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ORIGINAL ARTICLE

Inclusion complexes of sulphanilamide drugs and β-cyclodextrin: a theoretical approach

G. Venkatesh · T. Sivasankar · M. Karthick · N. Rajendiran

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Abstract PM3 theoretical methodology was used to access and compare the relative stability of inclusion complexes formed by sulphadiazene, sulphisomidine, sulphamethazine and sulphanilamide with β-cyclodextrin (β-CD). The study predicted that (i) the heterocyclic ring is encapsulated in the hydrophobic part and aniline ring is present in the hydrophilic part of the β-CD cavity and (ii) intermolecular hydrogen bonds were formed between host and guest molecules. The negative free energy and enthalpy changes indicated that all the four inclusion complexation processes were spontaneous and enthalpy driven process. HOMO and LUMO orbital investigation confirmed that the stability increased in the inclusion complexes and also proved no significant change in the electronic structure of the guest and host molecules after complexation.

Keywords Sulpha drugs · β-Cyclodextrin · PM3 method · Molecular modelling · Thermodynamic parameters

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophilic outer surface and a relatively less polar central cavity, compared to water, which are capable of encapsulating a wide variety of the drug molecules [1, 2]. The stability of drug molecules in general increases upon such encapsulation [3, 4]. The inclusion process of drug molecules to β-cyclodextrin (β-CD) leads to important modifications of pharmaceutical properties of drug molecules. For example, the pharmaceutical interest in β-CD extends to enhance solubility, chemical stability (increase the life time of the drugs) and bioavailability of poorly soluble drugs, to reduce toxicity and to control the rate of release. Great use is made of this property of CDs in drug delivery. β-CD are the most readily available and widely used amongst the naturally occurring CDs namely alpha (α), beta (β) and gamma (γ) composed of 6, 7 and 8 glucose units. The restricted space and relatively reduced polarity of the CD cavity influences the photophysical properties of the guest molecule included in the cavity [5, 6].

Since 1995, much research has focused on the study of inclusion complex of CDs by semi empirical methods AM1 and PM3 to obtain electronic properties and generate more information about geometry of the complex. The results suggested that PM3 should be more advantageous than AM1 and give results which coincide with the experimental observations [7–11]. In 2000, some studies were carried out on the performances of AM1 and PM3 methods on some model compounds including hydroxyethyl ether and α (1-4)-glucobiose. On the basis of that it was suggested that PM3 should be advantageous to AM1 in CD chemistry because PM3 can predict the $\bar{O}H\cdots O$ hydrogen bonds better than AM1.

The most important driving forces for the inclusion complexes are electrostatic, hydrophobic, hydrogen bonding, release of conformational strain and the entropy released by decomplexed water molecules [12, 13]. The property of CDs to form inclusion complexes has become the subject of intense interest in theoretical studies using molecular mechanics, molecular dynamics and quantum mechanics methods because the combination of experimental and theoretical leads to successful results in solving structural, energetic and dynamic problems [14, 15]. Recently we have studied [16, 17] the encapsulation of different sulphanilamide drug molecules in β-CD cavity in solution and solid

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state and it was observed that in all these guest molecules the aniline moiety preferred to occupy most of the available space in the β-CD cavity. In this paper we report the comparison of our experimental results with theoretical studies on the geometry and energy interaction of the inclusion complex calculated using molecular modelling methods.

Sulfonamides constitute a class of drugs, which are frequently used in pharmaceutical preparations, especially in veterinary practice. They are widely used as antibiotics and antimicrobial agents and are used for both therapeutic and prophylactic purposes in addition to their application as growth promoters. Sulfadiazine is one of the sulfonamides used in the treatment of urinary tract infections, pneumocystic pneumonia, chronic bronchitis, meningococcal meningitis, acuteotitis media and toxoplasmosis [18]. Further these compounds have been found in surface and ground water, liquid manure and soil [19, 20]. Interest in this field of the drugs studies are not only for gaining some fundamental insight into the determination of drugs in pharmaceutical samples [21] but also obtaining information about the structure, as well as the chelating behaviour of the sulpha drugs [22, 23].

Methods

The theoretical calculations were performed with Gaussian 03 W package. The initial geometry of the drugs and β-CD were constructed with the help of Spartan 08 software and then optimized by PM3. β-CD was fully optimized by PM3 without any symmetry constraint [24]. The glycosidic oxygen atoms of CD were placed onto the XY plane and their centre was defined as the centre of the coordination system. The primary hydroxyl groups were placed pointing toward the positive Z axis. The inclusion complexes were constructed from the PM3-optimized β-CD and guest molecules. The longer dimension of the guest molecule was initially placed onto the Z axis. The position of the guest was determined by the Z coordinate of one selected atom of the guest. The inclusion process was simulated by putting the guest in one end of β-CD and then letting it pass through the β-CD cavity. Since the semiempirical PM3 method has been proved to be a powerful tool in the conformational study of cyclodextrin inclusion complexes and has high computational efficiency [25–27], hence PM3 method is selected to study the inclusion process of β-CD with the sulpha drugs in this paper.

