Theoretical Study of the Correlation between ^{14}N NQCC and Its Partial Atomic Charge in Amino Derivatives of Adamantane

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The electronic structures and electrostatic potential of some amino derivatives of adamantane have been studied using density functional theory. The partial atomic charges and nuclear quadrupole coupling constants (NQCC) of ^{14}N nucleus of the considered molecules have been reported. The partial atomic charges are calculated with two methods for ^{14}N nucleus: Mulliken charges and natural bond orbital (NBO). All of the computations were carried out using the Gaussian 03 program at the B3LYP/6-311++G(d,p) level of theory. The results of both methods show reasonably good correlation with NQCC parameter, however, a much better correlation is found between NBO charges and NQCC of ^{14}N nucleus.

INTRODUCTION

Experimental and theoretical studies on adamantane and its derivatives have been carried out since the early 1960. In these years, a new drug named amantadine for influenza treatment was seen on the shelves. From these years, various derivatives of adamantane play some essential roles in medicine for treatment of some disease like as AIDS, cancer, and so on [1,2]. Adamantane is a highly symmetrical and very stable bridged polycyclic hydrocarbon. The carbon backbone of adamantane is the same as the structure of diamond. The special structure of adamantane causes many useful chemical and physical properties [3-6]. Another important stable bridged polycyclic hydrocarbon amine is memantine (aminoadamantane) that clinically used for Alzheimer illness [7-10]. From a medicinal chemist point of view, the amino adamantyl can be used either as a trellis for development of remedial agents, such as memantine and amantadine derivatives, or as an adjuster of the pharmaco kinetics of a compound [11]. In some studies the inhibitory activities of the memantine and some other amino

adamantane are reported

Knowledge about the relationships between structures and their inhibitory activities could greatly facilitate the drug discovery process. Quantitative structure-activity relationship (QSAR) method is the study to establish an empirical rule or function concerning to the structural descriptors of compounds under investigation to bioactivities. This rule or function is then utilized to predict the same bioactivities of the compounds not involved in the training set from their structural descriptors [12].

The structure dependent parameters can be used in QSAR method which can be calculated using density functional theory (DFT) and can be effective on the drug activity (DFT-based QSAR). QSAR has been widely used for years to provide quantitative analysis of structure and biological activity relationships of compounds [12]. Quantitative structure-antitumor activity and three interatomic distances that define the relative spatial dispositions of three significant atoms [13] were used as descriptors. The molecular structure, natural bond orbital, DFT calculations and biological activity analysis of antioxidant drug hydroxycoumarin were the quantum mechanical descriptors [14]. Also, an alkyl chain lengths,

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polarizability tense and entropy descriptors for governing the EC50 values of the toxicity of quaternary ammonium compounds have been used as descriptors [15]. The dipole moment, average polarizability, ionization potential, electron affinity, LUMO energy, HOMO energy, total energy, electronegativity, electrophilicity and differences between HOMO and LUMO energies were the calculated quantum mechanical descriptors for established QSAR models of the biological activity of sulfonamide compounds with carbonic anhydrase inhibitory activity [16]. Hence, there are a large number of molecular descriptors that can be used in QSAR studies. The findings can be used to predict the activities of untested compounds. Recently, computer-aided drug design based on QSAR has been successfully used to develop new drugs for the treatment of cancer, SARS, HIV and other diseases [12]. Also, the partial atomic charge of the main nucleus is the important descriptor affecting the activity of drugs [13,15,17]. On the other hand, some researches have shown the importance of the function and the role of the nitrogen nucleus in adamantane amine derivatives in terms of their drug properties [18,19].

The nuclear quadrupole resonance (NQR) spectroscopy is one of the effective methods for evaluating the electric field gradient (EFG) [20,21]. In addition, the NQR spectroscopy was interested due to its ability to straightly record the variations in the electronic environment of the nucleus [22-24]. Furthermore, the interplay between the nuclear electric quadrupole moments (eQ) of the quadrupolar nuclei (having spin I > 1/2) and the local molecular EFG has a special task in the NQR spectroscopy. The nuclear quadrupole coupling constant (NQCC) that is calculated through the NQR frequency provides information about the electron distribution in the molecule [25]. Also, more accurate determination of the local distribution of the electron density around the nucleus using the NQCC is possible, when compared with the NMR chemical shift [26,27]. Furthermore, NQR is a very suitable method because the magnetic field is no more required and hence does not disturb the structure of the molecule under study [28].

