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O. I. Kalchenko[1], S. O. Cherenok[1], A. V. Solovyov[1,2]

[1] Institute of Organic Chemistry, National Academy of Sciences of Ukraine
5, Murmanska str., Kyiv-94, 02660, Ukraine E-mail: oik@ioch.kiev.ua
[2] Department of Chemical and Biomolecular Engineering, University of California

The effect of 5,11,17,23-tetrakis(diisopropoxyphosphonyl)-25,26,27,28-terapropoxycalix[4]arene on the chromatographic separation of ecologically hazardous aromatic compounds

Aim. To study the effect of 5,11,17,23-tetrakis(diisopropoxyphosphonyl)-25,26,27,28-tetrapropoxycalix[4] arene additive to the MeCN/H_2O mobile phase on selectivity of the HPLC separation of aromatic compounds using a Zorbax ODS support.

Results and discussion. Calixarene improves the separation due to formation of the Host-Guest inclusion complexes. The linear dependence of 1/k' on the calixarene concentration allows calculating the stability constants K_A of the complexes. The correlation of the separation selectivity induced by the calixarene additives with the ratio of the stability constants of the Host-Guest inclusion complexes of the aromatic analytes was found. The complexation is influenced by *logP* and *pKa* parameters of the analytes. Short contacts between the calixarene Host and the aromatic Guest indicate that the inclusion complexes are stabilized by various hydrogen bonds, nonvalence van der Waals, π-π and hydrophobic interactions.

Experimental part. The energy minimized structures of the calixarene complexes with *p*-fluorophenol, guaiacol, toluene and trichloromethylbezene were calculated using Hyper Chem 8, PM3, vacuum.

Conclusions. The data obtained can be used in design of new phases for HPLC.

***Key words**:* calix[4]arenes; liquid chromatography; aromatic compounds; inclusion complexes; stability constants; separation selectivity

О. І. Кальченко, С. О. Черенок, А. В. Соловйов

Вплив 5,11,17,23-тетракіс(діізопропоксифосфоніл)-25,26,27,28-тетрапропоксикаліксарену на хроматографічне розділення екологічно небезпечних ароматичних сполук

Мета. Дослідження впливу добавки 5,11,17,23-тетракіс(діізопропоксифосфоніл)-25,26,27,28-тетрапропоксикалікс[4]арену до рухомої фази MeCN/H_2O на селективність ВЕРХ розділення ароматичних сполук з використанням насадки Zorbax ODS.

Результати та їх обговорення. Каліксарен покращує розділення завдяки формуванню комплексів включення Господар-Гість. Лінійні характеристики залежності 1/k' аналіту від концентрації каліксарену дозволяють розрахувати константи стійкості K_A комплексів. Встановлено кореляцію селективності розділення, індуковану додаванням каліксарену, зі співвідношенням констант стійкості комплексів включення ароматичних аналітів. На комплексоутворення впливають параметри *logP* і *pKa* аналітів. Короткі контакти між каліксареном та ароматичними аналітами свідчать про те, що комплекси включення стабілізуються водневими зв'язками, невалентними ван дер Ваальсовими, π-π та гідрофобними взаємодіями.

Експериментальна частина. Розраховані енергетично мінімізовані структури каліксаренових комплексів з п-фторофенолом, гваяколом, толуеном і трихлорметилбензеном (Hyper Chem 8, PM3, вакуум).

Висновки. Отримані дані можуть бути використані для розробки нових фаз для ВЕРХ.

