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A combined TD-DFT and spectroscopic investigation of the solute–solvent interactions of efavirenz

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ABSTRACT

Efavirenz, commercially known as Sustiva® or Stocrin®, is a first-line antiretroviral treatment for HIV/AIDS. The clinical efficacy of efavirenz is, however, hindered by its solubility. We sought to investigate the solute–solvent effects of efavirenz by means of a combined qualitative study implementing UV–visible spectrophotometry, ^{1}H NMR spectroscopy and time-dependent density functional theory (TD-DFT) calculations. The UV spectrum displayed two main absorbance maxima, band I and band II at 246–260 and 291–295 nm, respectively. A general bathochromic shift was noticed from the non-polar solvent cyclohexane to the most polar solvent DMSO (≈13.69 nm) in band I and a smaller bathochromic (≈2.17 nm) and hyperchromic shift was observed in band II. We propose that these observations are due to the role of the amino (NH) and carbonyl (CO) functionalities which induce charge-transfer and intra- and inter-molecular hydrogen bonding. The aromatic and amine protons showed the most deshielded effects in the observed chemical shifts (δ) in the more polar DMSO-d_6 solvent relative to $CDCl_3$. The ^{1}H NMR chemical shifts observed are due to the increased delocalization of the lone pair electrons of the amino nitrogen with increased polarity of the more polar DMSO solvent. The theoretical reproduction of the UV and ^{1}H NMR spectra by means of TD-DFT is in good agreement with the experimental results.

1. Introduction

Efavirenz, commercially known as Sustiva® or Stocrin® (Fig. 1), is a first-line antiretroviral treatment for HIV/AIDS [1]. Efavirenz is characterized by its benzoxazine scaffold and hydrophobic cyclopropane functionality which renders it a class 2 compound on the biopharmaceutical classification system (BCS). This entails low aqueous solubility, but high lipophility and permeability, which reduces oral bioavailability leading to decreased clinical efficacy [2]. The development of new alternative approaches to improve the bioavailability of poorly soluble active pharmaceutical ingredients (APIs), like efavirenz, has become a fundamental part of research and development within the pharmaceutical industry. This becomes more challenging as we move towards greener methods of chemistry with the utilization of less hazardous, water miscible organic solvents. Green chemistry syntheses can be applied to improve solubility but these reactions are dependent on the physical characteristics of the solvent. The solvent has an overall influence on the structure and conformational flexibility, which consequently has an effect on the chemical reactivity and reaction rate of the solute [3–6].

Most reactions occur in solution so before any reaction is performed an investigation into the effect of solvent polarity on the solute is an integral factor. Solvent polarity comprises all intermolecular interactions the solvent is capable of, such as specific (hydrogen bonding and charge-transfer interactions) and non-specific (dielectric effects) interactions. The solvent, additionally, serves as a potential reactant which modifies the chemical reactivity of a compound and produces an array of unwanted products. Furthermore, the complexity of the solute-solvent interactions of efavirenz is amplified due to its abundant hydrogen bonding sites, molecular flexibility which leads to structural rearrangements, as well as the possibility of amide-imidol interconversion which are all dependent on solvent polarity [7–10].

Efavirenz is a polycyclic aromatic hydrocarbon containing benzene and oxazinan-2-one chromophores. UV–visible spectrophotometry can thus be applied to investigate the solvent influence on the spectral profile of efavirenz. Efavirenz, can potentially also give rise to intramolecular charge-transfer (ICT) states as it has adjacent acceptor (carbonyl) and donor (amino) functionalities. The solute, consequently, interacts with the hydrogen bond acceptor (β) or donor abilities (α) of the solvent [11]. The solvent polarizability (π*) indicates the extent of charge stabilization or dipole in a medium. These values are approximately proportional to the molecular dipole moments calculated by TD-DFT [12–17]. Time-dependent density functional theory (TD-DFT) methods have effectively been used to reproduce experimental electronic absorption spectra, i.e. the UV–visible spectra, and the ground and excited electronic states of efavirenz were predicted in the gaseous phase [18] and in methanol for which an experimental comparison was made [19]. Further spectroscopic analysis of the solute-solvent interactions of efavirenz can be done via solvent-induced chemical shift deviations observable in the ^{1}H NMR spectra [20].

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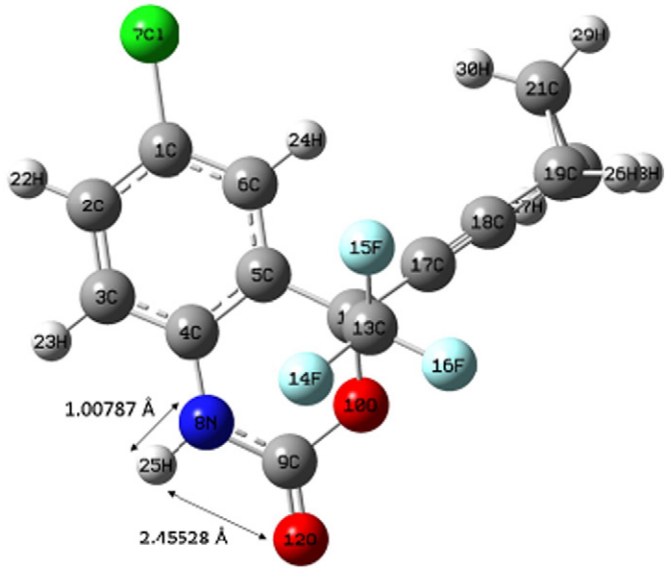

Fig. 1. Structure of efavirenz.

