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Isotropic magnetic shielding constants of retinal derivatives in aprotic and protic solvents

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We investigate the nuclear isotropic shielding constants $\sigma(^{13}C)$ and $\sigma(^{17}O)$ of isomers of retinoic acid and retinal in gas-phase and in chloroform, acetonitrile, methanol, and water solutions via Monte Carlo simulation and quantum mechanics calculations using the GIAO-B3LYP/6-311++G(2d,2p) approach. Electronic solute polarization effects due to protic and aprotic solvents are included iteratively and play an important role in the quantitative determination of oxygen shielding constants. Our MP2/6-31G+(d) results show substantial increases of the dipole moment of both retinal derivatives in solution as compared with the gas-phase results (between 22% and 26% in chloroform and between 55% and 99% in water). For the oxygen atoms the influence of the solute polarization is mild for $\sigma(^{17}O)$ of hydroxyl group, even in protic solvents, but it is particularly important for $\sigma(^{17}O)$ of carbonyl group. For the latter, there is a sizable increase in the magnitude with increasing solvent polarity. For the carbon atoms, the solvent effects on the $\sigma(^{13}C)$ values are in general small, being more appreciable in carbon atoms of the polyene chain than in the carbon atoms of the β-ionone ring and methyl groups. The results also show that isomeric changes on the backbones of the polyene chains have marked influence on the ^{13}C chemical shifts of carbon atoms near to the structural distortions, in good agreement with the experimental results measured in solution. © *2013 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4819694]

I. INTRODUCTION

Photophysical properties of retinal derivatives have been a subject of longstanding interest because they play an important role in photobiological process of the vision.[1–4] A photoisomerization process of a retinal chromophore is usually referred to as the primary step of the phototransduction mechanism in animals. Upon light absorption, the photoisomerization based on the *cis-trans* change of a retinal derivative (11-*cis* protonated Schiff base) triggers the activity of the rhodopsin, a prototype for the visual pigments located in the retina.[1,2] Even though spectroscopic properties of the chromophores are modified by the surrounding environment formed by the protein,[5] the study of electronic properties of geometric isomers of retinal derivatives in solution is important to a better understanding of this complex biological process.

Nuclear magnetic resonance (NMR) spectroscopy has shown some interesting results with respect to the conformational modifications of retinal molecules.[6–8] For example, Rowan and Sykes[6] have reported the ^{13}C NMR spectra of all-*trans*-, 9-*cis*-, 11-*cis*-, and 13-*cis*-retinals in solution. Their results showed that *cis-trans* isomerization causes upfield changes of the chemical shifts of carbon atoms near to the isomeric changes but for carbons far from the point of isomerization they are very similar to those of all-*trans*-retinal. A similar effect of *cis-trans* isomerization has been noted on the ^{13}C chemical shielding tensors of retinal derivatives in solid phase.[7] From a theoretical point of view, a previous investigation of ^{13}C chemical shifts for these isomers of retinal in gas-phase[9] have been obtained within the density functional theory (DFT) using the gauge invariant atomic orbital (GIAO)[10] method. The theoretical results were in general agreement with the experimental results measured in solution, although the former has overestimated the chemical shifts in upfield direction. Other theoretical studies have addressed the important role played by the protein environment effects,[11] but in this study we report a NMR investigation of the structural and functional properties of retinal derivatives in aprotic and protic solvents, which allow a meaningful comparison with available experimental results.

The isotropic magnetic shielding constants $\sigma(^{13}C)$ and $\sigma(^{17}O)$ of retinoic acid and retinal isomers in solution reported in this paper are based on the sequential Monte Carlo simulation/quantum mechanics (S-MC/QM) methodology.[12] In this approach, solute-solvent configurations are generated by the MC simulation and quantum mechanical calculations are performed on these configurations composed of one solute molecule surrounded by several solvent molecules treated as point charges or/and as explicit molecules. For the QM calculation of the NMR properties, we use the GIAO-DFT approach that offers a good compromise between computational cost and accuracy.[13,14] We verify that all values reported here are statistically converged. Four polar solvents were considered, being two aprotic solvents [chloroform ($CHCl_3$) and acetonitrile (CH_3CN)] and two protic solvents [methanol

