To study the interactions between saccharide/their derivatives and bactericidal cefadroxil drug: Volumetric, acoustic and molecular docking studies

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ABSTRACT

Volumetric, acoustic and molecular docking investigations are helpful to elucidate the molecular interactions occurring between saccharides/derivatives with cefadroxil drug in aqueous solution. The density, ρ and speed of sound, u were measured for saccharides and their derivatives, in molality, m_B = (0.001-0.004) mol·kg^{-1} aqueous solutions of cefadroxil at temperatures, T = (288.15, 298.15, 308.15, 318.15) K. These values were used to retrieve the corresponding values of standard partial molar volumes, V_2^o and partial molar isentropic compressibilties, $K^o_{s,2}$ at infinite-dilution. From these data, the transfer properties ($\Delta_{tr}V_2^o$ and $\Delta_{tr}K^o_{s,2}$) for saccharides from water to aqueous solutions of cefadroxil have been evaluated. These parameters provide an essence about the type and nature of interactions occurring between saccharide (solute) and cefadroxil drug. Further, the molecular docking studies have also been carried out, which give information about the active groups present in both solutes and cefadroxil molecules at the binding site. Both the experimental and theoretical studies show that the distinct stereochemical –OH group present in the studied saccharides/derivatives interact differently with the cefadroxil molecule. The theoretical studies also show that the –NH, –NH_2, >C=O and –COOH groups of cefadroxil participate more actively at the binding site.

Keywords: cefadroxil; saccharide; standard partial molar volume; transfer properties; stereochemistry.

1. Introduction

Carbohydrates such as saccharides and their derivatives show potential chemical diversity and serve as receptors grouped into enzymes, lectins, and antibodies, accelerate the distinct

molecular recognition mechanisms that prompt specific biological response [1-3]. In particular, the multi-faceted properties of carbohydrates make them very useful in the evolution of synthetic carbohydrate-based systems for therapeutic demand [4]. The formation of carbohydrate-based substances, especially, glyconanoparticles (GNPs) with their great biocompatibility and multivalency has become the topic of research in the last few decades [5,6].

Carbohydrates not only have the therapeutic effect but also help in drug delivery and vaccine development [7,8]. The oligosaccharides act as potential recognition sites for carbohydrate-mediated interactions between cells and drug carriers bearing suitable site directing molecules. The recognition of carbohydrate immunodeterminants has created great attention in the development of carbohydrate-based vaccines [5]. Cefadroxil is a broad spectrum β-lactam antibiotic of the cephalosporin type in which the β-lactam ring is fused to a 6-membered dihydrothiazine ring and thus forms the cephem nucleus. Cefadroxil is the bactericidal antibiotic used to treat a wide variety of bacterial infections, such as respiratory tract, skin, and urinary tract infections [9]. Dangerous or multidrug-resistant bacteria have become more common and increasing frequently over the past few decades. To combat the issue of multi-drug resistant strains various research efforts have been targeted to develop the newer antibiotics with novel modes of action [10].

The study of interactions between drug and macromolecule in the physiological medium is crucial for various processes such as delivery of therapeutic agents, drug targeting, protein binding, etc [11]. The pharmacodynamics, pharmacokinetics, safety and efficacy of drugs have been widely studied [12]. The drug interactions occurring outside the body may be grouped as physical or chemical, and they may occur during formulation, storage and during mixing of ingredients [13]. Occasionally, *in vitro* interaction appears without any observable changes like precipitation or color change, hence can be evaluated quantitatively by analyzing their thermodynamic parameters in solutions [14]. In the light of above facts, the study of saccharides in presence of drugs has its own importance, but no such studies have been carried out earlier.

The present study is the first report of attempts to decipher the type and traits of interactions occurring in-between saccharides/derivatives and cefadroxil drug at different temperatures through volumetric, acoustic and molecular docking studies. Volumetric and acoustic investigations are significant in understanding molecular interactions in the fluid medium. Also, molecular docking studies give further information about which specific active

groups of saccharide/derivative and cefadroxil molecules were interacting to throw further light on these systems. These studies provide the database which may provide experimental and theoretical background for the development of new antibiotics by the pharmaceutical companies.

2. Experimental

2.1. Materials

The chemicals of highest purity grade were used as delivered by the suppliers. However, the chemicals were dried over $CaCl_{2(anhyd)}$ in a vacuum desiccator for 48 h at room temperature, to ensure no water content (moisture) present in the chemicals. Then, the purity of the chemicals used was analyzed by C, H, N, S analysis method using Thermo Scientific FLASH 2000 Organic Elemental Analyzer, USA [15]. The description about the chemicals including abbreviation, molecular formula, mass fraction purity, source, and CAS number is given in Table 1. The carbon and hydrogen contents obtained in the analysis are comparable with the calculated values obtained using molecular formulae. The instrument measures the percent of carbon, hydrogen, nitrogen and sulphur in the studied samples with repeatability of 0.21%, 0.14%, 0.19% and 0.17% respectively.

2.2. Equipment and procedure

2.2.1 Volumetric and acoustic measurements

The density and speed of sound measurements of the solutions were carried out by employing the density and sound velocity meter DSA-5000 M (Anton Paar Gmbh, Graz, Austria) with a precision better than 1×10^{-3} kg m^{-3} in density and 0.1 m s^{-1} in speed of sound. The frequency for measuring sound velocity is 3 MHz. The working of vibrating-tube densimeter relies upon the time-lapse by estimation of the exact number of oscillations of the sample filled in the vibrating U-shaped sample tube [16-18]. The empty glass oscillating device is electronically energized in an undamped style toward the path opposite to the plane going through the inlet and outlet openings of the sample tube. The instrument was calibrated at 293.15 K by millipore water (given with the instrument) and dry air at atmospheric pressure. Also, before each series of measurements, the instrument was calibrated with degassed water, at the studied temperature. The chemical calibration of the densimeter was also performed by measuring the values of density and sound of velocity of aqueous sodium chloride at several molalities and at the experimental temperature range and comparing the results with the literature values [19], which

showed an excellent agreement. The temperature of cells was maintained constant using peltier device equipped within the instrument with precision of ± 0.001 K. The solutions were freshly prepared on mass basis using a Mettler balance (Model: AB265-S) with a precision of ± 0.01 mg in pure water procured from Ultra UV/UF Rions lab water system. The electrical conductivity for the pure water sample used was less than 1.29×10^{-4} S m^{-1}. The standard uncertainty of the density and speed of sound estimates after taken into account the impurity of the samples, purity of water, uncertainty of the resolution of the instrument (i.e., 0.001 kg m^{-3}) and uncertainty in measured temperature (i.e., 0.01 K) was found to be within ± 0.4 $kg \cdot m^{-3}$ and ± 0.5 $m \cdot s^{-1}$, respectively. The uncertainty in molality is $u_r(m) = u(m)/m = 0.01$.

2.2.2. Molecular docking

The computational studies were carried to predict the binding site and the binding energy of saccharide/derivative-cefadroxil complex using the AutoDock-Vina software [20]. The graphical user interface of AutoDock Tools (ADT) [21,22] was used to set up and perform molecular docking. The cefadroxil was obtained from ChemSpider Database [23]. Sugar molecules were read as macromolecule and the cefadroxil was read as ligand. In ADT Gasteiger charge method was adopted for computing atomic charges when preparing the structure for molecular docking for AutoDock-Vina software. All the non-polar hydrogens were merged to prepare the structure. In order to identify the active site of binding, a large space with the dimensions of 40 x 40 x 40 $Å^3$, along with the x, y and z directions was considered with the grid point spacing of 0.375 $Å^3$. Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm is used for optimization in AutoDock-Vina to get the global minimum structure of host-guest. In order to find the correct dock conformation the value of exhaustiveness parameter was set to 16. All the other parameters required for the molecular docking were fixed at their default values as available in software. All the simulation was performed in the gas phase.

