Advances in Health Sciences Research, volume 28
Proceedings of the International Conference "Health and Wellbeing in Modern Society" (ICHW 2020)

Inclusion Complexes of Cyclodextrins With Biologically Active Molecules in Water-Organic Solvents as a Promising Material for the Pharmaceutic Industry

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ABSTRACT
The paper provides the review of literature sources on thermodynamics of inclusion complexes reactions of cyclodextrin with biologically active hydrophobic molecules. The group of authors presents the results of their experimental studies of the inclusion complexes reaction of β-cyclodextrin (β-CD) with benzoic acid (BA) in water-ethanol solvents. Thermodynamic parameters of the reaction [BAβCD] are defined. In the transition from water to water-ethanol mixtures, the stability of the complex decreases, while the exothermicity of the reaction increases. The results were discussed on the basis of solvation-thermodynamic approach. The most popular application is the pharmaceutical industry, since this is connected with the development of vector delivery of medicines to living systems, which makes it possible not only to significantly increase the efficiency of the drug used, but also to significantly improve its consumer properties.

Keywords: *cyclodextrins, benzoic acid, water-ethanol solvent, isothermal titration calorimetry, complex formation, solvation*

1. INTRODUCTION

Cyclodextrins (CD) are able to form inclusion complexes by placing different drugs in the vids of their molecules [7] and selectively deliver them to human cells, tissues and organs (Figure 1). The development of new pharmaceutical compositions to improve bioavailability, targeted delivery, low toxicity, as well as controlled release of pharmacologically active components from the dosage form is one of the strategic directions of the pharmaceutical industry in the Russian Federation. The above requirements for modern innovative preparations can be achieved by encapsulating biologically active molecules with cyclodextrins.

Due to their structure, CDs are able to form water-soluble complex inclusions with different organic substrates. Such molecular encapsulation solves many pharmaceutical problems and offers a wide range of possibilities to improve the properties of already available medicinal compounds, namely allows the following:

1) increasing solubility, dissolution rate and bioactivity of pharmacologically active substances;
2) stabilizing and increasing the shelf life of medicines;
3) achieving controlled and prolonged drug release effect;
4) reducing undesirable side effects.

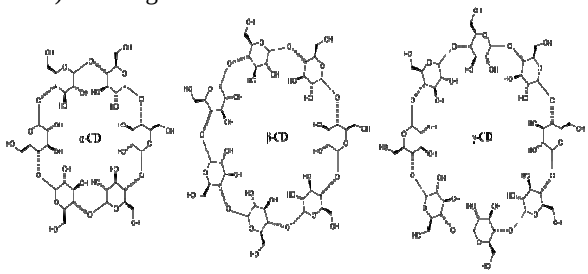

Figure 1 Structures of three main cyclodextrins

Molecular complexation in water is usually characterized by low stability of complexes, which makes their preparation and study difficult [15]. In contrast, in non-aqueous environments, such interactions are characterized by high stability of complexes. However, low solubility of "guests" in non-aqueous solvents may prevent the creation of optimal concentration of complexation. Based on previous studies of formation reactions of molecular complexes of macrocyclic ligands with amino acids and peptides [1], it can be assumed that the targeted change of solvent composition will allow

obtaining inclusion complexes with new thermodynamic properties, the formation of which is impossible in water.

Table 1 Characteristics of cyclodextrins [7]

Cyclodextrin	Abbreviation	Mole weight/g mol^{-1}	Water conten /%	Cavity diameter/Å
β-cyclodextrin	β-CD	1135	14.9	6.0–6.5
γ-cyclodextrin	γ-CD	1297	11.2	7.5–8.3
hydroxypropyl- β-cyclodextrin	HPβCD	1414	9.0	*

Table 2 Thermodynamic properties of cyclodextrin derivatives [7]

Cyclodextrin	Differential scanning calorimetry			Thermogravimetry	
	$T_{beginning}$ /^{0}C	ΔH/J g^{-1}	ΔH/ kJ mol^{-1}	$T_{beginning}$/^{0}C	Weight loss / %
β-CD	75	234	266	40–125	11.4
HPβCD	58	58	64	40–120	6.0
γ-CD	67	56	73	40–120	9.0

Benzoic acid (BA) is a monobasic carboxylic acid (Figure 2) found in the 16th century by sublimation of benzoic resin. It is a natural compound. It is contained in cranberry, blueberry, cowberry, raspberry, cherry tree bark. Benzoic acid shows antimicrobial, antifungal action, prevents reproduction of bacteria of butyric fermentation, yeast, suppresses activity of enzymes of pathogenic cells. However, high BA doses can affect liver and kidneys and cause skin and eye irritation [6, 3].