In this research the electronic structures of some pharmaceutical derivatives of adamantane amine are investigated by density functional theory (DFT). The Mulliken and NBO partial atomic charges and the nuclear quadrupole coupling constant for N nucleus are evaluated,

and correlations between atomic charges and NQCC are suggested. Then, the relation between NQR spectroscopy frequencies and the activity of the drugs is introduced.

COMPUTATIONAL METHODS

All computations including partial atomic charge, DFT computations and EFG calculations were carried out using the Gaussian 03 program [29]. The geometry optimization of the considered molecules was performed at the B3LYP level of theory and by employing 6-311++G(d,p) standard basis sets.

Previously, some researchers have used these methods for optimization of many other similar compounds successfully and have published good results [24,30]. The nuclear quadrupole coupling constant of ^{14}N was calculated using EFG tensor (q_{xx}, q_{yy} and q_{zz}) obtained from DFT computations by the following equation, [25]

$$NQCC = e^2 Qq_{zz}/h \qquad (1)$$

in which, NQCC, e, Q and h are nuclear quadrupole coupling constant (in MHz), the electronic charge (in atomic unit), the nuclear quadrupole moment of the ^{14}N nuclei (in millibarn) and the Plank's constant, respectively. The constant value of 20.44 millibarn was reported by Pyykko [31] set as the value of eQ of ^{14}N atom. The NQCC parameter is a measure of the interaction between the nuclear quadrupole moment and the EFG at the quadrupole nuclei site due to the non-spherical and non-cylindrical (anisotropic) charge distribution in the system.

RESULTS AND DISCUSSION

^{14}N EFG Tensors

In this work, forty structures of amino derivatives of adamantane, possesing antiviral properties, have been chosen for the study. The molecular structure and number of amino derivatives of adamantane are listed in Table 1. All of the structures are divided into three types as similarity between the structures (I, II, III). The components of EFG tensors (q_{xx}, q_{yy} and q_{zz}) were calculated at the B3LYP/6-311++G(d,p) level of theory in order to study the effect of substituted groups on the relationship between the NQCC

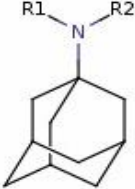**Table 1.** The Number, Type (I, II, III) and Open Structure of the Studied Structures
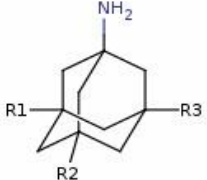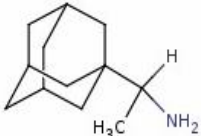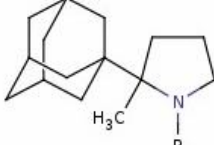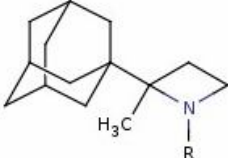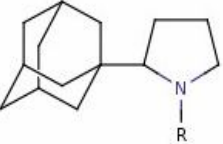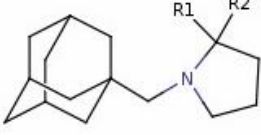

