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DFT calculations of the ^{1}H chemical shifts and ^{13}C chemical shift tensors of retinal isomers

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Abstract

An ab initio study on the accuracy of the prediction of ^{13}C isotropic chemical shifts and nuclear magnetic shielding tensors of several geometric isomers of retinal within the density functional theory framework at the B3LYP/6-31G level is presented. In addition, the accuracy of the calculated ^{1}H chemical shifts of the vinyl protons is investigated. The results are compared with available experimental data from solution and solid-state NMR. The calculated ^{13}C isotropic chemical shifts in the conjugated chain of the retinal isomers are in reasonable agreement with the experiment with a rms error of 4.1 ppm and a correlation coefficient $\rho = 0.982$. For the calculated ^{1}H isotropic chemical shifts of the vinyl protons, the overall rms error is 0.5 ppm and the correlation coefficient is $\rho = 0.993$. We conclude that, even with a small basis set, density functional theory provides a valuable tool in the prediction of ^{13}C NMR properties. A larger basis set is recommended to predict ^{1}H chemical shifts.

Keywords: Retinal-isomers; DFT; ^{13}C NMR tensor; ^{1}H NMR chemical shifts; Rhodopsin

1. Introduction

The geometric isomers of retinal serve as chromophores in light-transducing proteins, specifically rhodopsin, isorhodopsin and bacteriorhodopsin. Bovine rhodopsin is the photoreceptor protein that is responsible for dim light vision in vertebrates. The light-absorbing ligand in rhodopsin is a retinylidene group with a 6-s-*cis*-11-*cis*-12-s-*trans* conformation that is covalently bound to the Lys296 residue of the protein backbone by means of a protonated Schiff base linkage [1]. The visual cycle is initiated by an 11-*cis* to all-*trans* isomerization of the retinylidene chromophore upon absorption of a photon [2]. This process is completed within 200 fs with a quantum yield of 0.67, and is one of the fastest photochemical reactions [3,4]. In isorhodopsin, an analog of rhodopsin, the retinylidene chromophore assumes a 9-*cis* conformation. As in rhodopsin, the primary event in the photocycle is isomerization of the ligand to an all-*trans* conformation, but in this case the kinetics are much slower: the isomerization process takes place in 600 fs, and the corresponding quantum yield drops to 22% [5,6]. Bacteriorhodopsin is the protein pigment of the purple membrane of the microorganism *Halobacterium halobium* and serves as a light-driven pump of protons through the cell membrane. The light-absorbing ligand in bacteriorhodopsin is an all-*trans* retinylidene group that is covalently bound to the surrounding protein by means of a protonated Schiff base to the Lys216 residue [7]. The primary event in the proton-pumping photocycle is isomerization of the chromophore from all-*trans* to a 13-*cis* conformation upon illumination. This process takes place within 500 fs with a quantum yield of 60% [8,9].

The high efficiencies and quantum yields of the pigments are related to the fundamental structural properties of the retinylidene chromophores and their interactions with the corresponding protein environment. A large part of the structural characteristics of both rhodopsin and bacteriorhodopsin have been elucidated by various spectroscopic studies, including UV/VIS, solid-state NMR, FTIR, resonance Raman and X-ray diffraction, but the knowledge about

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the chromophore on the molecular level is still insufficient. Additional insight can be provided by theoretical modeling studies. Several ab initio studies on the spatial and electronic structure of the chromophore have already been performed [10–16]. An additional aid in resolving the essential details of the electronic structure of rhodopsin is the theoretical prediction of ^{1}H and ^{13}C NMR properties. For this purpose it is important to examine the accuracy that can be obtained with the available theoretical methods. In a previous study the ^{13}C NMR properties of retinylidene iminium salts have been studied within the density functional theory framework using the technique described by Mauri et al. [17,18]. In this paper we will discuss the accuracy of the calculation of ^{13}C nuclear magnetic shielding tensors and ^{1}H chemical shifts performed within the density functional theory (DFT) framework using the gauge invariant atomic orbital (GIAO) technique on several geometric isomers of retinal, i.e. all-*trans*-retinal, 13-*cis*-retinal, 11-*cis*-retinal and 9-*cis*-retinal [19,20]. For 11-*cis*-retinal, two distinct conformations have been studied, i.e. 11-*cis*-12-s-*cis* and 11-*cis*-12-s-*trans*. All model compounds are in the 6-s-*cis* conformation. The chemical structures of the model compounds and the corresponding numbering schemes used are shown in Fig. 1.

