The chromatographic study of complexation of functionalized calix[4,8]arenes with aromatic aldehydes


Results and discussion. The stability constants of Host-Guest complexes ($K_s$ = 57 M$^{-1}$ – 1649 M$^{-1}$) strongly depend on the calixarene structure and the aromatic aldehyde nature. The enhancement of the complexing properties of calixarenes is observed in the row of PRA < IC4A < PC4A < PC8A. The volume of the calixarene molecular cavity plays the most important role in binding of aldehydes.

Experimental part. The stability constants of calixarene complexes with aldehydes were determined by RP HPLC method in acetonitrile-water (80 : 20, v/v) solution. The RP HPLC analysis was performed using a LiChrosorb RP-18 column. Molecular modeling of calixarene complexes was carried out using a Hyper Chem 8.0 program.

Conclusions. The Host-Guest complexation data can be used as a useful tool in design of calixarene based sensor devices for determination of the aromatic aldehydes in air or preparation of chromatographic phases for analysis of aldehydes in solutions.

Key words: calixarenes; aromatic aldehydes; inclusion complexes; stability constants; liquid chromatography; molecular modeling
Calix[n]arenes [1] are three-dimensional macrocyclic compounds constituted by phenolic fragments linked via methylene bridges. In the 90s David Gutsche developed the preparative one-pot synthesis of the tert-butylicalix[4,6,8]arenes based on precision cyclodehydration of tert-butylphenol with formaldehyde (or paraform) in the presence of catalytic amounts of sodium hydroxide or potassium hydroxide. In the calixarene molecule conditionally the upper (wide) rim and the lower (narrow) rim are distinguished. The calixarene family extends to calix[4]resorcinarenes easily synthesized by cyclodehydration of resorcinol with aliphatic or aromatic aldehydes catalyzed by hydrochloric acid.

Calixarenes are easily amenable for chemical modification at the upper or the lower rim of the macrocycle. Due to the nanosized three-dimensional architecture, calixarenes functionalized with appropriate groups can be recognized with high selectivity, bind in supramolecular complexes and separate cations, anions, gases, neutral organic molecules, and biomolecules with the similar properties [2]. The supramolecular complexes can be stabilized by various non-covalent interactions, such as hydrogen bonds, π-π, CH-π, cation-π, anion-π, van der Waals, solvathophobic interactions, etc. The unique receptor properties provide broad prospects for the practical use of calixarenes in different fields of chemistry, biology, physics, nanotechnology [3-17].


Since the aromatic aldehydes are widely used as starting materials or aromatic ingredients in pharmaceutical and cosmetics industry [18, 19], the Host-Guest complexation data can be used as a useful tool in design of calixarene based sensor devices for determination of the aromatic aldehydes in air or preparation of chromatographic phases for analysis of compounds in solutions.

**Results and discussion**

Complexation of the calixarenes with aldehydes was studied in the acetonitrile-water solution by the RP HPLC method using the approach previously developed [20, 21]. The stability constants of calixarene complexes were calculated from the dependence of the aldehyde retention factor on the concentration of calixarenes in the mobile phase.

The calixarene additives to the mobile phase decrease the retention factors $k'$ of aldehydes 1-4 due to formation of the Host-Guest inclusion complexes. The linear plots of $1/k'$ vs the calixarene concentration (Fig. 1-4) indicates formation of the Host-Guest supramolecular complexes with stoichiometry of 1:1 and allows using the equation (1) for calculation of their stability constants $K_s$:

$$1/k' = 1/k'_0 + K_s \times [CA]/k'_0,$$  

where $k'_0$ is the capacity factors of the aldehyde molecule determined in the absence and the presence of the calixarene in the mobile phase.

The $K_s$ values and free Gibbs energies $\Delta G$ of the calixarene – aldehyde complexes are presented in Table.

As can be seen from Table, the stability constants ($K_s = 57 \text{ M}^{-1} - 1649 \text{ M}^{-1}$) strongly depend on the calixarene structure and the aromatic aldehyde nature. The enhancement of the complexing properties of calixarenes is observed in the row of PRA < IC4A < PC4A < PC8A. The volume of the calixarene molecular cavity plays the most important role in binding of aldehydes. PC8A exceeds PRA, IC4A and PC4A by 11-23 times for benzaldehyde, 6-15 times for salicylic aldehyde, 3-8 times for p-anisaldehyde, and 7-15 times for veratraldehyde complexation. It should be noted that the stability constant of the IC4A – benzaldehyde 1 complex ($K_s = 146 \text{ M}^{-1}$) is close to those of the cyclophane – benzaldehyde complex ($K_s = 120 \text{ M}^{-1}$) described in [22].