1: $R_1 = H$, $R_2 = (CH_2)_3OH$

2: $R_1 = H$, $R_2 = CH_2CH_2COOCH_3$

3: $R_1 = H$, $R_2 = C_6H_{11}$

4: $R_1 = H$, $R_2 = C_6H_5$

5: $R_1 = H$, $R_2 = CH_2CH_2\,C_6H_5$

6: $R_1 = H$, $R_2 = CH_2C_6H_5$

7: $R_1 = H$, $R_2 = OH$

8: $R_1, R_2 = (CH_2)_2CH_3$

9: $R_1 = CH_3$, $R_2 = CH_2CH_2OH$

10: $R_1 = CH_3$, $R_2 = CH_2CH_2NH_2$

11: $R_1 = CH_3$, $R_2 = CH_2CH_2Cl$

12: $R_1, R_2 = CH_2CH_2Cl$

13: R_1-$R_2 = $ -$(CH_2)_4$-

14: $R_1 = H$, $R_2 = H$

15: $R_1 = H$, $R_2 = CH_3$

16: $R_1 = H$, $R_2 = C_2H_5$

17: $R_1 = H$, $R_2 = (CH_2)_2CH_3$

18: $R_1 = H$, $R_2 = (CH_2)_3CH_3$

19: $R_1 = H$, $R_2 = (CH_2)_5CH_3$

20: $R_1 = CH_3$, $R_2 = CH_3$

21: $R_1 = C_2H_5$, $R_2 = C_2H_5$

22: $R_1, R_2 = H$, $R_3 = C_6H_5$

23: $R_1, R_2 = H$, $R_3 = CH_3$

24: $R_1, R_2 = H$, $R_3 = NH_2$

25: $R_1, R_2, R_3 = CH_3$

I

26

27: R = H

28: R = CH_3

29: R = H

30: R = CH_3

II

31: R = H

32: R = CH_3

33: R = CH_2CH_3

34: R = n-C_4H_9

35: $R_1 = CH_3$, $R_2 = CH_3$

36: R_1-$R_2 = $ -$(CH_2)_4$-

37: R_1-$R_2 = $ -$(CH_2)_5$-

38: $R_1 = H$, $R_2 = $ t-Bu

39: $R_1 = CH_2NMe_2$, $R_2 = H$

40: $R_1 = H$, $R_2 = CH_2NMe_2$

III

Table 2. The Number, Type (I, II, III) and the Mulliken Charges, NBO Charges and NQCC Parameters for ^{14}N Nucleus of the Studied Structures

Type	No.	Mulliken Charges	NBO charges	NQCC	Type	No.	Mulliken Charges	NBO charges	NQCC
	1	0.318618	-0.69377	5.796770		21	0.699941	-0.55476	6.426403
	2	0.341778	-0.68920	5.761808		22	-0.208840	-0.84410	5.160587
	3	0.427518	-0.70286	5.920272	I	23	0.089446	-0.84428	5.147001
	4	0.418012	-0.64483	5.530303		24	-0.256240	-0.84330	5.148423
	5	0.330449	-0.68727	5.772765		25	-0.233920	-0.84430	5.165685
	6	0.371040	-0.68403	5.839964		26	-0.321610	-0.84571	5.260377
	7	-0.099890	-0.35869	7.085961		27	-0.042730	-0.70197	6.153559
	8	0.941725	-0.54976	6.483716	II	28	0.255737	-0.54175	6.453757
	9	0.584732	-0.53982	6.433914		29	0.029176	-0.69090	5.496923
	10	0.576062	-0.53865	6.432799		30	0.060547	-0.52971	6.685156
I	11	0.579149	-0.53694	6.460250		31	-0.107710	-0.68236	6.016587
	12	0.718078	-0.55033	7.221670		32	0.307155	-0.53402	6.370224
	13	0.550208	-0.54018	6.135034		33	0.395817	-0.54129	6.590109
	14	-0.229470	-0.84460	5.141868		34	0.600875	-0.53545	6.825022
	15	0.089446	-0.67638	5.871229		35	0.577551	-0.55074	6.216096
	16	0.228192	-0.68869	5.774053	III	36	0.802302	-0.54502	6.224444
	17	0.274323	-0.68933	6.137095		37	0.760284	-0.54855	6.194081
	18	0.341043	-0.68561	5.809534		38	0.732209	-0.5479	6.385771
	19	0.410202	-0.68572	5.809447		39	0.366192	-0.55657	5.988027
	20	0.364014	-0.51980	6.350680		40	0.735068	-0.54001	6.392552

and the partial atomic charges of ^{14}N nucleus of the considered molecules. Then, the components of EFG tensors were applied to calculate the NQCC.

Nuclear Quadrupole Coupling Constant

As can be seen from the Eq. (1), the NQCC of the nucleus is directly related to q_{zz} value. The value of q_{zz} in a nucleus has also been related to the charge density on the nucleus and symmetry of electric field gradient around the quadrupolar nucleus [28]. The increasing of the charge density on the nucleus helps to increase the q_{zz} value and consequently the NQCC value. In addition, the increasing of the charge distribution (as the symmetry of EFG) helps to increase the q_{zz} value and consequently the NQCC value [28]. The calculated ^{14}N NQCC parameter for each structure is collected in Table 2. The results show that the highest calculated ^{14}N NQCC parameter is for structure 12 with two N-substitutde 2-chloroethyl groups, and the lowest calculated NQCC parameter is for structure 14 without any N-substituted groups. Although, there are no experimental results for ^{14}N NQCC parameter of amino derivatives of adamantane, there are many studies that show the experimental and calculated results for ^{14}N NQCC parameters are almost the same [32-35].