Result and discussion

The optimization

The energy, HOMO, LUMO, thermodynamic parameters (enthalpy, entropy, free energy), chemical potential (μ), stability (S), dipole moment (D), hardness (η), electrophilicity (ω), zero point vibrational energy and Mulliken charge of the guest [sulphadiazene(SDA), sulphisomidine (SFM), sulphamethazine (SMA) and sulphanilamide (SAM)], host (β-CD) and inclusion complexes are summarized in Table 1. The PM3 level optimized structures of the isolated guest, host and the inclusion complexes are shown in Fig. 1 and Fig. 2 respectively. From Fig. 2, it can be seen that the guest molecules formed stable inclusion complexes with β-CD. Interestingly, it can also be seen that the structure of the above four inclusion complexes are all similar to each other. Presumably, the fact that the SDA, SFM and SMA molecules having isoelectronic structure causes the above behaviour. Therefore, the slight structural difference is not likely factor that makes the complexation energies of the guests with β-CD are different.

Table 2 presents the most interesting bond distances, bond angles and dihedral angles of the drugs (guests) before and after complexation in β-CD obtained from PM3 calculations from the most stable structure (Fig. 2). It was evident that in β-CD the geometry of this sulphanilamide analogue drugs were slightly altered. The alterations were significant in dihedral angles, which indicated that the drugs adopted a specific conformation to form a stable complex. The internal diameter of β-CD is approximately 6.5 Å and the height is 7.8 Å; considering the shape and dimensions of β-CD, the drugs may not be completely embedded into the β-CD cavity. Since the vertical distance and length of the drugs are greater than the dimensions of the β-CD, the guest molecules cannot be fully present inside of the β-CD cavity. Further, the optimized structures of the inclusion complexes were also confirmed that the guest molecules partially included in the β-CD cavity.

The optimized inclusion structures in Fig. 2 demonstrated, hydrogen bond is formed in all the inclusion complexes. The intermolecular hydrogen bonds were formed between hydrogen atom of amino group of the drugs and oxygen atom of primary hydroxyl group of the β-CD with a d_{H-O} distance less than 3.00 Å and the d_{H-O} distance more than 3.00 Å indicates at that position H– bonding interactions were not formed. This justified the importance of both interaction energy between the drugs and β-CD necessary to ensure a better inclusion of the guest to the host. The above values were supported by the fact that the flexibility of the host molecule may be one of the structural requirements for inclusion complexes formation. The present calculations explained that hydrogen bonding brings the difference between the binding energies of β-CD complexation with the sulphanilamide analogue drugs.

Among structures of the four inclusion complexes shown in Fig. 2, we could notice that SFM presents three hydrogen bonds; one between H atom of amino group and oxygen atom of secondary hydroxyl group of the β-CD

Table 1 Energetic features, thermodynamic parameters and HOMO–LUMO energy calculations for SDA, SFM, SMA, SAM and its inclusion complexes by PM3 method

Properties	SDA	SFM	SMA	SAM	β-CD	SDA: β-CD	SFM: β-CD	SMA: β-CD	SAM: β-CD
E_{HOMO} (eV)	−9.24	−9.34	−9.13	−9.29	−10.35	−8.42	−8.96	−8.82	−8.73
E_{LUMO} (eV)	−0.72	−0.91	−0.74	−0.65	1.23	−0.91	−0.94	−0.62	−0.42
E_{HOMO}–E_{LUMO} (eV)	−8.52	−8.42	−8.38	−8.63	−11.58	−7.51	−8.01	−8.19	−8.31
μ	−4.98	−5.13	−4.94	−4.97	−4.56	−4.66	−4.95	−4.72	−4.57
η	4.26	4.21	4.19	4.32	5.79	3.75	4.01	4.09	4.15
ω	2.91	3.12	2.91	2.85	1.79	2.89	3.06	2.72	2.51
S	0.23	0.23	0.23	0.23	0.17	0.26	0.25	0.24	0.24
Dipole (D)	6.86	6.30	4.63	7.48	12.29	17.42	7.55	12.96	10.07
ΔD						−1.73	−11.04	−3.96	−9.7
E (kcal mol^{-1})	−6.45	−22.61	−23.49	−10.76	−1457.63	−1487.63	−1500.49	−1494.38	−1516.52
ΔE (kcal mol^{-1})						−23.55	−20.25	−13.26	−48.13
G (kcal mol^{-1})	144.54	115.03	133.86	64.15	−789.52	−648.47	−681.55	−683.32	−769.71
ΔG (kcal mol^{-1})						−3.49	−7.06	−27.66	−71.34
H (kcal mol^{-1})	126.60	146.41	193.63	95.47	−667.55	−548.79	−538.11	−533.08	−630.08
ΔH (kcal mol^{-1})						−7.84	−16.97	−59.16	−58.01
S (kcal mol^{-1} K^{-1})	0.127	0.138	0.152	105.04	0.409	0.428	0.481	0.503	0.468
ΔS (kcal mol^{-1} K^{-1})						−0.108	−0.066	−0.058	−0.046
Zero point vibrational energy	122.83	157.57	157.59	87.82	740.56	862.76	901.79	899.65	−829.57
Mulliken properties	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

