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Density functional calculations on meloxicam–β-cyclodextrin inclusion complexes

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ABSTRACT

The geometries of the cyclodextrin (CD) inclusion complexes with various tautomeric forms of meloxicam in gas phase were determined by DFT calculation (B3LYP/6-31G (d,p)). The interaction energies were estimated including basis set superposition error (BSSE) correction. Two orientations of the meloxicam guest were considered: the benzene ring located near the narrow rim and at the wider rim of the β-cyclodextrin, respectively. The calculations show that in all cases the molecules are located inside the CD cavity. The preferred complexation orientation is that one, in which the benzene ring of meloxicam is located near the wider rim with the secondary hydroxyl groups of the CD. The stabilization energies for the encapsulation of the meloxicam guest molecules show an overall affinity ranking for the meloxicam guest molecule in the following order: anionic (deprotonated) form > zwitterionic form ~ enolic form > cationic (protonated) form. A comparison of the enolic and zwitterionic neutral forms shows, that the zwitterionic structure is better stabilized upon complexation due to the geometry of two extra hydrogen bonds between host and guest.

1. Introduction

Cyclodextrins (CDs) are indispensable excipients not only in pharmacy and pharmaceutical technology, but also in many other scientific disciplines, like environmental, technical and analytical chemistry, for stereo-specific separations of diastereomers and optical isomers, for extraction of natural products, for protection and stabilization of light-, temperature- or oxidation-sensitive compounds. The reason for this broad field of various applications of CDs is their ability to form inclusion complexes with small or even medium-sized organic or inorganic compounds. Such an inclusion influences the physico-chemical behaviour of the guest molecules, like the reactivity or the solubility significantly. Emulsification of highly apolar compounds, change of the catalytic activities, support in organic syntheses, masking of odour or taste, increase of bioavailability and efficiency of the active substance as a consequence of solubility enhancement and the permission of controlled release are topics of actual CD research (Szejtli, 1982, 1998; Szejtli and Osa, 1996; Bender and Momiyama, 1978; Duchene and Wouessidjewe, 1992).

Native CDs are obtained by the degradation of starch ($\alpha(1 \rightarrow 4)$ linked polyglucose) by α-1,4-glucan-glycosyltransferases. Depending on the respective transferase, different types of CDs result, consisting of 6 (α-CD), 7 (β-CD), 8 (γ-CD) or more $\alpha(1 \rightarrow 4)$ linked glucose units. β-Cyclodextrin is one of the most widely used compound owing a cavity with an internal diameter of 6.5 Å and a depth of 8 Å.

Steric as well as electronic parameters of both the CDs and the guest molecules determine the driving forces of the complexation and the geometries of the inclusion complexes. Many review articles have been published, which give excellent overviews about detailed descriptions of structural properties of CDs and CD complexes (Del Valle, 2004; Dodziuk, 2006; Szejtli, 2004). Particularly, as a consequence of the high importance of CDs in pharmaceutical applications many reviews about pharmaceutical applications have been published (Vyas et al., 2008; Brewster and Loftsson, 2007; Challa et al., 2005; Davis and Brewster, 2004; Frömming and Szejtli, 1994; Loftsson and Duchene, 2007; Rajewski and Stella, 1996).

In CDs all hydroxyl groups of the glucopyranose subunits of the CD molecule are orientated to the exterior of the molecule, with the primary hydroxyl groups located at the narrow rim of the torus and the secondary hydroxyl groups on the wider rim. The CD exterior is therefore hydrophilic, whereas the central cavity, lined with skeletal carbon and ether oxygen atoms of the glucopyranose units, is relatively hydrophobic and comparable to the lipophilicity of an aqueous ethanolic solution (Frömming and Szejtli, 1994). The lipophilic cavity of a cyclodextrin molecule provides a microenvironment into which an appropriately sized nonpolar drug molecule, or more often nonpolar parts of the drug molecule, can enter to form an inclusion complex (Alcaro et al., 2004; Bodor and Buchwald,