The Electrostatic Potential

We also calculated the electrostatic potential (ESP) to gain a better insight into the active sites of the studied structures. The ESP shows that where the molecule site has less or more electron density. It shows the active and inactive sites of the molecule. Figure 1 shows the ESP for the studied molecules with numbers 14, 15, 26 and 32. The Esp of four structures, related to three studied group (I, II and III), has been shown for briefness. As can be seen from the ESP map, the nitrogen atom in all of the studied molecules has the red color indicating that the electrostatic potential of nitrogen site is more positive than that of the other sites. So, it is the active site of these molecules to interact with the negative sites of the molecule or compound. Accordingly, the charge distribution on the nitrogen atom of the studied structures was investigated.

The Mulliken Charges

The Mulliken partial atomic charges for the studied structures are presented in Table 2. The results show that the more positive Mulliken charge on the ^{14}N nucleus, 0.941725 e, belongs to the structure 8 whit two N-substituted n-propyl groups. On the contrary, the more negative Mulliken charge on the ^{14}N nucleus, -0.321610 e, belongs to the structure 32. The variations of NQCC parameter with the Mulliken charge are shown in Fig. 2A. As can be seen from this figure, the correlation coefficient for the Mulliken partial atomic charges and NQCC parameter for the forty studied structures is 0.3237. Also, as can be seen from Fig. 2B, by elimination some points (the structures that their relative errors are more than 5%) the correlation coefficient of the Mulliken partial atomic charges and NQCC parameter of the nitrogen nucleus for other remained structures (22 structures) become better (0.784). Therefore, about 55% of the studied structures of amino derivatives of adamantane show a liner relationship between the Mulliken partial atomic charges and NQCC parameter of nitrogen nucleus.