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(CH_3OH) and water (H_2O)]. The compounds studied here have been divided into two groups and termed according to Ref. 15: retinoic acid isomers (09-*cis*-retinoic acid – 09CAR, 11-*cis*-retinoic acid – 11CAR, 13-*cis*-retinoic acid – 13CAR, and all-*trans* retinoic acid – ATAR) and retinal isomers (09-*cis*-retinal – 09CRA, 11-*cis*-retinal – 11CRA, 13-*cis*-retinal – 13CRA, and all-*trans*-retinal – ATRA) defined by carboxyl and aldehyde functional groups, respectively. In this study we pay particular attention to the solute polarization effect for describing the isotropic shielding constants of retinal chromophores in aprotic and protic solvents. In addition, the dependence of these properties on hydrogen bonds (HBs) has been analyzed in water. To our knowledge, this is the first theoretical investigation of the magnetic properties of these solvated systems. Although we have studied also the isomers 09CAR, 11CAR, 09CRA, and 11CRA, the main conclusions can be drawn based on the results obtained for 13CAR, ATAR, 13CRA, and ATRA, whose chemical structures are showed in Figure 1.

II. COMPUTATIONAL DETAILS

The ground state geometry of the retinal derivatives in gas-phase and in the presence of chloroform, acetonitrile, methanol, and water was fully optimized with the second-order Møller–Plesset perturbation theory (MP2) using the 6-31G(d) basis set, without any symmetry constraint. The choice of this basis set follows a previous study by Lee *et al.*[16] that has shown that for the retinal isomers there is a close agreement between the MP2/6-31G(d) bond lengths calculated in gas-phase and those determined by X-ray diffraction.[17,18] The solvent dependence of the geometry has been included by employing the polarizable continuum model (PCM),[19] as implemented in the GAUSSIAN 03 package.[20]

The Monte Carlo (MC) simulations were performed using the DICE program[21] by using the Metropolis sampling technique in the *NPT* ensemble for a system composed by one molecule of retinal derivative and 903 molecules of solvent (chloroform, acetonitrile, methanol, or water) in normal conditions (temperature of 298 K and pressure of 1 atm). Both solute and solvent molecules are kept with rigid geometry during the MC simulations but the solute geometry used in the MC simulations was optimized in each solvent environment, using PCM. The intermolecular interactions are modeled by the standard Lennard-Jones (LJ) plus Coulomb potential with three parameters for each atomic site (ε_i, σ_i, and q_i) and the combination rules are $\varepsilon_{ij} = (\varepsilon_i \varepsilon_j)^{1/2}$ and $\sigma_i = (\sigma_i \sigma_j)^{1/2}$. For the retinal derivatives, we have used the LJ parameters of the optimized parameters for liquid simulation (OPLS) force field[22] (displayed in Table I) and the atomic charges were obtained using an electrostatic potential fit (CHELPG)[23] in a MP2/6-31+G(d) calculation. For chloroform the potential used was obtained from Ref. 24, for acetonitrile from Ref. 25, and for methanol from Ref. 22. For water the TIP3 model from Ref. 26 was used as force field.

Solute polarization effects have shown to be important for a reliable description of the molecular properties in polar solvents.[27–30] Here, we have used a reliable iterative

