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Influence of N–H…O and O–H…O hydrogen bonds on the ^{17}O, ^{15}N and ^{13}C chemical shielding tensors in crystalline acetaminophen: A density functional theory study

Mehdi D. Esrafili, Hadi Behzadi, Nasser L. Hadipour *

Department of Chemistry, Tarbiat Modares University, P.O. Box: 14115-175, Tehran, Iran

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Abstract

A computational investigation was carried out to characterize the ^{17}O, ^{15}N and ^{13}C chemical shielding tensors in crystalline acetaminophen. We found that N–H…O and O–H…O hydrogen bonds around the acetaminophen molecule in the crystal lattice have different influences on the calculated ^{17}O, ^{15}N and ^{13}C chemical shielding eigenvalues and their orientations in the molecular frame of axes. The calculations were performed with the B3LYP method and 6–311++G(d, p) and 6–311+G(d) standard basis sets using the *Gaussian 98* suite of programs. Calculated chemical shielding tensors were used to evaluate the ^{17}O, ^{15}N, and ^{13}C NMR chemical shift tensors in crystalline acetaminophen, which are in reasonable agreement with available experimental data. The difference between the calculated NMR parameters of the monomer and molecular clusters shows how much hydrogen-bonding interactions affect the chemical shielding tensors of each nucleus. The computed ^{17}O chemical shielding tensor on O(1), which is involved in two intermolecular hydrogen bonds, shows remarkable sensitivity toward the choice of the cluster model, whereas the ^{17}O chemical shielding tensor on O(2) involved in one N–H…O hydrogen bond, shows smaller improvement toward the hydrogen-bonding interactions. Also, a reasonably good agreement between the experimentally obtained solid-state ^{15}N and ^{13}C NMR chemical shifts and B3LYP/6–311++G(d, p) calculations is achievable only in molecular cluster model where a complete hydrogen-bonding network is considered. Moreover, at the B3LYP/6–311++G(d, p) level of theory, the calculated ^{17}O, ^{15}N and ^{13}C chemical shielding tensor orientations are able to reproduce the experimental values to a reasonably good degree of accuracy.

Keywords: Acetaminophen; NMR; Chemical shielding tensors; Hydrogen-bonding; Chemical shift, DFT

1. Introduction

Nuclear Magnetic Resonance, NMR, spectroscopy of ^{17}O, ^{15}N and ^{13}C nuclei has become an indispensable technique for studying biological structures both in the solid state and in solution. Many of NMR observables are resulted from anisotropic chemical shielding interaction between the nuclear spin and its environment. The chemical shielding interaction has been found to be a sensitive probe of structural features such as peptide backbone conformation, secondary structure and hydrogen bonding, H-bonding, interaction. This has resulted in numerous studies focusing on the relationship between the ^{17}O, ^{15}N and ^{13}C chemical shift tensors and these structural characteristics in both experimental and theoretical fields specifically in the last few decades [1–4].

It is good idea to investigate the nature of the intermolecular H-bonding interactions in acetanilide and its derivatives, especially acetaminophen, because of their key role in biosystems as pain reliever and fever reducer drugs. Numerous experimental techniques, including X-ray and neutron diffraction crystallography, infrared, Raman and NMR spectroscopies were applied to study the nature of the hydrogen bonds in acetanilide and its derivatives in the solid phase [5–8]. Recently, Nickols and Frampton pointed out in their studies that hydrogen bonds have a significant role in the morphology of acetaminophen, so the crystallization of three polymorphs of

* Corresponding author.
E-mail address: hadipour@modares.ac.ir (N.L. Hadipour).

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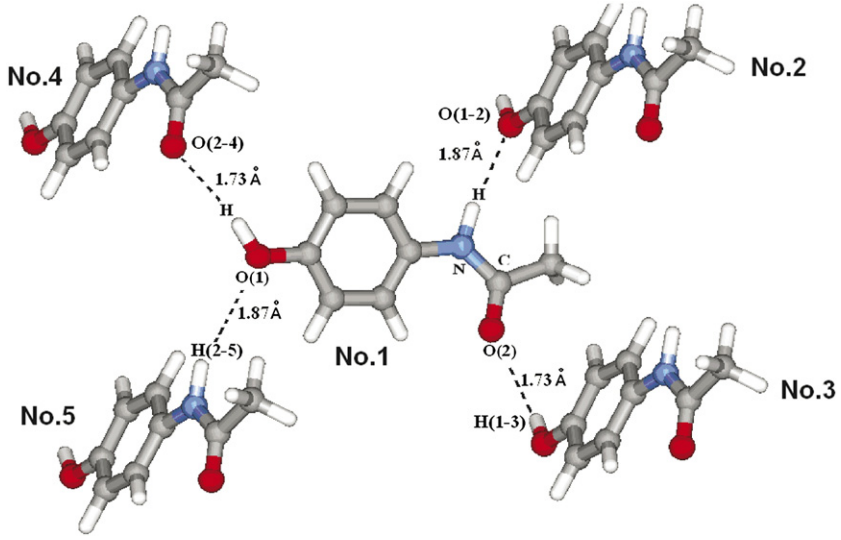