The NBO Charges

The partial atomic charges calculated by the NBO method for all of the structures are listed in Table 2. The results show that the less negative NBO partial atomic charge on the ^{14}N nucleus, -0.35869 e, belongs to the structure 7, while, the more negative NBO charge on the ^{14}N nucleus, -0.84571 e, belongs to the structure 22. The relationship between the calculated NBO partial atomic charges and NQCC parameter on the ^{14}N nucleus are shown in Fig. 2C. As can be seen from Fig. 2C, the correlation coefficient for the forty studied structures is 0.4466. Also, as can be seen from Fig. 2D, by elimination some points (the structures that their relative errors are more than 5%), a inear relationship is found between the NBO partial atomic charges and NQCC parameter of the nitrogen nucleus for the remained structures (33 structures). The correlation coefficient by these eliminations becomes better (0.9774) indicating that there is a good relationship between NBO partial atomic charges and NQCC parameter of nitrogen nucleus. Therefore, about 83% of the studied structures of amino derivatives of adamantane show a linear relationship between NBO partial atomic charges and NQCC parameter
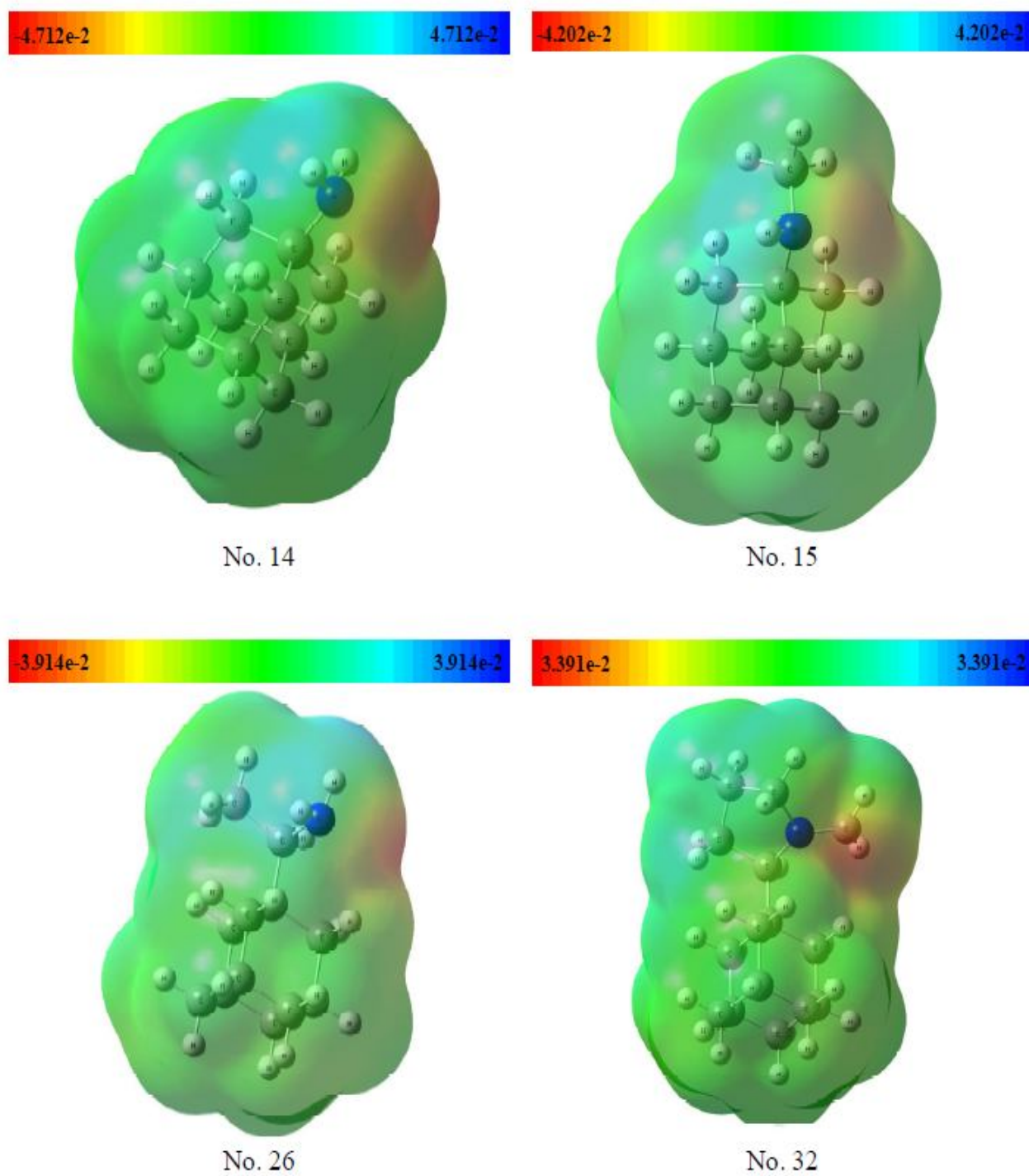
Fig. 1. The ESP of the molecules (number = 14, 15, 26 and 32) of the studied structures.
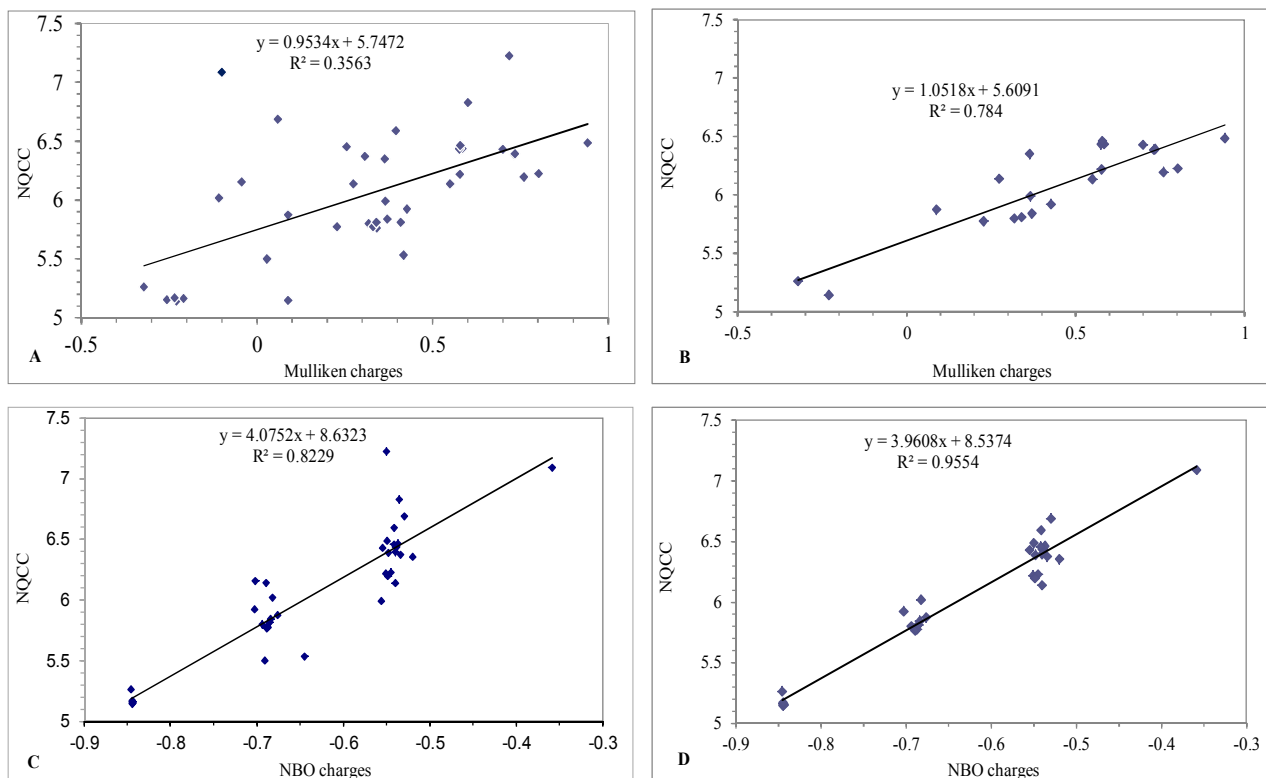
Fig. 2. The curve of the NQCC parameter *vs*. A) Calculated Mulliken partial atomic charges for all structures, B) Calculated Mulliken partial atomic charges for selected structures, C) Calculated NBO partial atomic charges for all structures, D) Calculated NBO partial atomic charges for selected structures for ^{14}N nucleus.
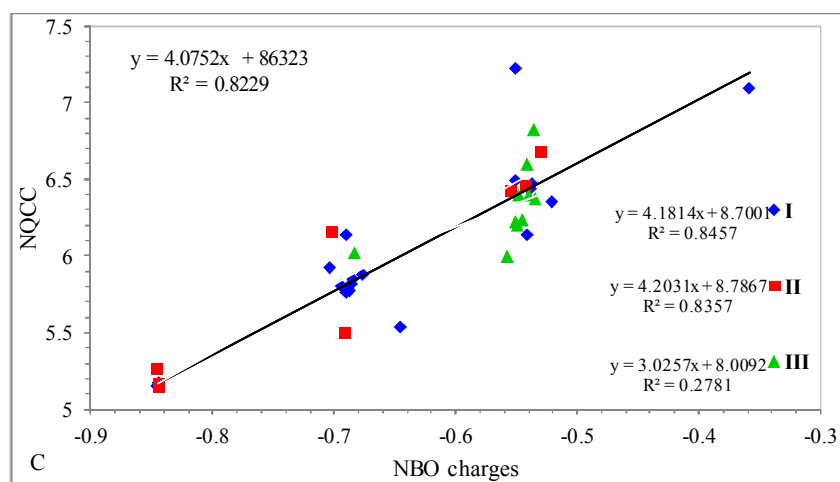