3. Results and discussion

3.1. Experimental studies

3.1.1. Apparent molar volumes ($V_{2,\phi}$) and apparent molar isentropic compression ($K_{s,2,\phi}$)

The $V_{2,\phi}$ and $K_{s,2,\phi}$ values for saccharides and their derivatives in m_B = (0.001, 0.002, 0.003, and 0.004) mol·kg^{-1} aqueous cefadroxil solutions and at different temperatures were calculated from density, ρ and speed of sound, u data using the following relations:

$$V_{2,\phi} = [M/\rho] - [(\rho - \rho_o) / (m_A \rho \rho_o)] \quad (1)$$

$$K_{s,2,\phi} = [K_s M/\rho] - [(K_s^o \rho - K_s \rho_o) / (m_A \rho \rho_o)] \quad (2)$$

where M is the molar mass of the solute (saccharide/derivative); m_A is the molality of the solute. The ρ, ρ_o and K_s, K_s^o are the densities and isentropic compressibilities of solution (saccharide/derivative + cefadroxil + H_2O) and solvent (cefadroxil + H_2O), respectively. The experimental density, ρ and speed of sound, u for studied saccharides in water show good agreement with the available literature data [24-39] (Fig. S1 & S2) and show some deviations from literature values in cases of (+)-D-glucose and (+)-maltose (anhydrous) (Fig. S1(A&C) & S2(A&D)). Dhondge et. al. [26] have reported the densities for binary solutions {(+)-D-glucose in water} over the concentration range (0.5 to 3.5) mol·kg^{-1} which are higher than the presently studied concentration range of (+)-D-glucose {Fig. S1A((v) & (vi))}. The deviation in the values may be due to differences in the concentration ranges studied. Oroian et al. [35] have reported the ρ and u for (0.01 to 0.10) mol·kg^{-1} (+)-D-glucose and (+)-maltose in water. The values of ρ reported [35] for (+)-D-glucose and (+)-maltose (anhydrous) are slightly lower than the present values at 308.15 & 318.15 K (Fig. S1-A & C). Whereas, the values of u reported [35] for (+)-D-glucose and (+)-maltose (anhydrous) are slightly higher than the present values at 298.15 K and lower than present values at 308.15 & 318.15 K (Fig. S2-A & D). Nikam et. al. [39] have reported the u for (0.0025 to 0.0600) mol·kg^{-1} (+)-maltose in water which are lower than present values at 298.15 K (Fig. S2-D). The factors like purity of materials, solution preparation, experimental methods etc. may be responsible for the discrepancies.

The K_s values for the solutions have been calculated using the measured u and ρ data by the following relation:

$$K_s = 1 / u^2 \rho \quad (3)$$

The ρ and u values (supplementary Table S1) increase with the increase of molalities of both solute and cosolute (cefadroxil). However, the ρ values decrease while u values increase with the increase of temperature. The $V_{2,\phi}$ and $K_{s,2,\phi}$ results for the studied solute are given in supplementary Table S2. For the hydrated solutes 6-Deoxy-D-mannose (6de-Man) and (+)-

Maltose monohydrate (Mal), the molality corrections have been applied and respective values of $V_{2,\phi}$ and $K_{s,2,\phi}$ for their anhydrous states are given in Table S2. The combined uncertainties in $V_{2,\phi}$ are; U_c ($V_{2,\phi}$) = ± 0.16×10^{-6} m^3·mol^{-1} at m_A = 0.04 mol·kg^{-1} and U_c ($V_{2,\phi}$) = ± 0.02 ×10^{-6} m^3·mol^{-1} at m_A = 0.20 mol·kg^{-1} (level of confidence = 0.95, K = 2) at low and high concentration of the solute respectively. The standard uncertainties in $K_{s,2,\phi}$, are $u(K_{s,2,\phi})$ = ± 0.44 × 10^{-15} m^3 ·mol^{-1} ·Pa^{-1} at m_A = 0.04 mol·kg^{-1} and ± 0.22 × 10^{-15} m^3 ·mol^{-1} ·Pa^{-1} at m_A = 0.20 mol·kg^{-1} at low and high concentration of the solute respectively. The $V_{2,\phi}$ considers the size of the hydrated entity in the solution, and henceforth the level of interaction of the solute with water structure. It is redeemed from Table S2 that $V_{2,\phi}$ values are positive for all the studied solutes and increase with the increase in molalities of solute and cosolute. The increase of $V_{2,\phi}$ values with increase of molalities of solute shows decline packing characteristics of water, hence decline interaction with water structure and consequently increase in solute-cosolute interactions. Also, the inspection of Table S2 shows that the $V_{2,\phi}$ values increases with increase in temperature. This may be attributable to the loosening of water molecules from the salvation layers of the solute molecules as the structure of the water is weakened by the elevation of temperature, and correspondingly solute-cosolute interactions increase with rise of temperature [33, 40-42]. The $K_{s,2,\phi}$ values for solutes so obtained are negative (except for 2de-Glc and Uro at higher temperature) indicating that the water molecules in the bulk solution are more compressible than the water molecules surrounding the solutes [43,44]. This, in turn, indicates about the strong solute-cosolute interactions in the aqueous medium.

3.1.2. Standard partial molar volumes (V_2^o) and partial molar isentropic compressibilities ($K^o_{s,2}$) at infinite-dilution

The V_2^o and $K^o_{s,2}$ values were obtained by least-squares fitting the following equations (4) and (5) proposed by Masson [45] to the experimental $V_{2,\phi}$ and $K_{s,2,\phi}$ data as:

$$V_{2,\phi} = V_2^o + S_v m_A \quad (4)$$

$$K_{s,2,\phi} = K^o_{s,2} + S_k m_A \quad (5)$$

where, S_v and S_k are the experimental slopes of the plots of apparent molar volumes and apparent molar isentropic compression, versus molalities of the solute, respectively. The V_2^o and $K^o_{s,2}$ results along with S_v and S_k values are given in Table 2. The comparison of V_2^o and $K^o_{s,2}$

values of solutes in water with literature values [24-29, 31, 46-62] show good agreement and tabulated in Table S3. The V_2^o gives information about the solute-solvent interactions. The V_2^o values increase with the rise of temperature which may be due to the fact that the interactions of water with the solute molecules get weakened, and the bound water molecules are released to the bulk and additionally, an expansion of solution at high temperature also leads to the larger values of V_2^o [62]. With an increase in molality of cosolute, the V_2^o values increase for the studied solutes except for 6de-Man and 2de-Glc. The decrease in V_2° values in cases of 6de-Man and 2de-Glc may be attributed to the decrease of electrostriction and in turn, less release of water molecules at higher m_B values leads to compression of volume.

Additionally, the S_v represents the volumetric virial parameter, and gives evidence for the solute-solute interactions. The S_v values have very small magnitudes in comparison to V_2^o which shows the predominance of solute-solvent interactions over the solute-solute interactions. The solute-solute interactions of the studied systems have also been analyzed using the approach proposed by Wawer and Krakowiak [63], which utilizes relative deviation of apparent molar volume, RC_v calculated from $V_{2,\phi}$ and V_2^o by using the following equation:

$$RC_v = [(V_{2,\phi} - V_2^o)\, V_2^o]100\% \quad (6)$$

The RC_v values obtained from Eq. (6) equate well with the RC_v values obtained from S_v and V_2^o by using the following relation:

$$RC_v = [mS_v/\, V_2^o]100\% \quad (7)$$

The RC_v values obtained from Eqs. (6) and (7) are tabulated in Table S4 given as Supplementary material. A careful perusal of Table S4 indicates that the RC_v values obtained from Eqs. (6) and (7) are compare well for saccharides in water and in cefadroxil drug solutions. The RC_v values are positive and small in magnitude and increase with increase in the concentration of solute. This further supports the above conclusion regarding the presence of weak solute-solute interactions (at infinite dilution) in these systems by using Mason's equation [45].

The variation of V_2^o values with absolute temperature, T for the studied saccharides and their derivatives in the presence of cefadroxil$_{(aq)}$ solutions was studied using the following equation:

$$V_2^o = \nu_o + \nu_1 T + \nu_2 T^2 \quad (8)$$

where, ν_o, ν_1 and ν_2 are the empirical constants. The values of standard partial molar expansion coefficients, V_E^o $\{V_E^o = (\partial V_2^o/\partial T)_P\}$ and their second-order derivatives, $(\partial^2 V_2^o/\partial T^2)_P$ are

summarized in Table 3. Generally, the $(\partial V_2^o/\partial T)_P$ values increase with the increase of temperature for saccharides and their derivatives in the presence of cefadroxil. However, in cases of 2de-Glc and Mal, the value decreases with the increase of temperature. The representative plots of standard partial molar expansion coefficients $(\partial V_2^o/\partial T)_P$ versus T are shown in Figure 1. The thermodynamic relation $\{(\partial C_{p,2}^o/\partial P)_T = -T(\partial^2 V_2^o/\partial T^2)_P\}$, used by Hepler [64] relates the modulation of heat capacity with pressure to the second-order derivative of volume with respect to temperature. The negative $(\partial^2 V_2^o/\partial T^2)_P$ values indicate the chaotropic nature of solutes, whereas the positive values reflect the kosmotropic character of solutes. Therefore, $(\partial^2 V_2^o/\partial T^2)_P$ data (Table 3), suggest that the studied saccharides and their derivatives act as kosmotropes, while 2de-Glc and Mal act as chaotropes, in water as well as in cefadroxil drug solutions.

