The theoretical study of bisphosphonate derivatives as drug for inhibition of cancer

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Abstract

DFT computations were carried out to characterize the ^{17}Oand ^{2}H electric field gradient, EFG, in various bisphosphonic acids derivatives. The computations were performed at the B3LYP level with 6-311++G (d, P) standard basis set. Calculated EFG tensors were used to determine the ^{17}O and ^{2}H nuclear quadrupole coupling constant, χ and asymmetry parameter, η. The results showed that various substituents have a strong effect on the Nuclear Quadrupole Resonance (NQR) parameters (χ, η) of ^{17}O in contrast with ^{2}H NQR parameters. The NQR parameters were studied in order to find the correlation between electronic structure and activity of structure. Investigations showed that substitutions on the carbon atom in P-C-P are important in bisphosphonates drug properties.

Keywords: Bisphosphonate; NQR; DFT calculations; Electrical field gradient

1. Introduction

Derivatives of bisphosphonate with and without nitrogen are a novel class of drug that has been

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registered for various clinical applications worldwide and clinical data confirm the role of bisphosphonate in metabolic in bone metastatic cancer and multiple myeloma, prostate and lung cancer patients, have been often included in trials. Recent reports suggest that bisphosphonate treatment may be associated with an increase in patient survival, raising the possibility that these compounds may have a direct effect on the tumor cells [1-6].

The site of action bisphosphonate has been shown to bethel mevalonate/isoprene biosynthesis pathway enzyme, farnesyl pyrophosphate (FPP) synthase. [7-12], Some bisphosphonates have been shown to be potent inhibitors of FPP synthase from the trypanosomatids *Trypanosoma cruzi* (the causativeagent of Chagas disease) and *Trypanosoma brucei* (the causative agent of African sleeping sickness))[13-14] and they are also potent activators of human γδ T cell. [15-16].

γδ T cells are the first line of defense against many infectious organisms and are also involved in tumor cell surveillance and killing. γδ T cells expressing the Vγ2Vδ2 (also known as Vγ9Vδ2) T cell receptor (TCR) play an important role in immune system surveillances and defense [17-22].

Recently, drug researchers have focused on a protein called Ras since nearly a third of all human cancers involve a mutation in the Ras gene. Therefore, bisphosphonates have attended. Because, bisphosphonates act on other enzymes, called FPPS and GGPPS, which are upstream of Ras in the cell survival pathway. Recently, clinical data confirm inhibiting these enzymes appears to be a more effective when used in combination with hormone therapy for killing cancer cells [23].

Recently, various derivatives bisphosphonate with and without nitrogen have been investigated by quantitative structure-activity relationship used Hartree-Fock theory with a 6-31G* basis set, the Merz-Sinhg-kollman (MSK) method [24] calculated atomic charges in the Gaussian 98 program. Comparative molecular field analysis (CoMFA) [25] calculates interaction energies between a

molecule and a series of probes (electrostatic, hydrogen bonding,and hydrophobic) and correlates variances in the interaction energies with activity consisting of steepest-descent and Powell. BFGS algorithms, using the Tripods force field in the Sybyl 6.9 [26] program using a partial least squares (PLS) approach and a Gasteiger-Marsili charge set,comparative analysis (CoMSIA) [27] [28]in Syby 6.9 program by using Gasteiger-Marsili (GM) calculated hydrophobic, electrostatic and steric and hydrogen-bond acceptor to make quantitative relationship between γδ TCells and activity of bisphosphonate. Catalyst program [28] is pharmacophore modeling using the Hip Hop module correlates activity with the presence of chemical feature such as hydrogen bond donors, negative ionizable groups, etc for investigated pharmacophor modeling [22,29-31].

The nuclear magnetic resonance chemical shift and nuclear quadrupole resonance parameters are the most powerful properties available for structure determination at the molecular level. Specifically, progress in the areas including the effects of an unpaired electron, electron correlation, and relativistic effects into *ab initio* chemical shielding calculations, the tensor nature of the chemical shift, and intramolecular and intermolecular effects on the chemical shift will be covered.