Fig. 3. The curve of the NQCC parameter *vs*. calculated NBO partial atomic charges for ^{14}N nucleus of all studied structures.

of nitrogen nucleus. Accordingly, there are about three islands of data that are shown in Fig. 3. However, this division is not exactly as similar as the structures divisions (I, II, III) that can be seen from Table 1. So, as can be seen from Fig. 3, each of three islands of data contains every type of the studied structures, indicating that the results are good for finding the relationship between NBO partial atomic charges and NQCC parameter for ^{14}N nucleus. Although, each of the three types of structures individually shows a good correlation between NBO and NQCC parameter for ^{14}N nucleus.

CONCLUSIONS

A theoretical investigation was carried out using the DFT method to study the NQCC parameter, electrostatic potential, and partial atomic charge of amino derivatives of adamantane. The results showed that the nitrogen atom of the studied structures is the active site. So, the relationship between the partial atomic charges and the NQCC parameter of ^{14}N nucleus for amino derivatives of adamantane was studied. The partial atomic charges of the structures were studied using two methods: Mulliken and NBO charges. The results showed that the NQCC parameters are extremely sensitive to the charge changes around the nuclei. This sensitivity for NBO method is more than that for the Mulliken method. There was an acceptable correlation between the calculated NBO charges and the NQCC parameter, and that about 83% of the studied amino derivatives of adamantane indicate a linear relationship between the NBO partial atomic charges and NQCC parameters for the ^{14}N nuclei. This study shows that the NQR spectroscopy frequencies can be used to evaluate the activity of drugs, because there is a good relationship between NQCC parameter and activity of drugs when the active site of drugs contains a quadrupolar nucleus.

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