It is evident from Table 2 that generally the $K^o_{s,2}$ values are negative for studied solutes in the presence of cefadroxil drug and become less negative with the increase of temperature indicating electrostriction of solute molecules reduces and water molecules are released to the bulk on addition of drug, rendering the solutions more compressible at higher temperatures [65-67]. This in addition, shows increase in solute-cosolute interaction with increasing temperature and these results are in good agreement with results obtained from partial molar volume studies. The magnitude of $K^o_{s,2}$ values generally decreases with the increase of molalities of cosolute except for 6de-Man and 2de-Glc. It also suggests about the dehydration of solute molecules which leads to the more compression as the molality of cosolute increase. The hydroxyl (–OH) groups at 2nd and 6th positions of saccharides are crucial for the hydration of solute molecules. Therefore, the absence of –OH groups in cases of 2de-Glc and 6de-Man, decreases the solute hydration with an increase in molality of cosolute, hence the $K^o_{s,2}$ values become more negative at higher molalities of cosolute.

3.1.3. Partial molar properties of transfer of solutes from water to cefadroxil drug

The standard partial molar volumes of transfer, $\Delta_{tr}V_2^o$ and partial molar isentropic compressibilities of transfer, $\Delta_{tr}K^o_{s,2}$ of saccharides/derivatives at infinite-dilution from water to cefadroxil solutions have been calculated using following relation:

$$\Delta_{tr}V_2^o/\Delta_{tr}K^o_{s,2}\{\text{water to cefadroxil}_{(aq)}\} = V_2^o/K^o_s\{\text{in cefadroxil}_{(aq)}\} - V_2^o/K^o_s\{\text{in water}\} \quad (9)$$

The plots of transfer properties ($\Delta_{tr}V_2^o$ / $\Delta_{tr}K^o_{s,2}$) as a function of molality, m_B of cefadroxil are given in Figure 2. Both transfer values ($\Delta_{tr}V_2^o$ and $\Delta_{tr}K^o_{s,2}$) have comparable magnitude for the studied systems, this may be due to fact that both density and speed of sound of solution are

inter-related (as speed of sound = √elasticity/density) [68] from which parameters V_2^o and $K^o_{s,2}$ have been derived. Additionally, from these parameters corresponding values of transfer values have been calculated. The transfer properties are negative for both 6de-Man and 2de-Glc (Fig. A(i,ii)), however, conversely the transfer properties are positive for both Uro and Mal (Fig. C and D) at all studied temperatures and m_B values of cefadroxil. The transfer properties are both positive and negative for Man and Glc (representative fig. B(i, ii)) solutes having negative transfer properties values at low m_B values of cefadroxil and turn into positive values at higher m_B values. The transfer properties decrease with the increase of temperature, but increase with molality of cefadroxil for all studied saccharide/derivatives. The trends in volumes of transfer, $\Delta_{tr}V_2^o$, can be further explained using the cosphere overlap model developed by Gurney [69]. The probable types of interactions occurring in the ternary solution of saccharide/derivative + cefadroxil + H_2O are: (A) Hydrophilic-ionic/hydrophilic interactions between polar interacting sites (–OH, –C=O, –O–) of saccharide/derivative (solute) and the zwitterionic (NH_3^+/COO^-) or polar (–COOH, –NH, –NH_2) sites of cefadroxil. (B) Hydrophobic-ionic/hydrophilic interactions between the interacting non-polar sites (R = –CH, –CH_2) of solute and the ionic/polar groups of cefadroxil. (C) Hydrophobic-hydrophobic interactions between the non-polar interacting sites of solute and cefadroxil.

As per cosphere overlap model, the hydrophilic-ionic/hydrophilic (A type) interactions tend to give positive contribution to $\Delta_{tr}V_2^o$ values in cases of Uro, Mal, and Glc, Man (at high m_B values). In contrast, hydrophobic-ionic/hydrophilic (B type) interactions and hydrophobic-hydrophobic (C type) interactions have negative contribution to the $\Delta_{tr}V_2^o$ values in cases of 6de-Man and 2de-Glc at all studied m_B values and for Glc and Man at low m_B values. Similarly, the positive $\Delta_{tr}K^o_{s,2}$ values for Glc, Uro, Mal, Man (at high m_B values) show that the compressibility of saccharide/derivative increases in the presence of cefadroxil which may be attributed to the more release of water molecules to the bulk water due to hydrophilic-ionic/hydrophilic interactions between saccharide and cefadroxil molecules and additionally, this decreases the effect of solutes on the structure of water. However, the negative $\Delta_{tr}K^o_{s,2}$ values indicate about the hydrophobic-ionic/hydrophilic/hydrophobic interactions between the solutes (6de-Man, 2de-Glc) and cefadroxil molecules which demonstrate different hydration characteristics of these solutes. The transfer parameters for various solutes at same molality of cosolute and temperature decrease in the following order: Uro > Mal > Glc > Man > 2de-Glc > 6de-Man. These trends in

transfer values of solutes depend on the arrangement of hydroxyl (–OH) groups present in saccharide/derivative (i.e., axial (a), equatorial (e), or exocyclic (exo)) and derivatization of (–OH) groups [70,71]. Glc (1e2e3e4e6exo) with all –OH groups at equatorial positions tends to interact more affirmly with the cefadroxil molecules with more $\Delta_{tr}V_2^o$ / $\Delta_{tr}K^o_{s,2}$ values in comparison to Man (1a2a3e4e6exo) containing both axial and equatorial –OH groups. The switching of –CHOH group by methylene (CHOH → CH_2) or carboxylic group (CHOH → COOH) in cases of derivatives of Glc and Man plays the important role and shows their different hydration characteristics in the presence of cefadroxil. 2de-Glc and 6de-Man derivatives with methylene (–CH_2) groups show lower transfer values with respect to their parent saccharides i.e., Glc and Man. However, Uro having acidic carboxylic (–COOH) group shows exclusively different hydration behavior as it is noticeable from very large $\Delta_{tr}V_2^o$ and $\Delta_{tr}K^o_{s,2}$ values. Hence, among the studied saccharides and their derivatives Uro interact more affirmly with the cefadroxil molecules. This suggests about its greater dehydration effect due to its interaction with cefadroxil, hence release of more hydrated water molecules to the bulk water which in turn leads to the positive transfer values. Indeed, Mal (a disaccharide) indicates more noteworthy susceptibility to interact with cefadroxil molecule however after the Uro. After concluding the experimental section which gives knowledge about the kind of interaction, and additionally to know about which specific active groups of saccharide/derivative and cefadroxil molecules were interacting, the molecular docking studies have been carried out to throw further light on these systems.

3.2. Theoretical studies

3.2.1. Molecular docking studies

As, it is already proposed from the experimental studies that discrimination of stereochemically distinct saccharide/derivatives towards the cefadroxil molecule is vital for the study of interactions between them, which may help in designing of new saccharide-based drugs. In addition to this, the molecular docking studies are used to quantify the binding affinity of saccharide/derivatives with a cefadroxil drug at the atomic level, which allows us to know the active groups present in the solute molecules at the binding site [20]. In molecular docking studies, the preferred orientations or conformations of the molecule with optimal binding energy at the binding site have been predicted in order to quantify the binding affinity between the two

molecules [21]. The images of saccharide/derivative docked at the active site of cefadroxil drug are represented in Figure 3. Additionally, the five lowest energy conformations of different saccharides with cefadroxil drug are given in the supplementary Figure S3 (a-f). The interactions of saccharide/derivative with cefadroxil molecule at the binding site are mainly polar within 2.3 Å distance and depend on the stereochemistry of saccharide/derivatives. The docking simulations demonstrate the inclination of saccharides/derivatives towards the –NH, $–NH_2$, >C=O and –COOH groups present in the cefadroxil drug. In case of 2de-Glc, the oxygen atom of pyranose ring and –OH group at anomeric carbon C1 interacts with both protons of –NH and $–NH_2$ groups of cefadroxil at the binding site. Whereas, in case of 6de-Man, the only –OH group at anomeric carbon C1 interacts with both protons of –NH and $–NH_2$ of cefadroxil drug. Similarly, among the monosaccharides; Man containing the –OH groups at C2, C3 and Glc containing –OH groups at C4, C6 show interaction with –NH and $–NH_2$ groups of cefadroxil. In case of Uro, the –OH groups present at C2, C3 and carboxylic (–COOH) group at C5 interact with the protons of –NH, $–NH_2$ as well as the carbonyl group present in the cefadroxil molecule. In case of disaccharide (Mal), the –OH groups present at C6, C3' and C6' interact with the protons of –NH, $–NH_2$, –COOH and >C═O groups of cefadroxil.

