ICC
Iranian Chemical Communication
Original Research Article
Payame Noor University http://icc.journals.pnu.ac.ir

Application of the extended solvation theory to study the interaction of β-CD with interpolymer of PEO and PAA

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Received: 3 March 2016, Accepted: 3 September 2016, Published: 3 September 2016

Abstract

Thermodynamic study on the interaction of β-CD with poly ethylene oxide and poly acrylic acid was performed by isothermal titration calorimetry at 298K. When β-CD is added to the interpolymer complex, competition is created between host-guest and Hydrogen bond. Enthalpy of interaction between the β-CD and interpolymer complex was calculated using the extended solvation theory. P=1 shows that willingness of β-CD to interact with both polymers is identical. The positive values of δ_θ^A and δ_θ^B show that interpolymer complex is stabilized by β-CD. The process is both enthalpy and entropy-driven. The results show that this interaction is exothermic and increases the interpolymer complex stability.

Keywords: β-CD; poly ethylene oxide; poly acrylic acid; isothermal titration calorimetry.

Introduction

Host–guest chemistry deals with the concept of molecular interactions and recognition by noncovalent bonding consisted of small molecules as guests which are noncovalently bound to larger molecules as hosts in a unique structural relationship [1]. Recently host-guest complexes are becoming increasingly important and have been broadly investigated [2]. Cyclodextrins(CDs) are normally water-soluble and toroidally formed polysaccharides contained a greatly hydrophobic central cavity that have the ability to produce inclusion complexes accompanied by a wide range of organic and inorganic substrates [3-9]. α−, β−, and γ−CD are the three major natural cyclodextrins which are made up from 6, 7, and 8 glucopyranose units, respectively. CDs are often observed as building blocks of supramolecular systems, chemical sensors, or self-assemblies [10–15]. The potential of CDs in forming inclusion complexes, in which the physicochemical features of the guest molecules affected by the free molecules, has engendered a wide range of applications [16–22]. The inclusion complexation with cyclodextrins (CDs) is a tempting and widely employed method for solubility improvement of imperfectly water-soluble drugs [23].

The polymers preserve CD/drug complexes with the help of ternary

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complexes configuration. Furthermore, ternary complexes comprising matrix-forming polymers(hydroxypropyl methylcellulose) are able to prompt drug release [24]. The CD-polymers can form nanoparticles or gels in aqueous media that can be explored as drug delivery systems [25]. Interpolymer complexes (IPCs) between polyacids and non-ionic polymers stabilized by hydrogen bonds have been studied for several decades [26-30]. The isothermal titration calorimetry (ITC) method is based on the evaluation of the heat absorbed or generated upon the interplay between two molecules. Data derived from ITC were obtained in many areas from chemistry to cellular biology [31–33]. ITC was used for the characterization of polyelectrolyte complexes [34], adsorption on vesicles [35], self-associating systems [36], micellarbased systems [37–39], nucleic acid interactions with multivalent cations together with the characterization of various functionalities conducted *via* nanoparticles. A special interest of ITC affects its implementation for the characterization of guest-CD interactions [40–45]. Owing to the knowledge of the polymer–CD interactions, various sorts of self-assembled drug delivery systems were developed such as a wide range of nanoparticles [46] and hydrogels [47]. ITC is the most sensitive method available for the determination of the stoichiometry of the interaction (N), K_a(the association constant), along with ΔH (the enthalpy variation), which reflects the heat released or taken up during the interaction. Furthermore, the entropy (ΔS) and the Gibbs free energy of the process (ΔG) can be calculated from the ITC data [33,40–48,49]. Since PEO(Poly ethylene oxide) is able to form the inclusion complex with CD and interpolymer complex with PAA(Poly acrylic acid), respectively, it is very interesting to observe what happens after mixing CD, PEO and PAA together. In this research, PEO and PAA ternary components are constructed dependent on the hydrogen bonding interaction between PEO and PAA and host-guest interaction between CD and PEO various novel supra molecular polymer systems consisting of β–CD. Thermodynamic study on the interaction with β-CD, poly ethylene oxide, and poly acrylic acid was performed at 298K using isothermal titration calorimetry.

