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Theoretical-experimental study of metronidazole solvatochromism

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INTRODUCTION & AIM

Metronidazole (MTZ) is a nitroimidazole antimicrobial widely used to treat various anaerobic bacteria and protozoa infections.
MTZ is a small lipophilic molecule with an oral bioavailability higher than 90 % (Figure 1).
An analytical theoretical-experimental solvatochromic study of MTZ that improves its pharmacokinetics understanding has not been done yet.
The aim of this research is to experimentally and theoretically study the MTZ solvatochromic behavior.

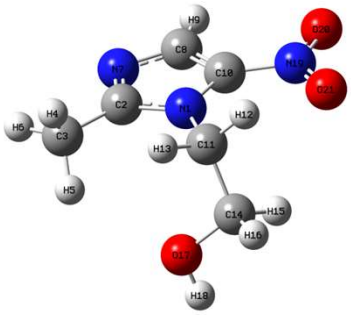

Figure 1. MTZ conformer obtained by B3LYP6-311+G(d,p) *ab-initio* calculation.

METHOD

To perform the experimental research twelve pure solvents: two non-polar (*n*-hexane and benzene), six polar aprotic (diethyl ether, dichloromethane, chloroform, ethyl acetate, acetonitrile and dimethyl sulfoxide), four polar protic (2-propanol, *n*-butanol, ethanol and methanol), and buffer pH 7.4 were chosen.
The spectrophotometric study was performed with $1x10^{-5}$ M MTZ solutions.
The theoretical UV–Vis spectra of MTZ were obtained using the TD-DFT B3LYP and CAM-B3LYP methods, combined with the PCM model in its IEFPCM formalism and the 6-311+G(d,p) basis set.
Kamlet and Taft, Catalán and Laurence multiparametric equations were utilized to analyze the effect of the solvent environment on MTZ.
Kamlet and Taft equation:

$$A = A_0 + s\pi^* + a\alpha + b\beta$$

Catalán equation:

$$A = A_0 + c_{SP}SP + d_{SdP}SdP + a_{SA}SA + b_{SB}SB$$

Laurence equation:

$$A = A_0 + di\ DI + e\ ES + a_1\ \alpha_1 + b_1\ \beta_1$$

RESULTS & DISCUSSION

Both, the experimental and theoretical analyses exhibit positive solvatochromism.
The mayor Kamlet and Taft's relative contribution was from non-specific π^* interactions, accounting for 65 %. Catalán and Laurence equations showed that these non-specific contributions were mostly due to polarizability and dispersion forces (65 % SP and 72 % DI). While hydrogen-bond specific interactions were much less relevant: 35 % β, 16 % SB, and 20 % β_1.

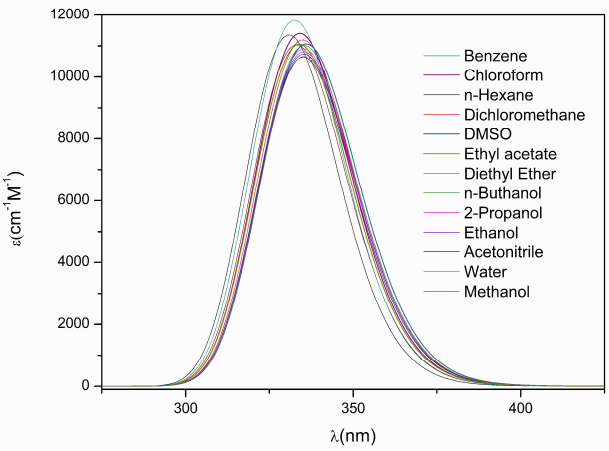

Figure 2. Theoretical UV-Vis spectra of MTZ calculated by ab-initio TD-DFT B3LYP.

All calculated maximum wavelengths (Figure 2), which correspond to the electronic transitions of the second singlet states for MTZ, were from HOMO to LUMO.
These results show that polarizability rises significantly in polar solvents, reflecting enhanced electron cloud distortion, besides the high polarity of MTZ.
Greater polarizability typically correlates with increased permeability through biological membranes, as the molecule can interact more effectively with the lipid environment and adapt to changes in polarity between the aqueous medium and the lipid bilayer membrane.

CONCLUSION

The obtained results provide further evidence suggesting that MTZ can easily penetrate microbial cells through passive diffusion.