Thermodynamic properties of benzoic acid obtained by differential scanning calorimetry and thermogravimetry are shown in Table 3 [7].

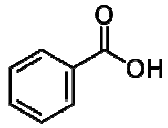

Figure 2 Structural formula of benzoic acid.

Table 3 Thermodynamic properties of benzoic acid [7]

Acid	Differential scanning calorimetry			Thermogravimetry	
	$T_{beginning}$/^{0}C	ΔH/J g^{-1}	ΔH/ kJ mol^{-1}	$T_{beginning}$/^{0}C	Weight loss / %
BA	115	131	16	85	98

The process of formation of β-cyclodextrin complex with benzoic acid corresponds to the reaction:

$$BA + \beta\text{-CD} \leftrightarrow [BA\beta CD] \quad (1)$$

It is known that β-CD is capable of forming complexes-inclusions provided the following condition is met: the molecule "guest" shall have a suitable size (steric factor) [4, 5, 8].

Besides, water also forms stable hydrates with cyclodextrin, which complicates complexation. Most studies of intermolecular interactions were focused on the study of selective recognition processes in aqueous solutions. Molecular complexation of cyclodextrins with aromatic carboxylic acid compounds in water is generally characterized by low stability of complexes and low exothermicity of complexation, which makes it difficult to obtain molecular complexes, study them and ensure their further practical application. Previous studies showed that the addition of a small amount of methanol or ethanol to water facilitates the complexation of β-cyclodextrin with hydrophobic guest [16].

On the basis of concentration dependencies of transport enthalpy ($\Delta_{tr}H$), change of a chemical shift ($\Delta\delta$) and apparent mole volume (V_Φ) it was found that α-cyclodextrin (α-CD) and β-CD form complexes with BC with 1:1 composition [2–5, 8].

The interaction of benzoic acid with β-CD, HPβ-CD and α-CD was studied in [8]. The studies were conducted

by differential scanning calorimetry and thermogravimetry combined with Fourier IR and X-ray powder diffraction.

Table 4 Thermodynamic parameters of complexation of cyclodextrins with benzoic acid in water at 298.15K [8, 4]

Complex	K^0	Δ_cG^0		Δ_cH^0	$T\Delta_cS^0$	Method
		kJ/mol				
α-CD/BA	897±75	-16.9±0.5	-38.8±0.5	-21.9±0.7		calorimetry ^{1}H NMR densimetry
	901±15	-16.9±0.1	-	-		
	845±96	-16.7±0.6	-	-		
β-CD/BA	372±47	-14.7±0.2	-13.4±0.4	1.3±0.8		calorimetry ^{1}H NMR densimetry
	363±15	-14.6±0.6	-	-		
	235±20	-13.5±1.1	-	-		

* – concentrations of reagents were expressed in mol/kg

Thermodynamic parameters of complex formation of BA with cyclodextrins (K, Δ_cG^0, Δ_cH^0 и $T\Delta_cS^0$) calculated by non-linear least-square method taking into account equation (1) are given in Table 4 [8, 4].

The authors of [16] carried out quantum-chemical calculations of the structure of α-CD inclusion complexes with aromatic guest molecules. It was shown that dipole-dipole interactions prevail in complex formation with BC and determine guest orientation within the host macrocyclic cavity. According to Levis and Hansen, high exothermicity of BA complexation with α-CD is caused by the preponderance of the negative contribution of the formation of hydrogen bonds between the guest and host molecules, as well as between water molecules, which are partially or completely released from the macrocyclic cavity and go into the volume of a solvent. Thus, contributions from all of these types of non-valent interactions determine high negative Δ_cH^0 and $T\Delta_cS^0$ values for the complexation of BA with α-CD.

The interaction of BA and benzenecarboxylic acids (BCA) with β-CD in aqueous solutions and on the surface of fine silica chemically modified β-CD was studied in [1]. The study was conducted using UV and IR spectroscopy, as well as thermal analysis and quantum-chemical calculations. The structure of β-CD complexes with BCA synthesized in aqueous solutions was established. Based on the results of quantum-chemical calculations, it was concluded that the formation of tail forward and head forward inclusion complexes is equally possible (Figure 3).