2. Computational methods

The ground state equilibrium structure and the ^{13}C NMR chemical shifts tensors of the retinals have been determined within the density functional theory framework [19]. The geometry optimization has been performed using gradient corrections to the local density approximation (LDA) in the form proposed by Becke and Perdew (BP86) [21–23]. This functional has been chosen for consistency with our previous work [10–13]. Only the valence electrons have been treated explicitly. The interaction with the inner core electrons is described by using soft first-principles pseudopotentials in the form proposed by Vanderbilt [24]. The Kohn–Sham single particle wavefunctions are expanded on a plane wave basis set with an energy cut-off of 25 Ry. The expansion of the wavefunctions in terms of plane waves implies the use of periodic boundary conditions. The simulation box has been chosen $30\times20\times20$ au^3, which is sufficiently large to avoid interaction with the images. The optimization of the electronic wavefunctions and the atomic positions has been performed using the direct inversion in the interactive subspace (DIIS) algorithm [25].

The calculation of the nuclear magnetic shielding tensor has been performed within the density functional theory

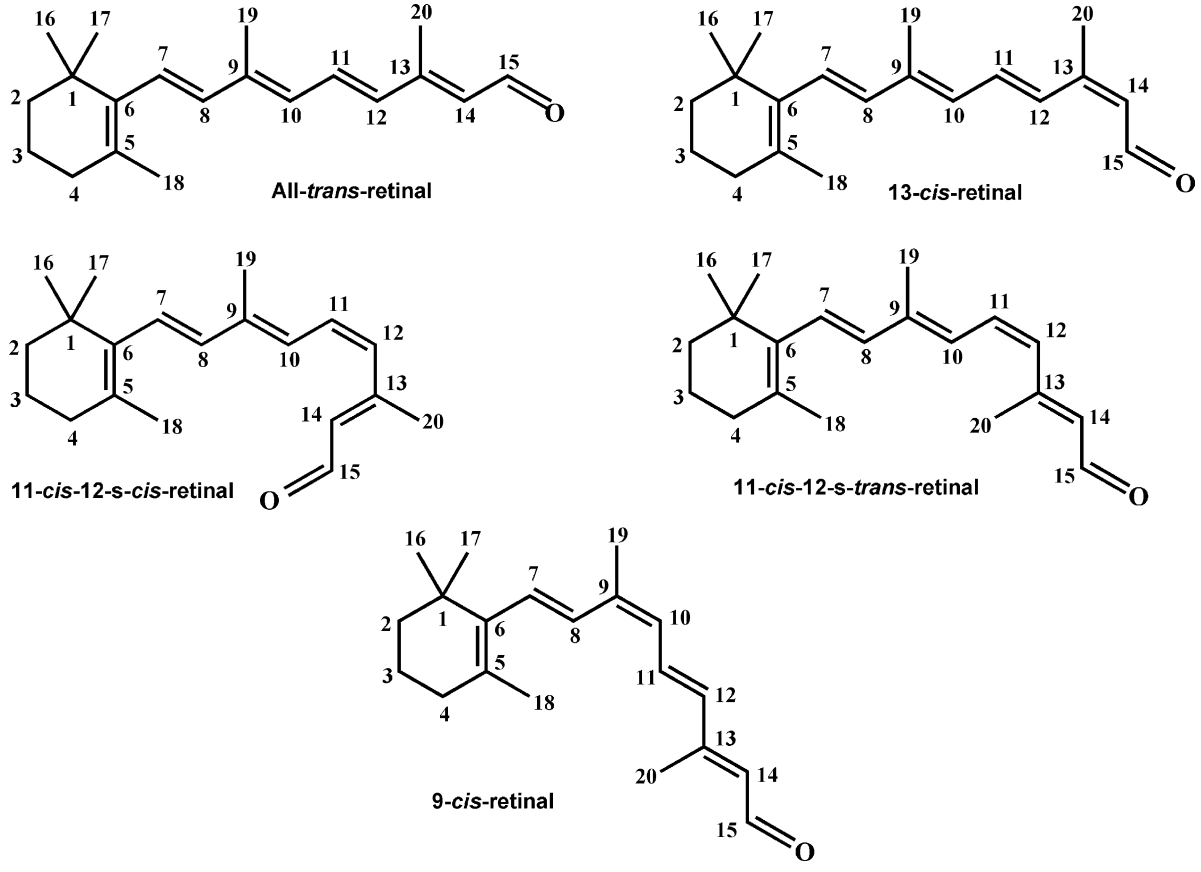

Fig. 1. Chemical structure of all-*trans*, 13-*cis*, 11-*cis*-12-s-*cis*, 11-*cis*-12-s-*trans* and 9-*cis* isomer of retinal. The numbering is in accordance to the International Union of Pure and Applied Chemistry rules for retinals.

framework, using the hybrid B3LYP exchange-correlation functional [26,27]. The B3LYP functional is the most widely used functional for predicting NMR properties. The calculations employed the GIAO method with the 6-31G GAUSSIAN basis set [20,28]. The isotropic ^{13}C chemical shifts δ_{iso}, and the principle components of the chemical shift tensor δ_{11}, δ_{22}, and δ_{33} are quoted in parts per million (ppm) relative to the ^{13}C chemical shift of tetramethylsilane (TMS), i.e. $\sigma_{iso} = 194.42$ ppm. Similarly, the isotropic ^{1}H chemical shifts are quoted in parts per million (ppm) relative to the ^{1}H chemical shift of tetramethylsilane (TMS), i.e. $\sigma_{iso} = 32.79$ ppm. These values have been determined theoretically by applying the same level of theory on an isolated molecule of TMS.

