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Encapsulation of fluoroaromatics by β-cyclodextrin and their derivatives theoretical studies

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ABSTRACT

Fluoroaromatics associate with β-cyclodextrin (β-CD) and their derivatives (per-modification at C6 position with fumaric acid monoamide and maleic acid monoamide) in gas phase with unexpected results. The complex forming abilities of b-CD and its derivatives modified at position C6 were compared. The complexation ability was found to strongly depend on the structure of both fluoroaromatics and β-CD derivatives. The –F and $–CF_3$ group of benzene ring could easily fit in the hydrophobic interior of β-CD and their derivatives. The other substituents were engaged in hydrogen bonds with β-CD ring or ester part of the host molecule. The formation of hydrogen bond is not necessary to ensure the stability of the complex.

1. Introduction

The monofluoro, difluoro or other aromatic compounds as well as fluorinated bioactive compounds have been known as components of common drugs [1]. Incorporation of even one or two fluorine atoms into an organic compound has been known to increase its lipophilicity and to cause changes in the geometry of molecule, bonds polarity and other physical properties (e.g. surface energies, dielectric constants and refracting indexes) changing also their chemical and biological properties [2]. Significant and unique features that trifluoromethylated compounds show in pharmaceuticals, agricultural chemicals, and functional materials have made the trifluoromethyl group one of the most important structural moiety in diverse organic molecules [3,4]. Since Umemoto and co-workers developed a new series of electrophilic trifluoromethylating reagents, e.g. (trifluoromethyl)dibenzoheterocyclic salts, the synthesis a new fluorinated building blocks has become more common [5–7].

Cyclodextrins have been widely used as pharmaceutical excipients, especially as solubilizing or stabilizing agents for lipophilic compounds [8,9]. They are also known to ensure the chemical stability of drug molecules and can be used to reduce side effects of drugs [10]. β-Cyclodextrin (β-CD) as a natural cyclic oligomer composed of seven 1,4-linked α glucose units per molecule has been the most popular in scientific literature of all known cyclodextrins [11–15]. Its hydrophobic cavity has been able to selectively host a wide range of guest molecules by forming inclusion complexes via non-covalent interaction such as van der Waals, hydrophobic or hydrogen bonding interactions [16,17]. The size of torus shaped of β-CD cavity has allowed to host not only aliphatic hydrocarbons but also aromatic compounds bearing various substituents [16]. Encapsulation [12,18–20] and supramolecular chemistry [11,21,22] have been the concepts applied recently to CDs and their derivatives.

Quantum chemical calculations of an organic system have been a powerful tool widely used for presentation of its structure or description of its interactions [23,24]. Thanks to computational chemistry it has been possible to calculate the energy and structural details of a new system. Some theoretical studies of CD system have been already published [15,21,25,26].

In this paper, we examined the possibility of formation of stable inclusion complexes by the interaction of modified β-CD with fluoro compounds. The geometrical isomers of butendioic monoamide acid were chosen as the agents for chemical modification of β-CD. Quantum chemical calculations were used for getting the information on geometry and energy of interactions of the inclusion compounds.

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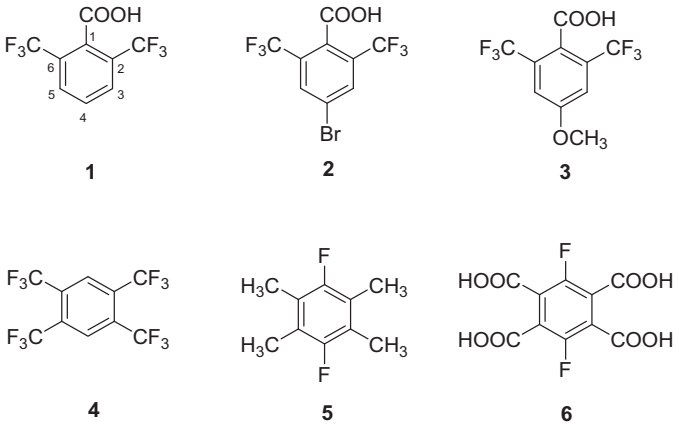

Fig. 1. Molecular structure of fluoroaromatics compounds.

2. Results and discussion

In the present study, the structure and heat of complex formation (E) of 42 inclusion complexes of β-CD and its derivatives were analyzed by means of quantum chemical methods. A series of six polyfluoro aromatics (**1**–**6**) presented in Fig. 1 was analyzed as guest compounds.