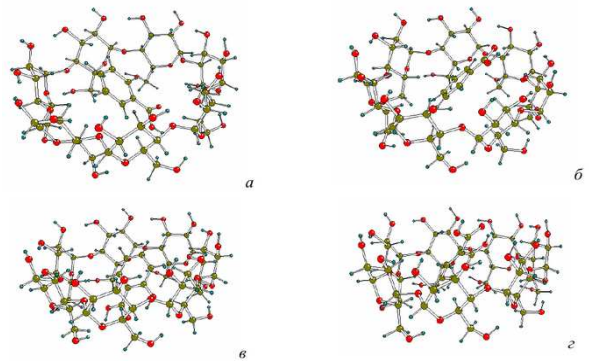

Figure 3 Spatial structure of β-cyclodextrin inclusion complexes with benzoic (a, b) and salicylic (c, d) acids: “tail forward” (a, c) and “head forward” (b, d) [1]

The obtained complexes relate to host-guest inclusion compounds and have 1:1 composition. The stability constants of complexes-inclusions and standard thermodynamic parameters of their formation are calculated (Table 5).

Table 5 Stability constants and standard thermodynamic parameters of formation of β-CD complex with BA in water [1]

Temperature, K	K_s, l/mol	ΔG^0, kJ/mol	ΔH^0, kJ/mol	ΔS^0, J/mol·K
βCD-BA				
291	124 ± 6	-11(11.66±0.58)	-(23±1)	-(39±2)
293	120 ± 6	-11(11.66±0.58)		
295	114 ± 6	-11(11.62±0.58)		
298	108 ± 5	-11(11.60±0.58)		
300	104 ± 5	-11(11.58±0.58)		

Low K_S of stability constants (Table 5) for the complex [BAβCD] indicate the presence of non-specific intermolecular interactions.

2. METHODS AND MATERIALS

2.1. Substances and their treatment

The following substances were used in this study:

1. Benzoic Acid (BA) by Sigma-Aldrich with BA≥99 % was used without additional treatment.

2. β-cyclodextrin (β-CD) by Fluka with β-CD≥99 % was used without additional treatment. The water content of β-CD was determined by thermogravimetry and taken into account in the calculation of the concentration. β-CD contained 7.5 % water.

3. Ethanol ("rectificate") was purified by distillation at atmospheric pressure. The water content was controlled densimetrically and did not exceed 5%. Residual water content in ethanol was taken into account in the preparation of solutions. The solutions were prepared by weight based on freshly distilled aqueous bidistillate.

2.2. Calorimetric method

The method of isothermal titration calorimetry is currently the only one that allows simultaneously defining all thermodynamic parameters of complex formation (or binding in biochemical terminology in the study of protein-ligand complexes), namely: stability constant of complexes (binding constant) expressing the interaction force and defining the change of the Gibbs energy, contribution of enthalpy and entropy in the change of the Gibbs energy $\Delta G=\Delta H-T\Delta S$), the reaction stoichiometry or the number of binding sites in biomolecule interaction (n).

In this work, calorimetric experiments were performed on isothermal titration calorimeter TAM III (TA Instruments, USA) with a titration module having with a 20 ml reaction cell to conduct experiments in order to study interactions in liquid media in the isothermal mode. The accuracy of temperature maintenance of the TAM III calorimetric unit makes ±0.0001 K.

The use of standard calorimetric titration with sequential addition of titrant to the calorimetric cell is limited by low solubility of BA in H_2O-EtOH mixtures. This did not allow obtaining the desired ratio of reactant concentrations during one titration experiment. Single addition of titrant to a cell with subsequent registration of heat release and reloading the calorimetric system allows creating optimal concentration conditions. Earlier this technique was successfully applied to calorimetric study of complex formation "host-guest" 18-crown-6 and cryptands [2.2.2] with some amino acids and peptides as well as for Cu (II) complexes with glycyl-glycyl-glycine [10–12]. In calorimetric experiment, the BA initial concentration in a cell was in the range of $1.34\cdot10^{-3}$–$5.68\cdot10^{-1}$ mol kg^{-3}. The concentration of β-CD in the syringe made $1.73\cdot10^{-2}$–$2.54\cdot10^{-2}$ mol kg^{-3}.