***Ключові слова**:* калікс[4]арени; рідинна хроматографія; ароматичні сполуки; комплекси включення; константи стійкості; селективність розділення

О. И. Кальченко, С. А. Черенок, А. В. Соловйов

Влияние 5,11,17,23-тетракис(диизопропоксифосфонил)-25,26,27,28-тетрапропоксикаликсарена на хроматографическое разделение экологически опасных ароматических соединений

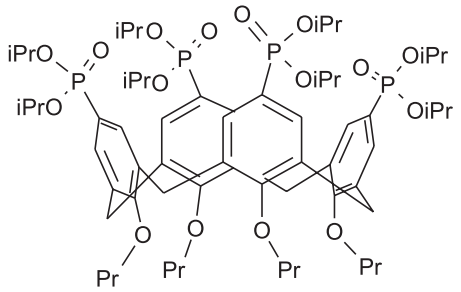
Цель. Исследование влияния добавок 5,11,17,23-тетракис(диизопропоксифосфонил)-25,26,27,28-тетрапропоксикаликс[4]арена к подвижной фазе MeCN/H_2O на селективность ВЭЖХ разделения ароматических соединений с использованием неподвижной фазы Zorbax ODS.

Результаты и их обсуждение. Каликсарен улучшает разделение вследствие образования комплексов включения Хозяин-Гость. Линейная зависимость 1/k' аналита от концентрации каликсарена позволяет рассчитать константы устойчивости K_A комплексов. Установлена корреляция селективности разделения, вызванная добавками каликсарена с отношением констант устойчивости комплексов включения Хозяин-Гость. На комплексообразование влияют параметры *logP* и *pKa* аналитов. Короткие контакты между каликсареном и ароматическим гостем свидетельствуют о том, что комплексы включения стабилизируются водородными связями, ван-дер-Ваальсовыми, π-π и гидрофобными взаимодействиями.

Экспериментальная часть. Рассчитаны энергетически минимизированные структуры комплексов каликсарена с п-фторфенолом, гваяколом, толуолом и трихлорметилбензолом (Hyper Chem 8, PM3, вакуум).

Выводы. Полученные данные могут быть использованы при разработке новых фаз для ВЭЖХ.

***Ключевые слова**:* каликс[4]арены; жидкостная хроматография; ароматические соединения; комплексы включения; константы устойчивости; селективность разделения



Scheme. **CA**

Calix[n]arenes are macrocyclic oligomers consisting of phenolic units linked by methylene spacers; they are the well known complexing agents that can be used for separation of organic molecules in solutions [1-10]. These compounds can form supramolecular complexes with different molecules and have been applied for the design of new stationary chromatographic phases [11-19], as well as additi-ves [20] to mobile phases that improve the HPLC separation of organic and inorganic analytes [21]. In this paper the effect of 5,11,17,23-tetrakis(diisopropoxyphosphonyl)-25,26,27,28-tetrapropoxycalix[4]arene (**CA**) additive to the acetonitrile-water mobile phase on the selectivity of the HPLC separation of some ecologically hazardous aromatic guest compounds is discussed (Scheme).

Results and discussion

As shown [22], the calixarene additive to the HPLC mobile phase decreases the capacity coefficients *k'* of aromatic compounds due to formation of the Host-Guest inclusion complexes. The linear dependence of 1/k' on the calixarene concentration indicates formation of the Host-Guest supramolecular complexes and allows calculating the stability constants K_A of the complexes using the equation (1) [22]:

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

where: k_0', k' – are the capacity coefficients of the Guest molecule determined in the absence and the presence of the calixarene additive to the mobile phase.

Table 1

The values of Δ*k'* of the analytes induced by **CA** additives and stability constants K_A [23] of their complexes with **CA**

Analyte	Δ*k'*	K_A, M^{-1}
Trichloromethylbenzene	0.07	13
o-Dibromobenzene	0.07	15
Hexafluorobenzene	0.15	23
p-Bromophenol	0.09	29
p-Chlorophenol	0.13	31
Benzene	0.18	32
Phenol	0.15	32
p-Xylene	0.27	44
Benzaldehyde	0.14	65
p-Cresol	0.21	84
Salicyl aldehyde	0.20	94
Guaiacol	0.73	130
p-Fluorophenol	0.35	146
Toluene	0.70	152

The capacity coefficient *k'* of the **CA** peak is 2.38. As is shown, **CA** possesses the linear adsorption isotherm (Fig. 1) at the chromatographic support. It means **CA** can be used as an additive to the mobile phase.