Therefore, in this research we investigated NQR of some derivatives of non-nitrogen bisphosphonates as anticancer drug. These results and approaches can be used for development of novel bisphosphonates.

2. Computational methods

The density functional theory (DFT) calculations were carried out using the Gaussian 98 suite of programs [32] and the geometry optimization was performed at the B3LYP/6-31G(d,p) level. To evaluate and ensure the optimized structures of the molecules, frequency calculations were carried

out using analytical second derivatives. In all cases, only real frequencies were obtained for the optimized structures.

To calculate the ^{2}H and ^{17}O EFG tensors in the principal axis system, DFT method including B3LYP [33, 34] with the basis set of 6-311++G (d,p) was employed. To investigate the influence of the substitution on the EFG tensors, all calculations were performed for derivatives of non-nitrogen bisphosphonates.

for EFG tensors q_{xx}, q_{yy} and q_{zz} have the following relationship:

$$|q_{zz}| \geq |q_{yy}| \geq |q_{xx}|$$

The nuclear quadrupole coupling constant (c) was obtained by [35]

$$c \text{ (MHz)} = e^2 Q q_{zz} / h$$

where "e" is the charge of electron, Q is the nuclear electric quadrupole moment, and "h" is the Planck's constant. Q value for ^{17}O and ^{2}H nuclei used in the calculation of c values has been reported to be 25.78 and 2.86 mb (1 mb= 1×10^{-31} m^2), respectively [36].

Another important parameter which refers to the deviation of charge distribution from cylindrical symmetry is the asymmetry parameter (h) obtained by [37].

$$h = \left| \frac{q_{yy} - q_{xx}}{q_{zz}} \right|.$$

3. Results and discussion

We investigate ^{2}H and ^{17}O EFG tensors, the nuclear quadrupole coupling constants (χ), asymmetry parameters (η) and ^{13}C, ^{17}O and ^{31}P chemical shielding for acid, Di halo, orto, meta and para acids. The B3LYP/6- 311++G (d,p) optimized geometries for desired bisphosphonate and its derivatives are shown in Fig. 1.

3.1. Electric field gradients

In this part, the DFT calculations at the B3LYP level of theory with the 6-311++G (d,p) basis set are carried out to study the substituents effect on the ^{2}H and ^{17}O EFG tensors of bisphosphonates. Also, NQR parameters are used for investigating of the effect of substitutions on acidic and medicinal properties of bisphosphonates. The calculated nuclear quadrupole coupling constants, χ, and asymmetry parameters, η, by EFG tensor principal components, q_{ii}, for these atoms are summarized in Tables 1 and 2.

As the results in Tables 1 and 2 indicate, different substitutions have influences on the calculated ^{2}H and ^{17}O EFG tensors. Also, the effect of substitutions on χ and η is studied. The investigations show that χ relate to charge density on the atom and its symmetry. χ increases with increase in the charge density and decreases with decrease in the atom symmetry. According to the results in Table 1, the decrease in the EFG tensor elements of oxygen atoms in P=O bond can be a result of delocalized electrons. Two factors control the value of q_{zz} for a quadrupolar nucleus: the charge density at the nucleus and the symmetry of the EFG around the nucleus. The double bond in around oxygen atom in P=O bond increases the charge density at both oxygen atoms. Since the contribution of nonbonding electrons (lone pairs of p and d electrons) to the nonspherical charge distribution is greater than that of bonding electrons, the EFG is more asymmetric in atoms with nonbonding electron pairs due to the increased charge density. On the other hand, if the asymmetry of EFG increases, then q_{zz} and consequently χ would decrease. As a result, the competing effects of charge density and EFG asymmetry on χ offset each other, leading to only a small increase in the χ values of the acidic ^{17}O at phosphonat groups and a decrease in the χ values of ^{17}O in P=O bonds. Thus, we conclude that the ^{17}O χ values are a good marker for distinguishing between the acidic

and nonacidic forms of oxygen atoms in phosphonate groups. Therefore the ^{17}O χ values are used as good marker for investigating of the effect of substitutions on the acidic and medicinal properties bisphophonates.