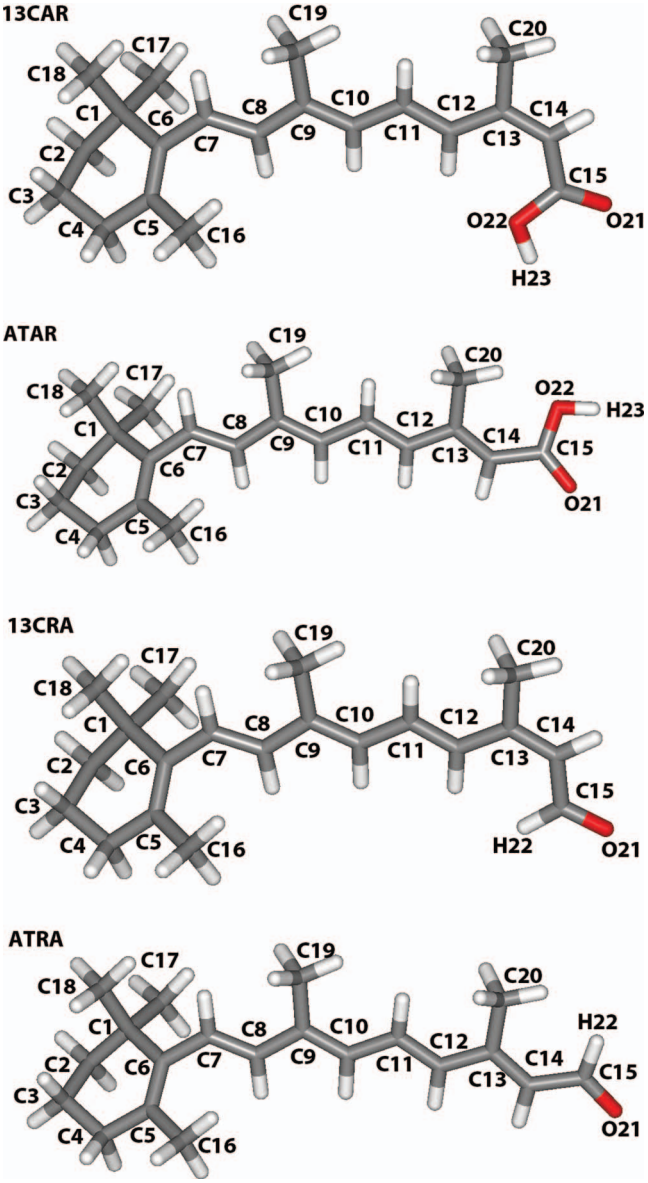

FIG. 1. Chemical structures of retinoic acid isomers [13-cis (13CAR) and all-trans (ATAR)] and of retinal isomers [13-cis (13CRA) and all-trans (ATRA)] with the numbering used in this study.

scheme to account for the electronic polarization of solute by the solvent, as reported in previous works.[27,28] We start the iterative procedure (iteration 0) by performing a MC simulation with the Coulombic term of the solute potential described by the atomic charges obtained in a gas-phase at the CHELPG/MP2/6-31+G(d) level. The results obtained with these configurations are referred to as unpolarized (UnPOL) model results and correspond to the first step in the iteration procedure. To initiate another step of the iterative process, we select statistically uncorrelated configurations to generate an electrostatic embedding around the solute. The average atomic charges of the solute are calculated using the average solvent electrostatic configuration (ASEC).[31] In all cases the ASEC is composed by a superposition of 100 statistically uncorrelated configurations of a solute molecule and 400 solvent molecules, treated as point charges. This procedure is repeated until convergence of the solute dipole

TABLE I. Lennard-Jones potential parameters of the Monte Carlo simulation. ε (kcal mol^{-1}) and σ (Å).

Atoms	ε	σ
Retinoic acid		
C(sp^3) → C1–C4; C16–C20	0.066	3.500
C(sp^2) → C5–C14	0.076	3.550
(Csp^2) → C15	0.105	3.750
(=O) → O21	0.210	2.960
(−OH) → O22	0.170	3.000
(−OH) → H23	0.000	0.000
H−C(sp^2) → H24–H26; H42; H46; H50	0.030	2.420
H−C(sp^3) → H27–H41; H43–H45; H47–H49	0.030	2.500
Retinal		
C(sp^3) → C1–C4; C16–C20	0.066	3.500
C(sp^2) → C5–C14	0.076	3.550
C(sp^2) → C15	0.105	3.750
(=O) → O21	0.210	2.960
(H−C=O) → H22	0.015	2.420
H−C(sp^2) → H23–H25; H41; H45; H49	0.030	2.420
H−C(sp^3)→ H26–H40; H42–H44; H46–H48	0.030	2.500