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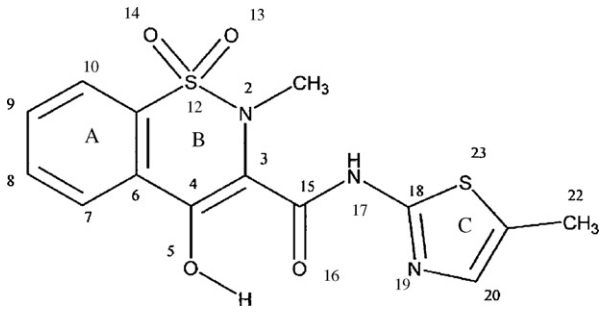

Fig. 1. Enolic conformation of meloxicam (atom numbering for reference only, not systematic).

2002; Connors, 1997; Kozar and Venanzi, 1997; Lawtrakul et al., 2003; Lebrilla, 2001; Liu and Guo, 2002; Rekharsky and Inoue, 1998; Viernstein et al., 2002).

The use of molecular modeling techniques for the study of cyclodextrins was somewhat limited in the past due to the size and flexibility of such molecules (Lipkowitz, 1998). Some studies using molecular calculations based on empirical force field methods or on low-level semiempirical quantum chemical methods have been performed (Liu and Guo, 2004; Liu et al., 1999), but only a limited amount of calculations based on ab initio and DFT methods with suitably high levels of theory and large basis sets, have been reported in the last years (Anconi et al., 2007; Avakyan et al., 2005; Karpfen et al., 2007, 2008; Pinjari et al., 2006, 2007; Snor et al., 2007; Weinzinger et al., 2007). However, the combination of experimental and computational studies has been recognized as a powerful tool for the study of the geometry of complexation.

In continuation of the work of Charumanee et al. (2006) the current study examines the inclusion complexation of meloxicam and β-CD by means of density functional calculations. Meloxicam [4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide] (Fig. 1), belongs to the class of nonsteroidal anti-inflammatory drugs (NSAID) of the enolic acid type of compounds. Previous studies reported the characterization of the stoichiometry and some insights on the 3D geometry of this inclusion complex (Abdoh et al., 2007; Banerjee et al., 2004; Luger et al., 1996; Naidu et al., 2004; Tsai et al., 1993). However, there are no unequivocal conclusions in the literature on the mode of inclusion and the conformation of the drug inside the CD cavity.

Tsai et al. (1993) reported that meloxicam exhibits only one pK_a (4.08) corresponding to the enolic OH. In contrast, Luger et al. (1996) estimated two pK_a values for meloxicam in aqueous solution, at 1.09 and 4.18, corresponding to ionization of the thiazole ring nitrogen and the enolic OH group, respectively. Thus, meloxicam exists as an anion at neutral pH and in weakly basic solutions, and is converted to cationic species at very low pH.

2. Materials and methods

We have analyzed the possible tautomers of all protonation states of meloxicam by DFT methods and have determined the geometries of the inclusion complexes with β-CD.

The initial structure of β-CD was obtained by manually building up the *Z*-matrix starting from the oxygen–oxygen distances of the primary hydroxyl groups at the more narrow rim of the β-CD molecule. The glycosidic oxygens of the CD were placed onto the *XY* plane and their center was defined as center of the coordinate system. Only a single combination of the OH-group orientations was considered (all hydroxymethyl and hydroxyl groups were oriented counterclockwise). This structure with C7 symmetry was then fully geometry optimized without symmetry restriction with a DFT B3LYP/6-31G (d,p) calculation using the program package GAUSSIAN 03 (Frisch et al., 2004). The obtained geometry was taken for further modeling of the inclusion complexes with meloxicam.

2.1. Selection of the tautomers of meloxicam

Four low-energy basic conformations of meloxicam, given in Fig. 2, were used to derive all theoretical possible tautomeric forms of the molecule.