The accuracy of the calculated chemical shifts has been assessed by determining the correlation with the experimental values. For any physical quantity x, the correlation coefficient ρ between the values of calculated quantities x_c and experimental quantities x_m is defined as:

$$\rho = \frac{\sum_{i=1}^{N} \Delta x_{m,i} \Delta x_{c,i}}{\sqrt{\sum_{i=1}^{N} \Delta x_{m,i}^2 \sum_{i=1}^{N} \Delta x_{c,i}^2}} \quad (1)$$

In Eq. (1) $\Delta x_{m,i}$ is the deviation of the measured value from the mean experimental value. Similarly, $\Delta x_{c,i}$ is the deviation of the calculated value from the mean calculated value.

The geometry optimizations have been performed using the CPMD program package [29]. The nuclear magnetic shielding tensors have been calculated with GAUSSIAN98 [30].

3. Results

We have calculated the ^{13}C NMR magnetic shielding tensors of our model compounds using density functional theory. Table 1 summarizes the ^{13}C isotropic chemical shifts of the model compounds and reports the corresponding experimental values [31,32]. For comparison with experimental values obtained by solution NMR, the calculated isotropic shifts for the 11-*cis*-12-s-*trans* and 11-*cis*-12-s-*cis* isomers have been averaged, since in solution both conformations are present. Averaged over all retinal-isomers, the overall rms error is 4.7 ppm and the correlation coefficient is $\rho = 0.998$. If only the conjugated carbon atoms are considered, the overall rms error for the isotropic shifts is 4.1 ppm, and the corresponding correlation coefficient is $\rho = 0.982$.

The ^{13}C magnetic shielding tensors of retinals contain valuable information with respect to the electronic structure, complementary to the isotropic shift. To obtain this additional information, we have calculated the ^{13}C magnetic shielding tensors within the density functional theory framework. The calculated principal Cartesian components of the ^{13}C chemical shift tensor and the corresponding isotropic chemical shifts of the carbon atoms in the conjugated chain of the model compounds are reported in

Table 1
Calculated and experimental isotropic ^{13}C chemical shifts for all-*trans*, 13-*cis*, 11-*cis*, and 9-*cis* isomers of retinal