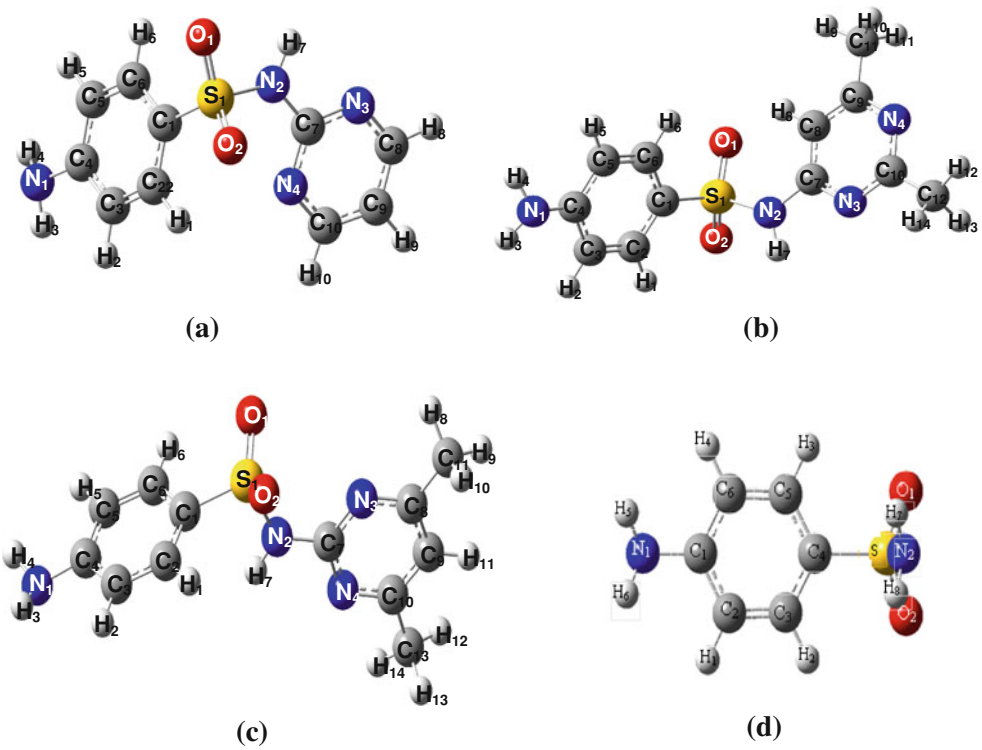

Fig. 1 The PM3 optimized structure of **a** SDA, **b** SFM, **c** SMA and **d** SAM