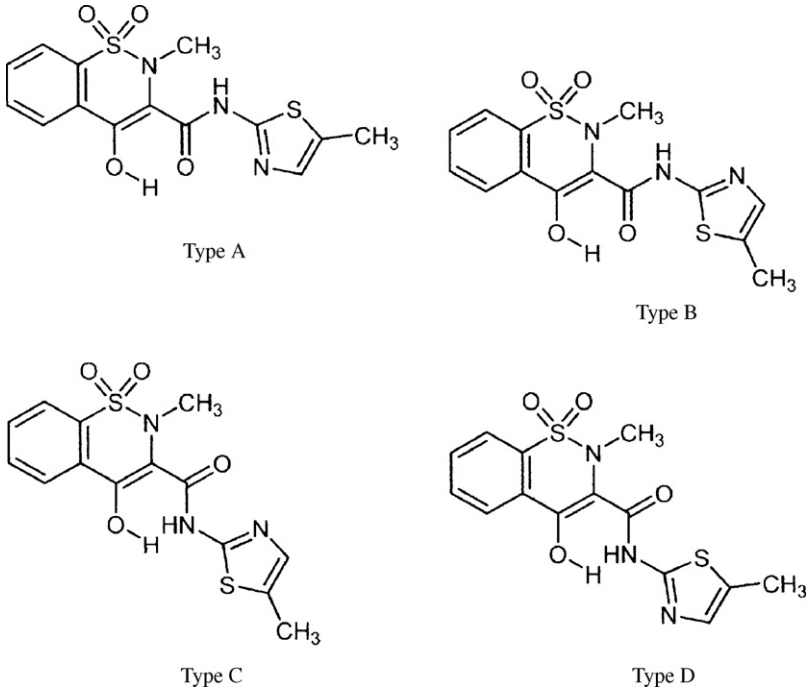

Fig. 2. Basic molecular structures of meloxicam.

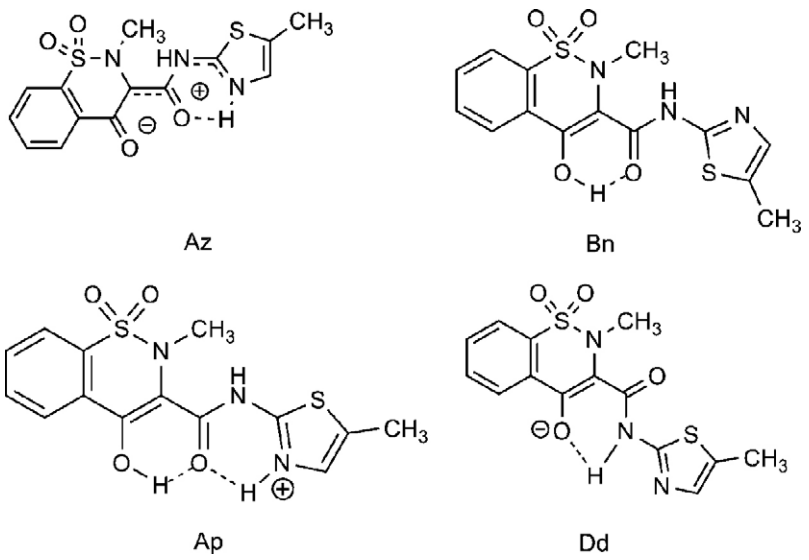

Fig. 3. Structures of the energetically most favourable enolic (Bn), zwitterionic (Az), anionic (Dd) and cationic (Ap) conformation of meloxicam. Hydrogen bonds are indicated by dotted lines.

Each of these possible tautomeric structures was subjected to a 5 ps simulated annealing run, using the MM+ force field and monitoring the three dihedral angles, viz. θ1, defined by C(4)–C(3)–C(15)–N(17), θ2, defined by O(16)–C(15)–N(17)–C(18), and θ3, defined by C(15)–N(17)–C(18)–N(19), respectively. Upon placing the dihedrals θ1, θ2 and θ3 at the positions with the energetically most favoured values, a new structure was created in either case and was fully energy optimized with B3LYP/6-31G (d,p). In this way a total amount of 16 structures was reached.

Out of these 16 structures the energetically most favourable enolic, zwitterionic, anionic (deprotonated) and cationic (protonated) form of meloxicam, viz. Bn, Az, Dd and Ap, respectively (Fig. 3) were used to build up the inclusion complexes with β-CD.