Fig. 1. Atomic numbering and hydrogen bonding network in crystalline acetaminophen. The target molecule (No. 1): (x, y, z); No. 2: ($-0.5+x$, $1.5-y$, $-0.5+z$); No. 3: ($0.5+x$, $1.5-y$, $-0.5+z$); No. 4: ($-0.5+x$, $1.5-y$, $0.5+z$); No. 5 ($0.5+x$, $1.5-y$, $0.5+z$).

acetaminophen are controlled by H-bonding interactions in the solid phase [9]. According to the model calculations, intermolecular hydrogen bonds in crystalline acetaminophen contribute up to 30% of the total lattice energy in [10]. In the crystalline structure, each acetaminophen molecule is linked to four neighboring acetaminophen via O–H...O and N–H...O hydrogen bonds; see Fig. 1.

It is well-known that quantum chemical calculations can provide an independent source of the chemical shielding tensor and their relative orientation in the molecular frame. Although the experimental studies are essential in obtaining information about the hydrogen bonds, however, the theoretical calculations can be confidently used as a complementary tool to interpret experimental NMR parameters. In a previous theoretical work, Wu et al. investigated the ^{17}O NMR tensors for secondary amide functional group in the crystal structure of acetanilide, benzanilide and *N*-methylbenzamide [11]. Their results indicated that ^{17}O NMR tensor of an amide group is sensitive to the H-bonding environment. Strohmeier and co-workers [12] also proposed that quantum chemical calculations can provide accurate ^{13}C and ^{15}N NMR chemical shifts in the hydrogen-bonded molecular crystals when the lattice effects, e.g. H-bonding interactions, are properly taken into consideration. Our previous theoretical studies on nucleic acids and polysaccharides also indicated the influence of H-bonding interactions on the ^{13}C, ^{15}N and ^{17}O NMR parameters [13–15]. Moreover, our recent theoretical work on the ^{17}O, ^{14}N and ^{2}H nuclear quadrupole resonance, NQR, parameters of crystalline acetaminophen indicated that quantum chemical calculations can provide better understanding about the relationship between the H-bonding strength and calculated NQR parameters [16].

Present work calculates ^{17}O, ^{15}N and ^{13}C chemical shielding tensors of crystalline acetaminophen by density functional theory, DFT, approach. Considering the presence of hydrogen bonds in the calculations, the most probable interacting molecules with the central molecule in the crystalline structure of acetaminophen was considered in a pentameric cluster; see Fig. 1 for details. To study systematically the influence of the H-bonding interactions on the various nuclei, chemical shielding tensors were calculated for three molecular models including: isolated gas phase (monomer), dimer and pentamer molecular models. The calculated chemical shielding tensors are exhibited in Tables 1–3. Finally, the relative orientation of the principal components of the ^{17}O, ^{15}N and ^{13}C chemical shielding tensors are obtained and the related angles and direction cosines are tabulated in Table 4.

Table 1
Calculated ^{17}O NMR parameters of acetaminophen

Model	Nucleus	Basis set	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	$\Delta\sigma$
Monomer	O(1)	6–311++G (d, p)	134.68	93.52	39.48	89.23	74.62
		6–311+G(d)	135.09	94.52	40.93	90.18	73.87
	O(2)	6–311++G (d, p)	713.01	502.49	−46.06	389.81	653.81
		6–311+G(d)	709.08	499.89	−47.48	387.16	651.96
Dimer	O(1)	6–311++G (d, p)	123.36	91.12	53.21	89.23	54.03
		6–311+G(d)	123.44	91.66	54.07	89.72	53.48
	O(2)	6–311++G (d, p)	703.81	499.69	−36.79	388.9	638.54
		6–311+G(d)	699.62	497.69	−36.42	386.96	635.08
Pentamer	O(1)	6–311++G (d, p)	150.54	94.66	69.55	104.92	53.05
		6–311+G(d)	149.61	94.47	67.89	103.99	54.16
	O(2)	6–311++G (d, p)	642.11	460.26	−28.23	358.05	579.42
		6–311+G(d)	637.1	456.32	−26.12	355.76	572.83
exp. [a]	O(2)		570	440	−20	330	525

[a] Experimental values of acetanilide from reference [11].