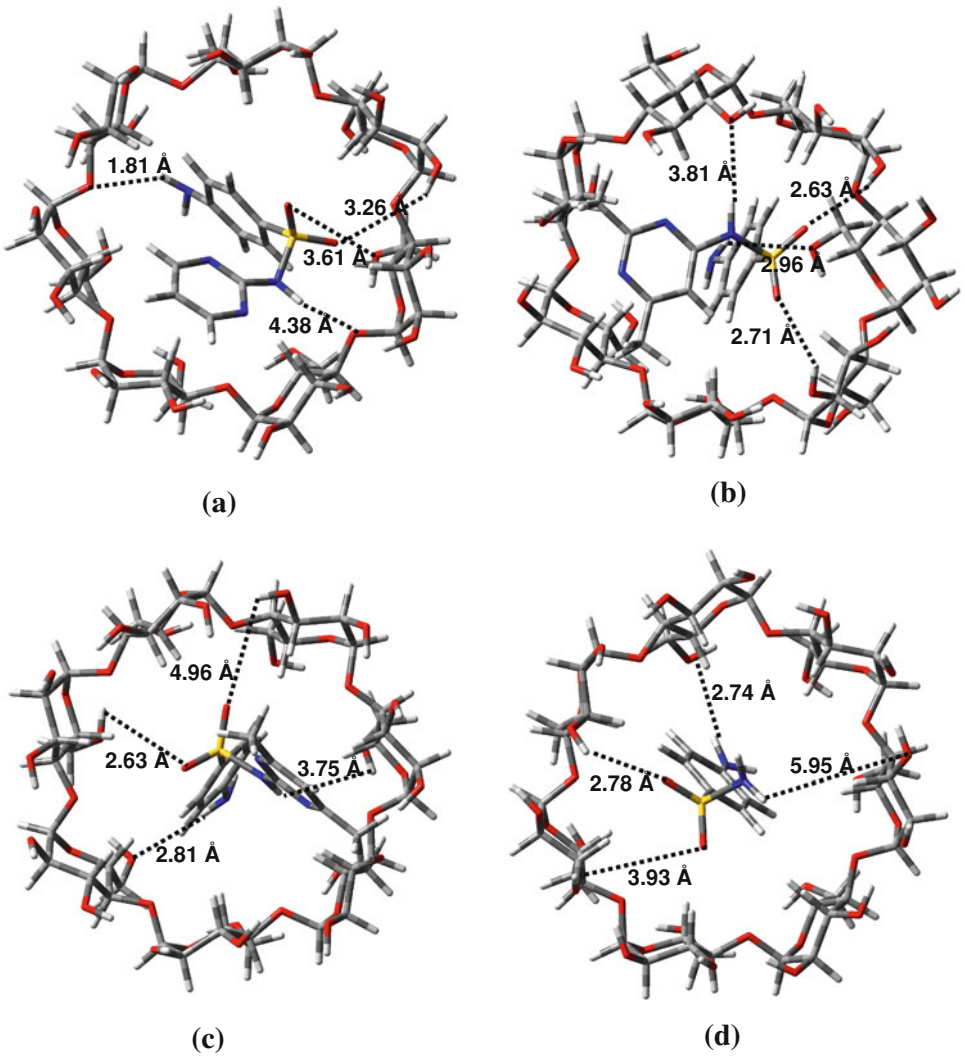

Fig. 2 Upper and side views of PM3 optimized structures of the β-CD complexes **a** SDA, **b** SFM, **c** SMA and **d** SAM

with hydrogen bonding interaction d_{H-O} distance of 2.96 Å. The two oxygen atoms of sulphonyl group ($-SO_2$) and the two hydrogen atoms of primary hydroxyl group CDs have hydrogen bonding interaction with d_{H-O} distance of 2.63 Å and 2.64 Å. Moreover, SAM (2.74 Å and 2.78 Å) and SMA (2.50 Å and 2.81 Å) molecules form two hydrogen bonds and SDA (1.81 Å) formed one hydrogen bond with host β-CD, the d_{H-O} distance and responsible groups are listed in the Table 2. Comparatively, a careful analysis of the energetic values obtained from PM3 method suggested that the mutual host–guest hydrogen bonding interactions contribute greatly to $E_{complexation}$ and are crucial in determining stability of the complex [28].

It is well known that the van der Waals forces including the dipole–induced dipole interactions are proportional to the distance between guest, the wall of the β-CD cavity and the polarizabilities of the two components. The interaction of the phenyl ring with β-CD would play an important role because the phenyl moiety may achieve a maximum contact area with the internal surface of the cavity of the CD. The above results imply that the inclusion of the drug molecules with β-CD cavity is affected by hydrophobic and electronic interactions. Since CD has a permanent dipole the primary hydroxyl end is positive and the secondary hydroxyl end is negative in the glucose units of CD. The stability of binding by hydrophobic interactions is partly the result of van der Waals force but is mainly due to the effects of entropy produced on the water molecules [29].

Dipole changes

The dipole moment of the SAM (7.02 D) is significantly larger than the other isolated SDA, SFM and SMA drugs molecules (Table 1). The dipole moment of the drugs and the inclusion complexes are present in the following order: SMA:β-CD > SDA:β-CD > β-CD > SAM:β-CD > SFM:β-CD > SAM > SDA > SFM > SMA. All the inclusion

Table 2 Geometrical parameters of SDA, SFM and SMA before and after inclusion in β-CD for the most stable inclusion complexes