2.2. Force field calculations on the complex geometry

The four energetically most favourable forms of meloxicam were used to create CD inclusion complexes. These meloxicam–β-CD complexes were constructed by manually introducing the meloxicam molecule into the β-CD cavity through the narrow and wide rim of the latter, respectively, centering it on a vector perpendicular to the mean plane through the glycosidic oxygen atoms.

For the complexation process, the CD was kept in this position while the meloxicam approached along the *z*-axis toward the narrow and wide rim of the CD, respectively. Two possible orientations of the guest molecule were considered. The relative position between meloxicam and CD was measured by the distance C3 of the meloxicam guest and the origin. The molecule was initially located at a distance of 10 Å from the origin and was moved in decreasing increments of 2 Å towards the center of the CD cavity. At each step the entire structure was optimized without any restriction, using the United Force Field (UFF) implemented in GAUSSIAN 03. Then the increments were increased and the meloxicam moved away from the CD. Once the meloxicam had been translated to 10 Å beyond the origin, the procedure was terminated. By this procedure local minima can be found and avoided.

2.3. Density functional theory calculations

To construct these inclusion complexes for the optimization with the DFT B3LYP/6-31G (d,p) method the results of the preliminary force field calculations (see Section 2.2) were used. For this purpose the C3 of the meloxicam molecule was placed in each case on the central axis of the CD molecule at a distance from the origin that corresponds to the energy minimum of the force field calculations (Fig. 4).

For the DFT calculation, no constraints were imposed on the whole system, especially no parameters were fixed. So the meloxicam molecule was free to move in the cavity of the β-CD during the whole optimization process. Therefore, conformational changes of the host as well as of the guest molecule were explicitly allowed.

In this way eight complex structures of CD/meloxicam complexes were fully optimized with B3LYP/6-31G (d,p). No restrictions

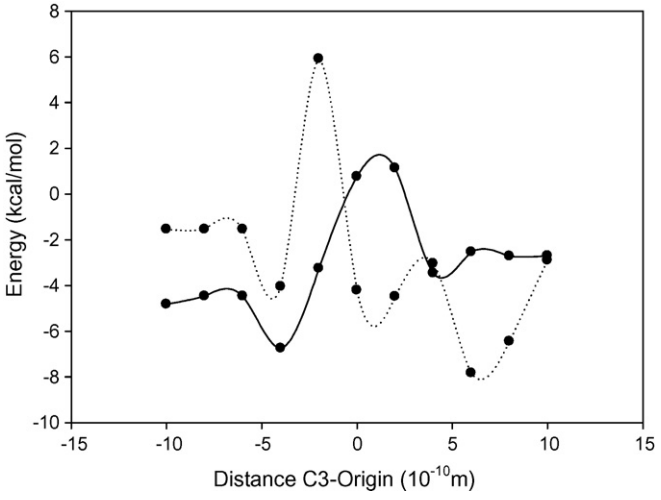

Fig. 4. Calculated force field energies as a function of the internal distance between C3 of the meloxicam guest molecule and the origin. The dotted line corresponds to form 2 of the anionic (deprotonated) complex, and the full line to form 1 of the anionic complex, respectively.

were imposed on the complexes during the geometry minimization process, and no close contacts have been established.

Table 1 lists particular free input parameters before and their respective output values after the optimization process.

The stabilization energy (ΔE) between meloxicam and β-CD was calculated for the minimum energy structure according to

$$\Delta E = E_{\text{complex}} - (E_{\text{meloxicam}} + E_{\beta\text{-CD}})$$

In order to take into account the basis set superposition error (BSSE) correction on the energy determination, the counterpoise (CP) correction (Boys and Bernardi, 1970) was estimated, and, additionally, a full geometry optimization was performed including BSSE correction.

3. Results and discussion

3.1. Force field calculations

As preliminary studies based on empirical force fields systematic conformational searches on the geometry of CD/meloxicam complexes were performed by varying the position of meloxicam inside the cavity. In Fig. 4 the calculated force field energies are plotted as a function of the internal distance between the CD ring and the meloxicam guest molecules.