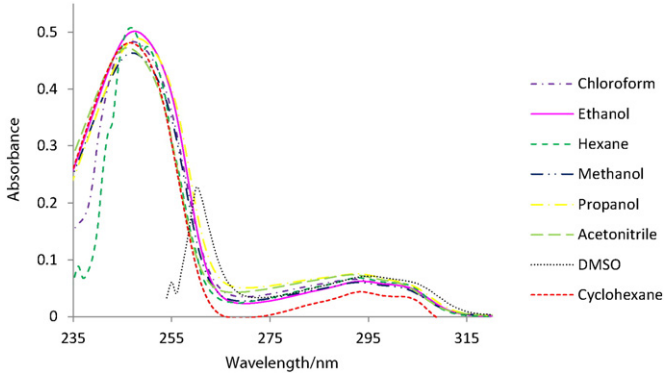

Fig. 2. Experimental UV spectra of efavirenz in polar protic, aprotic and nonpolar solvents.

In this study, a combined qualitative approach, by means of UV–visible spectrophotometry, ^{1}H NMR spectroscopy and TD-DFT calculations with the polarizable continuum model (PCM) to simulate bulk solvent effects, was applied to investigate the solute-solvent interactions of efavirenz. The solute-solvent interactions are discussed in terms of the charge transfer ability, excitation energies (eV), dipole moment (μ), absorption wavelength (λ) and chemical shift (δ) of the solute.

2. Experimental

2.1. Materials

A 98% pure efavirenz standard (SML0536) was supplied by Sigma Aldrich (South Africa) and obtained as a gift from Professor Thirumula Govender of the University of KwaZulu-Natal, Durban, South Africa. All the solvents used were of AR-grade and were purchased from Merck and used without further purification.

2.2. Experimental Procedure

UV–visible spectra were recorded on a Perkin Elmer Lambda 35 dual-beam UV–visible spectrophotometer in 1.0 cm quartz cells. The spectra were obtained over a wavelength range of 200–500 nm. All spectra were corrected for the solvent background by calibrating the instrument with the blank solvent and the spectra were recorded in duplicate. The concentration of efavirenz in each of the solvents was approximately 0.006 mol dm^{-3}.

NMR spectra were recorded on Bruker 400 MHz spectrometer. Efavirenz was dissolved in the following deuterated solvents: chloroform ($CDCl_3$), methanol (CD_3OD) and dimethylsulfoxide (DMSO-d_6) (all purchased from Aldrich), and was placed in 5 mm NMR tubes and run at 298 K.

2.3. Computational method

The conformations of efavirenz were generated by using the Generate Conformations algorithm embedded in Discovery Studio [21]. The full optimization of the lowest energy conformation of efavirenz was subsequently performed by using Becke's three parameter exchange-functional (B3) [22] and the gradient-corrected correlation functional of Lee, Yang and Parr (LYP) [23] with implementation of the 6-311 g + (2d,p) basis sets, in the Gaussian 09 programme package [24]. The polarized continuum model (PCM) model [25] with the integral equation formalism (IEF-PCM) embedded in the Gaussian programme was used to reproduce the effect of the solvents analysed. The true energy minima in each calculation were further verified by frequency calculations on the optimized geometry. The electronic transitions of the drug were calculated at the 6-311 g + (2d,p) level. The visualization of HOMO-LUMO orbitals was performed with Gauss View. The proton NMR chemical shifts of efavirenz (in $CDCl_3$, DMSO-

Table 1
Experimental (λ_{max}) and DFT computed (λ_{DFT}) wavelengths of maximum absorption, the electronic transitions, oscillator strength (*f*), dipole moment (μ) and excitation energy of efavirenz in different solvents.

Solvent	λ_{max}/ nm	λ_{DFT}/ nm	*f*	Electronic transitions	Excitation energy/ eV	μ/D
Cyclohexane	246.54	249.13	0.30	H → L + 2 (86%)	4.9767	4.60
	293.00	274.16	0.05	H → L (5.6%)		
n-Hexane	246.73	249.13	0.30	H → L + 2 (86%)	4.9756	4.63
	293.08	274.13	0.05	H → L (5.7%)		
Chloroform	247.11	249.47	0.30	H → L + 2 (85%)	4.9700	5.07
	291.71	275.81	0.06	H → L (6.1%)		
Propanol	248.01	249.34	0.29	H → L + 2 (83%)	4.9726	5.40
	292.53	276.02	0.06	H → L (6.2%)		
Ethanol	247.44	249.24	0.29	H → L + 2 (83%)	4.9744	5.42
	293.57	275.94	0.06	H → L (6.2%)		
Methanol	247.03	249.11	0.28	H → L + 2 (82%)	4.9771	5.45
	292.70	275.84	0.05	H → L (5.9%)		
Acetonitrile	245.97	249.18	0.28	H → L + 2 (82%)	4.9756	5.45
	291.43	275.86	0.06	H → L (5.9%)		
DMSO	260.23	249.50	0.30	H → L + 2 (83%)	4.9693	5.47
	295.17	278.98	0.06	H → L (7.4%)		