	SDA	SDA:β-CD		SFM	SFM:β-CD		SMA	SMA:β-CD		SAM	SAM:β-CD
Bond length (Å)											
H_4–H_9	9.34	9.95	H_4–H_{10}	11.48	10.82	H_4–H_9	11.81	11.88	H_5–O_2	7.26	7.26
H_3–H_8	9.71	9.34	H_3–H_{13}	10.72	10.69	H_4–H_{13}	12.59	12.53	N_1–N_2	6.60	6.62
N_1–H_9	8.01	7.92	H_5–H_2	4.34	4.37	H_5–H_2	4.34	4.37	N_1–S	6.00	5.97
H_2–H_5	4.34	4.30	H_9–H_{14}	5.71	5.93	C_4–H_{13}	9.78	9.35	H_1–H_4	4.34	4.36
H_8–H_{10}	4.36	4.27	C_4–N_4	8.33	7.60	H_8–H_{14}	6.34	6.63			
H-bond length (Å)											
(–NH_2)H···O(2° OH)		1.81	(–NH_2)H···O(2° OH)		2.96	(−NH_2)H···O(2° OH)		2.81	(–NH_2)H···O(2° OH)		2.74
(–SO_2)O···H(1° OH)		3.61	(–SO_2)O···H(1° OH)		2.63	(−SO_2)OH(1° OH)		2.63	(−SO_2)O···H(1° OH)		2.78
(–SO_2)O···H(1° OH)		3.26	(−SO_2)O···H(1° OH)		2.71	(−SO_2)O···H(1° OH)		4.96	(−SO_2)O···H(1° OH)		3.93
(–NH)H···O(1° OH)		4.38	(−NH)H···O(1° OH)		3.81	(−NH)H···O(1° OH)		3.75	(−SO_2–NH_2)H−O(1° OH)		5.95
Bond angle (°)											
H_4–N_1–C_4	113.94	113.94	H_4−N_1−C_4	112.99	114.85	H_4−N_1−C_4	112.84	114.07	H_5−N_1−C_1	112.83	114.05
C_1–S_1–O_1	109.47	109.47	C_1–S_1−O_1	110.96	111.69	C_1–S_1–O_1	110.30	111.19	C_4−S−N_2	100.94	102.19
S_1–N_1–H_7	116.34	113.58	N_4–C_9–C_{11}	119.11	117.45	S_1–N_2–H_7	112.50	119.18			
N_3–C_7–N_2	117.62	119.29	H_{12}–C_{12}–C_{10}	111.83	110.35	C7–N_2–H_7	112.95	113.24			
Dihedral angle (°)											
H_4–N_1–C_4–C_5	28.23	29.97	H_4–N_1–C_4–C_5	−27.86	−21.89	H_4–N–C_4–C_5	−28.01	−25.55	H–N–S–O_1	−175.19	−126.50
C_1–S_1–N_2–C_7	−74.58	−82.81	H_{12}–C_{12}–C_{10}–N_4	−48.04	−41.81	C–S_1–N–C_7	−180.00	−176.31	H–N–S-O_2	175.26	130.84
C_7−N_2−S_1−O_1	170.53	165.37	O_2−S_1−N_2−C_7	−160.54	−164.69	C_1−S_1−N_2−H_7	−0.34	0.63	H_7−N_2−S−C_4	−69.70	

complex showed dipole moment values higher than the corresponding isolated drugs molecules, where as compared to β-CD, the values were low or high. This indicates that the polarity of the β-CD cavity changed after the drug entered into the β-CD cavity. From these results it can be concluded that the dipole moment values show a strong correlation with the complexation behaviour of the molecules. However, the values of ΔG and ΔH clearly indicated that, the complexation of the sulpha drugs with β-CD is enthalphically more favourable [29].

HOMO–LUMO parameters

HOMO as ionization energy (IE) and LUMO as electron affinity (EA) are used for calculating the electronic chemical potential (μ) which is half of the sum of energies of the HOMO and LUMO:

$$\mu = (E_{HOMO} + E_{LUMO})/2 \quad (1)$$

The gap energy (G) is the different between the HOMO and LUMO, the hardness (η) is half of the energy gap between LUMO and HOMO.

$$Gap = E_{HOMO} - E_{LUMO} \quad (2)$$

$$\eta = E_{LUMO} - E_{HOMO}/2 \quad (3)$$

The electrophilicity (ω) of the drug molecules and their complexes are calculated using the following equation.

$$\omega = \mu^2/2\eta \quad (4)$$

Table 1, depicts that (i) HOMO and LUMO energy, chemical potential and electrophilicity of SFM is higher than that of other isolated SDA, SMA and SAM, (ii) hardness and dipole of SAM is higher with respect to other three drugs, (iii) the HOMO–LUMO gap of isolated SDA drug is higher than other drugs, (iv) chemical potential of SAM:β-CD is less negative with respect to SDA, SFM and SMA inclusion complexes, (v) with respect to other three complexes, SMA:β-CD inclusion complex is having more dipole moment, (vii) no significant difference in the stability of the four drugs and their complexes.