The change in the capacity coefficients Δ*k'* of the analytes induced by **CA** addition to the mobile phase was determined (Tab. 1). The correlation of the analyte Δ*k'* factors *vs* the stability constants K_A of their complexes with **CA** was found (Fig. 2).

The addition of **CA** to the mobile phase increases the selectivity of the chromatographic separation of analytes (Tab. 2).

The correlation of the separation selectivity induced by **CA** addition with the ratio of the stability constants of the Host-Guest inclusion complexes of the aromatic analytes is presented in Fig. 3.

As shown in Fig. 3, the greater is the ratio of the stability constants *S*, the better the separation selectivity ratio a_1/a_0 is. The separation ability depends

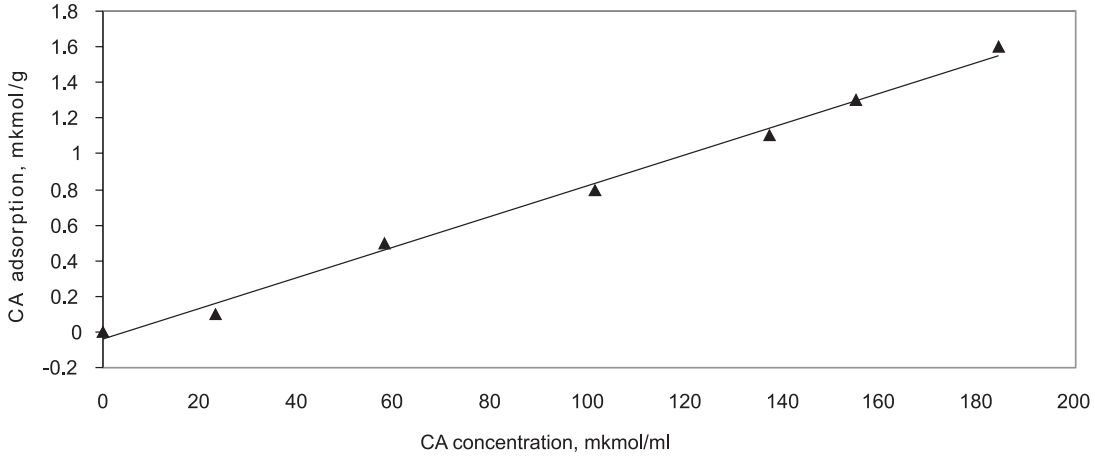


Fig. 1. The adsorption isotherm of **CA** (y = 0.0087x – 0.0455; r = 0.99)