moment in solution is achieved. The converged results obtained with these configurations are referred to as polarized (POL) model results. In general, the dipole moment values of the solute in solution present a rapid convergence as a function of the iteration step.[27,28] The magnetic shielding constants $\sigma(^{13}C)$ and $\sigma(^{17}O)$ were calculated using the GIAO approach with the B3LYP exchange–correlation functional with the 6-311++G(2d,2p) basis set, as implemented in the GAUSSIAN 09 program.[32] In the comparison with available experimental results,[6] the ^{13}C chemical shifts were calculated relative to isotropic shielding constant of tetramethylsilane (TMS), determined as 180.89 ppm at the B3LYP/6-311++G(2d,2p) level.[33]

III. RESULTS AND DISCUSSION

A. Optimized geometric parameters

A selected set of MP2/6-31G(d) bond lengths for a representative set of isomers (13CAR, ATAR, 13CRA, and ATRA) optimized in gas-phase and in water is presented in Table II. One can see that the bond lengths of the β-ionone ring are not substantially affected by the isomeric form nor by the functional group type, as previously reported by Lee *et al.*[16] for the retinal isomers. In comparison with gas-phase results, the modifications caused by the solvent on the bond lengths of the β-ionone ring and of the polyene chain are in general small, regardless of the isomeric form. For all compounds, more significant changes due to the solvent effect on the bond length are observed at the terminal part of the segment, including the functional groups. This is also true for the optimized bond distances for these isomers in chloroform, acetonitrile, and methanol as well as for the isomers 09CAR, 11CAR, 09CRA, and 11CRA (not shown in table). From results of Table II, we have that for both retinal derivatives there is a lengthening of R_{16}(C15 = O21) around 0.005 Å, whereas the bond length R_{17}(C15-O22) of the retinioc acids is shortened by −0.015 Å. As expected, the bond length R_{18}(O22-H23) of the isomers of the retinoic acid is more sensitive to the influence of the medium and suffers a lengthening of 0.024 Å, in going from gas-phase to water. The determination of the equilibrium geometry in each solvent is important because the shielding constants are, in general, sensitive to geometric changes.[29]

Table III shows the values of the dihedral angle φ_D (C5,C6,C7,C8), formed between the β-ionone ring and the

TABLE II. MP2/6-31G(d) results for selected bond distances (in Å) of the isomers 13CRA, ATRA, 13CAR, and ATAR optimized in gas-phase and in water with PCM.

	Gas-phase				Water			
	13CAR	ATAR	13CRA	ATRA	13CAR	ATAR	13CRA	ATRA
R_1(C1−C2)	1.535	1.535	1.535	1.535	1.535	1.535	1.535	1.535
R_2(C1−C6)	1.531	1.531	1.531	1.531	1.531	1.531	1.531	1.531
R_3(C2−C3)	1.521	1.521	1.521	1.521	1.521	1.521	1.521	1.521
R_4(C3−C4)	1.523	1.523	1.523	1.523	1.523	1.523	1.523	1.523
R_5(C4−C5)	1.511	1.511	1.511	1.511	1.511	1.511	1.511	1.511
R_6(C5=C6)	1.361	1.361	1.361	1.361	1.361	1.361	1.361	1.361
R_7(C6−C7)	1.471	1.471	1.471	1.471	1.472	1.472	1.472	1.472
R_8(C7=C8)	1.357	1.357	1.357	1.357	1.357	1.357	1.357	1.357
R_9(C8−C9)	1.453	1.453	1.453	1.453	1.454	1.454	1.454	1.454
R_{10}(C9=C10)	1.368	1.368	1.368	1.368	1.369	1.368	1.369	1.369
R_{11}(C10−C11)	1.438	1.439	1.438	1.438	1.440	1.440	1.439	1.439
R_{12}(C11=C12)	1.363	1.361	1.362	1.362	1.363	1.362	1.363	1.363
R_{13}(C12−C13)	1.453	1.456	1.453	1.452	1.455	1.457	1.453	1.452
R_{14}(C13=C14)	1.363	1.362	1.365	1.364	1.362	1.362	1.366	1.365
R_{15}(C14−C15)	1.471	1.470	1.463	1.462	1.473	1.472	1.458	1.456
R_{16}(C15=O21)	1.225	1.225	1.233	1.234	1.231	1.230	1.238	1.239
R_{17}(C15−O22)	1.366	1.366	...	...	1.351	1.351	...	...
R_{17}(C15−H22)	...	...	1.106	1.106	...	...	1.105	1.105
R_{18}(O22−H23)	0.980	0.980	...	...	1.004	1.004	...	...