Experimental

PEO and PAA (both with $M_W = 10000$) together with β-CD were provided from Aldrich Chem. β-CD purified once by recrystallization from deionized water before employment. The isothermal titration calorimetric experiments were performed with the four channel commercial microcalorimetric system, Thermal Activity Monitor 2277, Thermometric, Sweden. The microcalorimeter is composed of two identical cell made of a highly efficient thermal conducting material surrounded by an adiabetic jacket. The sample cell contained 1.8 mL PAA/PEO (0.031 μmol.L-1) and the reference cell was filled with β- CD (0.114 μmol.L-1) . The titration of PAA/PEO with β- CD involved 30 consecutive injections of the β- CD and each injection included 10 Ml of β-CD (2.5 mmol.L-1). The heat of injection was calculated by the 'Thermometric Digitam 3' software program. The measurements were carried out at a constant temperature (25 °C). The microcalorimeter was frequently calibrated electrically during the course of the study. The β-CD and the guest

concentrations in the syringe or in the measurement cell could be adjusted depending upon several factors, such as the solubility and the affinity of the β CD–guest interaction. The concentrations of the guest and the β-CD have to be adjusted to obtain titration curves that can be fitted properly. The observed heat signals obtained upon the titration are dependent on the concentrations used.

Results and discussion

The interaction between poly acids such as poly (acrylic acid) and poly bases such as poly ethylene oxide have been designed–based on the formation of interpolymer complex (IPC). If aqueous solution of two polymers mixes with a same volume becomes turbid immediately, hydrophilic groups of polymers lead to hydrogen bonds formation. Therefore, the PAA/PEO complexes coil up to compact structure and then aggregate to large particles. The internal cavity of CD is hydrophobic and external area of the cavity has hydrophilic properties. In fact, when β-CD is added to the interpolymer complex, competition is created between host-guest and Hydrogen bond. With adding β-CD, Hydrogen bonds between the polymer is gradually weakened.

The extended solvation model was used to analyze the heats of interaction between interpolymer complex (guest) and β-CD (host). As demonstrated before, the heats of interaction between a macromolecule and ligand in the aqueus solvent system could be analyzed by the following equation [50-54]:

$$q = q_{\max} x'_B - \delta_A (x'_A L_A + x'_B L_B) - (\delta_B - \delta_A)(x'_A L_A + x'_B L_B) x'_B \quad (1)$$

In this equation q is the generated heat because of binding of β-CD with IPC and q_{max} is the maximum necessary heat for saturating the β-CD molecule. The parameters δA and δB reflect the net effect of IPC on the β-CD stability in the low and high IPC concentrations, respectively. The positive values for δA and δB indicate that the IPC stabilized the β-CD structure, while the negative values of δA and δB show that β-CD is destabilized as a result of its interaction with the IPC. If the binding of β-CD with one polymer increases the affinity for β-CD at another polymer, the macromolectule exhibits positive cooperativity(p>1). Conversely, if the binding of β-CD with one polymer decrease the affinity for β-CD at another polymer, the host-guest system exhibits negative cooperativity (p<1) [55-57]. If the β-CD binds with each polymer independently, the binding is non-cooperative (p=1). L_A and L_B are the relative unbound and bound β-CD contributions to the heats of dilution in the absence of interpolymer complex.

x'_B can be expressed as follows:

$$x'_B = \frac{p x_B}{x_A + p x_B} \quad (2)$$

x'_B is a fraction of of bound β-CD with the interpolymer complex and $x'_A = 1 - x'_B$ is the fraction of unbound IPC. The x_B fractions are the IPC concentrations, after every injection divided by the maximum concentration of the IPC upon saturation of all β-CD, $[L]_{max}$, as follows:

$$x_B = \frac{[L]}{[L]_{\max}} \quad (3)$$

[L] is the concentration of β-CD after every injection and $[L]_{max}$ is the maximum concentration of β-CD upon saturation of interpolymer complex. In the fitting procedure, *p* was changed

until the best agreement between the experimental and calculated data was approached (Figure 1).

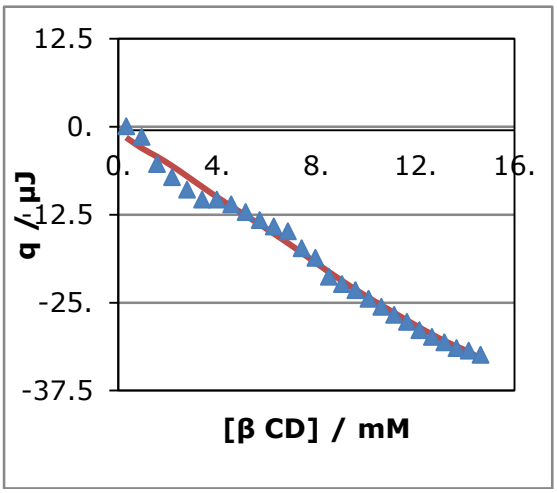

Figure 1. Comparison between the experimental heats for β-CD + interpolymercomplex interactions at 298 K (filled triangles) and calculated results (lines) *via* Eq. 1.

$$L_A = q_{dilut} + x_B(\frac{\partial q_{dilut}}{\partial x_B})$$

$$L_B = q_{dilut} - x_A(\frac{\partial q_{dilut}}{\partial x_B}) \quad (4)$$

L_A and L_B are the relative of unbound and bound IPC contributions to the enthalpies of dilution in the absence of β-CD.