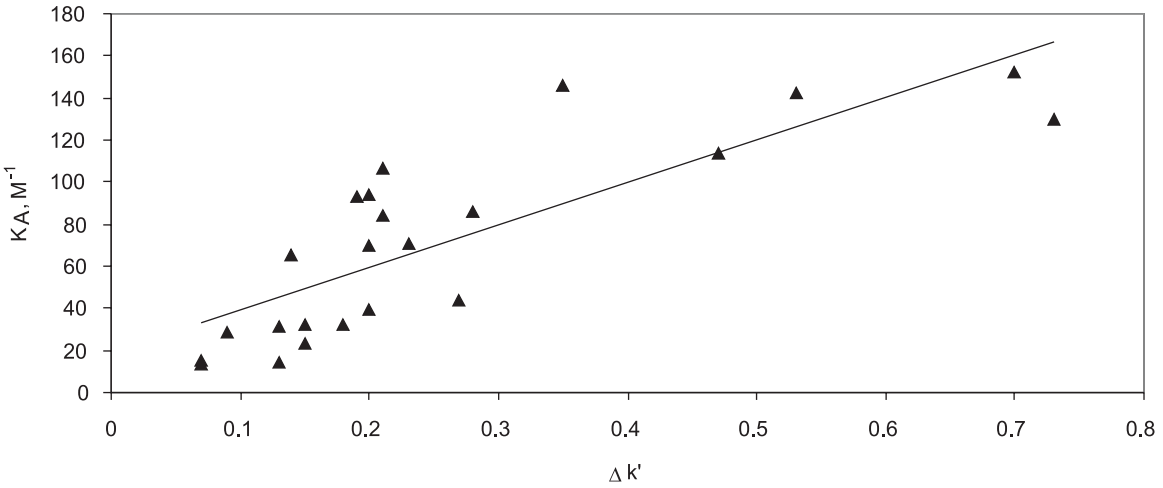


Fig. 2. The correlation of $\Delta k'$ values of the analytes *vs* their stability constants K_A with **CA** (y = 202.05x + 19.042; r = 0.82)

on the substituent's nature in the analyte molecules. The addition of **CA** to the mobile phase practically does not affect separation of *p*-xylene *vs* benzene (a_1/a_0 = 1.01), however, increases the separation selectivity ratio for trichloromethylbenzene *vs p*-fluorophenol and *p*-bromophenol *vs p*-fluorophenol (a_1/a_0 = 1.47 and 1.41, respectively). The increase of the separation can be explained by formation of the Host-Guest inclusion complexes between **CA** and the aromatic analyte molecules. Fig. 4 demonstrates the energy minimized structures of **CA** complexes with *p*-fluorophenol, guaiacol,

The complexes of *p*-fluorophenol and toluene demonstrate the largest K_A values (146 M^{-1} and 152 M^{-1}, respectively) (Tab. 1) [23]. As shown in Fig. 4a and 4b, *p*-fluorophenol and guaiacol are included into the calixarene cavity by their OH groups that form hydro-

Table 2

The separation selectivity of aromatic analytes induced by **CA** additive to the mobile phase

Analytes separated	Selectivity without **CA** additive, a_0	Selectivity after adding **CA**, a_1	Selectivity ratio, a_1/a_0	Stability constant ratio, *S*
Benzene *vs p*-fluorophenol	1.29	1.71	1.33	4.56
Benzene *vs* benzaldehyde	1.77	1.86	1.05	2.03
Benzene *vs* salicyl aldehyde	1.91	2.39	1.25	2.94
Benzaldehyde *vs* hexafluorobenzene	2.05	2.29	1.12	2.83
p-Cresol *vs* benzene	1.24	1.34	1.08	2.63
p-Cresol *vs* salicyl aldehyde	1.54	1.78	1.16	1.12
p-Xylene *vs* benzene	1.03	1.04	1.01	1.38
Hexafluorobenzene *vs* benzene	1.17	1.23	1.05	1.39
p-Xylene *vs p*- fluorophenol	1.34	1.66	1.24	3.32
Benzene *vs* trichloromethyl-benzene	1.0	1.10	1.10	1.46
Guaiacol *vs* toluene	1.16	1.24	1.07	1.17
Trichloromethyl-benzene *vs p*-fluorophenol	1.29	1.89	1.47	11.23
p-Fluorophenol *vs* phenol	1.02	1.28	1.25	4.56
p-Fluorophenol *vs p*-chlorophenol	1.55	1.58	1.02	1.03
o-Dibromobenzene *vs p*- fluorophenol	1.05	1.36	1.3	9.73
p-Bromophenol *vs p*- fluorophenol	1.04	1.47	1.41	5.03
p-Bromophenol *vs p*-cresol	1.0	1.15	1.15	2.90
Benzene *vs* salicyl aldehyde	1.91	2.39	1.25	1.07
Benzene *vs* benzaldehyde	1.75	1.86	1.05	1.39
p-Xylene *vs* hexafluorobenzene	1.12	1.27	1.13	6.17
Toluene *vs* hexafluorobenzene	1.12	1.38	1.23	6.61
Guaiacol *vs* salicyl aldehyde	2.91	2.65	0.91	1.38