Calorimetric measurements were made in water-ethanol solvents containing 0.00, 0.10, 0.20, or 0.30 mole fractions of EtOH. The solutions were prepared immediately before measurements, in phosphate buffer at pH=3.6, which correspond to the pH of BA solutions with concentrations used in the experiments. An example of primary thermochemical experimental data is given in Table 6. The concentration range of water-ethanol mixtures is limited by low solubility of β-CD in the water-ethanol mixture, which limits the set of BA:β-CD concentration ratios required for simultaneous calculation of stability constants of the complex [BAβCD] and the enthalpy of its formation reaction from calorimetric data. It was found that at X(EtOH) = 0.30 mole fraction and higher, according to calorimetric titration data, the complexation does not occur.

Table 6 Example of primary experimental data on complexation of β-CD with BA in solvent H_2O-EtOH, X_{EtOH} = 0.20 mol, T = 298.15K. Phosphate buffer, pH = 3.6

C^a(BA), mol·kg^{-1}	C^a(β-CD), mol·kg^{-1}	C^b(BA)10^{-3}, mol·kg^{-1}	C^b(β-CD) 10^{-4}, mol·kg^{-1}	Q_{com}, mJ	$-Q_{dil}$, mJ
β-CD in cell, BA in syringe					
0.5682	0.0138	0.0075	0.0136	375.2	249.7
0.5682	0.0138	0.0075	0.0136	369.7	249.7
0.5682	0.0056	0.0075	0.0054	165.1	249.7
0.5682	0.0056	0.0075	0.0054	151.8	249.7
0.5682	0.0056	0.0111	0.0054	155.9	258.0
0.5682	0.0056	0.0111	0.0054	138.8	258.0
BA in cell, β-CD in syringe					
0.0479	0.0172	0.0473	0.0002	23.1	-12.0
0.0287	0.0172	0.0288	0.0002	18.7	-12.0
0.1955	0.0172	0.1286	0.0002	14.0	-12.0
0.0172	0.0172	0.0173	0.0002	8.9	-12.0

C^a – initial concentration of reactants; C^b – analytical concentration of reactants in a cell; Q_{com} – thermal effect of complexation between BA and β-CD; Q_{dil} – thermal effect of dilution of solution of β-CD or BA in solvent.

The thermal effect of dilution of β-CD or BA solution in a corresponding solvent (Q_{dil}) was measured in a separate calorimetric experiment and taken into account in determining the thermal effect of complexation (Q_{mix}):

$Q_{com} = Q_{mix} - Q_{dil}$ (2)

Q_{mix} – thermal effect of mixing the BA solution with the β-CD solution; Q_{dil} – thermal effects of an experiment to dilute a solution of β-CD or BC in a mixed solvent. The experiments in a buffer solution made it possible to exclude possible acid-basic equilibrium of reagents.

3. RESULTS

There are some differences in complexation between BA and β-CD in water and in an aqueous-ethanol solvent: the part of internal cavity of β-CD in which the BA molecule is located may be more hydrophobic in water than in H_2O-EtOH mixture, and this may cause the growth of exothermicity of complexation in the transition from water to aqueous ethanol. The highest $\Delta_r H$ value in the solvent of the composition 0.10 mole fraction of EtOH is likely due to changes in solvation of the reactants at initial additions of EtOH to water. Previously, extremes were observed on dependencies of thermodynamic parameters of solvation of reagents and reaction of formation of d-metal complexes in water-ethanol mixtures at high water concentrations [13]. Such effects were correlated with the effect of forming a cavity in a solvent structure in initial additions of ethanol to water [3].

Thermodynamic parameters (lg$K$, $\Delta_r H$ $\Delta_r G$ $T\Delta_r S$) of complex formations were calculated in HEAT program. The analysis of experimental data processing in the study of molecular complex formation reactions by HEAT was previously described in [10–13]. The thermodynamic parameters of reaction (1) in H_2O-EtOH solvents are shown in Table 7.

The increase of EtOH concentrations in a mixed solvent leads to a decrease in the stability of the complex [BAβCD] and an increase in the exothermicity of its formation reaction. The increase in exothermicity of complexation is accompanied by a decrease in entropy contribution to the change of the Gibbs energy.