2. Definition and methods

Chemical shielding Hamiltonian acting on a spin, I, is given by [17]:

$$\hat{H} = -\gamma\hbar\sigma B_0\hat{I} \quad (1)$$

where γ, B_0 and $\hat{I}$ are magnetogyric ratio, applied magnetic field and nuclear spin operator, respectively. The term σ is a second-rank tensor called NMR chemical shielding tensor whose elements describe the size of chemical shielding as a function of molecular orientation respecting to the external magnetic field. In PAS, this tensor is converted to a diagonal matrix with σ_{11}, σ_{22} and σ_{33} components where $\sigma_{33}>\sigma_{22}>\sigma_{11}$. To describe a chemical shielding tensor, chemical shielding isotropy, σ_{iso}, and anisotropy, $\Delta\sigma$, are used in addition to the three principal components. These two NMR parameters are related to the principal components by following equations:

$$\sigma_{iso} = \frac{1}{3}(\sigma_{11} + \sigma_{22} + \sigma_{33}) \quad (2)$$

$$\Delta\sigma = \sigma_{33} - \frac{1}{2}(\sigma_{11} + \sigma_{22}). \quad (3)$$

DFT calculations were performed using *Gaussian 98* suite of programs [18]. This is done for calculating the chemical shielding tensors in their PAS for the oxygen, nitrogen and carbonyl carbon nuclei. Among various modern functionals for DFT calculation, Becke three parameter hybrid functional combined with Lee–Yang–Parr correlation functional designated B3LYP, with 6–311++G(d, p) and 6–311+G(d) standard basis sets were used [19,20]. As mentioned above, the crystal structure of acetaminophen was taken from X-ray diffraction study [8]. Since the hydrogen atom positions measured by X-ray diffraction are generally not accurate, partial geometry optimization was performed at the B3LYP/6–31++G(d, p) level of theory.

Chemical shielding calculations were performed using the gauge included atomic orbital, GIAO, method [21]. Since quantum chemical calculations yield absolute chemical shielding values, one must establish the absolute shielding values for a particular nucleus to obtain a direct relation between the calculated results and experimentally reported data. To evaluate the chemical shift tensor components, δ_{ii}, from the calculated $\sigma_{ii,cal.}$ values, we used

$$\delta_{ii} = \sigma_{ii,ref} - \sigma_{ii,cal.} \quad (4)$$

where $\sigma_{ii,ref}$ refers to the absolute chemical shielding of liquid water, liquid ammonia and tetramethylsilane (TMS) with the $\sigma_{iso,ref}$=307.9, 244.6 and 184.1 ppm, respectively [22–24].

Table 2
Calculated ^{15}N NMR parameters of acetaminophen

Model	Basis set	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	$\Delta\sigma$
Monomer	6–311++G(d, p)	245.038	127.28	52.3	141.54	133.86
	6–311+G(d)	245.74	126.72	51.09	141.18	135.14
Dimer	6–311++G(d, p)	246.72	106.79	75.19	142.9	101.56
	6–311+G(d)	247.37	106	73.92	142.43	102.77
Pentamer	6–311++G(d, p)	254.45	108.86	77.81	147.04	103.84
	6–311+G(d)	255.04	108.04	76.76	146.62	104.78
exp. [a]		246.6	89.6	76.60	137.6	91.5

[a] Experimental values of acetanilide from reference [7].

Table 3
Calculated ^{13}C NMR parameters of acetaminophen

Model	Basis set	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	$\Delta\sigma$
Monomer	6–311++G(d, p)	261.99	150.58	95.33	169.3	110.95
	6–311+G(d)	261.75	150.73	95.4	169.29	110.84
Dimer	6–311++G(d, p)	263.65	152.98	94.73	170.45	113.58
	6–311+G(d)	263.09	153.31	95.07	170.49	113.13
Pentamer	6–311++G(d, p)	253.52	165.88	92.1	170.5	117.60
	6–311+G(d)	253.31	166.27	92.05	170.55	117.74
exp. [a]		246.1	173.1	88.1	169.1	121.5

[a] Experimental values of acetanilide from reference [7].