The values of binding energy for direct interaction between saccharide/derivative and cefadroxil drug are as follows: Mal (11.71 $kJ \cdot mol^{-1}$) > Uro (11.29 $kJ \cdot mol^{-1}$) > Glc (9.62 $kJ \cdot mol^{-1}$) > Man (9.20 $kJ \cdot mol^{-1}$) > 2de-Glc (8.79 $kJ \cdot mol^{-1}$) ≈ 6de-Man (8.79 $kJ \cdot mol^{-1}$). These trends of binding energy are in line with the experimental studies. Among monosaccharides, cefadroxil molecules show more preference for Glc than Man, this shows inclination of cefadroxil towards the equatorial –OH group at C4 and the more flexible exocyclic –OH group present in Glc than axial –OH group present at C2 in Man [70,71]. Also, the cefadroxil has more binding affinity towards Glc than its deoxy derivative i.e., 2de-Glc, this may be due to absence of –OH group at C2 in 2de-Glc due to which 2de-Glc molecule orients itself at the binding site in such a way that it interacts weakly with cefadroxil molecules. Mal, being a disaccharide with more available –OH groups shows more binding affinity with cefadroxil than monosaccharides and their derivatives. Uro shows an exceptional behavior in the presence of cefadroxil molecules showing high binding affinity comparable to Mal which is disaccharide. This is due to involvement of –COOH group present in the Uro which makes stronger bond with the >C═O group of cefadroxil by making it more electrophilic in nature. The 2de-Glc and 6de-Man has almost comparable

binding affinity. This may be due to the fact that molecular docking is a computational method that aims to predict the favored orientation of a ligand (saccharide/derivative) to its receptor (cefadroxil), when these bound to each other to form a stable complex without taking account of water molecules surrounding the solute molecules in the aqueous medium i.e., the simulation studies is performed in gas-phase only; binding contribution due to the solvent interaction is not reflected in the binding energy. The computational studies confirm that the –NH, $–NH_2$, >C=O and –COOH groups of cefadroxil participate more actively at the binding site and form stronger polar bonds with the saccharides and their derivatives.

Conclusions

In the present investigation, from the data of densities, ρ and speed of sound, u standard partial molar volumes, V_2^o and partial molar isentropic compressibilties, $K^o_{s,2}$, transfer properties ($\Delta_{tr}V_2^o$ and $\Delta_{tr}K^o_{s,2}$) and hydration numbers have been computed for saccharides and their derivatives in water and aqueous cefadroxil solutions. The $V_{2,\phi}$ values suggest the prevalence of solute-cosolute interactions which get intensified with rise of temperature. The negative $K_{s,2,\phi}$ values in most of cases indicates that the hydrated water molecule is less compressible than the water molecules in the bulk. This, in turn, indicates about the strong solute-cosolute interactions in the aqueous medium. The transfer parameters show dominance of hydrophilic-ionic/hydrophilic interactions in cases of parent saccharides (Uro, Mal, and Glc, Man), in contrast to derivatives (6de- Man and 2de-Glc) where hydrophobic-hydrophobic/hydrophilic interactions dominates. Also, comparing the transfer parameters for various solutes studied at same molality of cosolute and temperature shows different interacting compatibility of solute with cosolute follows the decreasing order as: Uro > Mal > Glc > Man > 2de-Glc > 6de-Man. The differences in the interacting compatibility of studied saccharides/derivatives with cefadroxil drug suggest the cefadroxil drug prefer certain arrangement of hydroxyl (–OH) groups present in saccharide/derivative (i.e., axial (a), equatorial (e), or exocyclic (exo)) and derivatization of (–OH) groups. Uro, having acidic carboxylic (–COOH) group shows exclusively different hydration behavior from the rest of saccharide/derivatives with very large values of transfer. Also, the molecular docking studies support the above results as Uro show exception behavior having binding affinity comparable to the Mal which is disaccharide. In addition to this, it is found from the molecular docking studies that the –NH, $–NH_2$, >C=O and –COOH groups of

cefadroxil drug participate actively at the binding site. Such studies may be useful towards the synthesis of saccharide-based antibiotic drugs by providing the database which lay the foundation for the synthesis to meet future challenges.

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Table 1 Specification of the chemicals used.

Compound /(Abbreviations) [Molecular formula]	Molar mass $g \cdot mol^{-1}$	[a]Mass Fraction Purity	Source	CAS Number	C, H, N, S Analysis	
					Calculated **wt** %	Observed **wt** %
(+)-D-Mannose / (Man) $[C_6H_{12}O_6]$	180.16	≥0.99	Sisco Research Lab.	3458-28-4	C = 40.00 H = 6.71	C = 40.03 H = 6.68
6-Deoxy-D-mannose / (6de-Man) $[C_6H_{12}O_5.H_2O]$	182.18	0.99	Sisco Research Lab.	6155-35-7	C = 39.55 H = 7.74	C = 39.53 H = 7.77
(+)-D-Glucose / (Glc) $[C_6H_{12}O_6]$	180.16	≥0.99	Sigma Chemical Co.	50-99-7	C = 40.00 H = 6.71	C = 40.03 H = 6.69
2-Deoxy-D-glucose / (2de-Glc) $[C_6H_{12}O_5]$	164.16	0.99	Sisco Research Lab.	154-17-6	C = 43.90 H = 7.37	C = 43.88 H = 7.39
D- Glucuronic acid/ (Uro) $[C_6H_{10}O_7]$	194.14	≥0.98	Sigma Chemical Co.	6556-12-3	C = 37.12 H = 5.19	C = 37.14 H = 5.21
(+)-Maltose monohydrate / (Mal) $[C_{12}H_{22}O_{11}.H_2O]$	360.31	0.99	Sigma Chemical Co.	6363-53-7	C = 40.00 H = 6.71	C = 40.02 H = 6.69
Cefadroxil $[C_{16}H_{17}N_3O_5S]$	363.39	≥0.98	Sigma Chemical Co.	50370-12-2	C = 52.88 H = 4.71 N = 11.56 S = 8.82	C = 52.85 H = 4.72 N = 11.55 S = 8.81

[a] Declared by the supplier.

Table 2 Standard partial molar volumes, V_2^o and partial molar isentropic compressibilities, $K^o_{s,2}$ at infinite-dilution of saccharides and their derivatives, in cefadroxil$_{(aq)}$ solutions over the temperature range (288.15 to 318.15) K under atmospheric pressure, p = 0.1 MPa.

[a]m_B /mol·kg^{-1}	$10^6\times V_2^o$/m^3·mol^{-1}				$10^{15}\times K^o_{s,2}$/ m^3·mol^{-1}·Pa^{-1}			
	T/K=288.15	298.15	308.15	318.15	288.15	298.15	308.15	318.15
(+)-D-Mannose								
0.000	111.020±0.022 (4.004±0.197)[b] 0.020[c]	111.672±0.020 (3.886± 0.174), 0.018	112.283±0.020 (4.391± 0.176), 0.018	112.978±0.018 (4.235± 0.154), 0.016	-22.897±0.003 (0.180±0.026), 0.002	-16.305±0.003 (0.105±0.029), 0.003	-13.847±0.003 (0.148±0.027) 0.002	-11.009±0.004 (0.203±0.039), 0.004
0.001	110.932±0.016 (4.224±0.140), 0.014	111.493±0.020 (4.591±0.178), 0.018	112.001±0.026 (4.817±0.228), 0.023	112.616±0.017 (4.590±0.156), 0.016	-23.017±0.004 (0.292±0.034), 0.003	-16.553±0.004 (0.349±0.037), 0.004	-14.172±0.004 (0.309±0.036), 0.003	-11.445±0.004 (0.326±0.035) 0.003
0.002	111.395±0.010 (3.745±0.082), 0.010	111.934±0.020 (4.578±0.057) , 0.021	112.452±0.029 (4.568±0.026), 0.010	113.005±0.010 (3.776±0.080), 0.010	-22.527±0.003 (0.289±0.025), 0.003	-16.033±0.003 (0.328±0.027) 0.003	-13.653±0.003 (0.328±0.027), 0.003	-10.905±0.003 (0.284±0.023), 0.003
0.003	111.866±0.022 (3.902±0.068), 0.023	112.371±0.025 (4.321±0.093), 0.021	112.825±0.020 (4.120±0.054), 0.021	113.348±0.012 (3.745±0.098), 0.013	-22.274±0.003 (0.314±0.023), 0.003	-15.756±0.003 (0.297±0.027), 0.003	-13.374±0.003 (0.314±0.023), 0.003	-10.608±0.003 (0.303±0.029), 0.004
0.004	112.203±0.018 (4.264±0.043), 0.019	112.627±0.010 (3.636±0.081), 0.011	113.111±0.014 (4.244±0.011), 0.015	113.656±0.007 (4.008±0.056), 0.002	-22.006±0.002 (0.266±0.021), 0.002	-15.532±0.003 (0.320±0.022), 0.003	-13.150±0.002 (0.248±0.019), 0.002	-10.430±0.004 (0.299±0.031), 0.004
6-Deoxy-D-mannose (anhydrous)								
0.000	110.198±0.015 (4.033±0.085), 0.009	110.587±0.013 (3.897±0.159), 0.007	111.536±0.021 (3.391±0.248), 0.012	112.891±0.026 (3.566±0.310), 0.015	-17.960±0.009 (1.350±0.114), 0.005	-13.095±0.004 (1.525±0.052), 0.002	-11.103±0.008 (1.477±0.101), 0.005	-8.993±0.008 (1.477±0.101), 0.005
0.001	110.119±0.025 (4.669±0.270), 0.017	110.437±0.027 (4.584±0.286), 0.018	111.300±0.009 (4.239±0.098), 0.006	112.579±0.019 (4.336±0.206), 0.013	-17.996±0.005 (0.292±0.055), 0.003	-13.244±0.004 (0.320±0.050), 0.003	-11.324±0.004 (0.351±0.050), 0.003	-9.294±0.004 (0.343±0.050), 0.003
0.002	110.011±0.009 (4.659±0.097), 0.006	110.322±0.013 (4.219±0.140), 0.009	111.174±0.007 (4.021±0.077), 0.005	112.447±0.008 (4.119±0.093), 0.006	-18.084±0.004 (0.245±0.049), 0.003	-13.344±0.004 (0.342±0.050), 0.003	-11.444±0.004 (0.342±0.050), 0.003	-9.399±0.004 (0.147±0.048), 0.003
0.003	109.907±0.024 (4.616±0.258), 0.016	110.204±0.005 (4.095±0.058), 0.003	111.048±0.009 (4.579±0.095), 0.006	112.323±0.009 (3.995±0.099), 0.006	-18.219±0.004 (0.240±0.049), 0.003	-13.439±0.004 (0.240±0.049), 0.003	-11.544±0.004 (0.337±0.047), 0.003	-9.519±0.004 (0.240±0.049), 0.003