Carbon atom	All-*trans*-retinal		13-*cis*-retinal		11-*cis*-retinal		9-*cis*-retinal	
	Exp.[a]	DFT	Exp.[a]	DFT	Exp.[b]	DFT	Exp.[a]	DFT
C1	34.1	35.9	34.3	37.6	32.9	37.3	34.1	37.4
C2	39.6	41.1	39.7	41.2	38.4	40.3	39.7	41.1
C3	19.3	20.6	19.3	21.4	17.9	20.1	19.3	21.0
C4	33.2	33.2	33.2	35.4	31.6	33.5	33.2	36.1
C5	130.3	128.7	130.3	131.0	128.5	131.7	130.4	132.5
C6	137.6	136.7	137.6	136.2	136.5	138.6	138.1	139.4
C7	129.6	134.8	129.6	128.7	127.9	130.9	131.1	128.9
C8	137.1	131.1	137.0	133.4	136.5	134.7	129.4	127.0
C9	141.1	140.8	141.3	136.3	139.7	140.6	140.0	136.4
C10	129.4	122.7	129.4	132.5	125.0	125.6	127.9	128.9
C11	132.4	130.3	133.4	125.3	129.6	128.8	131.2	125.5
C12	134.5	127.0	126.5	126.3	129.6	127.1	133.8	132.6
C13	154.5	147.1	154.2	144.4	153.9	148.0	154.3	146.4
C14	128.9	124.0	127.7	123.4	128.7	124.3	128.9	126.7
C15	190.7	192.3	189.6	192.5	189.2	193.0	190.6	195.1
C16	29.0	33.5	29.0	29.7	27.3	31.2	29.0	31.2
C17	29.0	39.3	29.0	33.1	27.3	32.2	29.0	31.9
C18	21.7	29.8	21.7	22.9	19.9	24.5	21.8	26.6
C19	13.0	17.2	13.0	14.2	10.4	27.5	20.9	24.0
C20	13.0	18.0	21.1	22.0	15.9	18.5	13.2	14.4

All values are reported in ppm relative to TMS.
[a] Data from G. Englert [31].
[b] Data from R. Rowan III and B.D. Sykes [32].

Table 2
Calculated principal Cartesian components of the ^{13}C chemical shift tensor in the conjugated chain of the all-*trans*, 13-*cis*, 11-*cis*-12-s-*cis* and 11-*cis*-12-s-*trans*, and 9-*cis* isomers of retinal

Carbon atom	All-*trans*-retinal				13-*cis*-retinal				11-*cis*−12-s-*cis*-retinal				11-*cis*-12-s-*trans*-retinal				9-*cis*-retinal			
	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	δ_{iso}
C5	214.0	143.8	28.2	128.7	213.5	150.7	28.7	131.0	216.0	150.7	27.1	131.3	218.9	148.4	29.3	132.2	217.6	151.0	28.9	132.5
C6	224.8	130.2	55.0	136.7	223.1	138.3	47.3	136.2	223.8	138.2	50.0	137.4	224.4	140.9	54.4	139.9	226.5	143.9	47.8	139.4
C7	226.9	148.4	29.0	134.8	219.5	137.3	29.3	128.7	220.8	142.8	28.8	130.8	221.0	144.6	27.6	131.0	215.2	141.3	40.3	128.9
C8	219.7	126.4	47.0	131.1	216.6	128.0	55.4	133.4	219.2	129.6	52.1	133.7	218.8	127.7	60.5	135.7	217.7	134.3	29.2	127.0
C9	227.3	163.5	31.6	140.8	219.0	160.8	29.2	136.3	227.7	165.7	28.9	140.8	224.7	166.7	30.1	140.5	221.6	159.7	27.8	136.4
C10	199.2	127.8	41.1	122.7	207.9	124.2	65.5	132.5	202.7	133.4	37.0	124.4	206.2	132.1	42.3	126.9	206.9	118.5	61.3	128.9
C11	226.6	140.0	24.2	130.3	209.9	145.5	20.4	125.3	222.8	136.5	25.5	128.2	222.6	138.8	26.9	129.4	217.1	141.7	17.8	125.5
C12	202.7	131.1	47.1	127.0	209.4	129.8	39.6	126.3	215.5	121.4	43.9	126.9	209.4	124.5	47.9	127.2	209.7	131.1	57.1	132.6
C13	241.2	172.9	27.2	147.1	242.8	167.7	22.8	144.4	245.3	169.1	28.7	147.7	241.9	174.9	28.1	148.3	240.0	173.9	25.3	146.4
C14	195.6	122.0	54.5	124.0	195.7	116.0	58.4	123.4	197.0	125.7	45.3	122.7	198.0	122.9	56.6	125.9	197.7	123.3	59.1	126.7
C15	289.7	206.8	80.5	192.3	288.9	212.9	75.8	192.5	287.9	206.0	79.2	191.0	293.2	213.5	78.5	195.1	293.3	212.0	80.1	195.1

All values are reported in ppm relative to TMS.