2.1. Modeling the hydrogen bond network in crystalline acetaminophen

As mentioned above, acetaminophen in its crystalline structure makes extensive intermolecular hydrogen bonds with its neighboring molecules, to provide one with the chance to study the influence of these interactions on the chemical shielding tensors of the oxygen, nitrogen and carbon nuclei. However, to study systematically the H-bonding effects in crystalline acetaminophen, we used three molecular models in the quantum mechanical calculations. The first model involves of only one isolated acetaminophen molecule. This simplest model serves as a baseline for the chemical shielding calculations, in which there is no H-bonding interaction. Second model contains two acetaminophen molecules, molecules No. 1 and No. 2, where the target molecule interacts with the other via one N–H…O hydrogen bond; see Fig. 1. In this case, two molecular planes are perpendicular to each other. The main objective of taking this model into account is to investigate the N–H…O hydrogen bond effect on the chemical shielding tensors of the ^{17}O (2), ^{15}N and ^{13}C nuclei. Pentamer model involves all neighboring molecules that interact directly with the target acetaminophen molecule. This is the smallest unit of actual acetaminophen crystalline phase which consequently represents a complete quantitative description of the H-bond network around the target acetaminophen in crystalline lattice. As will be shown in the following sections, this model is able to produce quite satisfactory results for the chemical shielding calculations.

It might also mention that the dependency of the theoretically calculated chemical shielding and electric field gradient tensors on the molecular cluster size was also reported elsewhere [25–31]. Ludwig and et al. [32] concluded on the basis of calculation of the chemical shielding of *N*-methylacetamide that for the ^{1}H and ^{15}N chemical shielding tensors, considering a tetramer cluster is able to reproduce the strong cooperative properties compatible with the

Table 4
Orientation of calculated ^{17}O, ^{15}N and ^{13}C chemical shift tensors of the target acetaminophen molecule in pentamer cluster

Nucleus	δ_{ii}	Angle of the principal axes system/deg			Directional cosine of the principal axes system		
		x	*y*	*z*	*x*	*y*	*z*
O(1)	δ_{11}	32.72	77.06	119.48	0.84	0.22	−0.49
	δ_{22}	121.45	54.93	129.10	−0.52	0.57	−0.63
	δ_{33}	98.13	141.93	126.89	−0.14	−0.79	−0.60
O(2)	δ_{11}	127.95	93.18	38.13	−0.61	−0.06	0.79
	δ_{22}	40.46	107.67	55.01	0.76	−0.30	0.57
	δ_{33}	78.06	17.97	76.78	0.21	0.95	0.23
N	δ_{11}	160.95	106.99	98.40	−0.95	−0.29	−0.15
	δ_{22}	101.30	81.39	14.28	−0.20	0.15	0.97
	δ_{33}	105.15	19.16	101.47	−0.26	0.94	−0.20
C	δ_{11}	128.57	92.31	38.66	−0.62	−0.04	0.78
	δ_{22}	85.40	175.35	89.27	0.08	−1.00	0.01
	δ_{33}	38.94	85.95	51.36	0.78	0.07	0.62

experimental values found in the liquid phase. On the other hand, pervious study on the ^{17}O, ^{14}N and ^{2}H nuclear quadrupole coupling tensors in crystalline acetaminophen [16], demonstrates that a pentamer cluster is adequate for predicting the principal component and orientation of theoretical quadrupole coupling tensors which are in good agreement with available experimental data.

3. Results and discussion

In this study, chemical shielding tensors of the ^{17}O, ^{15}N and ^{13}C of crystalline acetaminophen were calculated to investigate the influences of the intermolecular H-bonding interactions. To achieve the objective, the calculations were performed on various molecular models including the monomer, dimer and pentamer of acetaminophen molecules. The H-bonding distances between the target molecule and its neighboring molecules in the solid phase are illustrated in Fig. 1. Chemical shielding tensor calculations were carried out at the B3LYP method using 6–311++G(d, p) and 6–311+G(d) basis sets. Tables 1–3 exhibit the calculated principal components, chemical shift isotropy and anisotropy of the ^{17}O, ^{15}N and ^{13}C nuclei in the monomer and the target molecule in the dimer and pentamer models of crystalline acetaminophen. A quick look at the results, reveals that the calculated parameters with the 6–311++G(d, p) and 6–311+G(d) basis sets are consistent with each other.