0.004	109.793±0.022 (3.580±0.233), 0.016	110.044±0.015 (4.183±0.156), 0.010	110.902±0.008 (3.328±0.085), 0.005	112.172±0.013 (4.190±0.136), 0.009	-18.272±0.004 (0.317±0.049), 0.003	-13.532±0.004 (0.317±0.049), 0.003	-11.635±0.002 (0.324±0.030), 0.002	-9.602±0.004 (0.244±0.051), 0.003
(+)-D-Glucose								
0.000	111.178±0.017 (2.787±0.143), 0.016	111.862±0.032 (4.825±0.267), 0.020	112.819±0.026 (4.327±0.214), 0.020	113.624±0.012 (3.735±0.103), 0.011	-24.538±0.007 (4.651±0.062), 0.007	-17.815±0.024 (4.565±0.204), 0.020	-15.798±0.008 (3.127±0.069), 0.007	-10.922±0.010 (3.122±0.086), 0.009
0.001	110.717±0.005 (4.052±0.044), 0.006	111.376±0.015 (4.029±0.113), 0.016	112.164±0.012 (3.844±0.095), 0.013	112.862±0.007 (4.135±0.059), 0.008	-24.655±0.005 (0.626±0.040), 0.005	-18.051±0.003 (0.518±0.029), 0.004	-16.155±0.005 (0.436±0.044), 0.006	-11.369±0.003 (0.188±0.023), 0.003
0.002	111.718±0.008 (3.675±0.059), 0.008	112.319±0.013 (3.814±0.098), 0.014	113.057±0.007 (3.761±0.057), 0.008	113.712±0.010 (4.369±0.076), 0.011	-23.995±0.002 (0.178±0.021), 0.003	-17.452±0.004 (0.176±0.031). 0.004	-15.687±0.002 (0.184±0.020), 0.003	-11.032±0.002 (0.230±0.020), 0.002
0.003	112.245±0.017 (4.480±0.127), 0.018	112.846±0.011 (4.697±0.083), 0.011	113.579±0.014 (4.967±0.103), 0.014	114.248±0.010 (4.231±0.075), 0.010	-23.125±0.003 (0.254±0.022), 0.003	-16.572±0.002 (0.217±0.016), 0.002	-14.776±0.003 (0.268±0.024), 0.003	-10.089±0.003 (0.234±0.023), 0.003
0.004	112.947±0.011 (4.322±0.089), 0.012	113.534±0.006 (4.580±0.047), 0.006	114.230±0.010 (4.805±0.077), 0.011	114.859±0.011 (4.310±0.085), 0.012	-22.323±0.005 (0.443±0.037), 0.005	-15.841±0.003 (0.273±0.023), 0.003	-14.070±0.003 (0.304±0.029), 0.004	-9.426±0.003 (0.274±0.021), 0.003
2-Deoxy-D-glucose								
0.000	111.823±0.018 (5.153±0.224), 0.010	112.741±0.018 (3.756±0.225), 0.010	113.525±0.010 (4.886±0.123), 0.005	114.323±0.014 (4.165±0.173), 0.007	-10.603±0.023 (4.446±0.279), 0.012	-5.345±0.009 (3.970±0.108), 0.004	-1.895±0.016 (2.665±0.199), 0.008	3.196±0.015 (4.409±0.188), 0.008
0.001	111.676±0.018 (5.446±0.354), 0.014	112.501±0.030 (5.155±0.373), 0.015	113.212±0.017 (4.830±0.214), 0.008	113.879±0.006 (4.774±0.075), 0.003	-10.716±0.006 (0.330±0.075), 0.003	-5.542±0.006 (0.218±0.079), 0.003	-2.187±0.008 (0.380±0.101), 0.004	2.833±0.006 (0.330±0.075), 0.003
0.002	111.531±0.017 (4.029±0.017), 0.009	112.324±0.029 (4.234±0.360), 0.015	112.991±0.011 (4.690±0.143), 0.006	113.666±0.019 (4.336±0.235), 0.010	-10.834±0.005 (0.307±0.068), 0.003	-5.681±0.006 (0.201±0.074), 0.003	-2.314±0.005 (0.307±0.068), 0.003	2.694±0.007 (0.353±0.093), 0.004
0.003	111.373±0.021 (4.909±0.256), 0.011	112.137±0.010 (3.817±0.124), 0.005	112.841±0.014 (3.982±0.174), 0.007	113.520±0.017 (4.187±0.208), 0.009	-10.944±0.005 (0.310±0.071), 0.003	-5.794±0.005 (0.310±0.071), 0.003	-2.435±0.007 (0.357±0.097), 0.004	2.574±0.007 (0.357±0.097), 0.004
0.004	111.180±0.013 (5.055±0.159), 0.007	111.986±0.018 (4.670±0.225), 0.010	112.680±0.020 (4.369±0.247), 0.011	113.393±0.025 (4.574±0.308), 0.013	-11.164±0.008 (0.342±0.099), 0.004	-6.003±0.005 (0.300±0.068), 0.003	-2.643±0.005 (0.300±0.068), 0.003	2.359±0.006 (0.198±0.072), 0.003
D- Glucuronic acid								