For a set of identical and independent binding sites, the number of binding sites (g) and dissociation equilibrium constant (K_d) can be calculated by equation 5 from the slope $\frac{1}{g}$ and the vertical-intercept of ($\frac{K_d}{g}$) of the linear plot.

$$(\frac{\Delta q}{q_{\max}})M_0 = (\frac{\Delta q}{q})L_0\frac{1}{g} - \frac{K_d}{g} \quad (5)$$

The term Δq represents the heat value at a certain concentration of β-CD in interpolymer complex . M_0 and L_0 are concentrations of guest and host, respectively.

The molar enthalpy of binding for each binding site (ΔH°) will be $\Delta H = \frac{q_{\max}}{g}$.

The standard Gibbs free energy, ΔG°, is able to be calculated from association constant ($K_a = \frac{1}{K_d}$) as follows:

$$\Delta G = -RT\ln K_a \quad (6)$$

ΔS (enthropy) With the values of ΔG and ΔH could be calculated from the following equation:

$$\Delta S = \frac{\Delta H - \Delta G}{T} \quad (7)$$

The binding parameters for β-CD+IPC interactions were achieved from equation 1 are listed in Table 2. The agreement between the calculated and experimental results (Figure 1) is striking, and gives considerable support to the use of equation 1.

Table 1. The heats of β-CD binding to interpolymercomplex

[β CD] / mM	**q / µJ**	q_{dilut} **/ µJ**
0.315789	-1.5213	0.11166
0.942149	3.02728	1.40735
1.561644	4.24294	5.29309
2.174387	5.58066	7.14904
2.780488	7.04349	8.90109
3.380054	8.52892	10.313
3.97319	9.95819	10.3373
4.56	11.3095	11.0088
5.140584	12.6058	12.0829
5.71504	13.8883	13.2186
6.283465	15.1922	14.1285
6.845953	16.5325	14.8109
7.402597	17.9015	17.2455
7.953488	19.2739	18.589
8.498715	20.618	21.3094
9.038363	21.9068	22.3519
9.572519	23.1266	23.1945
10.10127	24.2799	24.4152
10.62469	25.3822	25.564
11.14286	26.4536	26.7166
11.65586	27.5072	27.6993
12.16377	28.5388	28.8807
12.66667	29.5238	29.8282
13.16462	30.4263	30.6101
13.6577	31.2303	31.4447
14.14599	31.9996	31.7971
14.62954	32.9752	32.3899

Table 2. Thermodynamic parameters of β-CD to interpolymercomplex *via* Eq. (1)

p	**g**	**Ka/L.mol^{-1}**	**ΔH/ kJ.mol^{-1}**	**ΔG/kJ.mol^{-1}**	**ΔS / kJ.mol^{-1}.K^{-1}**	δ_θ^A	δ_θ^B
1	0.4238	4.9673	-0.0058	21.0857	0.07073	1.062677	1.9946

Conclusion

P=1 shows that willingness of β-CD to interact with both polymers is identical (Table 2). The positive values of δ_θ^A and δ_θ^B show that interpolymer complex is stabilized by β-CD[58] . Binding includes two steps: first step is breaking some bind to make a cavity that needs consuming some energy which is positive. The second step is rearranging the IPC around the cavity and formation of complex around the β-CD which releases some energy. Then the summation of energy in the bulk solvent system is positive, consequently; it is possible to conclude that the system of β-CD and IPC in the solvation shell is stable.

The value of g indicate that 2 mole of β-CD were bound to one mole of IPC. The process is enthalpy driven. The small values of enthalpy indicate that the hydrogen bonds between the PAA and PEO has been weakened becuase competition has happened between host-guest and hydrogen bonds. All of these results suggest that PAA/PEO/βCD materials are suitable for drug delivery and biological application.

Acknowledgments

The authors gratefully acknowledge the financial support from the University of Imam Khomeini (Qazvin).

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