Journal of Physical and Theoretical Chemistry
of Islamic Azad University of Iran, 12 (1) 69-75: Spring 2015
(J. Phys. Theor. Chem. IAU Iran)
ISSN 1735-2126

Theoretical study of structure spectral properties of Tacrine as Alzheimer drug

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Received August 2014; Accepted February 2015

ABSTRACT

Tacrine (9-amino-1,2,3,4-tetrahydroacridine) as a reversible inhibitor of acetylcholinesterase (AChE), was the first drug for the symptomatic treatment of Alzheimer's disease (AD). NMR structure determination still presents some considerable challenges: the method is limited to systems of relatively small molecular mass, data collection times are long, data analysis remains a lengthy procedure, and it is difficult to evaluate the quality of the final structures but calculation of a structure itself has become extremely rapid, and new labeling methods have significantly improved both spectral quality and automated analysis, whilst rigorous standards and data formats afford compatibility of different software packages. In this theoretical study, we used HF and DFT (BLYP, B3LYP) method for chemical shift nucleus magnetic resonance DFT-NMR. The basis set used were 6–31G, 6–31G** and 6-31G++. The results show a reasonably good correlation between calculated and experimental chemical shifts. Agreement of experiment and calculated data suggesting that studies of drug structures can be pursued with some degree of confidence with this level of theory.

Keywords: Tacrine; Alzheimer's disease; DFT-NMR; Basis set

INTRODUCTION

Dementia is the most common psychiatric disorder of old age, and Alzheimer's disease (AD) [1] is its most common cause. Alzheimer's disease (AD) involves the degeneration of cholinergic neurones in the cerebral cortex and hippocampus, areas of the brain particularly associated with memory, higher intellectual functioning, and consciousness [2]. The biochemical deficits also extend into other neurochemical systems, affecting the levels of monoamine transmitters for example [3], but the most profound and consistent loss is that of cholinergic and glutamatergic transmission.

Tacrine (9-amino-1,2,3,4-tetrahydroacridine or THA) is a reversible inhibitor of acetylcholinesterase (AChE), and was launched in 1993 as the first drug for the symptomatic treatment of Alzheimer's disease (AD) [4,5]. However, the use of tacrine in AD has been limited by serious side effects such as hepatotoxicity, which often forces patients

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to discontinue treatment [6-8]. Tacrine has also been shown to possess a much broader pharmacological profile than cholinesterase inhibition: blockage of potassium channels [9,10] inhibition of neuronal monoamine uptake processes [11], and inhibition of monoamine oxidase [12] have all been reported.

Although the concept of a relationship between the chemical structure of a chemical compound and its biological activity appeared several years ago, prediction of the compound activity on the basis of its structural stability still comes across serious difficulties. Moreover, it was understood that the chemical structure of a compound and its physical and chemical properties has significant influence on its activity both therapeutic and toxicity [13].

Modern computational chemistry methods, especially DFT, have proven to be excellent tools for determining molecular structures [14]. All calculations have been in the gas phase, while gas phase predications are appropriate for many purposes and inadequate for describing many systems in solutions. Solvent effects on electronic structure of molecules have been investigated by many chemists and physicists to understand molecular structure, mechanism of chemical reactions in solution etc. by using quantum chemical calculations and molecular dynamics simulations. Physical properties such as geometry of molecules and charge distribution in solution often vary from those in vacuum [15]. IR absorption spectroscopy has been applied to elucidate a drug structure by overcoming these problems experimentally and theoretically. Recently, such capabilities have been broadened to span spectroscopic properties such as NMR chemical shifts and couplings. DFT calculations can predict ^{13}C and ^{1}H-NMR chemical shifts to a degree of accuracy that has enabled researchers to sort out many issues in the structural elucidation of complex organic molecules such as natural products [16-18].

For better understanding the relationship between the chemical structure, physical and chemical properties of Tacrine and its biological activity we performed theoretical investigation on Tacrine.

The geometric optimizations and calculation of ^{13}C and ^{1}H-NMR chemical shifts were done on Tacrine using density functional theory (DFT). We have reported non empirical calculation of ^{13}C and ^{1}H-NMR chemical shifts of tacrin in chloroform as solvent.

COMPUTATIONAL ANALYSIS

NMR Parameters

The calculation of NMR parameters using semi-empirical, ab initio and DFT techniques has become a major and powerful tool in the investigation to look at how variations in the molecular structure occurs. The ability to quickly evaluate and correlate the magnitude and orientation of the chemical shielding anisotropy tensor with variations in bond length, bond angles and local coordination and nearest neighbor interactions has been a number of recent applications in the investigation of molecular structure. Nuclear magnetic resonance (NMR) was shown that it is possible to calculate chemical shifts of Individual amino acid residues of proteins without a detailed knowledge of the complete protein structure. The calculations also provide valuable information for exploring the experimental NMR chemical shifts with the molecular geometry and environment. Also NMR chemical shifts are quite sensitive to intermolecular interactions .

