Probing inclusion complexes of 2-hydroxypropyl-\(\beta\)-cyclodextrin with mono-amino mono-carboxylic acids: physicochemical specification, characterization and molecular modeling

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\textbf{ABSTRACT}

Density (\(\rho\)), viscosity (\(\eta\)) and surface tension (\(\gamma\)) of three amino acids (valine, alanine, and glycine) have been measured at a different mass fraction (0.002 - 0.009) of aqueous hydroxypropyl-\(\beta\)-cyclodextrin (HP\(\beta\)CD) mixtures and different temperatures (278.15 - 295.15 K). The formation of inclusion complexes has been analyzed via evaluating the amounts of apparent and limiting apparent molar volumes, limiting apparent molar expansibilities, activation energy, kinematic, relative, intrinsic, spatial, and dynamic viscosities. The surface tension studies indicated that the inclusion complexes have been formed with 1:1 stoichiometry and mediated by hydrophobic effects and electrostatic forces. Additionally, the \(\rho\) and \(\eta\) parameters were evaluated by molecular modeling experiments to provide more details on the mechanisms of the complexation.

1. Introduction

Cyclodextrins (CDs) are a family of cyclic oligosaccharides consisting of six (\(\alpha\)-CD), seven (\(\beta\)-CD) and eight (\(\gamma\)-CD) glucose subunits constructed from starch by enzymatic conversion (Chen et al., 2017). They are vastly used for the controlled release of compounds due to their exceptional ability to form inclusion complexes with a variety of guest molecules, represented an major duty to follow whether a molecule forms an inclusion complex with cyclodextrins (Chen et al., 2017; Szojtli, 1998). They have applications majorly in food, pharmaceutical, drug delivery, and chemical industries, and also environmental engineering (Wimmer, 2012; Adeoye and Cabral-Marques, 2017; Gao et al., 2006). In the pharmaceutical industry, \(\beta\)-CDs have mostly been used as complexing agents to increase aqueous solubility of imperfectly soluble drugs and to increase their bioavailability and stability. Thus, improved and comparatively safe \(\beta\)-CDs have been synthesized and used properly (Costa et al., 2015). 2-Hydroxypropyl-\(\beta\)-cyclodextrin (2-HP \(\beta\) CD) is a derivative of \(\beta\)-CD that hydroxypropyl groups replace the hydroxyl groups of C2, C3 and C6 of \(\beta\)-CD (Chen et al., 2017). HP\(\beta\)CD is known to be a mixture of various isomers (disparate orientation of hydroxypropyl groups) and comparable with different degree of substitution (Stella et al., 1997; Tablet et al., 2012). Amino acids have important interactions with cyclodextrins and have been intensively studied due to their properties that are similar to enzyme-substrate complexes (Huang et al., 2016). So, the physicochemical features of amino acids in aqueous solutions are mediated by solute-solute interactions and solute-solvent interactions that are important in several biochemical and physiological processes taken place in living systems (Zhao et al., 2005; Huang et al., 2016). Based on this insight, the present study focuses on the evaluations of density and viscosity of non-polar amino acids (valine, alanine, and glycine) from 0.002 to 0.009 mol kg\textsuperscript{-1} in aqueous solutions of HP\(\beta\)CD at different temperatures (278.15, 283.15, 288.15, 293.15, and 295.15K).

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Figure 1. Density of the solution against molality of the Amino acids at different temperatures and $w_{\text{HP\beta CD}} = 0.002$.

Figure 2. Density of the solution against molality of the Amino acids at different temperatures and $w_{\text{HP\beta CD}} = 0.009$.

Figure 3. Density of the solution against molality of the Amino acids at different mass fraction of HP\beta CD and $T = 278$ K.
Furthermore, the nature of the complexes will be defined using thermodynamic parameters, based on density, viscosity measurements by devising the portion to the various physicochemical parameters such as \( \Phi_V, \Phi_0V, S_V, \Phi_0E, E, \eta \) which are computed within the experimental data. Finally, the results will be explicated in terms of solute solvent and solute-solute interactions in these complexes (Chen et al., 2017).

