**) with active pharmaceutical ingredients of antiviral drugs Remdesivir, Nevirapine, Vesatolimod, Bictegravir, Emtricitabine and Tenofovir in the water medium depend on the structures of the calixarene and the antiviral drug.

According to the energy minimization calculation, **CMPO** and **CEPO** molecules exist in the *cone* conformations stabilized by intramolecular hydrogen bonds or voluminous propyl groups, respectively, which restrict the rotation of the benzene ring through the macrocyclic annulus.

The **TCMPO** molecule, having rather weak intramolecular hydrogen bonds O-H···O-H, exists in the symmetrical conformation *1,3-alternate*.

Quantum-chemical calculations show that the calixarene-phosphine oxides form supramolecular complexes with molecules of the antiviral drugs. These complexes are stabilized by intermolecular hydrogen bonds between the proton acceptor P=O groups and the proton donor groups of the drugs.

Thus, the synthetically available water-soluble calixarene-phosphine oxides **CMPO**, **CEPO**, and **TCMPO** have the potential for application in formulations of antiviral drugs and in the creation of vectors for their delivery systems.

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