NMR is based on the quantum mechanical property of nuclei. The chemical shielding refers to the

phenomenon which associated with the secondary magnetic field created by the induced motions of the NMR is an ideal tool for investigating the structural elucidation of complex organic molecules such as natural products. The ab initio calculation of nuclear magnetic shielding has become an indispensable aid in the investigation of molecular structure and accurate assignment of NMR spectra of compounds [14]. NMR is based on the quantum mechanical property of nuclei. The chemical shielding refers to the phenomenon which associated with the secondary magnetic field created by the induced motions of the electrons that surrounding the nuclei when in the presence of an applied magnetic field.

For chemical shielding (CS) tensors, which describe how the size of shielding varies with molecular orientation, we often use the following convention for the three principle component:

$$\sigma_{11} \leq \sigma_{22} \leq \sigma_{33} \quad (1)$$

The three values of the shielding tensor are frequently expressed as the isotropic value (σ_{iso}), the anisotropy shielding ($\Delta\sigma$), and the asymmetry parameter (η). NMR computations of absolute shielding were performed using the gauge including atomic orbital (GIAO) method [19] on the HF and DFT-optimized structure with 6-31G, 6-31G** and 6-31G++ basis sets in the presence of chloroform as solvent. The ^{1}H and ^{13}C chemical shifts were calculated as $\delta = \sigma_{ref}$, where σ_{ref} is the shielding constant of $(CH_3)_4Si$ calculated at the same level of theory and at the same solvent. NMR parameters are very sensitive to small changes in molecular geometry and chemical environment exhibited significant sensitivity to the intra molecular interactions. So, our obtained theoretical results emphasized on the influence of the environment factors.

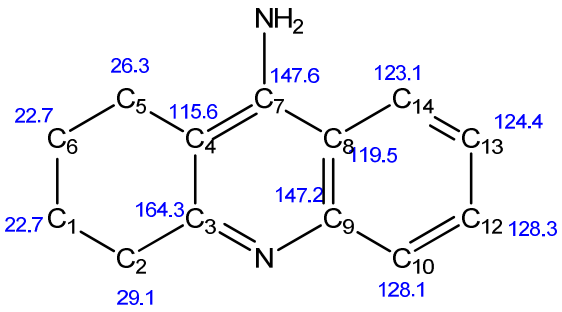

Fig. 1. ^{13}C NMR chemical shifts of Tacrine obtained from ChemDraw Ulltra 12.0.

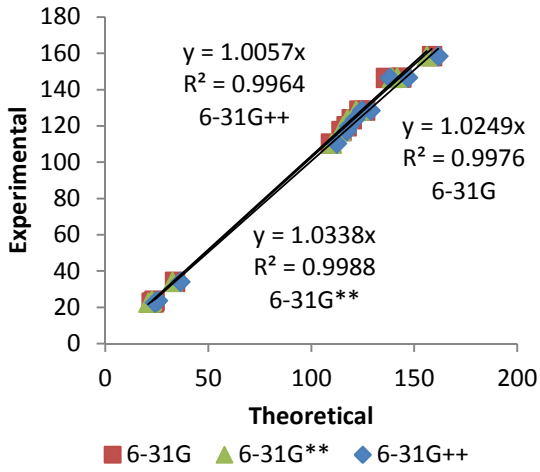

Fig. 2. correlation between calculated and experimental ^{13}CNMR chemical shifts of Tacrine at B3LYP levels with different basis sets.

RESULTS AND DISCUSSIONS

NMR computations of absolute shielding were performed using the gauge including atomic orbital (GIAO) method [19] on the HF and B3LYP optimized structure with 6-31G, 6-31G** in the presence of chloroform as solvent. These calculations extended to 6-31G++ basis set for consideration of hydrogen bonding that was existed between solute and solvent. The calculated ^{1}H and ^{13}C chemical shifts

were reported in Table 1 and Table 2. By consideration of structural parameters, the highest chemical shift was belonged to C3 because the bond length between C3 and N26 is the shortest length among the other carbon atoms that connected to N26 and N27. This short length added contribution of "s" character of sp^2 orbitals, so C3 becomes more electronegative and deshield than C9 and C7. The C7 is more deshield than C9, because C7 is attached to positive N27 (for participation of its lone pair in ring aromatization). For more comparison of ^{13}C NMR chemical shifts, we obtained ^{13}C NMR from ChemDraw Ultra 12.0 (Figure 1). Figure 2 and 3 show that there are good agreements between calculated and experimental [20] ^{13}C NMR chemical shifts, especially those were calculated at B3LYP/6-31G** level.