Table 7 Thermodynamic parameters of the reaction of complex formation [BAβCD] (lg$K$, $\Delta_r H$, $\Delta_r G$, $T\Delta_r S$) in a binary solvent H_2O-EtOH of variable structure at T = 298.15 K

X_{EtOH}	lg$K$	$-\Delta_r H$, kJ mol^{-1}	$-\Delta_r G$, kJ mol^{-1}	$-T\Delta_r S$, kJ mol^{-1}	Method, pH
0.00	2.4 ±0.1	12.2 ±0.5[a]	13.7±0.6[a]	1.5±0.8[a]	Isothermic titration calorimetry, pH=3.6
	1.94		11.3		Solubility method, pH=2.9
	2.6±0.1	13.4 ± 0.4	14.7	-1.3	Isothermic titration calorimetry, acid medium
	2.5	22.3±0.3	14.4	7.9	CD spectroscopy
	2.5	−	14.2	−	^{1}H NMR, acid medium
	2.1	32±11	12	20	Isothermic titration calorimetry
	2.4	−	13.7	−	Densimetry, acid medium
0.10	1.9 ± 0.1	36.8 ± 0.2[a]	10.8±0.6[a]	26.0±0.7[a]	Isothermic titration calorimetry, pH=3.6
0.20	0.70 ±0.1	44.3 ± 0.6[a]	3.9±0.6[a]	40.4±0.8[a]	Isothermic titration calorimetry, pH=3.6

The effect of the water-ethanol solvent on the formation reaction (1) is discussed based on the solvation-thermodynamic approach. According to the solvation-thermodynamic approach, the effect of changing the solvent composition on the reaction (3) ($\Delta_r Y_{(solvent)}$, $\Delta_r Y_{(water)}$) and on thermodynamic solvation parameters of each reagent and product ($Y(Z)_{(solvent)}$, $Y(Z)_{(water)}$) can be quantified by the following equations:

$\Delta_{tr} Y_r = \Delta_r Y_{(solvent)} - \Delta_r Y_{(water)}$ (3)

$\Delta_{tr} Y(Z) = Y(Z)_{(solvent)} - Y(Z)_{(water)}$, (4)

where $\Delta_{tr} Y_r$ и $\Delta_{tr} Y(Z)$ – thermodynamic transfer functions ($\Delta_{tr} H$, $\Delta_{tr} G$, $T\Delta_{tr} S$) for reaction and reagents, respectively.

The ratios of thermodynamic characteristics of the formation reaction [BAβCD] and solvation of the reagents are shown in Figures 4 and 5.

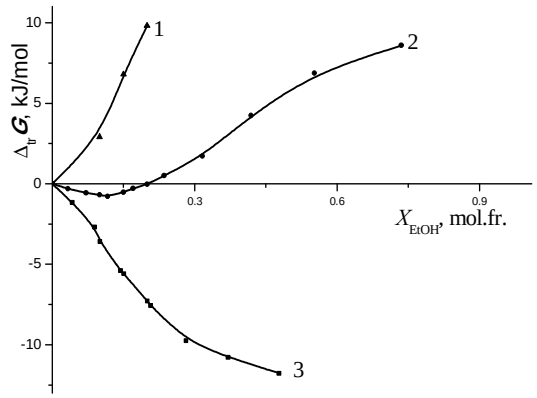

Figure 4 Effect of H_2O-EtOH solvent composition on the Gibbs energy change of the formation reaction [BAβCD] and solvation characteristics of reagents 1 – $\Delta_{tr}G_r$; 2 – $\Delta_{tr}G_r$(CD) [7]; 3 – $\Delta_{tr}G$(BA).

The $\Delta_{tr}G$(β-CD) values are close to zero at concentrations X(EtOH) = 0.0 0.2 mol.fr. Thus, the decrease in the stability of the complex is determined by the change in the solvate state of BA (Δ_{tr}G(BA)) and desolvation of the complex.

When a small amount of EtOH is added to the solvent (X(EtOH)<0.05 mol.fr.), the increase in exothermicity of the complex formation reaction ($\Delta_{tr}H_r$) is determined by desolvation of β-cyclodextrin (Figure 4 (2)).