They had different structural formula but all of them were encapsulated in β-cyclodextrin with good calculated result (Table 1 and Fig. 1). The β-CD ring with the 0.62 nm bay has been known as a good host molecule in inclusion processes [27]. The CDs have a torus with hydrophobic interior and hydrophilic extremities and that is why they have a tendency to capture lipophilic compounds [28]. A series of six fluorinated aromatics was dissolved in saturated solution of β-CD in H_2O (alkaline pH) [29]. It was not possible without the addition of cyclodextrin. It was not possible without the addition of cyclodextrin. It was the convincing evidence that water molecules inside CD were exchanged for fluorinated aromatic compounds.

The 1,4 di fluoro aromatics **5** and **6** were included with their long axis perpendicular to the -β-CD cavity while compound **4** was included with their short axis in this direction. The three and four substituted benzoic acids were fitted with diagonal axis in the above position. Four of them **1**, **2**, **3** and **6** formed hydrogen bonds inside the hydrophobic cavity. In our calculations, the most stable inclusion complex of β-CD was the complex with 3,6-difluorobenzene-1,2,4,5-tetracarboxylic acid (**6**) (E = −52 kJ). This complex contained three hydrogen bonds between 2.45–2.67 Å and 138.1–157.0° bond angle (Table 2).

Thanks to these bonds a molecule of **6** was fitted near C1 and C2 of the glucose ring. Compounds **2** and **1** were included almost at the same position inside of the CD body, they were bonded to one of seven oxygen atoms of the 1,4-glycosidic bond. The next energetically favorable complex of β-CD with 1,4-difluoro-2,3,5, 6-tetramethylbenzene (**5**) had no hydrogen bonds as well as the complexes with aromatics **3** and **4**. The analyzed new inclusion complexes of β-CD with variously substituted aromatic compounds had E values from −69.18 kJ to −152.91 kJ. The formation of inclusion complexes depended on the structure of aromatic guests, which is a proof of β-CD selectivity [16]. The ability to form hydrogen bonds by the guest molecules was helpful but not necessary. The β-CD cage was large enough to accommodate at least the hydrophobic part of the guest from the series studied (Fig. 2).

Our intention was to analyse new structures of inclusion complexes of modified β-CD and selected benzene derivatives. The

Table 2
Heat of complex formation E^* (kJ) for inclusion complexes β-CD derivatives with fluoroaromatics **1**–**6**.

Guest	Hydrogen bond		
	Length [Å]	Angle [°]	Location near oxygen (at group or bond)
Maleic(R_1amido) ester-β-CD			
Ring			
2	2.47	108.7	Hemiacetal
3	2.92	159.6	Glycosidic
6	2.75	135.7	Glycosidic
	2.68	148.9	Hemiacetal
Maleic(R_2amido) ester-β-CD			
Ring			
6	2.50	144.0	OH(C2)
	2.98	129.8	OH(C2)
	2.40	101.2	Ester
	2.72	138.4	Ester
Tunnel			
2	2.67	152.7	Amide
3	2.65	161.9	Amide
Fumaric(R_1amido)ester-β-CD			
Ring			
1	2.63	123.3	Glycosidic
Fumaric(R_1amido)ester-β-CD			
Ring			
1	2.82	149.2	Ester
2	2.88	130.6	Glycosidic
3	2.93	134.1	Glycosidic
6	2.60	144.7	OH(C2)
	2.48	105.7	Glycosidic
	2.13	128.2	Ester
Tunnel			
1	2.77	165.8	Amide
2	2.68	169.6	*O* Amid
3	2.68	167.3	*O* Amid
6	2.83	150.6	*O* Est
	2.64	141.8	*O* Est

Table 1
Heat of complex formation E^* (kJ) for inclusion complexes β-CD with fluoroaromatics **1**–**6**.

	β-CD	Maleic(R_1amido)ester-β-CD			Fumaric(R_2amido)ester-β-CD		
		R_1	R_2		R_1	R_2	
		Ring		Tunnel	Ring		Tunnel
1	−69.18	44.08	60.59	1.13	−24.33	−182.93	−117.82
2	−76.26	−25.16	−4.13	−32.23	−105.87	−207.26	−162.06
3	−97.4	60.92	0.44	−22.3	27.4	−228.31	−126.88
4	−58.19	35.87	26.52	−11.77	97.17	−108.27	−68.55
5	−107.01	45.16	−8.14	−17.48	20.18	−143.57	−128.75
6	−152.91	−27.59	−23.5	−25.71	13.9	−216.73	−206.17

$^*E = E_{\text{inclusion complex}} - (E_{\text{host}} + E_{\text{guest}})$.