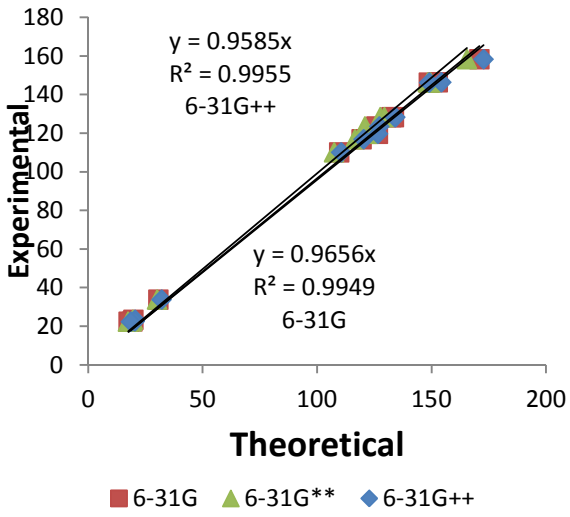

Fig. 3. correlation between calculated and experimental $^{13}CNMR$ chemical shifts of Tacrine at HF levels with different basis sets.

In ^{1}H NMR calculations, the highest chemical shift was belonged to H11. Calculated chemical shifts for H11, H19, H20 and H21 were in the range of aromatic protons. Calculated chemical shifts for H17, H22, H18, H23, H15, H24 and H16, H251 confirm these protons belong to methylene group in cyclohexyl, and finally calculated chemical shift of 4.50 confirmed that H28, H29 are connected to nitrogen atom in primary aromatic amine. For more comparison of ^{1}H NMR chemical shifts, we obtained ^{1}H NMR from ChemDraw Ultra 12.0 (Figure 4). Figure 5 and 6 show good correlation between calculated and experimental ^{1}HMR chemical shifts, especially those were calculated at B3LYP/6-31G++ level.

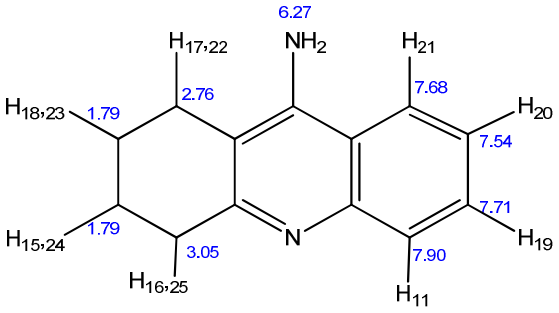

Fig. 4. ^{1}H NMR chemical shifts of Tacrine obtained from ChemDraw Ulltra 12.0

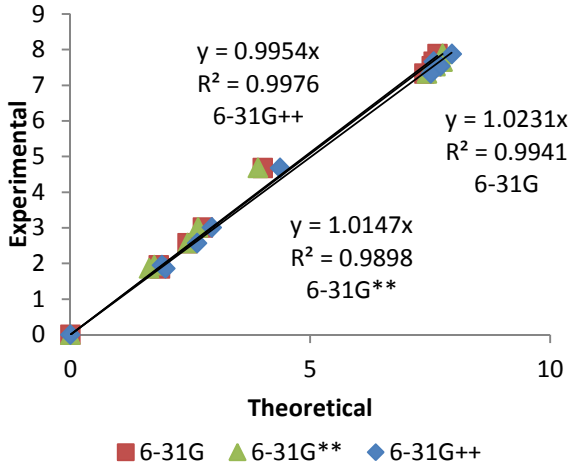

Fig. 5. correlation between calculated and experimental $^{1}HNMR$ chemical shifts of Tacrine at B3LYP levels with different basis sets

Table 1. calculated ^{13}C NMR chemical shifts of Tacrine at B3LYP and HF levels with different basis sets in chloroform as solvent

	HF			B3LYP			Exp
	6-31G	6-31G**	6-31G++	6-31G	6-31G**	6-31G++	
C3	170.91	165.45	172.72	158.54	156.04	161.64	158.3
C9	152.79	148.51	154.38	143.71	141.60	146.91	146.5
C7	148.87	149.52	148.98	136.12	139.12	138.03	146.3
C10	132.45	127.57	134.20	126.10	124.17	128.70	128.4
C12	133.69	129.47	134.02	123.31	121.72	124.62	128.3
C13	125.89	120.90	127.22	119.55	117.58	121.30	123.6
C14	126.70	122.59	126.59	117.10	115.41	118.38	119.8
C8	119.52	116.63	120.37	114.65	114.26	117.17	117
C4	109.69	107.54	110.50	109.41	109.97	112.41	110.1
C2	30.73	30.11	32.10	33.87	32.60	36.45	33.9
C5	19.77	19.51	20.51	23.82	22.65	25.61	23.5
C6	19.44	19.12	20.40	23.57	21.97	24.52	22.6
C1	17.65	17.47	18.63	22.44	20.91	23.98	22.5