Fig. 1, which is constructed using X-ray diffraction data, shows that acetaminophen makes intermolecular hydrogen bonds in the solid phase. Considering this fact, an isolated gas phase (monomer), dimer and pentamer clusters were created. To demonstrate the importance of H-bonding interactions, three sets of calculations were performed. First we calculated the chemical shielding tensors for isolated molecule and then we did the same for target molecule in the dimer and pentamer clusters, respectively. Finally we compared the calculations for the monomer and target molecule. In the following sections, we will discuss the B3LYP/6–311++G(d, p) results of the chemical shielding calculations for the ^{17}O, ^{15}N and ^{13}C nuclei and orientation of their principal components in the molecular frame axes, separately.

^{17}O chemical shift tensors. In this section, we will focus on the ^{17}O chemical shift tensor calculations of crystalline acetaminophen. Fig. 2 shows the effects of H-bonding interactions on the ^{17}O chemical shift tensors through the change in the molecular models. At first glance, several general trends are observed from the calculated results. First, for both oxygen nuclei involved in the H-bonding interactions, the chemical shift isotropy results exhibit significant dependency on the cluster model used in the calculations. For example, monomer model predicts $\delta_{iso}=89.23$ ppm for O(1), whereas pentamer model yields $\delta_{iso}=104.92$ ppm. Second, for those nuclei contributing to the strong hydrogen bonds, the ^{17}O anisotropy value decrease significantly from the monomer to the pentamer; see Table 1. From the monomer to the target molecule in the dimer model, it is obvious that the principal components of chemical shift tensor of O(1) nucleus is influenced by the intermolecular interactions. More specifically, the principal component corresponding to the most shielding, δ_{33}, exhibits a remarkable sensitivity (ca. 14 ppm), whereas the change in the intermediate shielded component, δ_{22}, is quite small (ca. 1 ppm). This trend is in agreement with our previous theoretical study on anhydrous chitosan [15]. Since the changes in the δ_{11} and δ_{33} are of the opposite sign, the isotropy parameter of the chemical shift tensor exhibits no change on going

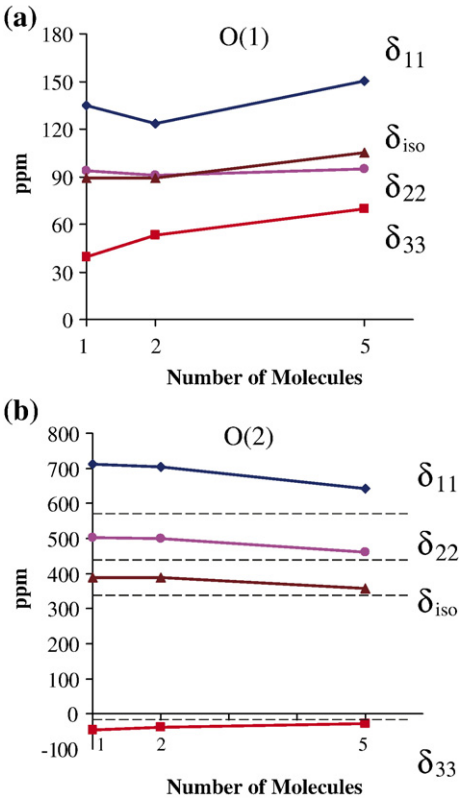

Fig. 2. Calculated (B3LYP/6–311++G(d, p)) ^{17}O chemical shift tensor components at (a) O(1) and (b) O(2) site of the monomer, dimer and pentamer models of crystalline acetaminophen. The dashed lines indicate the experimental values.

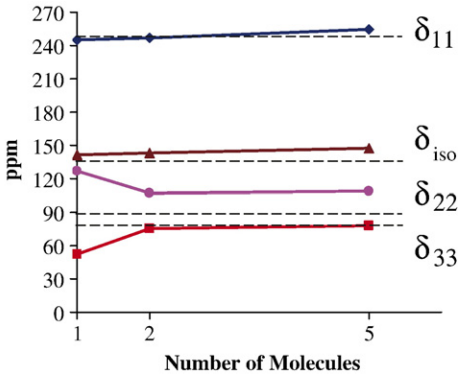

Fig. 3. Calculated (B3LYP/6–311++G(d, p)) ^{15}N chemical shift tensor components of the monomer, dimer and pentamer models of crystalline acetaminophen. The dashed lines indicate the experimental values.

from the monomer to the dimer model. Including the molecules No. 3–5, reveals the chemical shift tensor of the O(1) is influenced greatly by the H-bonding interactions, $\Delta\delta_{iso}$=15.69 ppm. Besides the difference in the H-bonding distances, $r_{N-H(2-1)...O(1-2)}$= 1.87 Å vs. $r_{O-H(1-1)...O(2-4)}$=1.73 Å, that contributes to the different charge distribution around the O(1), this nucleus also experiences different H-bonding nature, as a proton acceptor and proton acceptor/donor, from the dimer to the pentamer model, respectively. Interestingly, as compared with previous results on chitosan, the ^{17}O NMR parameters in the acetaminophen exhibit a considerably greater sensitivity to the hydrogen bond, indicating that O–H...O H-bonding interaction is much stronger in acetaminophen than in chitosan. These features reveal the importance of the O(1) nucleus in contributing to the O–H...O and N–H...O hydrogen bond interactions in the crystalline acetaminophen.