From Table 1, it can be observed that the stabilities of the drug complexes with β-CD are almost same. The chemical potential of all the inclusion complexes are negative which indicates that all the inclusion process are spontaneous. However, SFM:β-CD inclusion complex was more negative than other complexes suggesting this complexation process is more spontaneous than other complexes. The HOMO–LUMO value of the SAM:β-CD inclusion complex was slightly higher than other three inclusion complexes.

The ($E_{HOMO}-E_{LUMO}$) gap is an important scale of stability [30] and chemicals with large ($E_{HOMO}-E_{LUMO}$) values tend to have higher stability. So, we investigated the electronic structure of these complexes using the PM3 method. The HOMO and LUMO energies of these drugs and their inclusion complexes are shown in Table 1 and Fig. 3, which exposed that the energy gap and the chemical activity of the molecules. The LUMO as an electron acceptor represents the ability to obtain an electron and HOMO represents the ability to donate electron. Moreover, a lower HOMO–LUMO energy gap explained the eventual stability of the complex; i.e., isolated molecule had lower stability than complex molecule.

The HOMO–LUMO of the SFM:β-CD inclusion complex was slightly higher than other three inclusion complexes. Figure 3 illustrates the HOMO and LUMO energy orbital pictures of all these complexes are significantly varied. The energy gap between HOMO and LUMO of each complex suggested that there will be a significant change in the electronic structures of these guest molecules while molecular recognition and binding. The HOMO–LUMO gap for SFM:β-CD inclusion complex was more negative, which advocate that this complex is more stable than other inclusion complexes.

Though the results are not readily understandable according to the driving forces listed in the introduction, the Morokuma theory of energy decomposition analysis [31] can offer a reasonable explanation. According to the theory, when a supramolecule was formed electrons will lose their identity as belonging to one or other component molecule. Four types of interactions should be considered in the formation of a supramolecule: (a) electrostatic interaction, which is favoured by large permanent charges and dipoles, (b) polarization interaction, which is favoured by large volume and polarizability of the molecules, (c) exchange energy, or Pauli repulsion and (d) charge-transfer interaction, which is contributed from the mixing of the filled orbital of one component molecule with the vacant orbital of the other. The charge-transfer interaction is always attractive and the most important terms in this interaction are contributed from the charge-transfer between the HOMO of one component and the LUMO of the other. These first three interactions constitute the canonical driving forces in CD chemistry, i.e., dipole–dipole interaction, dipole-induced dipole interaction and steric effect. However, they cannot explain the unexpected theoretical and experimental observations. The higher HOMO of the guest molecule, the stronger is the charge-transfer interaction in the complexation. Herein, the semiempirical calculations indicate that no charge-transfer interactions formed between the guest and host. Further, the Mullikan charge for the complexes has zero values confirmed there is no charge transfer interactions present between the guest and host molecules. The thermodynamic parameter values (ΔE, ΔG and ΔH) indicated that, the complexation of the sulpha drugs with β-CD is enthalphically more favourable [29].

