Effect Of Solvent On The Absorption Spectra
Of Deferasirox

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Abstract: Density functional theory (DFT) and Time dependent density functional theory (TDDFT) calculations have been carried out to study the electronic structure and the UV absorption spectra of deferasirox. The UV spectra have been investigated with inclusion of solvent effect. The B3LYP functional with 6-31G(d,p) basis sets have been used for geometry optimization and also to compute absorption energies. The solvent effects have been included using the polarizable continuum model (PCM). The vertical absorption energies both in gas phase and in polar solvents such as ethanol, methanol and water were computed. The absorption maximum both in gas phase and in polar solvents is discussed in terms of electrostatic interaction energy, oscillator strength and dipole moment.
Keywords: DFT; TDDFT; 6-31G(d,p); PCM; Deferasirox.

Introduction

Deferasirox is a rationally-designed[1] oral iron chelator. Its main use is to reduce chronic iron overload in patients who are receiving long-term blood transfusions for conditions such as beta-thalassemia and other chronic anemias.[1-6] It is the first oral medication approved in the USA for this purpose.[6] Deferasirox is chemically [4-[(3Z,5E)-3,5-bis(6-oxo-1-cyclohexa-2,4-dienylidene)-1,2,4-triazolidin-1-yl]benzoic acid with a molecular formula $C_{21}H_{15}N_3O_4$ and molecular weight of 373.362 gm/mol.

The density functional theory (DFT)[7] with B3LYP[8, 9] functional combined with 6-31G(d,p)[10-12] basis sets are most use full to optimize the geometries of molecules. The Time-Dependent Density Functional Theory (TDDFT)[13-15] has been used to simulate the electronic absorption spectra of free molecules. The calculated excitation energies are well agreed with experimental data for various compounds. Moreover, the inclusion of solvation effect *via* a PCM[16-19] model tends to change the excitation energies, due to a stabilization of the LUMO orbital. Thus, the location of the first absorption band and the energy of the HOMO orbital were used as parameters to evaluate the absorption maximum (λ_{max}). The absorption maximum is an important parameter of the UV spectrophotometric methods in pharmaceutical formulations especially in quantitative estimation.[20-25]

In this work, the absorption maxima of deferasirox both in gas phase and in polar solvents such as ethanol, methanol and water are simulated using the DFT/TDDFT method.

Computational Details

Deferasirox molecule was modeled using Avogadro.[26] The ground state geometry was optimized using DFT/B3LYP hybrid functional with 6-31G(d,p) basis sets. The effects of the solvents (ethanol, methanol and water) were added using the polarizable continuum model (PCM) of solvation. The optimized geometries are utilized to get the frontier orbitals and to carry out the TDDFT studies. λ_{max} of deferasirox is calculated at the level of TDDFT/6-31G(d,p). All calculations are performed using GAMESS-US software suit.[27,28] Molecular

orbitals were plotted using wxMacMolPlt[29] and UV spectra were plotted using Gabedit[30].

Results and discussion

The optimized structure of the deferasirox has non-planar geometries, as can be seen in Fig. 1. Table 1 list the various torsion angles. Plane of the benzene ring of C17,C19,C20,C21,C22,C23 is twisted by -41.58° from C26-N30 and -46.83° from C29-N30, respectively. Fig. 2 displays the highest occupied molecular orbitals (HOMO), lowest unoccupied molecular orbitals (LUMO) and their computed isodensity surfaces. Both HOMO and LUMO show -character. LUMO are localized on C1, C2, C4, C6, C8, C10 ring, where as HOMO are localized on N28, N29, benzene rings of C11,C12,C13,C14,C15,C41 and C17,C19,C20,C21, 22,C23. This is desirable and leads to the intra-molecular charge separation upon excitation (push-pull effect).