2. Results and discussion

2.1. Density study: group contributions and interactions between amino acids and cyclodextrins

Initially, the density of solutions increases with increasing mass fraction of HP\( \beta \)CD at constant temperature due to structure built from a contribution of CDs with water molecules. The density of HP\( \beta \)CD decreases with increasing temperatures at constant mass fraction of HP\( \beta \)CD (Figures 1, 2, 3 and 4).

Then, to achieve our purpose, the values of \( \Phi_V \) are determined from the experimental values of density of the solutions using the proper equation (Masson, 1929) by taking 0.002, 0.004, 0.006, 0.008, 0.009 mass fractions of HP\( \beta \)CD at different temperatures (278.15 K–295.15 K).

The results demonstrate that the magnitude of \( \Phi_V \) is larger and more positive for Valine rather than for alanine and glycine. This would describe that the values of \( \Phi_V \) increase linearly with the increase in the size of the alkyl chain of the amino acids and also with the increase in the mass fraction of HP\( \beta \)CD (0.002, 0.004, 0.006, 0.008, 0.009) in aqueous medium (Figures 5, 6, 7, 8, 9 and 10). In this regards, the apparent molar volume of valine at 295.15 K and the mass fraction of 0.009 are greater than that of alanine and glycine, respectively under the same conditions (\( \Phi_V \) (Valine, \( W_{HP\beta CD} = 0.009, T = 295.15 K \)) > \( \Phi_V \) (Alanine, \( W_{HP\beta CD} = 0.009, T = 295.15 K \)) > \( \Phi_V \) (Glycine, \( W_{HP\beta CD} = 0.009, T = 295.15 K \)).

These findings also indicate stronger solute-solvent interactions of valine than alanine and alanine relatively to glycine at 295.15 K and 0.009 mass fraction of HP\( \beta \)CD (solute-solvent interactions increase with increasing concentration of HP\( \beta \)CD, size of the alkyl side chain of amino acids and temperature (Roy et al., 2016a, b). At all temperatures (278.15 K–295.15 K), the values of \( \Phi_0V \) increase the size of the alkyl group from glycine to valine. Considering particular amino acids (such as Glycine, Valine, alanine), it is ascertained that the values of \( \Phi_0V \) increase with increasing the mass fraction of HP\( \beta \)CD and temperature (Figures 11, 12 and 13). That means that the ion-hydrophilic group interactions, between zwitterionic centers of the amino acids and the –OH groups of HP\( \beta \)CD, are stronger than the ion-hydrophobic group interactions, between zwitterionic centers and non-polar parts of HP\( \beta \)CD, and hydrophobic-hydrophobic interactions, between non-polar parts of the amino acids and HP\( \beta \)CD (Roy et al., 2016a, b). Due to these interactions,
the electrostriction of water caused by the charged centers of the amino acids will be reduced resulting in an increase in the volume and the order glycine < alanine < valine at each investigated temperature.

The increase of $\Phi V$ with increasing temperature may be identified to the release of some solvated molecules from the loose solvated layers of the solutes in solution. The apparent molar volume ($\Phi V$) and limiting apparent molar volume ($\Phi V/C_1^0$) are considered to be sensitive tools for understanding the interactions taking place in solutions (Roy et al., 2014; Das et al., 2018). Where $\Phi V = V_0$ is the apparent molar volume at infinite dilution ($m < 0.1$ mol kg$^{-1}$). At infinite dilution, each monomer of solute is surrounded only by the solvent molecules, and being infinite distant with other ones. So, this would tell us that $\Phi V$ is unaffected by solute-solute interaction and it is a measure only of the solute-solvent interaction (Ekka and Roy, 2013). $S^*_V$ is found to be investigated for all the studied systems, suggesting that the pairwise interaction is restricted by the interaction of the charged functional group one molecule to chain of the other amino acids (Chen et al., 2017). A quantitative comparison between $\Phi V$ and $S^*_V$ values show that the magnitude of $\Phi V$ values is higher than $S^*_V$, suggesting the solute-solvent interactions at the different temperatures (278.15–295.15 K). Furthermore, $S^*_V$ values are negative and have an irregular trend at all temperatures which are indicative of the fact that solute-solute interactions are influenced by number of effects (Figure 14) (Chen et al., 2017). The values of $S^*_V$ faintly increase with the increase of temperatures, and consequently the entropy of the solution increases with increasing temperature.