Tables 1 and 2 indicate that the NQR parameters of the acidic hydrogen atom on the 14P (28H) in bisphosphonic acid change considerably with respect to other acidic hydrogens on the bisphosphonic acid. χ (28 H) decreases by 55 KHz and η (28 H) increases by 0.03 through position this hydrogen atom with respect to benzene ring. Furthermore, the change of substitution affect on the NQR parameters of the acidic hydrogen atom on the 14P (28H) in bisphosphonic acid and their derivative. The present calculations show that the O–H distance in the acidic hydrogen (28H) increases (Fig. 1a). The decrease of χ (28 H) and increase of the O–H distance in bisphosphonic acid and their derivatives the increased acidity of the hydrogen atom in the 21 O–28 H (Fig. 1a) bond.

4. Conclusion

Based on DFT calculations, it is concluded that the EFG tensors of oxygen atoms are good indicators to characterize the acidic property of hydrogen atoms phosphate groups. The NQR parameters of oxygen atom in P=O bond change significantly through delocalized electron. The results show that the electronic environments of oxygen atoms are affected by benzene ring and its substitutions. The position of 19O and 28H causes notable changes in the EFG tensors of these atoms. Furthermore, the change of substitution affect on the NQR parameters of the acidic hydrogen atom on the 14P (28H) in bisphosphonic acid and their derivative. The decrease of χ (28 H) and increase of the O–H distance in bisphosphonic acid and their derivatives the increased

acidity of the hydrogen atom in the 21 O–28 H bond. The bromine substitution and its position on the ring affect more than other substitutions.

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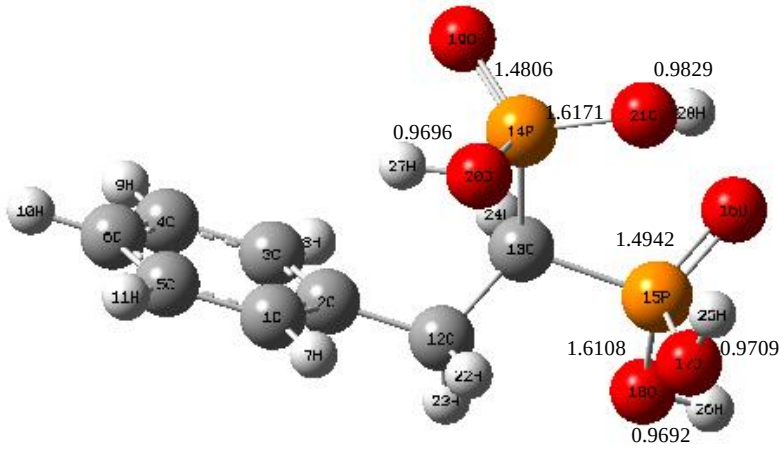
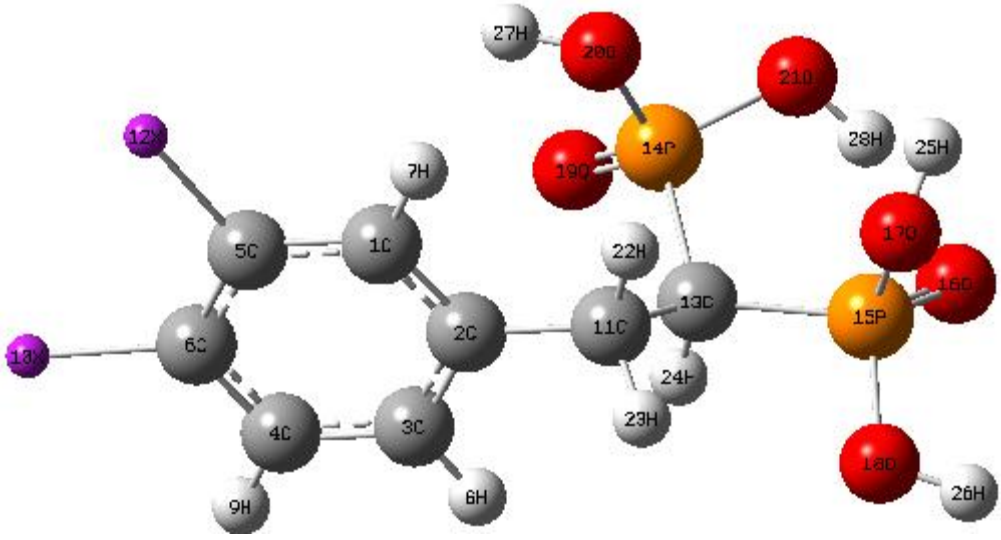


(a)



(b)

Fig 1. The optimized geometry using B3LYP/6-31G (d,p) for bisposphonate (a) and its derivatives (X=Cl, Br, F and OMe) (b).