Table 2. Calculated ^{1}H NMR chemical shifts of Tacrine at B3LYP and HF levels with different basis sets in chloroform as solvent

	HF			B3LYP			Exp
	6-31G	6-31G**	6-31G++	6-31G	6-31G**	6-31G++	
H11	8.45	8.19	8.68	7.65	7.76	7.95	7.88
H21	8.26	8.17	8.34	7.57	7.76	7.57	7.67
H19	8.21	7.99	8.36	7.53	7.61	7.71	7.54
H20	7.93	7.68	8.07	7.38	7.43	7.51	7.33
H28	4.10	3.82	4.28	4.27	4.16	4.52	4.68
H29	3.62	3.49	4.02	3.75	3.66	4.22	4.68
H16	2.80	2.69	2.91	2.65	2.63	2.85	3.01
H25	2.76	2.55	2.92	2.87	2.69	3.04	3.01
H22	2.41	2.23	2.62	2.52	2.54	2.70	2.57
H17	2.39	2.47	2.59	2.45	2.34	2.58	2.57
H18	1.87	1.81	1.92	2.01	1.91	2.11	1.95-1.86
H23	1.48	1.32	1.55	1.61	1.37	1.70	1.95-1.86
H15	1.86	1.80	1.91	1.99	1.88	2.13	1.95-1.86
H24	1.60	1.50	1.63	1.76	1.62	1.83	1.95-1.86

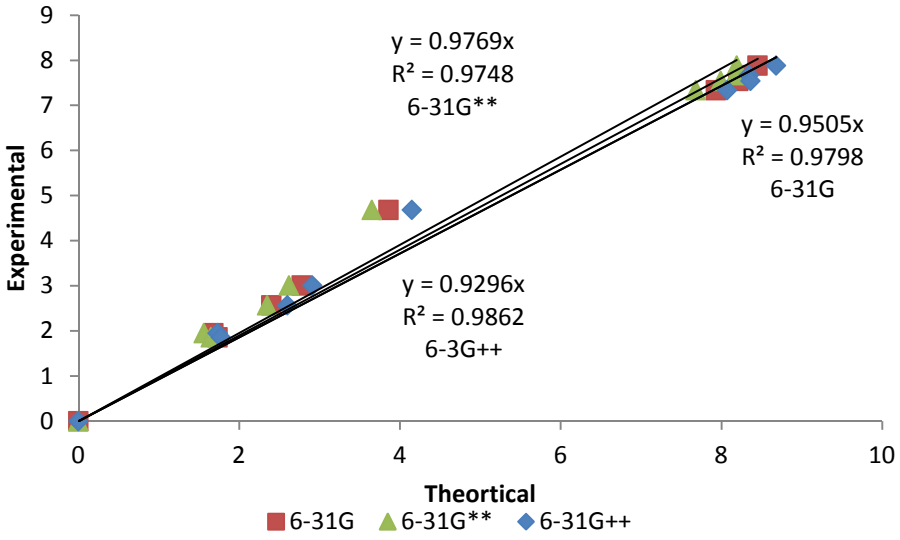

Fig. 6. correlation between calculated and experimental ^{1}HNMR chemical shifts of Tacrine at HF levels with different basis sets.

CONCLUSION

NMR parameters are very sensitive to small changes in molecular geometry and chemical environment exhibited significant sensitivity to the intramolecular interactions. So, our obtained theoretical results emphasized on the influence of the environment factors. This especially refers to the second-order magnetic response properties (NMR), since the magnetic resonance based techniques have gained substantial importance in chemistry and biochemistry that NMR data shown with two parameters isotropic (σ *iso*) and an isotropic (σ *aniso*) shielding.

In this theoretical study, we used HF and DFT (BLYP, B3LYP) method for calculation of energy, chemical shift nucleus magnetic resonance on Tacrine by DFT-NMR. The basis set used were 6–31G, 6–31G** and 6-31G++ for better evaluation and in order to obtain its optimal molecular geometry and vibrational modes in chloform as solvent. The ^{1}H and ^{13}C NMR calculations show good agreement with experimental data. The present study should take measures toward complete understanding of the present system. Generally, structures agree with the experiment, suggesting that studies of drug structures can be pursued with some degree of confidence with this level of theory. The environment does not only affect the Tacrine structure, but also its functionality. The presents study help to understand

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