Generally, 3D diagrams confirm the results obtained from the density section (Figures 15 and 16).
The values of limited apparent molar expansibility ($\Phi/C_1E$) for complexation of the studied three amino acids at different temperatures. $\Phi_e$ are also employed to interpret the structure-making or breaking properties of various solutes (Kumar and Kaur et al., 2012). Positive expansibilities increase the volume with the increase at considered temperature for all the amino acids in aqueous HPβCD solutions (Wang et al., 2014). If limiting apparent molar expansibility is positive, the molecular is a structure maker. This trend in $\Phi_e$ values indicates the presence of strong solute-solvent interactions and such interactions further strengthen at elevate temperature. $\Phi_e$ values for valine is higher than alanine and glycine, respectively.

2.2. Viscosity: group contribution and solvation number: the degree of solvation by cyclodextrin molecules

Next, the viscosity of the aqueous solution of CD increases with the increase of mass fraction for HPβCD at constant temperature due to the structure making from contribution of HPβCD with water molecules. In the studied ternary systems the viscosity and activation energy (Arrhenius model: $\mu(T) = \mu_0 \exp\left(\frac{E}{RT}\right)$) of HPβCD-AA were found to be increased with the increase of molar concentration for valine, alanine and glycine (Figures 17 and 18). These consequences reveal that the values of dynamic viscosity increases with the increase in the mass fraction of HPβCD.
energy increases with increasing molality of amino acids at constant mass fraction of HPβCD. The magnitude of $E_a$ is higher for valine rather than alanine and glycine, respectively (Figures 23 and 24). It can be concluded from the above discussion that the rate constants decrease with increasing molality and thus the rate of complex formation decreases. This decrease is larger for glycine than alanine and valine respectively ($E_a$ (valine) > $E_a$ (alanine) > $E_a$ (alanine); $k$ (glycine) > $k$ (alanine) >$k$ (valine)).

Additionally, we turned our attention to reduced viscosity that refers to the ratio of specific viscosity to the concentration of amino acids. Here, the reduced viscosity diagram versus concentration gives us intercept (intrinsic viscosity) and the gradient (slope) of the chart on the intrinsic viscosity ($\eta_{int}$). The internal viscosity and the reduced viscosity are measured for each concentration that has a different viscosity. The intercept of the reduced viscosity graph is intrinsic in the viscosity concentration and the slope of the graph is dependent on the intrinsic viscosity. Usually, the intrinsic viscosity is calculated from both methods and if they fit each other, we realize that we have done all the steps correctly by shown the diagrams obtained from the two methods together in a coordinate system. The reduced viscosity of aqueous HPβCD decreases with increasing molal concentration of the above three amino acids and decreases with increasing temperature and increases with increasing mass fraction of HPβCD. The magnitude of reduced viscosity for valine is more than alanine whereas alanine is larger than glycine. The relative viscosity refers to the ratio of discharge time dissolved to solvent drain time. Spatial viscosity refers to the ratio of the difference in discharge time dissolved and solvent drain time to solvent drain time ($\frac{\text{discharge time} - \text{solvent time}}{\text{solvent drain time}}$). Spatial viscosity was obtained at different temperature and different mass fraction of HPβCD. Therefore, Figures 25, 26, 27, 28 and 29 confirm our findings for this research.