TABLE III. MP2/6-31G(d) results for the dihedral angle φ_D (C05, C06, C07, C08) (in °) formed between the β-ionone ring and the polyene chain, for all isomers optimized in gas-phase and in solution with PCM.

Isomers	Gas-phase	$CHCl_3$	CH_3CN	CH_3OH	H_2O
		Retinoic acid			
09CAR	52.7	52.1	51.8	52.1	52.5
11CAR	53.6	53.6	54.0	54.4	53.7
13CAR	53.5	53.8	53.8	54.0	53.5
ATAR	53.6	53.9	53.8	53.7	53.6
		Retinal			
09CRA	52.7	52.5	51.8	52.3	53.1
11CRA	53.4	53.4	53.5	53.6	53.7
13CRA	53.5	53.8	53.8	53.8	53.7
ATRA	53.5	53.8	53.6	53.8	53.5

conjugated segment, for all isomers of the retinoic acid and retinal in gas-phase and in solution. The results show that the relative orientation between the β-ionone ring and the conjugated segment is almost not affected neither by isomerization nor by the solvent polarity. For example, for all isomers the differences between the values of φ_D obtained in gas phase and in each solvent do not exceed 1°. This very small solvent dependence of φ_D is a strong indication that the rigid geometry model is a good approximation to study nuclear magnetic properties of these compounds in solution. For comparison, the gas-phase MP2/6-31G(d) result of 53.5° for φ_D of ATRA is identical to that reported by Lee *et al.*[16] but is little underestimated by 8.5° as compared to the experimental values obtained in solid phase of 62°.[17]

B. Solute polarization

The results for the dipole moment (μ) in gas-phase and in solution (using the POL and UnPOL solute models) calculated with MP2/6-31+G(d) for all isomers of the retinoic acid and retinal, are quoted in Table IV. Figure 2 shows the evolution of the results for μ of all isomers as a function of the number of iterations. Each displayed point corresponds to a statistically converged result obtained from 100 statistically uncorrelated configurations (less than 10%) using the ASEC solvation model,[31] where the solvent molecules are treated as point charges. One can see that the convergence of the dipole moment with respect to the number of iterations is rapid, as also seen for other molecular systems in solution.[14,27,28] In comparison with the gas-phase results, the increases in the POL values of μ for isomers of retinoic acid are between 22% and 26%, 16% and 28%, 36% and 46%, and 55% and 88% in chloroform, acetonitrile, methanol, and water, respectively. Increments in the UnPOL results in relation to gas-phase are of 15%–22%, 13%–17%, 12%–30% and 19%–51%. For the retinal isomers the corresponding increases for the POL [UnPOL] values of μ in relation to the gas-phase results are between 23% and 26%, 25% and 29%, 42% and 55%, and 80% and 100% [17%–19%, 20%–23%, 18%–38%, and 31%–54%]. These assignments, for both retinal derivatives, reflect the importance of the inclusion of solute polarization effects, especially in protic solvents. The in-water [in-chloroform] μ values for the isomers of retinal are between 37% and 90% [42% and 58%] larger than those obtained for the retinoic acid isomers, which is as a consequence that the aldehyde functional group has one electron acceptor character stronger than the carboxyl functional group.

