Density Functional Calculations on Meloxicam-β-cyclodextrin Inclusion Complexes

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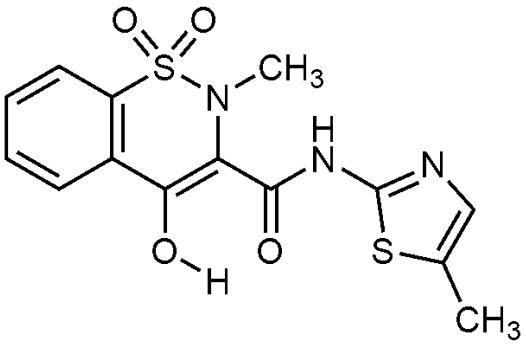
Introduction

β-Cyclodextrin (β-CD) serves as an effective drug delivery system for several nonsteroidal antiinflammatory drugs (NSAIDs) [Loftsson, T. (1999)]. This native CD, obtained from enzymatic degradation of starch consists of seven α-1,4-linked D-glucopyranose units and forms an interior in which small and medium-sized organic molecules can be inserted. The shape of the molecule resembles a truncated cone, with a smaller and a larger diameter opening at the primary hydroxyl and secondary hydroxyl faces of the cyclic sugar network, respectively. The exterior of the molecule is somewhat hydrophilic as a consequence of the hydroxyl groups and the inner cavity is postulated to be hydrophobic to some extent. The internal diameter of the cavity is 6.5 Å and the depth is 8 Å. Because of its ability to form inclusion complexes with various molecules (guests) of appropriate dimension, leading to the modification of some physicochemical properties of the guest, it has found extensive application in the pharmaceutical industry. A very important feature should be mentioned also, this is the rather low toxicity of most of CDs.

Meloxicam (MEL) is a new highly potent NSAID of the enolic acid class of oxicam derivatives. It has a wider spectrum of anti-inflammatory activity, combined with less gastric and local tissue irritation than NSAIDs available prior to its discovery [Luger, P. 1996].



In recent years, CD complexation has been successfully used to improve solubility, chemical stability and bioavailability of meloxicam [Naidu, N. B.(2004)] The major driving forces for the complex formation have been proposed to include the release of entropy-rich water molecules from the cavity, van der Waals interactions, hydrophobic interactions, hydrogen bonding and release of ring strain in the CD molecule.

However, the relative contributions and even the nature of the different forces are not well-known. Due to the limitations of the experimental methods, molecular modeling is frequently used to rationalize experimental findings concerning molecular and chiral recognition by CDs.

Molecular modeling methods of CD complexes are powerful tools for deriving information on the geometry and the interaction energy of the inclusion compounds [Alcaro, S. (2004)].

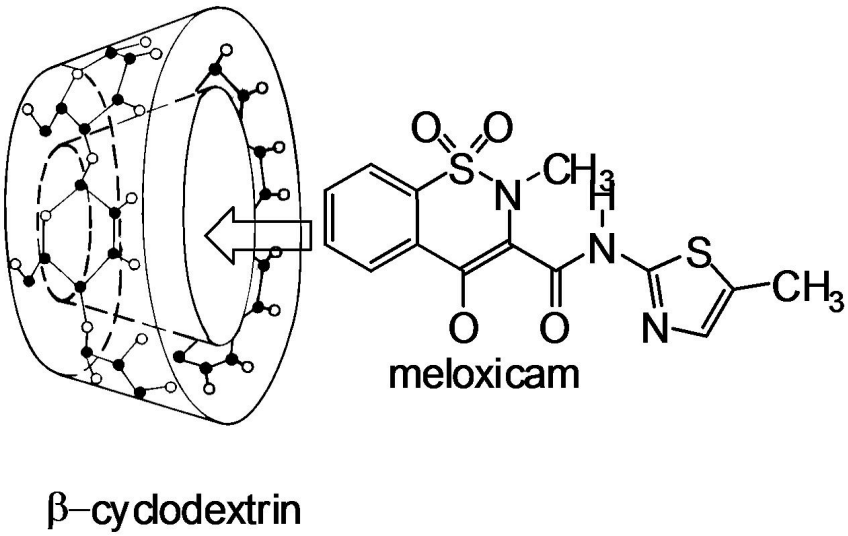
Material and methods

Density functional studies at the B3LYP/6-31G(d,p)-level have been used to calculate the geometries and enthalpies of formation of the inclusion complexes of β-CD with neutral, deprotonated and protonated forms of the nonsteroidal antiinflammatory drug meloxicam .