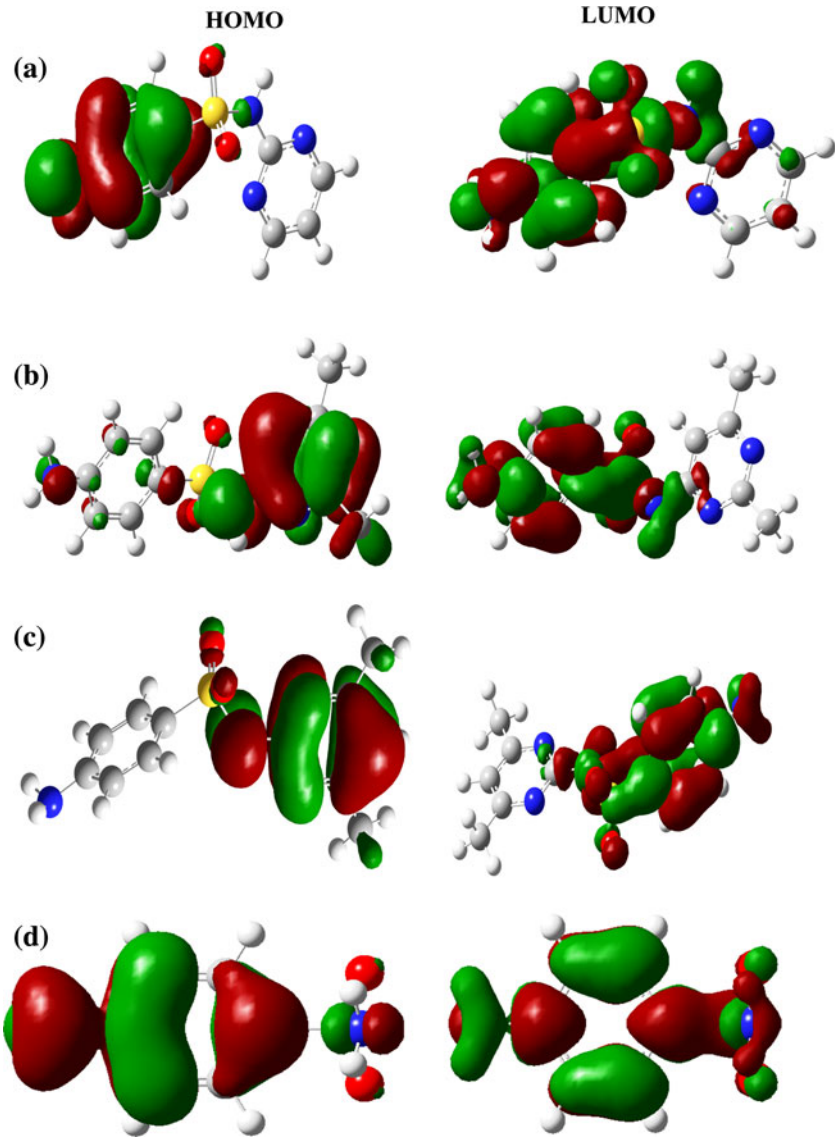

Fig. 3 The HOMO, LUMO energy structure of **a** SDA, **b** SFM, **c** SMA and **d** SAM

Thermodynamics parameters

To investigate the thermodynamic parameters of the binding process, the statistical thermodynamic calculation was carried out at 1 atm pressure and 298.15 K temperature by PM3 method. The thermodynamic quantities the binding energies (ΔE), Gibbs energy changes (ΔG), enthalpy changes (ΔH) and entropy changes (ΔS) contributions are depicted in Table 1. The complexation energy allowed us to evaluate the inclusion process and to find the most stable inclusion complex between the complexes under study. The ΔE of the inclusion process can be calculated by using the following equation

$$\Delta E_{complexation} = E_{complex} - \left(E_{\beta-CD} + E_{drug}\right) \quad (5)$$

where $E_{complex}$, $E_{\beta\text{-CD}}$ and E_{drug} represent the total energy of the optimized complex, free β-CD and the free drugs respectively. The complexation reactions of SDA, SFM, SMA and SAM with β-CD were exothermic, which was judged from the negative energy and enthalpy changes. The negative energy, enthalpy and Gibbs free energy changes suggested that the inclusion processes were energetically and enthalpically favourable in nature. The binding energy (ΔE) of the four inclusion complexes are higher than that of corresponding isolated drug molecule suggesting that stability of complexes are more. Among the four inclusion complexes, SAM:β-CD (-48.13 kcal mol^{-1}) inclusion complex had lowest energy when compared to other three complexes SDA:β-CD (-23.55 kcal mol^{-1}), SFM:β-CD (-20.25 kcal mol^{-1}) and SMA:β-CD (-13.26 kcal mol^{-1}). The above results proved that SAM and β-CD formed more stable inclusion complex than other three drugs (because high negative value is more stable). The calculated interaction energies, as discussed above can be

promptly understood in terms of the formation of intermolecular hydrogen bonds only. In this respect β-CD glycosyl and hydroxyl oxygen atoms (mainly the primary hydroxyl groups) play a major role for stability of these sulphanilamide analogues drugs inclusion complexes. For all these complexes, favourable hydrogen bonding interactions have been predicted based on the distance between oxygen atoms of host (β-CD) and amine group (–NH_2) or sulphonyl (SO_2) groups of the guest molecules. For these four inclusion complexes several hydrogen bonds are possible, but we could find only minimum number of hydrogen bonds (Table 2). According to the optimized geometries we found three hydrogen bonds in SFM, two hydrogen bonds in the case of SMA and SAM while only one hydrogen bond in SDA complex. These finding hints that dispersion forces must play an important role in these complex formation [32]. The smaller but significant ΔE values may vary with the number of hydrogen bonds has been predicted. From the Table 1 interaction energies of these four systems slightly differs each other; this is due to the hydrogen bond between different groups (Fig. 2). Nonetheless, it is often difficult to explain the difference in interaction energies of these complexes at PM3 level of computing.