Table 2. Table 3 reports the calculated and experimental ^{1}H isotropic chemical shifts of the vinyl protons [33]. Again, for comparison with experimental values obtained by solution NMR, the calculated isotropic shifts for the 11-*cis*-12-s-*trans* and 11-*cis*-12-s-*cis* isomers have been averaged. The overall rms error is 0.5 ppm and the correlation coefficient is $\rho = 0.993$.

4. Discussion

The calculated isotropic ^{13}C chemical shifts of the carbon atoms in the polyene chain of the retinal isomers and the corresponding experimental value are illustrated in Fig. 2.

The calculated and experimental values are in reasonable agreement for all four isomers. Specifically, the correlation coefficient is $\rho = 0.979$ for all-*trans*-retinal, $\rho = 0.976$ for 13-*cis*-retinal, $\rho = 0.986$ for 11-*cis*-retinal and $\rho = 0.985$ for 9-*cis*-retinal. The rms errors are 4.8, 4.7, 3.1 and 3.7 ppm, respectively. The results are consistent with previous plane-wave pseudopotential calculations on neutral retinylidene compounds, thus showing that the computed chemical shifts are not very sensitive to the specific basis set used [17]. The best agreement is obtained for 11-*cis*-retinal. This can be ascribed partly to the fact that we averaged the calculated results for the 11-*cis*-12-s-*cis* and 11-*cis*-12-s-*trans* conformations. The theoretical values were compared with ^{13}C chemical shift values measured in solution, were the different conformations are both present. As a result the measured values represent an average over all conformations present in the solution. The 11-*cis*-12-s-*cis* conformation is energetically favorable over the 11-*cis*-12-s-*trans* conformation, due to the absence of the steric hindrance between the C-13 methyl group and the proton bound to C-10 in the former conformation. Thus, the equilibrium in solution will be shifted toward the 11-*cis*-12-s-*cis* form.

cis–trans isomerization causes upfield shifts of the ^{13}C resonances at one bond distance from the isomerized bond itself, due to steric interactions between protons across *cis* linkages [32]. Solution spectra of retinal isomers have shown that ^{13}C-12 of 13-*cis*-retinal is upfield shifted by 8 ppm from the corresponding

Table 3
Calculated and experimental isotropic ^{1}H chemical shifts for the vinyl hydrogen atoms in the all-*trans*, 13-*cis*, 11-*cis*, and 9-*cis* isomers of retinal

Hydrogen atom	All-*trans*-retinal		13-*cis*-retinal		11-*cis*-retinal		9-*cis*-retinal	
	Exp.[a]	DFT	Exp.[a]	DFT	Exp.[a]	DFT	Exp.[a]	DFT
H7	6.36	7.18	6.35	6.89	6.32	7.01	6.31	6.84
H8	6.18	6.54	6.18	6.58	6.14	6.42	6.64	6.95
H10	6.20	6.38	6.23	6.28	6.54	6.79	6.06	6.35
H11	7.15	7.62	7.05	6.98	6.69	7.00	7.20	7.28
H12	6.37	6.52	7.28	7.46	5.92	6.26	6.27	6.51
H14	5.98	6.15	5.85	6.00	6.07	6.29	5.94	6.16
H15	10.12	11.27	10.20	11.52	10.10	11.14	10.07	11.29

All values are reported in ppm relative to TMS.
[a] Data from D.J. Patel [33].