The dipole moment of the free deferasirox molecule is 3.381 Debye and it increases to fivefold in the exited state. The interaction energy between deferasirox molecule with solvent molecules (fourth column of Table 2) is negative in polar solvents. The excited state dipole moment of deferasirox molecule in polar solvents is decreased and the total dipole moment of the system including PCM surface charge effect is slightly increased (sixth and seventh column of Table 2). The change in electronic charge distribution between HOMO and LUMO is also indicative of a large dipole moment and is the possible reason for the increase in oscillator strength (fifth column of Table 2) for the HOMO LUMO transition in polar solvents. The large dipole moment of deferasirox molecule in the excited state is additionally stabilised by polar solvent molecules that leads to the slight increase in the excitation energy and the corresponding blue shift of the spectral maximum.
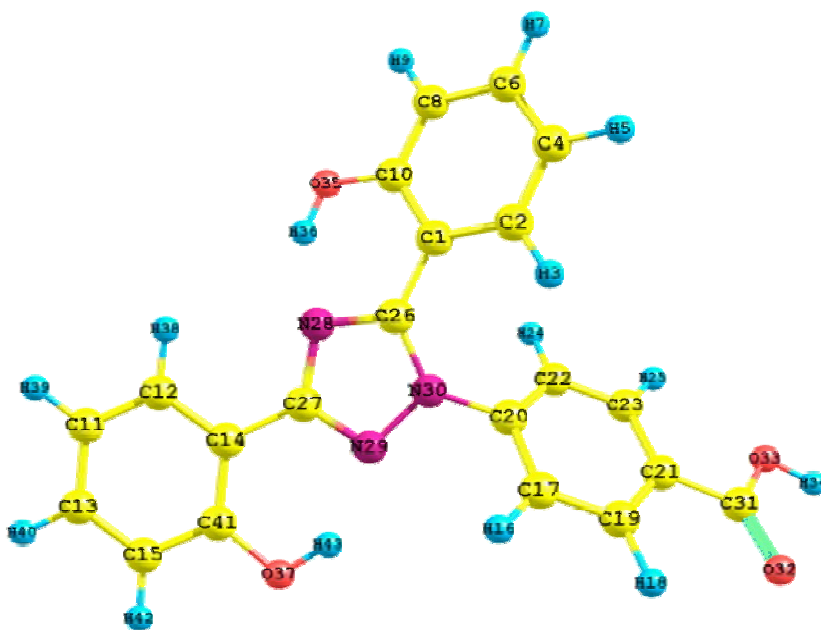

Fig. 1. Optimized structure of deferasirox. Yellow-C, Red-O, Magneta-N and Cyan-H

Table 1. Torsion angles

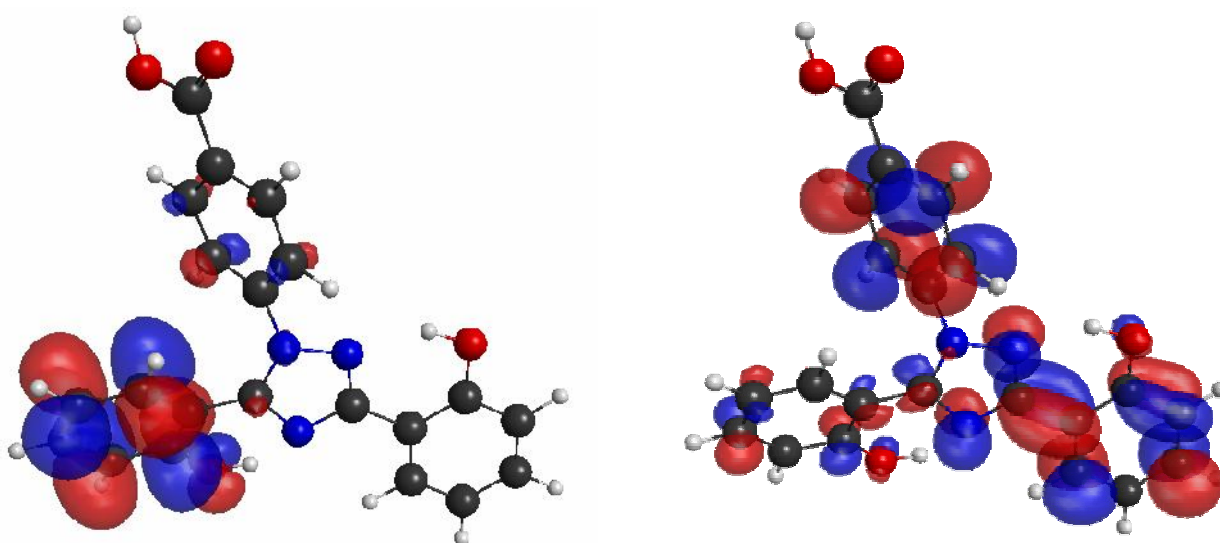| Sl. No	Chain	Angle(°)
1	C26-N30-C20-C22	-41.58
2	C29-N30-C20-C17	-46.83
3	N30-C26-C1-C2	-23.56
4	N28-C26-C1-C10	-23.01
5	N29-C27-C14-C41	-2.01
6	N28-C27-C14-C12	-1.90