The calculated chemical shift tensor at the O(2) site also shows significant dependency on the H-bonding interactions; see Fig. 2. As Fig. 2 indicates, when the O–H(1–3)...O(2–1) interaction is considered in the pentamer model, the discrepancies between the calculated δ_{iso} and $\Delta\sigma$ values with the monomer results are increased, $\Delta\delta_{iso}$=30.85 and $\Delta(\Delta\sigma)$= 59.12 ppm. In addition, from the monomer to the target molecule in the pentamer cluster, H-bonding interactions decrease the δ_{11} and δ_{22} components whereas δ_{33} exhibits opposite tendency. As shown in Fig. 2, except for δ_{11} component of the ^{17}O(2) chemical shift tensor, the calculated results from the pentamer model are in good agreement with the experimental data [11]. First, δ_{11} overestimation is a typical difficulty in the ^{17}O chemical shielding DFT calculations as previously reported by Wu and co-workers [11,33]. Second, their work on the crystalline urea and acetanilide also showed that the cluster incompleteness and ignoring the long-range O═C–N–H...O═CNH intermolecular interactions can produce significant errors in the ^{17}O δ_{11} calculations. Third, the obtained theoretical calculations in this case were compared with the experimental ^{17}O NMR parameters of acetanilide. Since the interaction of the chemical shielding is fundamentally a local phenomenon, therefore, it is expected that any change in the nature of H-bonding interaction leads to a major error in the NMR calculations. Comparing two compounds, from the acetanilide to the acetaminophen, O...N changes to the O...O type H-bonding. Furthermore, the change in the hydrogen bond distance is also remarkable: from 2.96 Å in acetanilide [6] to 2.76 Å in acetaminophen [8].

^{15}N chemical shift tensor. In this section, the influence of the H-bonding interactions on the chemical shielding tensors at the site of the ^{15}N nucleus of the monomer as a baseline for the ^{15}N NMR tensors in acetaminophen and the target molecule in the dimer and pentamer models is discussed, see Table 2 and Fig. 3. The calculated NMR chemical shielding tensor was referred to the absolute nitrogen chemical shielding of ammonia at 20 °C; 244.6 ppm [23].

As shown in Fig. 1, the amide group of acetaminophen molecule in the dimer and pentamer models is involved as a proton donor group in a N–H...O hydrogen bond. Due to this participation in the H-bonding interaction, ^{15}N chemical shift tensor for the target molecule in the dimer and pentamer models deviates significantly from the monomer values. Although the δ_{11} and δ_{33} components increase from the monomer to the cluster, δ_{22} exhibits an opposite trend. More specifically, from the monomer to the target acetaminophen in the pentamer cluster, H-bonding interactions cause a 5.50 ppm increase in the ^{15}N δ_{iso} of the target molecule. It is also remarkable to see that the ^{15}N $\Delta\sigma$ value changes approximately 20 ppm depending on whether the acetaminophen molecule is in the monomer or in the pentamer cluster lattice. However, the comparison of the calculated NMR parameters with the experimental ^{15}N chemical shift tensor [7] also supports this assignment, see Table 2 and Fig. 3. This illustrates that the amide site of the target molecule in the pentamer model approximately feels the same chemical environment as in the actual acetanilide solid phase. In addition, the experimental study has been done at 298 K where our calculation has been performed on the acetaminophen crystalline structure determined in 293 K. Therefore, a portion of variation between the calculated and the experimental data can be attributed to this temperature difference.