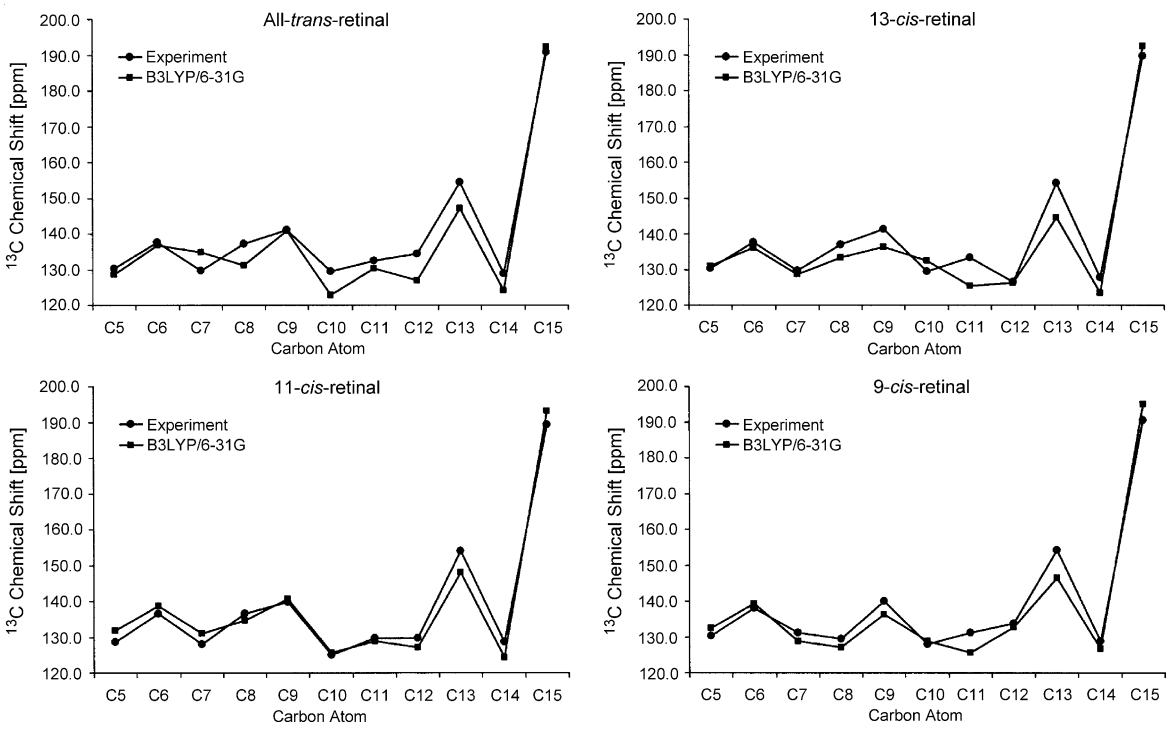

Fig. 2. Calculated ^{13}C NMR chemical shift in the conjugated backbone chain of retinal isomers compounds compared with the experimental ^{13}C NMR chemical shifts measured in solution [31,32]. All values are reported in ppm relative to TMS.

all-*trans* isomer. Similarly, ^{13}C-10 of 11-*cis*-retinal shows an upfield shift of 4.4 ppm from 13-*cis*-retinal, and ^{13}C-8 of 9-*cis*-retinal shows an upfield shift of 7.1 ppm from the 11-*cis* isomer [31,32]. These trends are well reproduced by our DFT calculations.

For all isomers, the calculated ^{13}C isotropic chemical shift of C-13 exhibits an appreciable deviation from the experimental value in the upfield direction. The largest deviation is observed for the 13-*cis*-retinal, for which the calculated value is 9.8 ppm below the experimental value. These discrepancies are most probably due to the poor description of the polarizability of long conjugated chains by the commonly used exchange-correlation functionals [34].

Fig. 3 presents a comparison of the experimental and calculated values of the principle Cartesian components of the ^{13}C chemical shift tensor for the carbon atoms in the conjugated chain of all-*trans*-retinal [35]. The agreement between the experiment and the theory is very good. Especially, the odd–even oscillations in the δ_{33} component, which is oriented perpendicular to the plane of the conjugate chain, are reproduced well, with a rms error of 5.4 ppm and the correlation coefficient $\rho = 0.967$. The in-plane components of the chemical shift tensor, δ_{11} and δ_{22}, are sensitive to the π-electron distributions and the accuracy of the calculated values are expected to be more subject to the particular exchange-correlation functional used in the calculations. Specifically, the rms errors for the δ_{11} and δ_{22} components are 11.9 and 8.4 ppm, and the corresponding correlation coefficient are $\rho = 0.909$ and 0.945, respectively. As for the isotropic ^{13}C chemical shifts, the accuracy of the calculated ^{13}C tensor elements is very similar to that obtained with previous plane-wave pseudopotential calculation on all-*trans*-retinal, again indicating that the results do not depend strongly on the specific basis set used [17]. Thus, although plane wave basis calculations are more appropriate to describe the periodicity in the crystal, the performance of the small 6-31G basis set for the prediction of ^{13}C NMR properties is similar to the computationally much more expensive plane wave basis set.