2.3. Surface tension study explains the inclusion as well as the stoichiometric ratio of the inclusion complexes

The surface tension ($\gamma$) measurement provides a considerable implication about the formation of inclusion complexes (IC) and also the stoichiometry of the host-guest assemblage. Each plot also indicates that there is a breakpoint at certain concentrations after which the slopes become less (Roy et al., 2016a, b). Finding of breakpoint in surface tension curve not only indicates the formation of IC but also provides information about its stoichiometry, i.e., the appearance of single, double and so on break point in the plot indicates 1:1, 1:2 and so on the stoichiometry of host: guest ICs (Roy et al., 2016a, b). In the present study the guest amino acids molecules exist in zwitterionic forms and contain basic side groups hence having a charge in their molecules. Therefore, it might be some ionic interactions between the charged groups resulting in an increase in surface tension of the aqueous medium, which would be definitely affected in the presence of HPβCD. Here a set of solutions has been prepared to have 4 mmol.L$^{-1}$ concentration of alanine, valine, and glycine with increasing concentration of HPβCD and the surface tension is measured at 295 K surface tension curve is found to be steadily come down with increased concentration of HPβCD, which perhaps ascribed to the formation of the inclusion complex (Figure 30). The curves for all the amino acids are similar, but the slope of valine is higher than that of alanine and alanine higher glycine, which may be due to a greater number of valine molecules present in the charged structure than that of alanine and glycine, HPβCD of which is encapsulated in the cyclodextrin cavity as the inclusion occurs. Single discernible breaks at about 4 mmol.L$^{-1}$ concentration of HPβCD are found for all

![Figure 11](image1.png)

Figure 11. Plot of limiting apparent molar volume against mass fraction of HPβCD for Glycine at different temperature.

![Figure 12](image2.png)

Figure 12. Plot of limiting apparent molar volume against mass fraction of HPβCD for Alanine at different temperature.

![Figure 13](image3.png)

Figure 13. Plot of limiting apparent volume against mass fraction of HPβCD for Valine at different temperature.
the possible for three cases indicating the 1:1 stoichiometric ratio for each of the inclusion complexes formed (Table 1) (see Tables 2 and 3).

2.4. Solid-state characterization of the inclusion compounds

The freeze-dried solids were studied by a range of techniques to confirm amino acids inclusion and to evaluate the purity and stability of the compounds and to study the geometry of inclusion of amino acids into HPβCD and the supramolecular packing of the complex units in the solid state.

2.5. X-ray powder diffraction studies

XRD is an impressive procedure for exploring the complexation process of HPβCD and molecules in the powder or microcrystalline states. The powder X-Ray diffraction patterns of the aforementioned amino acids, 2-HPβCD, the physical mixture and the complex were shown in Figures 31, 32 and 33. The XRD patterns of amino acids display such sharp and intense vertex of the amino acids which are suggestive of its crystalline character are shifted, disappeared or become less intense in complexed forms due to encapsulations of amino acids into the hydrophobic cavity of 2-HPβCD. However, 2-HPβCD showed the amorphous lacking crystalline peaks.
2.6. FTIR (Fourier transform infrared spectra) studies

Characterization of the inclusion complex was performed in order to obtain further information on AA-2-HPβCD. The results showed a better host-guest formation in aqueous solution. To evaluate any possible interaction of the amino acids with 2-HPβCD in the solid state, the FTIR technique was employed (Liang et al., 2018). The FTIR spectra of amino acids (glycine, alanine and valine), 2-HPβCD, amino acids/2-HPβCD physical mixture and amino acids-2-HPβCD inclusion complex were shown in Figures 34, 35 and 36. Comparison of the FTIR spectra of amino acids with amino acids-2-HPβCD, our findings reveal that the stretch vibration of carbonyl groups (C=O) of glycine, alanine and valine were shifted from 1647 cm\(^{-1}\) to 1664 cm\(^{-1}\), 1626 cm\(^{-1}\) and 1613 cm\(^{-1}\) respectively after encapsulating by the 2-HPβCD. The FTIR characteristic peaks of amino acids/2-HPβCD physical mixture induce changes compared with amino acids and 2-HPβCD, it could be inferred that amino acids and 2-HPβCD were mixed with host-guest interaction. FTIR spectra results clearly support the formation of the complexation between amino acids and 2-HPβCD.
3. Materials and methods

3.1. Experimental methods

The solubility of the HPβCD and that of the selected amino acids in medium solution with HPβCD has been exactly studied in Milli-Q water and it can be noted these were soluble in all amounts of aqueous Solution of HPβCD. All the solutions of the amino acids were prepared by mass (measured using Sartorius AG Gottingen with uncertainly 0.0001 g), and the working solutions were obtained by mass fraction at 295 K. The densities (ρ) of the solvents were measured by means an Anton Paar mPDS5 densitometer (DMA-HPM) with a precision of ±0.5 kg m⁻³ maintained at ±0.01 K of the desired temperature. It was calibrated by passing Milli-Q water and Glycerol and dry air. The viscosities (η) were measured using an Ostwald viscometer.

