

MODELING NMR PARAMETERS OF OXIMES IN WATER AND IONIC LIQUIDS – IMPLICATIONS OF SOLVATION SHELL STRUCTURE

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Abstract: Organophosphophorus compounds (OP) has been widely used as pesticides and as warfare nerve agents. They act by phosphorylating the hydroxyl group of the Ser 203 residue of the Acetylcholinesterase (AChE) active site, inhibiting its catalytic activity, causing the cholinergic Syndrome [1]. Currently, the OP poisoning treatment consists in the use of reactivators, for example oximes, a class of compounds that is able to reactivate the inhibited enzyme [2]. Typically, expensive techniques are employed for the detection of OPs, such as GC and HPLC, but new techniques have been developed for this purpose using sensors, biosensors and electrolytes [3]. Currently, the use of ionic liquids (IL) as reactional medium for these sensors is little explored, but very promising [4]. In this sense, modern spectroscopic techniques, such as NMR Spectroscopy seems to be adequate for the characterization of this system [5]. In line with that, this work aims to investigate the solvent and thermal effects on NMR parameters of oximes in two different solvents, water and 1-Butyl-3-methylimidazolium tetrafluoroborate (BMIM-BF₄). By using the OPLS force field in the GROMACS 4.6.510 program, 10 ns of classical molecular dynamics simulations were performed the for oxime 3-fluoro-4-[(hydroxyimino)methyl]-1-methyl-pyridinium (3-Fluoro-4-PAM) (Figure 1) in water and ionic liquid.



Figure1 Structures of 4-PAM and 3-Fluoro-4-PAM, respectively.

Ab Initio MD simulations were also performed at the B3LYP/6-31G level at 310K. For NMR calculations, the GIAO method was employed for both dynamics and static systems. Molecular docking calculations between studied oximes and the AChE enzyme, PDB code 5HFA, were performed with the Molegro Virtual Docker software. Finally, theoretical calculations with 4-PAM (Figure 1) were employed to compare with experimental data and to validate the theoretical strategy.

From our theoretical findings, it was possible to notice that the ¹³C chemical shift values are good agreement with experimental data [6] for the level of approximation δ^{310K} [(H₂O//B3LYP/H₂O), as shown in Table 1.

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Table 1: Experimental [6] and theoretical ¹³C NMR chemical shifts (ppm) for 4-PAM.

Level of approximation ⁺	δ^{13} C						
	C1	C2	C3	C4	C5	C6	C7
δ Experimental	146.4	125.3	148.5	125.3	146.4	146.6	49.3
δ_{e} (//B3LYP)	145.4	129.9	144.5	132.1	146.2	145.1	53.1
δe [//B3LYP/PCM(H ₂ O)]	147.4	130.9	144.5	131.9	147.8	147.8	53.8
δ_e (//B3LYP/H ₂ O)	153.6	130.2	145.0	131.2	143.7	146.2	51.2
δe [PCM(H2O)//B3LYP/PCM(H2O)]	147.9	131.7	144.3	131.9	147.5	148.3	52.7
δe (H2O//B3LYP/H2O)	144.4	116.7	122.7	119.9	143.9	186.0	32.7
δ ^{310K} (//B3LYP)	147.1 ± 5.6	128.9 ± 6.4	142.8 ± 4.2	129.6 ±5.9	147.5 ±5.9	149.2 ± 5.9	50.4 ± 4.5
δ ^{310K} [PCM(H2O)//B3LYP/PCM(H2O)]	143.5 ± 3.8	127.2 ± 2.7	145.7±2.0	130.5 ± 2.4	144.0 ± 2.9	146.2 ± 3.9	51.2 ± 3.0
δ ^{310K} [(H ₂ O//B3LYP/H ₂ O)	145.9 ± 3.2	125.2 ± 3.8	148.0 ± 3.7	125.9 ± 3.9	146.9 ± 2.9	147.5 ±2.9	50.4 ± 2.9

⁺Notation 'level of chemical shift computation//level of geometry optimization or MD simulation'

Now, the results considering the ¹⁹F NMR chemical shifts for 3-Fluoro-4-PAM is described in Table 2.

Table 2: theoretical ¹⁹F NMR chemical shifts (ppm) for 3-Fluoro-4-PAM in H₂O and BMIM-BF4.

Level of aproximation	¹⁹ F	
δ_{e} [AChE //B3LYP]	-64.0	
$\delta_{e}(//B3LYP)$	-147.4	
δ_{e} [//B3LYP/PCM(H ₂ O)]	-147.4	
$\delta_{e}(//B3LYP/H_{2}O)$	-151.5	
δ_{e} [PCM(H2O)//B3LYP/PCM(H ₂ O)]	-137.6	
δe (H2O//B3LYP/H2O)	-140.9	
δ_{e} (BMIM-BF4//B3LYP/BMIM-BF4)	-171.3	
δ^{310K} (//B3LYP)	-193.5 ± 4.7	
δ^{310K} [PCM(H2O)//B3LYP/PCM(H2O)]	$\textbf{-195.2} \pm 4.1$	
δ^{310K} (H ₂ O//B3LYP/H ₂ O)	-207.3 ± 5.9	
δ^{310K} (BMIM-BF4//B3LYP/ BMIM-BF4)	-213.4 ± 5.3	

On going from δ^{310K} (BMIM-BF4//B3LYP/ BMIM-BF4) to δ_e [AChE //B3LYP], the ¹⁹F NMR chemical shift changes from -213 to -64 ppm for 3-F-4-PAM, respectively. The values obtained corroborate with those reported by Lindon and Wilson (2015) and reveal that it is essential to incorporate the dynamics and solvent effects in NMR calculations in the condensed phase.

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