0.000	109.206±0.011 (4.562±0.138), 0.005	110.013±0.010 (3.676±0.123), 0.005	110.720±0.012 (4.617±0.152), 0.006	111.571±0.003 (4.566±0.044), 0.001	-10.014±0.007 (0.155±0.092), 0.003	-4.874±0.007 (0.155±0.092), 0.003	-3.119±0.007 (0.159±0.089), 0.003	-1.334±0.007 (0.155±0.092), 0.003
0.001	111.054±0.021 (5.149±0.263), 0.011	111.435±0.015 (4.801±0.184), 0.008	111.763±0.013 (5.042±0.165), 0.007	112.152±0.015 (4.203±0.192), 0.008	-8.170±0.006 (0.348±0.081), 0.003	-3.540±0.005 (0.198±0.069), 0.003	-2.210±0.006 (0.348±0.081), 0.003	-0.860±0.006 (0.348±0.081), 0.003
0.002	112.000±0.014 (4.393±0.181), 0.007	112.052±0.021 (4.339±0.263), 0.011	112.228±0.026 (5.390±0.317), 0.013	112.542±0.007 (4.026±0.091), 0.003	-7.581±0.005 (0.210±0.072), 0.003	-2.986±0.007 (0.366±0.089), 0.003	-1.714±0.006 (0.312±0.075), 0.003	-0.461±0.005 (0.210±0.072), 0.003
0.003	112.655±0.030 (5.018±0.384), 0.016	112.751±0.017 (4.815±0.222), 0.009	112.865±0.021 (3.897±0.273), 0.011	113.165±0.014 (4.982±0.180), 0.007	-7.094±0.006 (0.318±0.082), 0.003	-2.521±0.005 (0.216±0.072), 0.003	-1.227±0.006 (0.383±0.075), 0.003	0.072±0.006 (0.383±0.075), 0.003
0.004	113.462±0.033 (4.603±0.402), 0.018	113.555±0.023 (4.354±0.286), 0.012	113.590±0.027 (4.852±0.338), 0.015	113.674±0.013 (3.664±0.168), 0.007	-6.163±0.005 (0.296±0.071), 0.003	-1.824±0.006 (0.347±0.084), 0.003	-0.543±0.005 (0.296±0.071), 0.003	0.656±0.005 (0.296±0.071), 0.003
(+)-Maltose (anhydrous)								
0.000	208.567±0.005 (4.645±0.049), 0.005	210.182±0.006 (4.270±0.055), 0.005	211.667±0.015 (4.148±0.135), 0.014	213.012±0.020 (3.824±0.178), 0.018	-36.818±0.018 (3.897±0.159), 0.016	-33.268±0.017 (2.579±0.149), 0.015	-26.938±0.019 (3.345±0.163), 0.017	-23.804±0.010 (2.903±0.092), 0.009
0.001	212.087±0.008 (4.190±0.062), 0.008	213.374±0.006 (4.077±0.053), 0.006	214.415±0.009 (5.123±0.072), 0.009	215.336±0.012 (4.041±0.098), 0.012	-33.801±0.003 (0.371±0.024), 0.003	-30.479±0.003 (0.281±0.026), 0.003	-24.402±0.003 (0.364±0.027), 0.003	-21.558±0.002 (0.406±0.021), 0.002
0.002	212.356±0.020 (4.113±0.164), 0.020	213.524±0.012 (4.318±0.101), 0.012	214.606±0.012 (4.469±0.096), 0.012	215.599±0.010 (4.553±0.081), 0.010	-33.501±0.002 (0.166±0.022), 0.002	-30.203±0.002 (0.245±0.021), 0.002	-24.118±0.003 (0.421±0.025), 0.003	-21.224±0.003 (0.347±0.027), 0.003
0.003	212.510±0.004 (4.211±0.034), 0.004	213.723±0.018 (4.178±0.141), 0.017	214.817±0.026 (4.309±0.204), 0.020	215.801±0.004 (4.720±0.038), 0.004	-33.394±0.003 (0.296±0.025), 0.003	-30.015±0.003 (0.370±0.026), 0.003	-23.938±0.003 (0.363±0.026), 0.003	-21.087±0.003 (0.297±0.023), 0.002
0.004	212.676±0.013 (4.622±0.104), 0.013	213.881±0.009 (3.866±0.070), 0.009	215.001±0.004 (3.814±0.037), 0.004	216.010±0.012 (4.358±0.100), 0.013	-33.146±0.003 (0.336±0.025), 0.003	-29.844±0.002 (0.338±0.020), 0.002	-23.748±0.002 (0.297±0.021), 0.002	-20.916±0.002 (0.367±0.022), 0.002

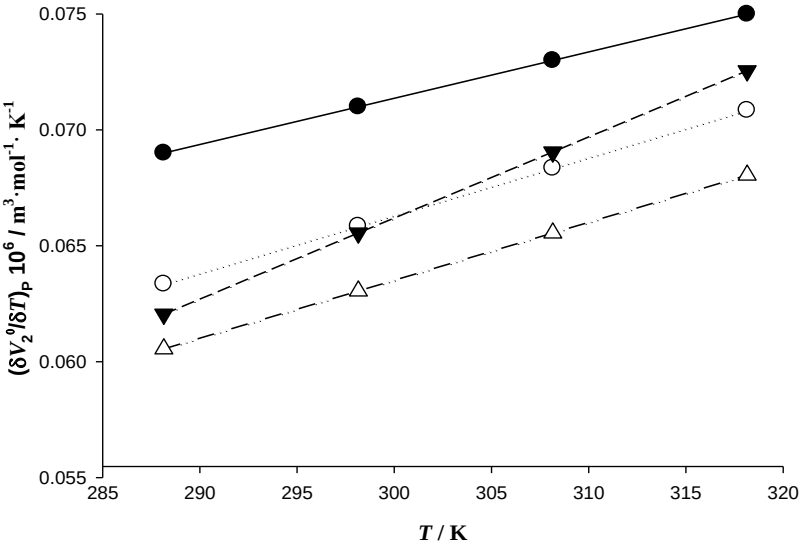
[a] m_B is the molality of cefadroxil in water. '±' are the error values in the respective parameters. [b]Parentheses contain slope, S_v of V_2^o ($m^3 \cdot kg \cdot mol^{-2}$) and S_k of $K^o_{s,2}$ ($m^3 \cdot mol^{-2} \cdot kg \cdot Pa^{-1}$) values. [c]Standard deviation of fitting of equation (4 & 5).

Table 3 Standard partial molar expansibility coefficients, V^{o}_{E} of saccharides, and their derivatives in water and cefadroxil$_{(aq)}$ solutions over the temperature range (288.15 to 318.15) K under atmospheric pressure, p = 0.1 MPa.

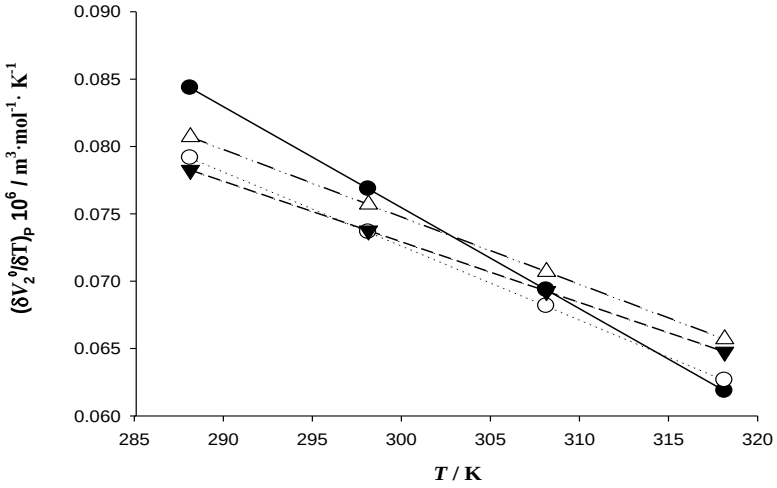
[a]m_B mol·kg^{-1}	$10^6 \times V^{o}_{E}$ / m^3·mol^{-1}·K^{-1}				$10^6 \times (\partial^2 V_2^{o}/\partial T^2)_P$ m^3·mol^1·K^{-2}	m_B mol·kg^{-1}	$10^6 \times V^{o}_{E}$ / m^3·mol^{-1}·K^{-1}				$10^6 \times (\partial^2 V_2^{o}/\partial T^2)_P$ m^3·mol^1·K^{-2}	
T(K) = 288.15	298.15	308.15	318.15	SD[b]		T (K) = 288.15	298.15	308.15	318.15	SD		
2-Deoxy-D-glucose						6-Deoxy-D-mannose (anhydrous)						
0.000	0.090	0.086	0.082	0.078	0.031	-0.0004 ± 0.00001[c]	0.000	0.013	0.064	0.115	0.165	0.042	0.0050 ± 0.0004
0.001	0.084	0.077	0.069	0.062	0.015	-0.0007 ±0.0001	0.001	0.010	0.058	0.107	0.155	0.033	0.0048 ± 0.0003
0.002	0.079	0.074	0.068	0.063	0.029	-0.0005 ± 0.0001	0.002	0.009	0.058	0.105	0.153	0.033	0.0047 ± 0.0003
0.003	0.078	0.073	0.068	0.063	0.011	-0.0004 ± 0.0001	0.003	0.008	0.056	0.105	0.152	0.026	0.0049 ± 0.0002
0.004	0.077	0.072	0.067	0.062	0.031	-0.0005 ± 0.0001	0.004	0.007	0.055	0.105	0.152	0.020	0.0046 ± 0.0002
(+)-D-Mannose							(+)-D-Glucose						
0.000	0.063	0.064	0.065	0.067	0.029	0.0001 ± 0.00001	0.000	0.077	0.081	0.084	0.088	0.046	0.0003 ± 0.0001
0.001	0.052	0.055	0.057	0.060	0.029	0.0002 ± 0.00001	0.001	0.069	0.071	0.073	0.075	0.044	0.0002 ± 0.00002
0.002	0.051	0.053	0.054	0.056	0.011	0.0001 ±0.00002	0.002	0.063	0.066	0.068	0.071	0.050	0.0003 ± 0.00001
0.003	0.047	0.048	0.049	0.051	0.022	0.0001 ±0.00001	0.003	0.062	0.065	0.068	0.069	0.042	0.0003 ± 0.00001
0.004	0.040	0.046	0.049	0.050	0.004	0.0006 ± 0.00003	0.004	0.060	0.063	0.066	0.068	0.042	0.0003 ± 0.00001
D- Glucuronic acid							(+)-Maltose (anhydrous)						
0.000	0.074	0.077	0.079	0.082	0.049	0.0002 ± 0.00001	0.000	0.167	0.155	0.143	0.131	0.001	-0.0012 ± 0.0001
0.001	0.036	0.036	0.037	0.037	0.024	0.0001 ± 0.00001	0.001	0.135	0.117	0.098	0.081	0.035	-0.0018 ± 0.0003
0.002	0.008	0.023	0.035	0.035	0.001	0.0001	0.002	0.128	0.116	0.104	0.095	0.006	-0.0008

						± 0.00001							± 0.00001
0.003	0.001	0.022	0.034	0.034	0.033	0.0001 ± 0.00001	0.003	0.127	0.116	0.105	0.093	0.001	-0.0011 ± 0.00002
0.004	0.001	0.005	0.006	0.006	0.027	0.0001 ± 0.00001	0.004	0.125	0.116	0.105	0.092	0.006	-0.0009 ± 0.00002

[a] m_B is the molality of cefadroxil in water. [b] SD is the standard deviation calculated using equation 8. [c] Error in $(\partial^2 V_2^o/\partial T^2)_P$ values.