C. Hydrogen bonds

Previous studies have shown that the polarization effect of the solute can affect considerably the specific interactions between solute and solvent molecules.[14,27,34] Considering that atoms of the aldehyde and carboxyl functional groups can form hydrogen bonds in protic solvents, in this section we present an analysis of the number of hydrogen bonds in water, where marked polarization effects are expected. Results were obtained for the isomers 13CAR, ATAR, 13CRA, and ATRA.

Figure 3 presents the radial distribution functions between the oxygen atoms O21 and O22 and the oxygen atom of the water molecule, $G_{O21\text{-}O}(r)$ and $G_{O22\text{-}O}(r)$, obtained with the POL and UnPOL solute models, for isomers 13CAR and ATAR. Figure 3 also presents the radial distribution function between the oxygen atom O21 and the oxygen atom of the

TABLE IV. MP2/6-31+G(d) results for the dipole moment (in D) of retinal derivatives in gas-phase and in aprotic and protic solvents. The dipole moments for each type of solution are calculated with ASEC solvation model.

		$CHCl_3$		CH_3CN		CH_3OH		H_2O	
Isomers	Gas-phase	UnPOL	POL	UnPOL	POL	UnPOL	POL	UnPOL	POL
				Retinoic acid					
09CAR	3.779	4.396	4.658	4.350	4.646	4.776	5.212	5.718	6.963
11CAR	3.764	4.572	4.609	4.367	4.616	4.904	5.122	5.680	6.926
13CAR	3.715	4.517	4.672	4.345	4.737	4.702	5.442	4.409	6.974
ATAR	3.519	4.046	4.310	3.976	4.083	3.939	4.846	4.452	5.470
				Retinal					
09CRA	5.577	6.533	6.897	6.760	7.182	6.759	7.933	8.286	11.146
11CRA	5.615	6.556	6.889	6.730	7.004	6.610	7.997	7.527	10.996
13CRA	5.315	6.320	6.616	6.477	6.853	6.773	7.688	6.985	9.572
ATRA	5.396	6.379	6.793	6.626	6.975	7.442	8.359	8.309	10.403