The free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) for the all the inclusion complexes are negative than the corresponding isolated drug molecules. The negative free energy change (ΔG) of the inclusion complexes imply that the inclusion preceded spontaneously at room temperature. The high negative ΔG value noticed for SAM:β-CD (-27.66 kcal mol^{-1}) inclusion complex specify that this inclusion process is more spontaneous than other three inclusion process. The theoretical ΔG values (SDA:β-CD ~ -3.49; SFM:β-CD ~ -7.06; SAM:β-CD ~ -17.91 kcal mol^{-1}) were different from our earlier experimental (SDA:β-CD ~ -12.74; SFM:β-CD ~ -12.84; SAM:β-CD ~ -13.42 kcal mol^{-1}) findings [16].

The difference in ΔE and ΔG can be explained by the solvent effect. The actual experiments are conducted in aqueous medium but the computational work was done at vacuum phase. Unfortunately, because of limitations in the calculation ability of our computer and the large molecular size of β-CD, the statistical thermodynamic calculations for these systems could not be performed in aqueous phase as well as in excited state. However, it was observed that the solvent effect on the host–guest interactions easily changes the inclusion reaction from a non-spontaneous process in the gas phase to a spontaneous one in the aqueous phase. The host–guest interaction causes an enthalpy-entropy compensating process in the gas phase whereas the same interaction causes an enthalpy-entropy co-driven process in aqueous solution, because inclusion complexation releases a number of water molecules from the cavity of β-CD.

Recently, some authors who encountered this discrepancy turned to experimental values to solve their calculations. For example in the case of the complexes of both *cis* and *trans* isomers of Brooker's mercyanine inserted within the β-CD cavity, the author's preliminary calculations of ΔG values predicted the complex would not form spontaneously and the magnitude and the sign of ΔS and ΔG values were very different from the experiment values [33]. They argued that since experimentally the entropy of complexation depends on both the insertion of the dye molecule and the concurrent displacement of water molecules that are trapped within the β-CD cavity, the water molecule should be included in the calculations and then they found thermodynamic values closer to the experimental results and the sign matched the reported values in all cases. Further, Xing et al. [34] proposed a model to calculate ΔS of the inclusion complex in aqueous solution with the assumptions that the effect of water molecules on the entropy changes of the 2-hydroxy-5-methoxy acetophenone:β-CD system is mainly determined by the water molecules in the β-CD cavity and the effect of the H_2O molecules out of the cavity is less important and thus can be negligible.

To best of our knowledge the very small negative ΔH values indicated that the inclusion formation of drugs with β-CD are an exothermic and enthalpy-driven. It should be noted that ΔH and ΔS values contain contributions from (i) release of cavity bound water, (ii) partial destruction of hydration shells of the reagents, (iii) non covalent interactions (van der Waals, hydrophobic and electrostatic interactions as well as hydrogen bonding) and (iv) hydration of the complexes. All these process should be taken into account while discussing thermodynamic parameters of complex formation.

ΔH for SMA is more negative (-59.16 kcal mol^{-1}) than other three drug complexes. Probably geometrics factor have plays a considerable role in complexation process. The small negative ΔS values are further confirm the restriction of freedom of the molecule and formation of less compact structures. As it is evident from Table 1, hydroxyl groups reduce binding affinity of β-CD to drugs, making the complexation process more enthalpy and less entropy favourable [35]. It is believed that the β-CD cavity size and drug substituents serve as a steric hindrance for the drug inclusion.

The observed small negative ΔS values are assumed to be due to enhancement of disorder in the system. Moreover hydrophobic interactions, which are long range interactions, can be important in the β-CD complex formation. The inclusion complex structure shown in Fig. 2 also suggested that the benzene ring was partially inside the cavity and interacts with β-CD cavity through hydrophobic interactions. Further the small ΔH values can be explained

by the prevalence of hydrophobic interactions. With regard to ΔG and ΔH values for the four drugs with β-CD confirmed the four inclusion complexes are stable. Comparison of ΔH and ΔS confirm that enthalpy changes are higher and entropy changes are lower for the complexation. Therefore complexes of the drugs with β-CD are more enthalpy stabilized.

Conclusion

The complexations of SDA, SFM, SMA and SAM with β-CD were studied by semi-empirical PM3 quantum mechanical calculations. The results propose that the complexation of these four sulphanilamide analogues significantly more favourable in nature. The optimized host–guest inclusion complexes structures proved sulphanilamide molecules are partially embedded into the β-CD cavity. In addition to that, the statistical thermodynamic calculations advocate that the formations of these inclusion complexes were enthalpy-driven process. The overall theoretical results suggest that hydrogen bonding and hydrophobic effect play an important role in the complexation process.

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