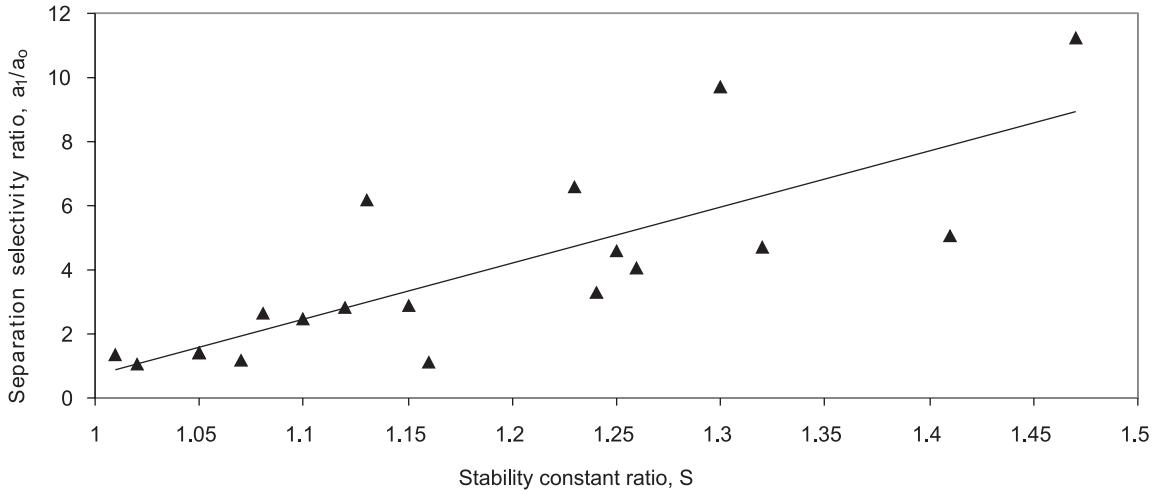


Fig. 3. Plots of the separation selectivity ratio a_1/a_0 *vs* the ratio of the stability constants *S* of **CA**–analyte complexes (y = 17.522x – 16.796; r = 0.80)

gen bonds with oxygen atoms at the lower rim of **CA**. The hydrophobic part in the *p*-fluorophenol and guaiacol molecules is oriented outside of the **CA** cavity. In the complex of toluene-**CA** (Fig. 4c) the toluene molecule is deeply included into the **CA** hydrophobic cavity by its hydrophobic CH_3 group (K_A = 152 M^{-1}). As can be seen in Fig. 4d, trichloromethylbezene bearing the bulky CCl_3 group (K_A = 13 M^{-1}) is included into the calixarene cavity by the benzene ring. The complexation does not change the **CA** regular *cone* conformation.

Short contacts between the **CA** and aromatic molecules (Fig. 4) indicate that the inclusion complexes are stabilized by various hydrogen bonds, non-valence van der Waals, π-π and hydrophobic interactions.

Fig. 5 presents the linear dependence of the stability constants K_A of the **CA** complexes from the *log P* of the aromatic compounds, thus confirming the role of the hydrophobic interaction in the process of the Host-Guest complexation.

An increase of the *log P* values of the aromatic compounds decreases the K_A values of their complexes with **CA** (Fig. 5). Fig. 6 demonstrates the correlation of K_A of **CA** complexes with *pKa* of phenol derivatives.

Experimental part

CA was synthesized by the method described in [23]. Acetonitrile was obtained from the Acros Orga-