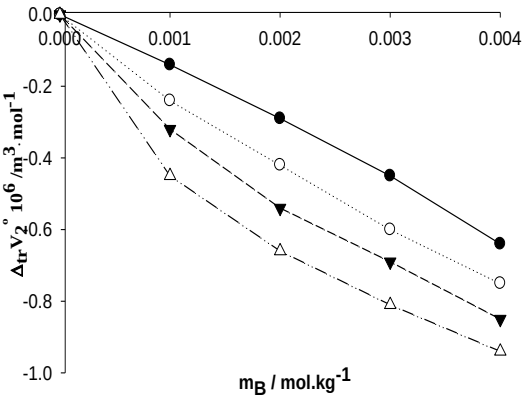
(a)



(b)

Figure 1 Standard partial molar expansion coefficients $(\partial V_2^{\circ}/\partial T)_P$ versus T of (a) (+)-D-glucose (b) 2-deoxy-D-glucose in ●, m_B = 0.001 mol·kg^{-1}; ○, m_B = 0.002 mol·kg^{-1}; ▼, m_B = 0.003 mol·kg^{-1}; Δ, m_B = 0.004 mol·kg^{-1}.

(A(i))



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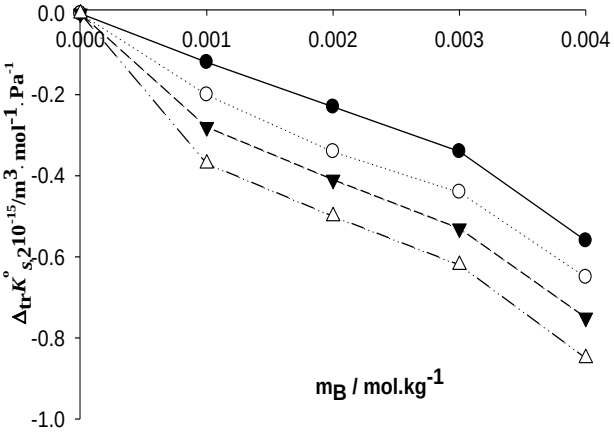

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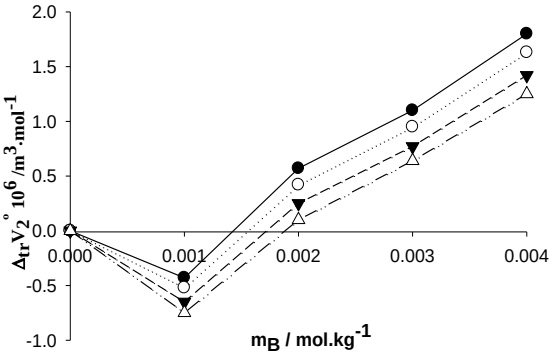

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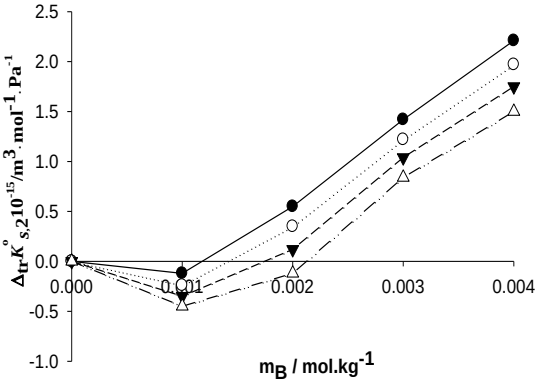

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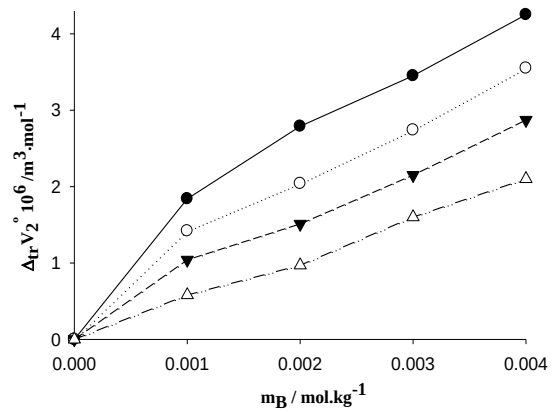
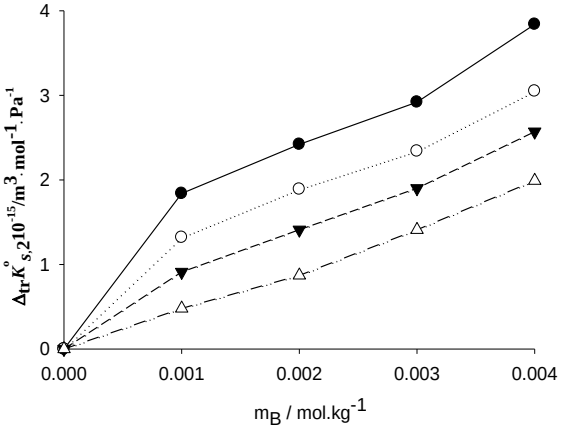


(C(ii))



(D(i)) (D(ii))

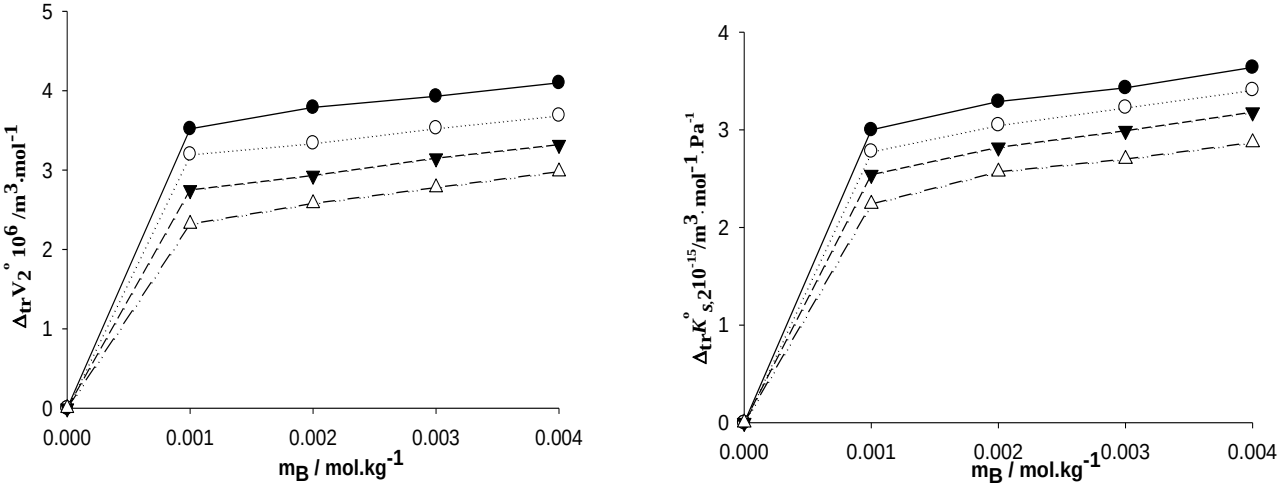
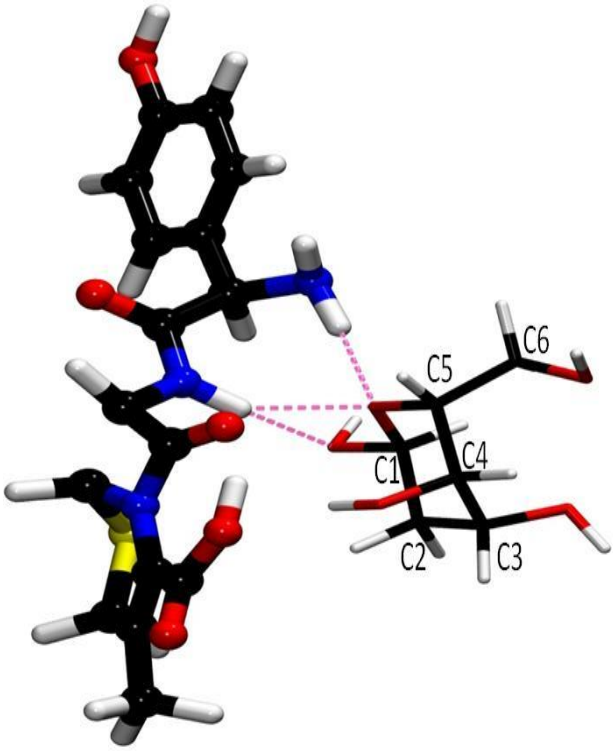
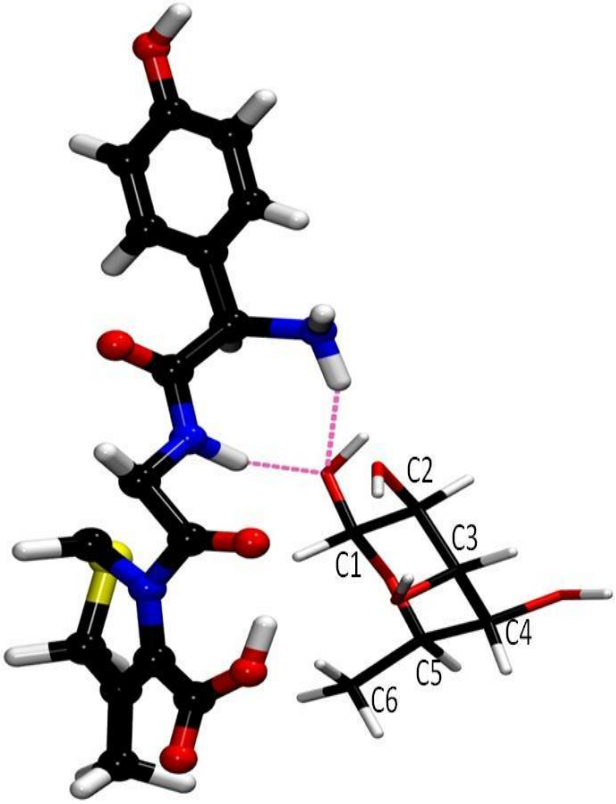