^{13}C chemical shift tensor. As discussed above, the including of the H-bonding interactions in the calculations affect remarkably the chemical shift components of both ^{17}O and ^{15}N nuclei. In this part, we will discuss about the H-bonding

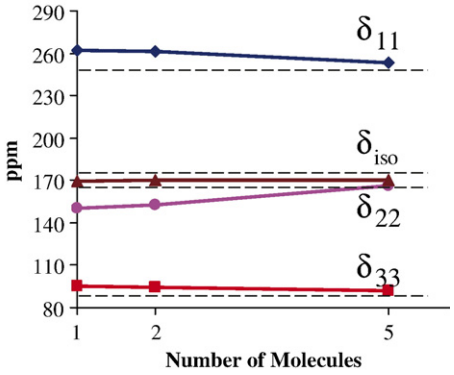

Fig. 4. Calculated (B3LYP/6–311++G(d, p)) ^{13}C chemical shift tensor components of the monomer, dimer and pentamer models of crystalline acetaminophen. The dashed lines indicate the experimental values.

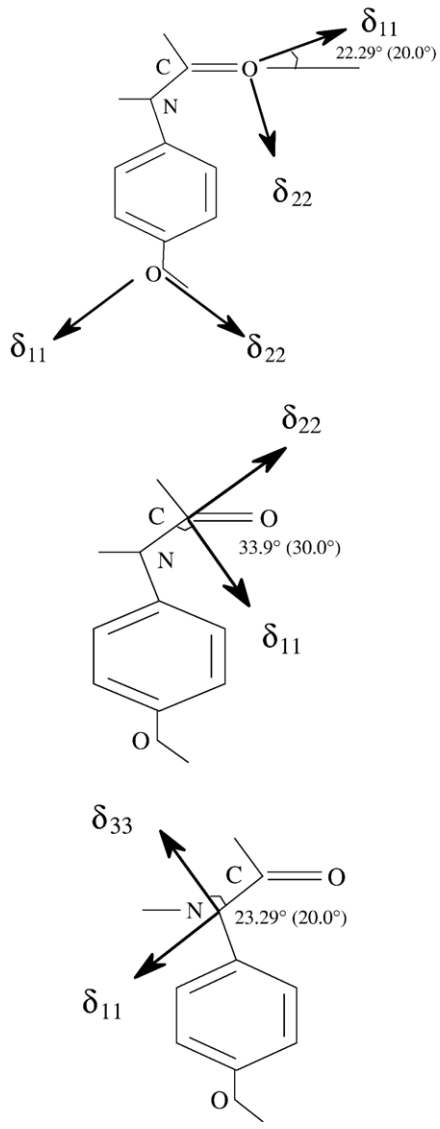

Fig. 5. Calculated relative orientations of the ^{17}O, ^{15}N and ^{13}C chemical shift tensors in acetaminophen. The values within the parentheses indicate the experimental values. (The component not represented is perpendicular to the molecular plane).

effects on the calculated ^{13}C chemical shift tensors. Table 3 shows the effects of the H-bonding interactions on the calculated ^{13}C chemical shift tensors. Consistent with the previous studies, H-bonding interactions decrease the ^{13}C isotropy values [34–37]. As Fig. 1 illustrates, the target molecule in the pentamer cluster makes one intermolecular H-bonding interaction via O═C–N functional group with the molecule No. 3. As seen from Table 3 and Fig. 4, results obtained from the both computational levels reveal that due to the H-bonding interactions, the δ_{iso} of the ^{13}C is decreased by 1.20 ppm from the monomer to the target molecule in the pentamer model. As another interesting trend observed in Table 3 and Fig. 4, both δ_{11} and δ_{22} components show a remarkable dependency to the H-bonding network. Including the H-bonding interactions makes approximately a 7 and 15 ppm reduction in δ_{11} and δ_{22}, respectively, from the monomer to the target molecule in the pentamer model. This trend also is reflected in the anisotropy parameter. For example, $\Delta\sigma$ value increases approximately 7 ppm depending upon whether the acetaminophen molecule is in the monomer or in the pentamer cluster.

The availability of ^{13}C solid state NMR experimental data [7] on acetanilide allows for additional examination of the accuracy of our calculated data. As the results of Fig. 4 illustrate, our calculated ^{13}C principal components values meet reasonably the experimental values. In addition, the calculated δ_{11}, δ_{22} and δ_{33} components deviate only 3.0, 2.4 and 0.8% from the experimental values, respectively. Clearly, remaining small disagreement between the calculated and experimental data may be largely attributed to the neglecting other intermolecular interactions produced by the neighboring acetaminophen molecules not directly involved in the H-bonding network. Similar lattice interactions resulted from the neighbor molecules has been previously observed for the ^{13}C chemical shielding calculations on α-glycine [34].