The calixarene Host-Guest complexes can be stabilized by hydrogen bonds, Van der Waals, π-π, C-H-π, and hydrophobic interactions. The role of the hydrophobic interaction is confirmed by the linear dependences of the binding constants $K_s$ on the $\log P$ of aldehydes (Fig. 5).

The intermolecular hydrogen bonds between the Host and Guest molecules are clearly manifested in the energy
minimized structures of the IC4A, PC4A, PC8A complexes with salicylaldehyde (Fig. 6). In the IC4A complex, the molecule of salicylaldehyde is included into the molecular cavity of the calixarene. In this case, the aldehyde hydroxyl group forms a hydrogen bond with the OH group oxygen atom on the lower rim of the macrocycle (O-H···O distance 2.84 Å).

In the inclusion complexes of PC4A and PC8A, the salicylaldehyde OH group is associated with oxygen atoms of P=O groups located at the upper or the lo-
wer rim of the macrocycle, respectively. The lengths of hydrogen bonds O-H···O=P are 2.38 Å for the PC4A complex and 2.87 Å for the PC8A complex.

As it is shown on Fig. 7, the experimental free Gibbs energies ∆G of calixarene complexes (Table) well correlate with relative energies ∆∆E of these complexes calculated by the molecular modeling method.

**Experimental part**

Calixarenes were synthesized by the methods early described: PRA [27], IC4A [28], PC4A [29] and PC8A [20]. Acetonitrile was obtained from Acros Organics (Thermo Fisher Scientific, New Jersey, USA) and aldehydes were purchased from Sigma-Aldrich (St. Louis, MO, USA).

**RP HPLC analysis**

The 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). Experiments were performed in isocratic conditions. The acetonitrile-water (80 : 20, v/v) mixture was used as a mobile phase. The calixarene concentrations in the mobile phases were 0.05-0.6 mM. The UV detector was operated at 254 nm, and the flow rate was

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**Table**

The values of $K_A$ (M$^{-1}$) and $\Delta G$ (kJ/mol) of the complexes PRA, IC4A, PC4A, and PC8A with aldehydes 1-4 (RSD = 8-20 %)

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>PRA</th>
<th>IC4A</th>
<th>PC4A</th>
<th>PC8A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde 1</td>
<td>97</td>
<td>146</td>
<td>71</td>
<td>1649</td>
</tr>
<tr>
<td>Salicylaldehyde 2</td>
<td>57</td>
<td>142</td>
<td>94</td>
<td>858</td>
</tr>
<tr>
<td>p-Anisaldehyde 3</td>
<td>104</td>
<td>195</td>
<td>242</td>
<td>797</td>
</tr>
<tr>
<td>Veratraldehyde 4</td>
<td>91</td>
<td>179</td>
<td>112</td>
<td>1330</td>
</tr>
</tbody>
</table>

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**Figures**

- Fig. 3. Plots of $1/k'$ for aldehydes 1-4 vs the PC4A concentration in the mobile phase ($R^2 = 0.95-0.99$).
- Fig. 4. Plots of $1/k'$ for aldehydes 1-4 vs the PC8A concentration in the mobile phase ($R^2 = 0.97-0.99$).
- Fig. 5. Correlation of $K_A$ of the calixarene complexes with log P of benzaldehyde 1 (1.50) [23], salicylaldehyde 2 (1.80) [24], p-anisaldehyde 3 (1.53) [25], veratraldehyde 4 (1.61) [26], $r = 0.94$ (PRA), 0.73 (IC4A), 0.88 (PC4A) and 0.89 (PC8A).
- Fig. 6. The energy minimized structures of the Host-Guest complexes of salicylaldehyde with: IC4A (a), PC4A (b) and PC8A (c). Hydrogen bonds are shown as dotted lines.
Molecular modeling

Molecular modeling of calixarene complexes was carried out using a Hyper Chem 8.0 program in the force field (PM3) [30]. The RMS (standard deviation of the root mean square) gradient was equal to 0.01 kcal/A mol.

Conclusions

Calix[4]arenes functionalized with two N-tolyl-iminomethyl groups or four disopropoxypyrophosphonyl groups at the upper rim, calix[8]arene functionalized with eight disopropoxyphosphoryl groups at the lower rim, and calix[4]resorcinarene functionalized with eight diphenyoxyphosphoryl groups at the upper rim form the Host-Guest inclusion complexes with the aromatic aldehydes in acetonitrile-water solutions. The stability constants of the complexes ($K_s$ = 57 M$^{-1}$ – 1649 M$^{-1}$) strongly depend on the calixarene structure and the aromatic aldehyde nature. The enhancement of the complexing properties of calixarenes is observed in the row: PRA < PC4A < PC8A. The Host-Guest complexation data can be used as a useful tool in design of calixarene based sensor devices for determination vapors of aldehydes in air or preparation of chromatographic phases for the analysis of aldehydes in solutions.

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

References

12. Conclusions

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References


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