Figure 2 Plots of standard partial molar volumes of transfer, $\Delta_{tr}V_2^{\circ}$ and partial molar isentropic compressibilities of transfer, $\Delta_{tr}K^{o}_{s,2}$ versus m_B, molalities of cefadroxil for (A (i & ii)) 2-deoxy-D-glucose, (B (i & ii)) (+)-D-glucose, (C (i & ii)) D-glucuronic acid, (D (i & ii)) (+)-maltose (anhydrous) at ●, 288.15 K; ○, 298.15 K; ▼, 308.15 K; Δ, 318.15 K.

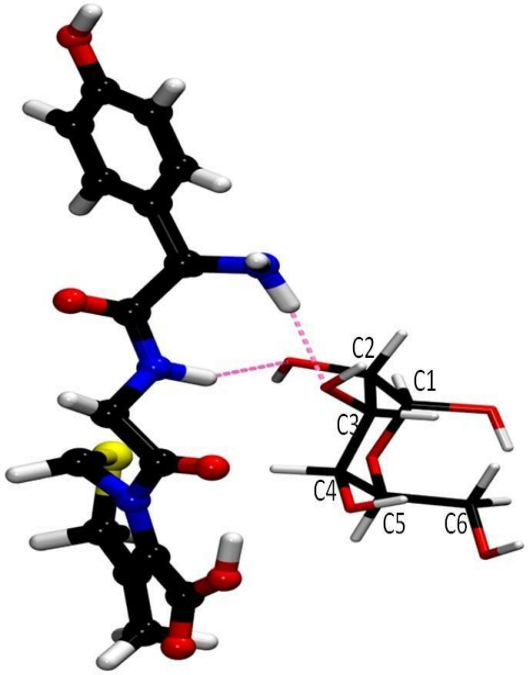
(a)



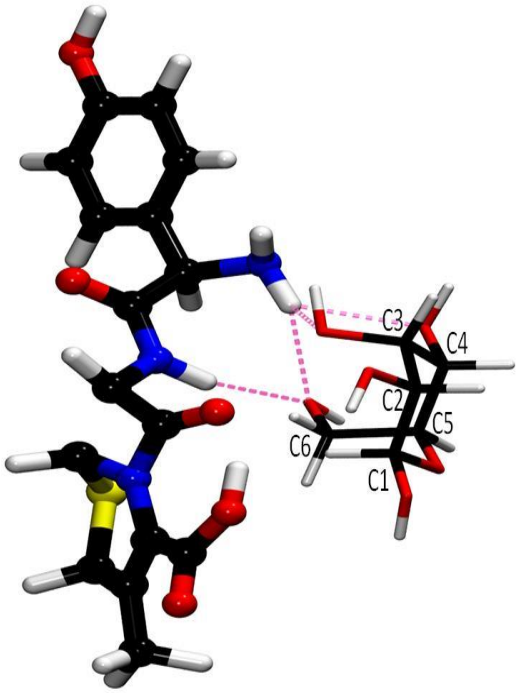
(b)



(c)



(d)



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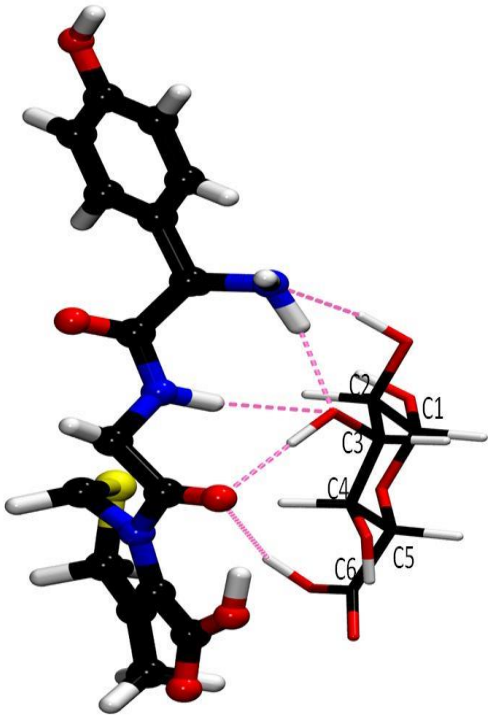
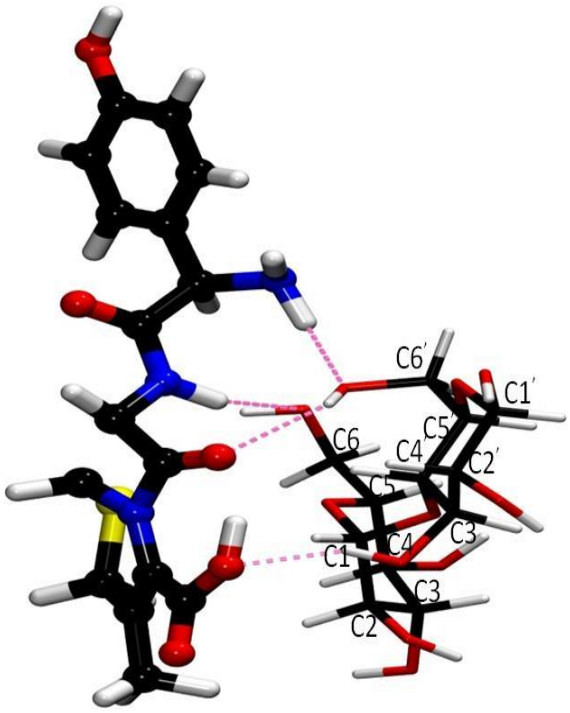


(f)



Atomic color code: Blue (N), Red (O), Black (C), Yellow (S), White (H)

Figure 3 Molecular docking images depicting binding of cefadroxil with different saccharide/derivative (a) 2-deoxy-D-glucose, (b) 6-deoxy-D-mannose, (c) (+)-D-mannose, (d) (+)-D-glucose, (e) D-glucuronic acid, (f) (+)-maltose monohydrate.

Highlights

- The $V_{2,\phi}$ values suggest the prevalence of solute-cosolute interactions which get intensified with ascension of temperature.
- The negative $K_{s,2,\phi}$ values indicates that the hydrated water molecule is less compressible than the water molecules in the bulk.
- Uro, having acidic carboxylic group shows exclusively different hydration behavior.
- Molecular docking studies shows that –NH, $–NH_2$, >C=O and –COOH groups of cefadroxil participate more actively at the binding site.

Graphical Abstract