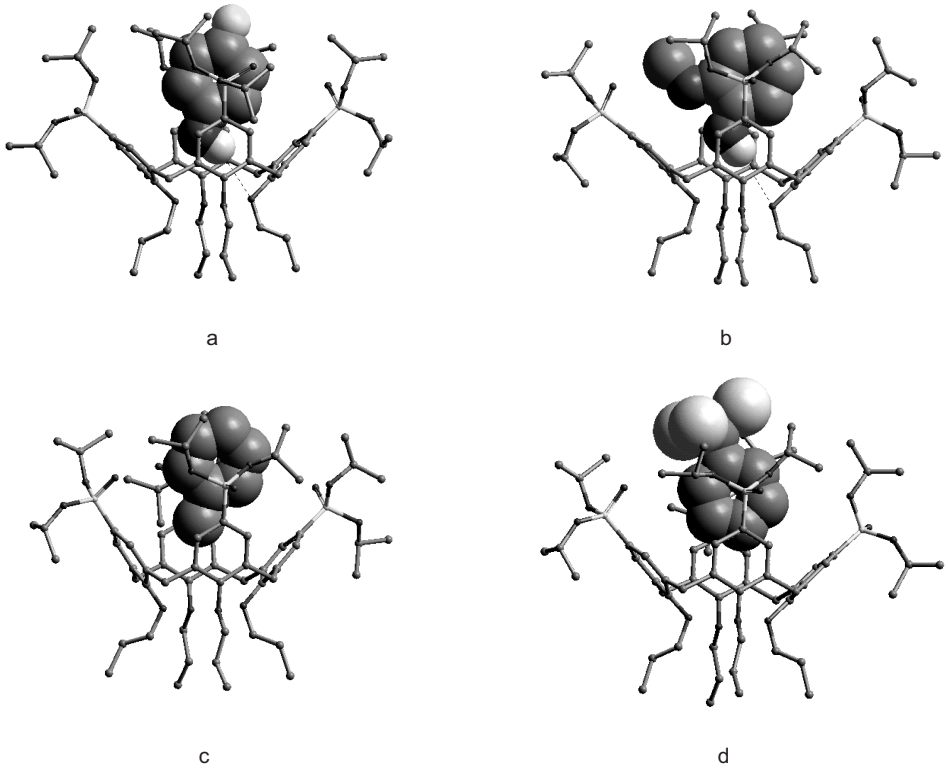


Fig. 4. The energy minimized structures of **CA** complexes with *p*-fluorophenol (a), guaiacol (b), toluene (c) and trichloromethylbezene (d) (Hyper Chem 8, PM3, vacuum). Hydrogen atoms are not shown

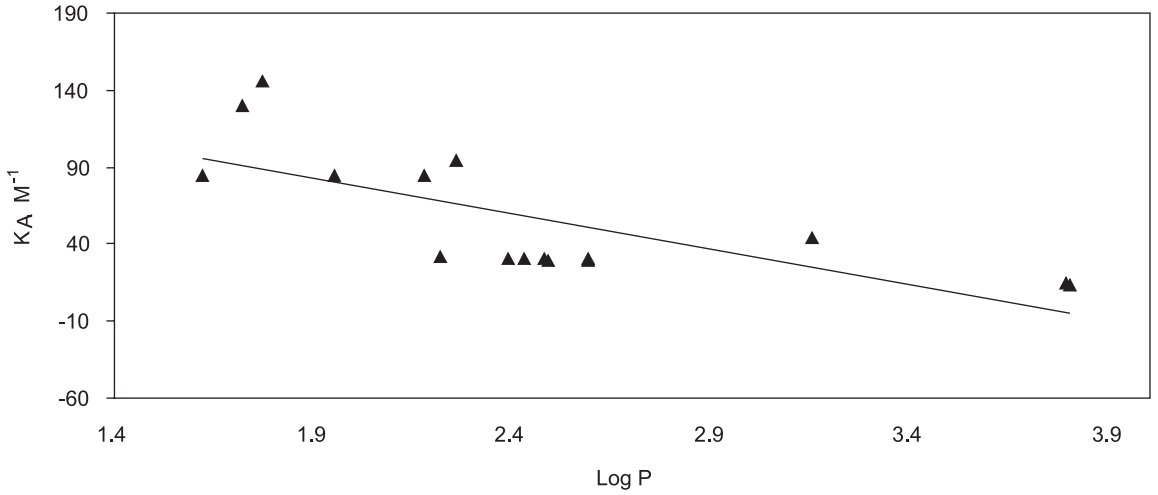


Fig. 5. Plots of K_A *vs log P* of the aromatic Guests (y = -46.488x + 171.31; r = 0.73)