3.1. Orientation of chemical shielding principal components in the molecular frame axes

High level quantum chemical calculations have proven to be an excellent approach for obtaining chemical shift tensor orientations in the molecular frame axes. Previously, Wu et al. have indicated that quantum chemical calculation at the B3LYP/6–311++G(d, p) level can produce reliable results for the chemical shielding tensor orientations, although the magnitude of the individual principal components computed by this level is less accurate [38]. Therefore, at this point, it is of much interest to characterize the relative orientation of the ^{17}O, ^{15}N and ^{13}C chemical shift tensors in the molecular frame of axes. To fulfill this aim, the calculated chemical shielding tensors of the oxygen, nitrogen and carbon atoms have been analyzed systematically to obtain their relative orientations, see Fig. 5. Furthermore, the angles and direction cosines of the PAS of the ^{17}O, ^{15}N and ^{13}C chemical shift components for the target acetaminophen molecule in the pentamer cluster were calculated at the B3LYP/6–311++G(d, p) level and tabulated in Table 4.

As Fig. 5 shows, it is remarkable to see that the orientation of the principal components of chemical shift tensor at the oxygen sites is different. It is well-known that for ^{17}O nucleus involved in a carbonyl group, the most contribution to the paramagnetic shielding is expected to be from the $n\rightarrow\pi^*$ mixing [39,40]. This is expected, since the contribution of two other mixing, $\sigma\rightarrow\pi^*$ and $\pi\rightarrow\sigma^*$, in carbonyl compounds is negligible. However, this suggests that the direction along the C═O bond should give rise to the least shielded environment at the oxygen nucleus. As Fig. 5 represents, the least shielded component, δ_{11}, of the O(2) atom tilts 22.29° from the C–N bond direction. However, this calculated value is in reasonably good agreement with the experimental value; $\angle\delta_{11}-C-N=20°$. On the other hand, the δ_{22} component lies in the molecular plane and is approximately perpendicular to the C═O bond. This general observation was found to be essentially the same with respect to the other carbonyl compounds such as amides [26,29,33], peptides [41], ketones

[42] and carboxylic acids [30,43]. In comparison to the O(2), the obtained relative orientation of chemical shift components illustrates that from the difference in the chemical environments, δ_{11} of the O(1) nucleus orientates along the O–H bond direction and makes a small angle with this bond; see Fig. 5.

It is indicated from Fig. 5 that at the nitrogen site, the unique component of the chemical shift tensor is δ_{22} that orientates normal to the amide plane whereas the δ_{33} component makes a 23.47° angle with the N–C bond direction. Since δ_{11} and δ_{33} are both in-plane components, the paramagnetic shielding contribution to each of these must be governed by out-of-plane excitation, i.e. $\sigma \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$. Interestingly, for the ^{13}C also the situation is fundamentally same as the experimentally available data [7]. As depicted in Fig. 5, δ_{33} tends to lie perpendicular to the molecular plane where the least shielded component is tilted 33.9° from C–N direction which differs only 3.9° from the experimentally obtained orientation for acetanilide.

3.2. Concluding remarks

We have presented a theoretical investigation of the ^{17}O, ^{15}N and ^{13}C chemical shielding tensors for crystalline acetaminophen. On the basis of the results obtained in this investigation, it is concluded that the chemical shielding tensors of the oxygen, nitrogen and carbon nuclei in the H-bonding interactions are appropriate parameters to characterize the property of these interactions. Our obtained results indicated that the calculated ^{17}O, ^{15}N and ^{13}C NMR parameters change via H-bonding interactions within the molecular clusters. Considering the available experimental and theoretical errors in determination of the NMR parameters, the calculated principal components, δ_{ii}, δ_{iso} and $\Delta\sigma$ values of the ^{17}O, ^{15}N and ^{13}C nuclei meet reasonably the available experimental values. There is also a remarkable reduction in the δ_{iso} value of the O(2) whereas O(1) shows apposite trend from the monomer to the target molecule in the pentamer model. It is noteworthy to mention that considering the results obtained for the nitrogen and carbon nuclei reveal the important role of O═CNH group in contributing to the H-bonding interactions in the crystalline acetaminophen. Moreover, the quantum mechanical calculation demonstrate that intermolecular H-bonding interactions play an essential role in determining the relative orientation of the principal components of the ^{17}O, ^{15}N and ^{13}C chemical shift tensors. All calculated orientations are in reasonable agreement with the reported experimental data. Specifically, for the $^{17}O(2)$ nucleus, the intermediate principal component, δ_{22} lies approximately along the C═O bond and tilts 22.9° from this bond direction.

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