Table1. Nuclear quadrupole coupling constants (NQCC), χ, and asymmetry parameters calculated for ^{2}H and ^{17}Onuclei for bisphosphonate and its derivatives using DFT-B3LYP/6-311++G (d, p) level.

compounds		acid		Di Bromo acid		Di Chloro acid		Di Fluoro acid		Chloro and Bromo		Meta -Br		Meta-Cl		Meta-F	
Number		χ	η	χ	η	χ	η	χ	η	χ	η	χ	η	χ	η	χ	η
H(13C)	24	187.80	0.02	186.45	0.03	186.39	0.03	190.21	0.02	186.26	0.03	185.90	0.03	186.46	0.03	187.34	0.03
O(14P)	19	3.36	1.01	3.11	2.09	3.08	2.12	3.39	1.91	3.07	2.13	3.24	1.95	3.24	1.95	3.32	1.86
	20	7.82	1.11	7.84	1.15	7.85	1.15	7.24	1.09	7.82	1.15	7.82	1.13	7.82	1.13	7.82	1.12
	21	7.12	1.11	6.96	1.15	6.96	1.16	7.71	1.13	6.96	1.17	7.03	1.14	7.03	1.14	7.08	1.12
O(15P)	16	3.16	2.20	3.09	2.29	3.08	2.30	3.31	2.06	3.07	2.32	3.13	2.25	3.13	2.25	3.15	2.22
	18	7.76	1.13	7.69	1.18	7.68	1.19	7.91	1.17	7.67	1.19	7.74	1.16	7.74	1.16	7.76	1.14
	17	8.13	1.13	8.11	1.13	8.10	1.13	7.12	1.10	8.09	1.13	8.11	1.13	8.11	1.13	8.12	1.13
H	25	290.76	0.11	295.54	0.11	295.52	0.11	295.07	0.11	296.67	0.11	293.76	0.11	294.93	0.11	291.97	0.11
	26	298.21	0.12	298.41	0.11	298.03	0.11	287.70	0.12	298.61	0.11	298.60	0.11	298.11	0.11	298.06	0.11
	27	292.72	0.12	296.97	0.11	297.16	0.11	297.22	0.11	296.44	0.11	296.85	0.11	296.11	0.11	293.495	0.12
	28	243.77	0.14	235.36	0.14	234.69	0.14	224.84	0.16	232.71	0.14	237.81	0.14	235.74	0.14	241.06	0.14
Compounds		Orto-Br		Orto-Cl		Orto-F		P-Br		P-Cl		P-F		P-OMe			
Number		χ	η	χ	η	χ	η	χ	η	χ	η	χ	η	χ	η		
H(13C)	24	182.31	0.02	183.42	0.02	184.93	0.02	187.76	0.03	187.08	0.03	187.50	0.03	187.67	0.02		
O(14P)	19	3.01	2.21	2.93	2.31	3.19	2.00	3.34	1.84	3.26	1.93	3.30	1.88	3.16	2.20		
	20	7.87	1.14	7.88	1.14	7.82	1.13	7.83	1.12	7.82	1.13	7.83	1.12	7.77	1.13		
	21	6.91	1.18	6.90	1.19	6.97	1.15	7.09	1.12	7.02	1.14	7.06	1.13	8.13	1.13		
O(15P)	16	3.17	2.21	3.15	2.22	3.15	2.22	3.16	2.21	3.12	2.26	3.16	2.21	3.36	1.83		
	18	7.75	1.17	7.73	1.17	7.75	1.16	7.75	1.14	7.72	1.17	7.75	1.15	7.82	1.10		
	17	8.12	1.14	8.12	1.14	8.12	1.13	8.12	1.13	8.11	1.13	8.12	1.13	7.11	1.11		
H	25	294.94	0.11	296.00	0.11	294.73	0.11	291.85	0.11	294.58	0.11	292.47	0.11	292.15	0.12		
	26	297.90	0.11	298.45	0.11	298.40	0.11	297.92	0..11	298.13	0.11	298.21	0.11	242.71	0.11		
	27	297.23	0.11	297.88	0.11	295.69	0.11	294.61	0.11	295.45	0.11	294.74	0.11	291.57	0.11		
	28	231.91	0.14	228.82	0.15	234.12	0.14	242.27	0.14	237.14	0.14	239.96	0.14	298.29	0.14		