To find the lowest energy conformations of meloxicam, forty possible tautomeric forms of the drug molecule were constructed and fully geometry optimized. The resulting energetically most favourable conformations of protonated (MEL P), neutral (MEL N) and zwitter ionic (MEL Z) as well as deprotonated (MEL D) forms of meloxicam were used to build up the inclusion complexes with β-CD. In the table the lowest energy geometry is set to zero.

CONFORMER	TYP	E (kcal/mol
MEL P	protonated	0
MEL N	neutral	242.8
MEL Z	zwitter ionic	248.2
MEL D	deprotonated	576.7

For the calculations of the meloxicam/β-CD inclusion complexes two different orientations of the guest molecules in the cavity were considered and energetically minimized.



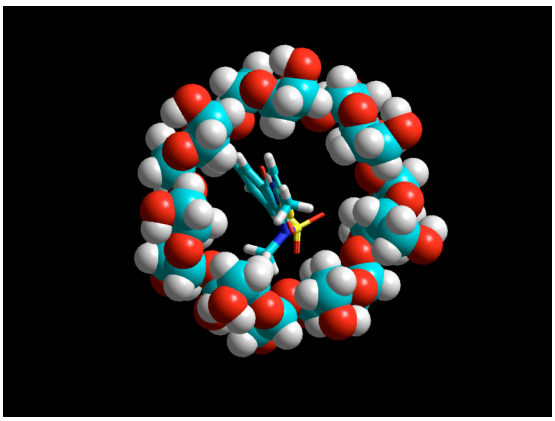
The inclusion complexes were constructed by moving the guest along the z-axis perpendicular to the plane of the cyclodextrin linkage oxygens, entering the host at the wider rim with the benzene ring first (form 1). To define a reproducible relationship between the guest and the CD, the mass centers of both the host and guest were superimposed. The guest molecule was then rotated by 180° and the insertion process repeated in the same way (form 2). The complexes were then fully geometry optimized.

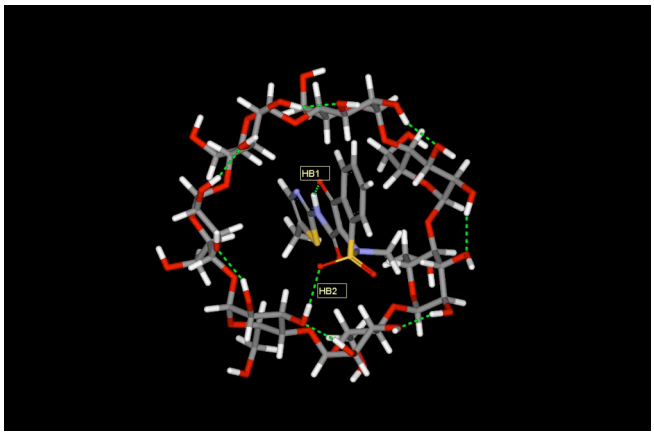
A comparison of the B3LYP/6-31G(d,p) energy differences between host and guest and the corresponding complexes in the minimum energy forms of various β-CD complexes is shown in the next table. Again the lowest energy geometry difference is set to zero.

COMPLEX	FORM	E (kcal/mol)
β-CD + MEL P	1	25.3
β-CD + MEL P	2	23.3
β-CD + MEL N	1	23.5
β-CD + MEL N	2	16.5
β-CD + MEL Z	1	20.0
β-CD + MEL Z	2	23.2
β-CD + MEL D	1	3.1
β-CD + MEL D	2	0

Results and Discussion

These calculations show that in all cases the molecules are located inside the cavity. Both orientations are energetically possible. 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: Deprotonated form > neutral form ~ zwitter ionic form > protonated form.

The stabilization of the complexes is also caused by hydrogen bonding. In the case of the deprotonated structure hydrogen bonds are depicted in the figure.

Conclusions

The application of B3LYP/6-31G(d,p) on CD-inclusion complexes leads to more reliable geometries than the widely used semiempirical methods. Also the interaction energies can be obtained with higher accuracy. Nevertheless, the calculations are performed on molecules in gas phase, neglecting the fact that complex formation results from differences in solvation energies of the host and the guest compared with the solvation energies of the host-guest complex system.

References

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