![Figure 18. Dynamic Viscosity against molality of Glycine at w = 0.009 and different temperatures.](image)

![Figure 19. Kinematic Viscosity against mass fraction of HPβCD and T = 278 K.](image)
3.2. Computational methods

The amino acid and HPβCD structures were obtained from the PubChem database or from our previously published experimental data (Shityakov et al., 2016a, b). The AMBER 16 suite (Case et al., 2005), including AMBER Tools utilities, was used to perform all the molecular dynamics (MD) calculations. Prior to MD simulations, Gasteiger partial charges were assigned to the analyzed structures and complexes, which were further solvated using the TIP3P water model (Gasteiger, Marsili, 1978; Mark and Nilsson, 2001). The GAFF and FF99SB force fields without modifications were utilized to generate the corresponding topologies (Wang et al., 2004; Wickstrom et al., 2009). The minimization, heating (NVT ensemble), and production protocols were implemented to calculate the self-diffusion coefficients and density parameters using the previously published MD protocol (Eckler and Nee, 2016). Production runs of 250 ps in the NPT ensemble with a step size of 1 fs provided ample data to determine the viscosity values from the mean-squared displacement by means of by the Einstein-Smoluchowski and Stokes-Einstein equations (Eckler; Nee, 2016).
Figure 22. Kinematic Viscosity against molality of amino acids in different temperatures and $\beta_{CD} = 0.009$.

Figure 23. Activation Energy against molality of amino acids in different temperatures and $\beta_{CD} = 0.002$. 
Figure 24. Activation Energy against molality of amino acids in different temperatures and $\beta_{CD} = 0.009$.

Figure 25. 3D diagram for inclusion of HPβCD-AA.
Figure 26. 3D diagram for inclusion of HPβCD-AA.

Figure 27. 3D diagram for inclusion of HPβCD-AA.
4. Conclusion

Thermodynamic properties of amino acids in different mass fraction of HPβCD at different temperatures (278–295 K) have been determined. From the experimental results, various parameters; $\Phi_{V}$, $\Phi_{0}$, $S_{V}$, $E_{a}$, $\nu$, $\eta_{int}$, $\eta_{s}$ and $\eta$ were calculated. The results indicate that the solute-solvent interaction is dominant over the solute-solute interaction in the systems. The structural effect of HPβCD gives the favorable support in the molecular interaction with retention of configuration and the difference side groups of amino acids affect the solute-solvent interaction. The variation of $\Phi_{0}$ with temperature indicated that amino acids (alanine, glycine, valine) as structure-maker in different mass fraction of HPβCD. Surface tension studies reveal that 1:1 inclusion complexes have been formed. Evidently, the
Table 1. Values of surface tension ($\gamma$) at the break point with corresponding concentration of aqueous HPβCD at 295 K.

| HPβCD | Glycine Conc./mM | $\gamma$/mN m$^{-1}$ | Alanine Conc./mM | $\gamma$/mN m$^{-1}$ | Valine Conc./mM | $\gamma$/mN m$^{-1}$ |
|-------|------------------|----------------------|-------------------|----------------------|-----------------|----------------------|
|       | 4                | 69.2                 | 4                 | 70                   | 4               | 70.2                 |

Table 2. Average density ($\rho$) of amino acids and their HPβCD complexes in water solution at different temperature parameters calculated for 250 ps using molecular dynamics with the GAFF force field.