Only one pronounced energy minimum can be observed for each orientation together with some smaller local minima, which means that the inclusion complexes should have well-defined geometries depending only on the orientation of the inserted molecule. Also the rotation of the molecule inside the cavity leads to a single geometry only.

3.2. Density functional theory calculations

From the 16 tautomeric forms of meloxicam of lowest energy four energetically most favourable enolic, zwitterionic, anionic (deprotonated) and cationic (protonated) forms of meloxicam, viz. Bn, Az, Dd and Ap, respectively (Fig. 3) were used to investigate the inclusion complexes with β-CD. Full geometry optimizations without any constraint with the DFT B3LYP/6-31G (d,p) method were employed in the study of the complexation process of these tautomeric forms of meloxicam with β-CD.

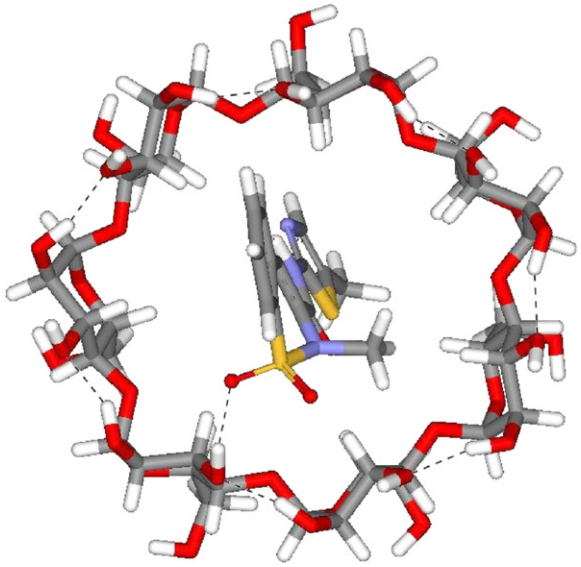

Fig. 5. B3LYP/6-31G (d,p) energy minimized structure of the meloxicam Dd-β-cyclodextrin complex (form 2). View along the *z*-axis. Hydrogen bonds are indicated by dotted lines.

Figs. 5–8 show the top view and side view of the most stable deprotonated (anionic) and neutral (zwitterionic) inclusion complexes, respectively.

3.3. Structural behaviour of the meloxicam–CD complexes

In all complex geometries, a considerable part of the guest molecule is accommodated in the β-CD cavity. The long axis of the meloxicam guests is oriented along the axis of the β-CD, with the B and C rings (Fig. 1) lying within the cavity. Both orientations, form 1 as well as form 2, are energetically possible and lead to conformational minima. The preferred complexation orientation is that one, in which the benzene ring of meloxicam is located near the wider rim with the secondary hydroxyl groups of the CD (form 2). In all cases, the ring of seven hydrogen bonds of the CD, comprising the secondary OH groups at the wider rim, remains unchanged upon complexation.

Table 1
Comparison of particular parameters of various meloxicam guest molecules in their free and complexed form, respectively. θ1, θ2 and θ3 are defined by C(4)–C(3)–C(15)–N(17), O(16)–C(15)–N(17)–C(18) and C(15)–N(17)–C(18)–N(19), respectively. A represents a hydrogen acceptor atom and D a hydrogen donor atom, respectively.

Guest	Complex-form	θ1 (°)	θ2 (°)	θ3 (°)	H-Bond D → A	Length (Å)	Angle, D–H···A (°)
Bn	–	−170.5	178.7	−177.3	O5–O16	1.64	149.0
	1	−169.0	177.6	−177.4	O5–O16	1.71	144.8
	2	−172	−179.3	−178.8	O5–O16	1.67	146.4
Az	–	179.6	−177.3	−179.7	O5–O16	1.58	150.6
					N19–O16	1.87	125.8
	1	174.9	−172.5	−179.2	O5–O16	1.57	151.1
					N19–O16	1.98	120.6
	2	178.3	−177.6	179.4	O5–O16	1.57	150.1
					N19–O16	1.86	126.0
Dd	–	177.9	179.5	−179.2	N17–O5	1.73	140.6
	1	−177.8	174.2	−169.4	N17–O5	1.67	143.0
	2	178.1	178.5	−177.9	N17–O5	1.7	141.5
Ap	–	165.6	−177.6	176.4	N19–O16	1.9	126.7
					O5–O16	1.76	144.2
	1	166.3	−175.5	−168.9	N19–O16	2.16	112.9
					O5–O16	1.81	140.6
	2	166.3	179.5	177.5	N19–O16	1.86	127.6
					O5–O16	1.81	140.0