Fig. 2. The Molecular orbitals of deferasirox. LUMO (top) and HOMO (bottom).

The computational UV absorption spectra of deferasirox in gas phase and in polar solvents are shown in the **Fig. 3.** Spectra show a similar profile in all phases; they present intense bands in polar solvents than in gas phase. The spectra show absorption energies corresponding to the λ_{max} of 359.06, 358.96 and 358.65 nm in ethanol, methanol and water, respectively. In isolated state, the spectrum presents the absorption peak at 376.05 nm. It can also be observed that the λ_{max} is nearly equal in polar solvents. (Table 2 and Fig. 3.).

energy calculation shows blue shift of λ_{max} in the presence of polar solvents. The absorption intensity of deferasirox molecule in isolated state is considerably lesser as compared with the absorption intensities in polar solvents. It has been observed that the λ_{max} is nearly equal in ethanol, methanol and water.

Conclusions

In this study UV absorption energy of deferasirox in isolated state and in polar solvents has been carried out using DFT/TDDFT *via* the PCM model for solvation. From the results, some parameters such as excitation energy, oscillator strength, electrostatic interaction energy, dipole moment of deferasirox have been chosen to evaluate λ_{max}. Absorption

Table 2. λ_{max} corresponding to TDDFT absorption energy, electrostatic interaction energy, oscillator strength (*f*), dipole moment (D_D) of deferasirox in isolated state and in polar solvents, and total dipole moment (D_T) of solvated deferasirox.

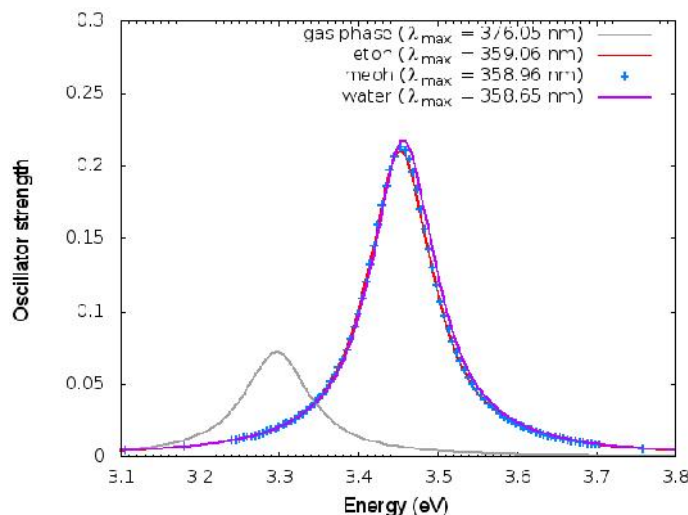| Isolated state/ Solvent	λ_{max} (nm)	E (eV)	Electrostatic interaction energy (kCal/mol)	*f*	D_D (Debye)	D_T (Debye)
Isolated state	376.05	3.297	-	0.072	15.333	-
Ethanol	359.06	3.453	-10.52	0.211	13.648	16.021
Methanol	358.96	3.454	-10.66	0.213	13.619	16.008
Water	358.65	3.457	-10.90	0.218	13.568	15.983

Fig. 3. Calculated UV absorption spectra of deferasirox.

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