| $\rho$ (g/cm$^3$) | Temperature (K) |
|-------------------|------------------|
|                   | 278.15           |
|                   | 283.15           |
|                   | 288.15           |
|                   | 293.15           |
|                   | 295.15           |
| Alanine           | 0.97             |
|                   | 0.96             |
|                   | 0.96             |
|                   | 0.95             |
|                   | 0.95             |
| Glycine           | 0.95             |
|                   | 0.95             |
|                   | 0.95             |
|                   | 0.96             |
|                   | 0.96             |
| Val               | 0.97             |
|                   | 0.97             |
|                   | 0.96             |
|                   | 0.97             |
| Ala-HPβCD         | 0.99             |
|                   | 0.99             |
|                   | 0.98             |
|                   | 0.98             |
|                   | 0.98             |
| Gly-HPβCD         | 0.99             |
|                   | 0.99             |
|                   | 0.99             |
|                   | 0.99             |
|                   | 0.99             |
| Val-HPβCD         | 0.99             |
|                   | 0.99             |
|                   | 0.99             |
|                   | 0.99             |
|                   | 0.99             |

Table 3. Average viscosity ($\eta$) of amino acids and their HPβCD complexes in water solution at different temperature parameters calculated for 250 ps using molecular dynamics with the GAFF force field.

| $\eta$ ($\mu$Pa·s) | Temperature (K) |
|---------------------|------------------|
|                     | 278.15           |
|                     | 283.15           |
|                     | 288.15           |
|                     | 293.15           |
|                     | 295.15           |
| Alanine             | 198.49           |
|                     | 156.9            |
|                     | 170.41           |
|                     | 165.9            |
|                     | 135.43           |
| Glycine             | 175.01           |
|                     | 214.09           |
|                     | 208.87           |
|                     | 169.48           |
|                     | 207.49           |
| Val                 | 199.21           |
|                     | 210.97           |
|                     | 143.19           |
|                     | 128.01           |
|                     | 192.58           |
| Ala-HPβCD           | 199.21           |
|                     | 225.59           |
|                     | 194.28           |
|                     | 176.92           |
|                     | 168.25           |
| Gly-HPβCD           | 210.77           |
|                     | 187.16           |
|                     | 181.37           |
|                     | 198.05           |
|                     | 213.64           |
| Val-HPβCD           | 220.94           |
|                     | 222.82           |
|                     | 216.8            |
|                     | 209.46           |
|                     | 223.87           |

Figure 31. XRD patterns (a) Glycine, (b) 2-HP-β-CD, (c) Glycine/2-HP-β-CD physical mixture, (d) Glycine/2-HP-β-CD inclusion complex.
Figure 32. XRD patterns (a) Alanine, (b) 2-HP-β-CD, (c) Alanine/2-HP-β-CD physical mixture, (d) Alanine/2-HP-β-CD inclusion complex.

Figure 33. XRD patterns (a) Valine, (b) 2-HP-β-CD, (c) Valine/2-HP-β-CD physical mixture, (d) Valine/2-HP-β-CD inclusion complex.
Figure 34. IR patterns (a) Glycine, (b) 2-HP-β-CD, (c) Glycine-HP-β-CD physical mixture, (d) Glycine-2-HP-β-CD inclusion complex.
Figure 35. IR patterns (a) Alanine, (b) 2-HP-β-CD, (c) Alanine-HP-β-CD physical mixture, (d) Alanine-2-HP-β-CD inclusion complex.
Figure 36. IR patterns (a) Valine, (b) 2-HP-β-CD, (c) Valine-HP-β-CD physical mixture, (d) Valine-2-HP-β-CD inclusion complex.
experimental results in this study complement each other and there are a consistency with the molecular modeling. The resulted de-
tections demonstrate the formation of the inclusion complexes. 
Finally, the present work illustrates its proportion to various appli-
cations as a controlled delivery system in the field of modern bio-
medicinal sciences.

Declarations

Author contribution statement

Sergey Shityakov: Analyzed and interpreted the data; Wrote the paper.
D. Esmaeilpour: Performed the experiments; Analyzed and interpret-
ed the data.
A. K. Bordbar, F. A. Almalki, A. A. Hussein: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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