χ of ^{17}O is in MHz and for ^{2}H in KHz.

Table 2. Calculated the largest component of the EFG tensor, q_{zz}, for ^{2}H and ^{17}Onuclei in bisphosphonate and its derivatives using DFT-B3LYP/6-311++G (d, p) level.

compounds		acid	Di Bromo acid	Di Chloro acid	Di Fluoro acid	Chloro and Bromo	Meta -Br	Meta-Cl	Meta-F
Number		q_{zz}	q_{zz}	q_{zz}	q_{zz}	q_{zz}	q_{zz}	q_{zz}	q_{zz}
H(13C)	24	0.28	0.28	-0.28	0.28	-0.28	-0.28	-0.28	-0.27
O(14P)	19	-0.38	-0.79	-0.79	-0.81	-0.79	-0.79	-0.79	-0.78
	20	1.22	-1.40	-1.39	-1.25	-1.39	-1.37	-1.38	-1.36
	21	-1.24	-1.24	-1.24	-1.35	-1.25	-1.24	-1.23	-1.24
O(15P)	16	-0.83	-0.84	-0.84	-0.84	-0.84	-0.84	-0.84	-0.84
	18	-1.36	-1.38	-1.38	-1.42	-1.39	-1.38	-1.38	-1.37
	17	-1.43	-1.42	-1.42	-1.23	-1.42	-1.42	-1.43	-1.43
H	25	-0.43	-0.44	-0.44	-0.33	-0.44	-0.44	-0.44	-0.43
	26	-0.44	-0.44	-0.44	-0.43	-0.44	-0.44	-0.44	-0.44
	27	-0.43	-0.44	-0.44	-0.44	-0.44	-0.44	-0.44	-0.44
	28	-0.36	-0.35	-0.35	-0.33	-0.35	-0.35	-0.35	-0.36
Compounds		Orto-Br	Orto-Cl	Orto-F	P-Br	P-Cl	P-F	P-OMe	
Number		q_{zz}	q_{zz}	q_{zz}	q_{zz}	q_{zz}	q_{zz}	q_{zz}	
H(13C)	24	-0.27	-0.27	-0.27	-0.28	-0.28	-0.28	-0.28	
O(14P)	19	-0.80	-0.80	-0.79	-0.78	-0.79	-0.78	-0.78	
	20	-1.39	-1.39	-1.37	-1.37	-1.37	-1.37	-1.35	
	21	-1.24	-1.25	-1.24	-1.24	-1.24	-1.24	-1.24	
O(15P)	16	-0.84	-0.84	-0.84	-0.84	-0.84	-0.84	-0.84	
	18	-1.38	-1.39	-1.38	-1.37	-1.38	-1.37	-1.37	
	17	-1.43	-1.39	-1.43	-1.42	-1.42	-1.43	-1.43	
H	25	-0.44	-0.44	-0.44	-0.43	-0.44	-0.43	-0.43	
	26	-0.44	-0.44	-0.44	-0.44	-0.44	-0.44	-0.36	
	27	-0.44	-0.44	-0.44	-0.44	-0.44	-0.44	-0.43	
	28	-0.34	-0.34	-0.35	-0.36	-0.35	-0.36	-0.44	

q_{zz} values in atomic units, 1 au = $9.717365\times10^{21}Vm^{-2}$.