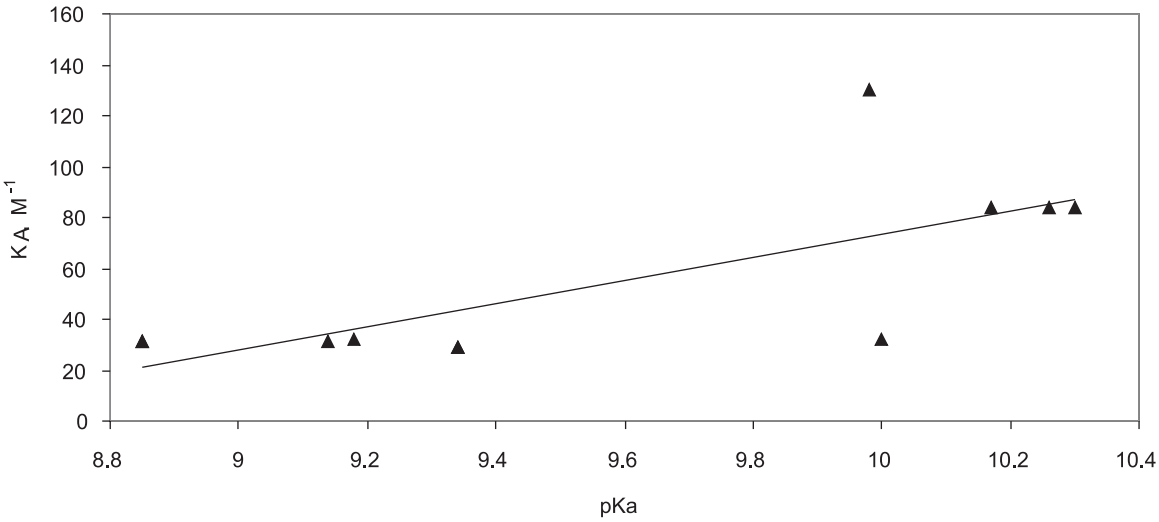


Fig. 6. The correlation of K_A of **CA** complexes with phenol derivatives pKa_1 (y = 45.425x – 381.02; r = 0.73)

nics (Thermo Fisher Scientific, New Jersey – USA), and analytes were purchased from Sigma-Aldrich (St. Louis, MO, USA). The chromatographic experiments were performed in isocratic conditions. The RP HPLC analysis was performed using the Zorbax ODS column support. The mobile phases contained calixarene in the concentrations of 0.76×10^{-3} M – 3.05×10^{-3} M. The UV detector was operated at 254 nm. The samples of the analytes for the RP HPLC analysis were prepared by dissolution of benzene derivatives in the solvent with the identical composition of the mobile phase ($MeCN/H_2O$, 86/14, v/v). The molecular modeling of the calixarene complexes were carried out using the Hyper Chem 8.0 program in the force field (PM3) [24]. The structures were calculated by the semi-empirical method. The RMS gradient was 0.01 kcal/A mol.

Conclusions

Addition of 5,11,17,23-tetrakis(diisopropoxyphosphonyl)-25,26,27,28-tetrapropoxycalix[4]arene to the $MeCN/H_2O$ mobile phase improves the RP HPLC separation of benzene derivatives on a Zorbax ODS support. The separation selectivity depends on the ratio of the stability constants of the analytes with the calix[4]arene and is influenced by the analytes *log P* and *pKa* parameters. The molecular modeling of the complexes demonstrates that the complexes are stabilized by hydrogen bonds, van der Waals, π-π, hydrophobic interactions. The data obtained can be used for design of the new stationary phases for RP HPLC.

Conflict of interests. The authors have no conflict of interests to declare.

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