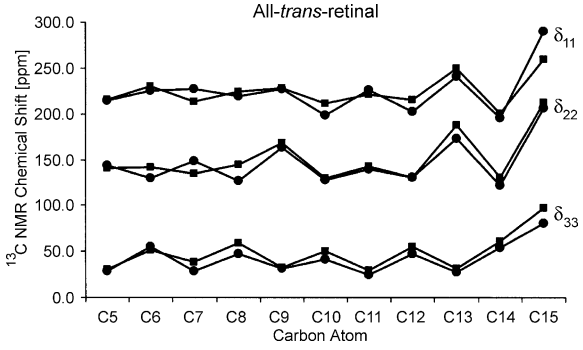

Fig. 3. Calculated (●) versus experimental (■ [35]) principal Cartesian components of the ^{13}C NMR chemical shift tensor in the conjugated backbone chain of all-*trans*-retinal. All values are reported in ppm relative to TMS.

The largest difference between the ^{13}C NMR properties of the 12-s-*cis* and 12-s-*trans* conformational isomers of 11-*cis*-retinal is observed in the δ_{33} component of the chemical shift tensor for C-14. In the 12-s-*cis* conformation this component is 45.3 ppm, while in the 12-s-*trans* conformation this value is 56.6 ppm. For the other geometric isomers, i.e. all-*trans*, 13-*cis*, and 9-*cis*, this component assumes the values 54.5, 58.5 and 59.1, respectively. The reduced value for the 11-*cis*-12-s-*cis* isomer reflects the steric interaction of the proton bound to C-14 with the proton on C-10.

For the calculated ^{1}H isotropic chemical shifts of the vinyl protons, the overall rms error is 0.5 ppm and the correlation coefficient is $\rho = 0.993$. Although this accuracy seems reasonable, closer inspection of Table 3 reveals some large discrepancies. For example, the experimental solution spectra of retinal isomers have shown that ^{1}H-11 of 13-*cis*-retinal is upfield shifted by only 0.10 ppm from the corresponding all-*trans* isomer, while the DFT calculations predict a downfield shift of 0.64 ppm. Thus, the accuracy obtained with the B3LYP/6-31G DFT calculations is not sufficient for predictions of experimental trends in the ^{1}H NMR chemical shifts. For more accurate calculations of the ^{1}H shifts, we recommend to use a large basis set that includes polarization functions.

5. Conclusions

We have calculated the ground state structures and the nuclear magnetic shielding tensors of the all-*trans*, 13-*cis*, 11-*cis*-12-s-*cis*, 11-*cis*-12-s-*trans* and 9-*cis* isomers of retinal, within the density functional theory framework. We applied the GIAO method in combination with the hybrid B3LYP exchange-correlation functional and the 6-31G basis set. The calculated ^{13}C isotropic chemical shifts in the conjugated chain of the retinal isomers are in reasonable agreement with the experiment with an overall rms error of 4.1 ppm and a correlation coefficient $\rho = 0.982$. Although the absolute values of the calculated isotropic ^{13}C chemical shifts and the principal Cartesian components of the ^{13}C chemical shift tensor are not in quantitative agreement with the experiment, qualitative trends observed in the measurements are well reproduced. Thus, it can be concluded that, even with a small basis set, density functional theory provides a valuable tool in the prediction of ^{13}C NMR properties. For the calculated ^{1}H isotropic chemical shifts of the vinyl protons, the overall rms error is 0.5 ppm and the correlation coefficient is $\rho = 0.993$. For the predictions of experimental trends in the ^{1}H NMR chemical shifts this accuracy is not sufficient. A larger basis set that includes polarization functions is recommended for more accurate results.

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