Earlier it was established that the increase of the content of nonaqueous co-solvent in such solvents as water-ethanol, water-dimethyl sulfoxide and water-acetone increases the stability of molecular "guest-host" complexes formed by macrocyclic ligand crown ether 18-crown-6 (18C6) and glycyl-glycyl-glycine, glycine, D, L-alaninom and L-phenylalanine ([AK18C6]) and the growth of exothermicity of their formation reactions [10-13, 14]. However, for both the molecular complex [B βCD] and the 18C6 complexes with amino acids and peptides, the change in the Gibbs energy is determined by the change in solvate state of the "guest" molecule.

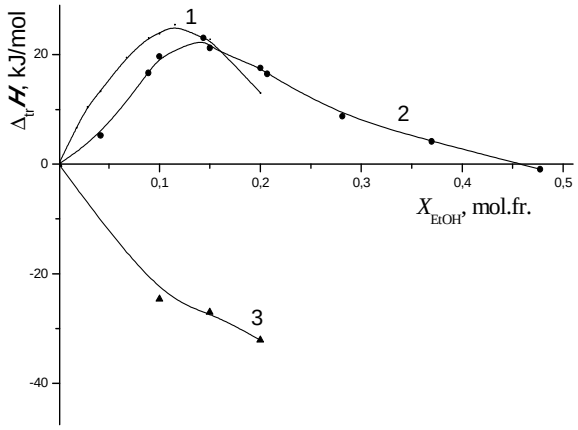

Figure 5 Effect of H_2O-EtOH solvent composition on enthalpy change in the formation reaction [BAβCD] and solvation enthalpy of reagents. 1 – $\Delta_{tr}H$(CD) [5]; 2 – $\Delta_{tr}H$(БК) [24]; 3 – $\Delta_{tr}H_r$.

In case of molecular complexes of amino acids with 18C6 the desolvation of "guests" is observed, and in the formation of the [BCβCD] complex the solvate BA complexes are strengthened during the transition from water to water-ethanol mixtures.

Despite various influences of water ethanol solvents on the stability of complexes [18C6AK] and [BAβCD], both types of reactions are characterized by the increase in exothermicity of complex formation in mixed H_2O-EtOH solvents with the growth of the content of ethanol.

4. CONCLUSION

The work defines thermodynamic parameters (lg*K*, $\Delta_r H$, $\Delta_r G$, $T\Delta_r S$) of the formation reaction of molecular inclusion complex of β-cyclodextrin with benzoic acid in H_2O-EtOH solvents of variable composition at T = 298.15 K. It was found that the increase of EtOH concentration in a solvent leads to the decrease of the stability of complex [BAβCD] and to the growth of exothermicity of its formation reaction. The analysis of solvation contributions of reagents to the change of stability of complex [BAβCD] and enthalpy of complex formation was carried out. Besides, the obtained results with those earlier presented in literature for complexes 18C6 with amino acids and peptides were compared:

- H_2O-EtOH solvent has an opposite impact on the stability of a complex of crown ether 18-crown-6 (18C6) with glycyl-glycyl-glycine, glycine, D, L-alaninom and L-phenylalanine: stability of complexes increases upon transition from water to water-ethanol mixtures.
- There is an increase in exothermicity of both types of complexation reactions in mixed H_2O-EtOH solvents with an increase in ethanol content.
- For molecular complexes [BAβCD] and 18C6 complexes with amino acids and peptides, the change in the Gibbs energy from water to water-ethanol solvents is determined by the change in solvate state of the "guest" molecules. In the case of molecular complexes of amino acids with 18C6, the desolvation of "guests" is observed, and in complexes [BAβCD] the solvate BA complexes are strengthened during transition from water to water-ethanol mixtures.

The obtained results can be used to assess the stability of inclusion complexes of cyclodextrins with benzoic acid and its derivatives in non-aqueous media, as well as as reference thermodynamic data for the development of synthesis technologies for new pharmaceuticals.

ACKNOWLEDGMENT

The study is conducted at the Institute of Thermodynamics and Kinetics of Chemical Processes of Ivanovo State University of Chemistry and Technology (ISUCT) with the use of the equipment of the ISUCT Center of Collective Use under financial support of the Russian Foundation for Basic Research and the Vietnamese Academy of Sciences and Technology within scientific project No. 19-53-54004, and under financial support of the National Fund of Scientific and Technical Development of Vietnam (NAFOSTED) [grant No. 104.06-2017.329].

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