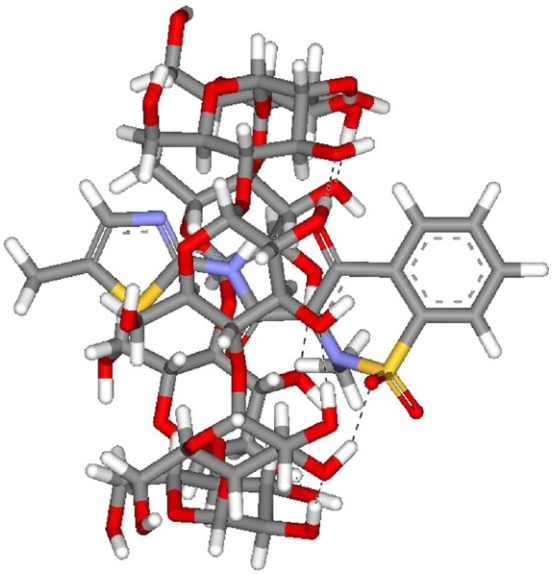

Fig. 6. B3LYP/6-31G (d,p) energy minimized structure of the meloxicam Dd-β-cyclodextrin complex (form 2). View perpendicular to the *z*-axis. Hydrogen bonds are indicated by dotted lines.

Moreover, extra hydrogen bonds are formed between the meloxicam guest and secondary OH groups of β-CD in the case of the anionic and zwitterionic complexes, respectively.

While in form 1 of the anionic complex one extra hydrogen bond has been established between N19 of the meloxicam guest and a secondary OH group of the CD (not shown in the figures), in form 2 of the anionic complex one extra hydrogen bond between O13 of meloxicam and a secondary OH group of CD was observed (see Figs. 5 and 6).

In the case of form 1 of the zwitterionic complex, one extra hydrogen bond was established between N19 of the meloxicam and a secondary OH group of the CD (not shown in the figures). In form 2 of the zwitterionic complex, both sulfur oxygens of the meloxicam guest molecule, viz. O13 and O14, were found to be involved in an extra hydrogen bond to a secondary OH group of the CD (see Figs. 7 and 8), respectively.

Upon complexation, the CD remains basically undistorted. To confirm this, the mean distance of the CD's mass center (centroid) to the seven glycosidic oxygens was calculated in each case. It was found that the extent of variation of this distance was marginal (5.09 ± 0.15 Å). The corresponding values of the uncomplexed CD were 5.11 ± 0.002 Å.

Table 1 comprises a comparison of certain parameters of meloxicam and meloxicam in the cavity of CD complex. The calculated parameters show, that the geometry of the meloxicam guest remains to a great extent undistorted, too.

According to the parameters calculated for the extra hydrogen bonds considered above between the meloxicam guest and secondary OH groups of the CD host in the anionic (deprotonated) and neutral (zwitterionic) inclusion complexes, respectively, these interactions can be classified as moderate hydrogen bonds (Scheiner, 1979). The criteria employed in this classification state that moderate hydrogen bonds are characterized by A···H–D distances between 1.5–2.2 Å and D–H···A angles between ≈130 and 180°, where A represents a hydrogen acceptor and D a hydrogen donor atom, respectively.

As an example, the partial charges on the different atoms of the meloxicam conformation Az have been calculated and are depicted in Fig. 9.

3.4. Energetic behaviour of the meloxicam–CD complexes

To examine the stability of the respective complexes, the stabilization energy was obtained from the difference between the complex energy and the sum of the energy of the isolated host and guest molecules. The calculated stabilization energies for the encapsulation of the meloxicam guest molecules show an overall affinity ranking for the meloxicam guest molecule in the following order: deprotonated form > enolic form ~ zwitterionic form > protonated form.

Table 2 presents the DFT B3LYP/6-31G (d,p) interaction energies (ΔE) of the minimum energy forms of various 1:1 meloxicam–β-CD complexes. The uncorrected and BSSE-corrected energy values are depicted.

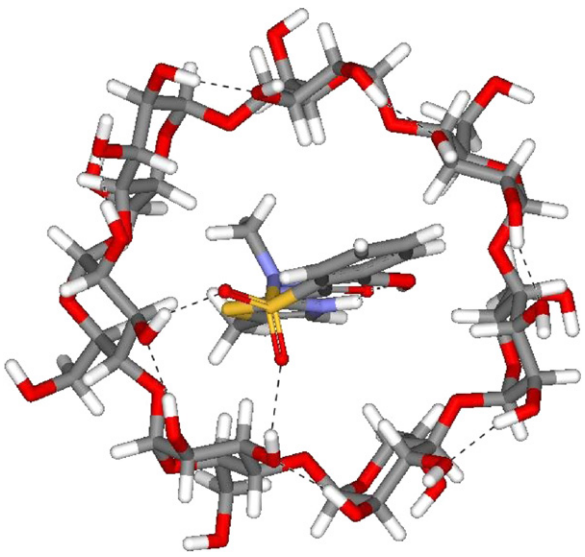

Fig. 7. B3LYP/6-31G (d,p) energy minimized structure of the meloxicam Az-β-cyclodextrin complex (form 2). View along the *z*-axis. Hydrogen bonds are indicated by dotted lines.

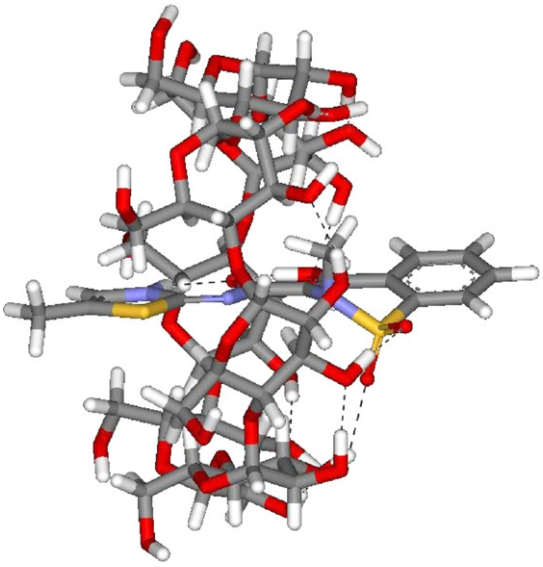

Fig. 8. B3LYP/6-31G (d,p) energy minimized structure of the meloxicam Az-β-cyclodextrin complex (form 2). View perpendicular to the *z*-axis. Hydrogen bonds are indicated by dotted lines.

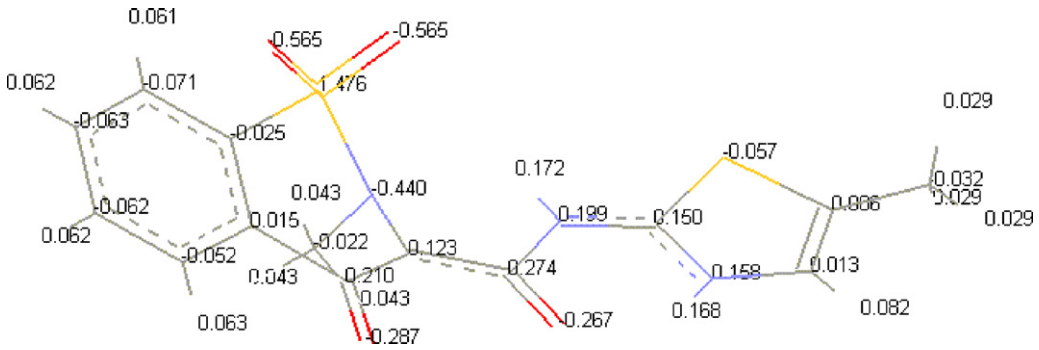

Fig. 9. B3LYP/6-31G (d,p) energy minimized structure of the meloxicam Az tautomer; the partial charges on each atom are depicted.

Table 2
DFT B3LYP/6-31G (d,p) interaction energies (ΔE, kcal/mol) of the minimum energy forms of various 1:1 meloxicam–β-cyclodextrin complexes. The uncorrected and BSSE-corrected energy values are depicted.

Components	Form		
	B3LYP uncorr.	BSSE-energy	B3LYP corr.
β-CD+Bn/1	−3.3	4.79	1.49
β-CD+Bn/2	−9.9	7.53	−2.37
β-CD+Dd/1	−25.8	10.76	−15.04
β-CD+Dd/2	−28.9	8.91	−19.99
β-CD+Ap/1	−3.6	8.71	5.11
β-CD+Ap/2	−5.6	7.45	1.85
β-CD+Az/1	−8.9	7.37	−1.53
β-CD+Az/2	−10.5	11.43	0.93

4. Conclusions

The complexation of neutral, zwitterionic, anionic (deprotonated) and cationic (protonated) meloxicam with β-CD was studied by force field and density functional B3LYP/6-31G (d,p) calculations, in the latter case including a fully optimized Counterpoise correction of the BSSE effect. The application of the DFT method leads to more reliable geometries than the widely used molecular mechanics and semiempirical methods. More possibilities of interactions as Van der Waals forces and H-bonds are taken into account by these accurate calculations, leading to well defined complexes and interaction energies with higher accuracy compared to the other methods.

The tautomeric forms of meloxicam studied here show that they are capable of forming stable inclusion complexes with the host β-cyclodextrin.

The optimized structures of the inclusion complexes reveal an overall affinity ranking for the meloxicam guest molecule in the following order: deprotonated form > enolic form ∼ zwitterionic form > protonated form.

In the case of the deprotonated (anionic) complex, in both forms one extra hydrogen bond has been established between the meloxicam guest and the CD host which may account for the stabilization of these complexes. In the case of the neutral forms of meloxicam, the better stabilization of the zwitterionic form over the enolic form may be contributed to the establishment of two extra hydrogen bonds between host and guest.

Upon complexation, no remarkable distortion of the β-CD host and the meloxicam guest molecules were detected. For the β-CD this was confirmed by comparing the variation of the mean distances between the centroid of the CD and the seven glycosidic oxygen atoms. In the case of the meloxicam guest molecules, certain parameters such as dihedral angles before and after the complexation process have been compared (see Table 1).

Nevertheless, the calculations were performed on molecules in the gas phase. There is, however, a discussion about the binding forces. In water, cyclodextrins are believed to form inclusion complexes that are mostly stabilized by hydrophobic interactions between the unpolar surface inside the cyclodextrin cavity and the surface of the guest. In the gas phase, the energetics that benefit from this arrangement do not exist because there are no water molecules that surround the complex. Consequently, there are no benefits from hydrophobic interactions in the gas phase. Rather, van der Waals forces and, if possible, hydrogen bonding remain.

It should also be mentioned, that the absence of explicit solvent did not allow us to consider the hydrophobic effect in a proper way. Despite this drawback, we still get a favourable interaction energy between the two components of the respective host–guest complexes. The solvophobic effect will further improve the stabilization of the complex. The aryl moieties in the meloxicam molecule, viz., rings A and B, being predominantly hydrophobic in nature should be partially stabilized by the solvophobic effect, while the interaction of the third ring C with β-CD is expected to be guided by the electrostatic effect.

Moreover, stronger interactions can be expected for a host with so many hydroxy dipoles that may arrange in a favourable fashion around a ionic guest. For an optimization of the number of such interactions, it is likely that the guest is located inside the cavity to provide a geometrically reasonable fit between guest and cavity. The conclusion from these considerations is that the complexes exist in solution as well as in the gas phase, but for different reasons.

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