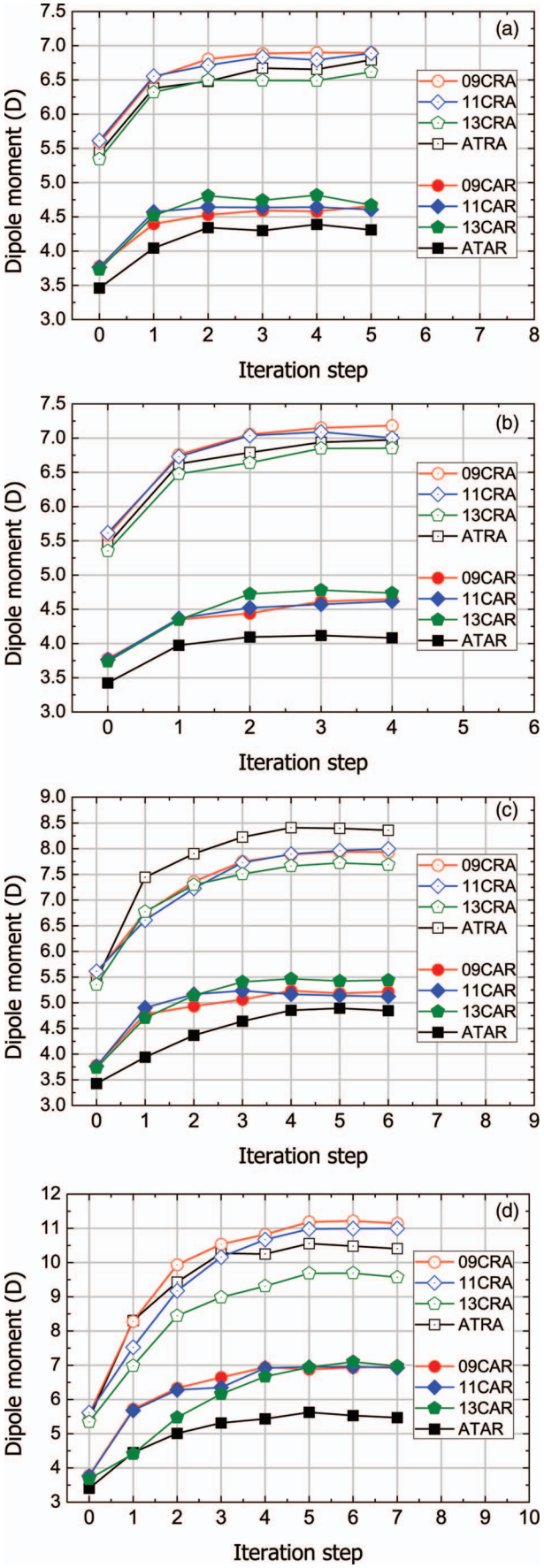

FIG. 2. Evolution of the MP2/6-311+G(d) results for the dipole moment of retinoic acid and retinal isomers in chloroform (a), acetonitrile (b), methanol (c), and water (d) as function of the number of iterations.

water molecule, $G_{O21\text{-}O}(r)$, obtained for the POL and UnPOL models, for 13CRA and ATRA isomers. In comparison with the UnPOL result, one can see a marked influence of the solute polarization on the distribution of the solvent molecules around O21. For all isomers, the first peaks of the radial distribution functions are centered between 2.6 and 2.8 Å (typical length of HBs between solute and solvent) and the first shells of coordination lie between 2.4 and 3.2. As results of the integration of the first coordination shell, we obtain for the POL model, for the 13CAR and ATAR isomers, the average numbers of 2.7 and 2.2 water molecules closest to the O21, respectively. The corresponding UnPOL results are 1.4 and 2.0. The numbers of water molecules linked to the polarized solute are increased by 93% and 10%. For O22 the polarization effects are in the opposite direction decreasing the number of HBs linked to the solute. The corresponding POL [UnPOL] average numbers of HBs are of 1.6 and 1.7 [1.7 and 2.0]. These findings lead to the numbers of HBs reduced by −6% and −15%. In addition, for O21 of the retinal isomers the average number of HBs are of 3.2 and 3.1 [2.5 and 2.5] for the POL [UnPOL] model, for 13CRA and ATRA, indicating an increase around of 25% in the number of water molecules linked to the polarized solute.

It is clear that not all molecules within the first solvation shell are indeed making HB with the solute. To obtain the specific number additional criterion is necessary. Thus, we also present a quantitative analysis of the average number of HBs in aqueous solution using geometric and energetic criteria.[35] Results were obtained for the POL solute model, for the 13CAR, ATAR, 13CRA, and ATRA isomers. In this case we use 100 uncorrelated configurations for selection of water molecules that form HBs, considering the following criteria: maximum distance between the sites ($O_{Soluto}\ldots O_{Solvente}$) less than or equal to 3.3 Å, with $\angle O\ldots O\text{–}H \leq 30^{o}$, and the solute-solvent interaction energy less than −0.10 kcal/mol. Thus, for the 13CAR [ATAR] molecule the average number of HBs between O21 and water is of 2.4 [2.2]. These findings show that using the geometric and energetic criteria 88% of the water molecules in the first hydration shell around O21 of 13CAR are hydrogen bonded. In the case of ATAR this number is 100%. For O22 the average number of HBs is 0.7 [0.5], what represents a reduction of more than one water molecule. The average number of HBs for O21 of 13CRA [ATRA] molecule is of 2.5 [2.7], indicating a reduction of 22% [13%]. As it will be shown, the treatment of explicit molecules can be particularly relevant for a reliable determination of the shielding constants of the oxygen atoms involved in hydrogen bonds.

D. Shielding constants in gas-phase and in solution

In Subsections III D 1–III D 3, the solvent effects on $\sigma(^{13}C)$ and $\sigma(^{17}O)$ of the retinoic acid and retinal isomers will be discussed in terms of the results obtained in water with the POL solute model. Similar results are also obtained for the other solvents considered. The shielding constants in solution were obtained using the ASEC solvation model that considers only the electrostatic contributions of the solvent molecules

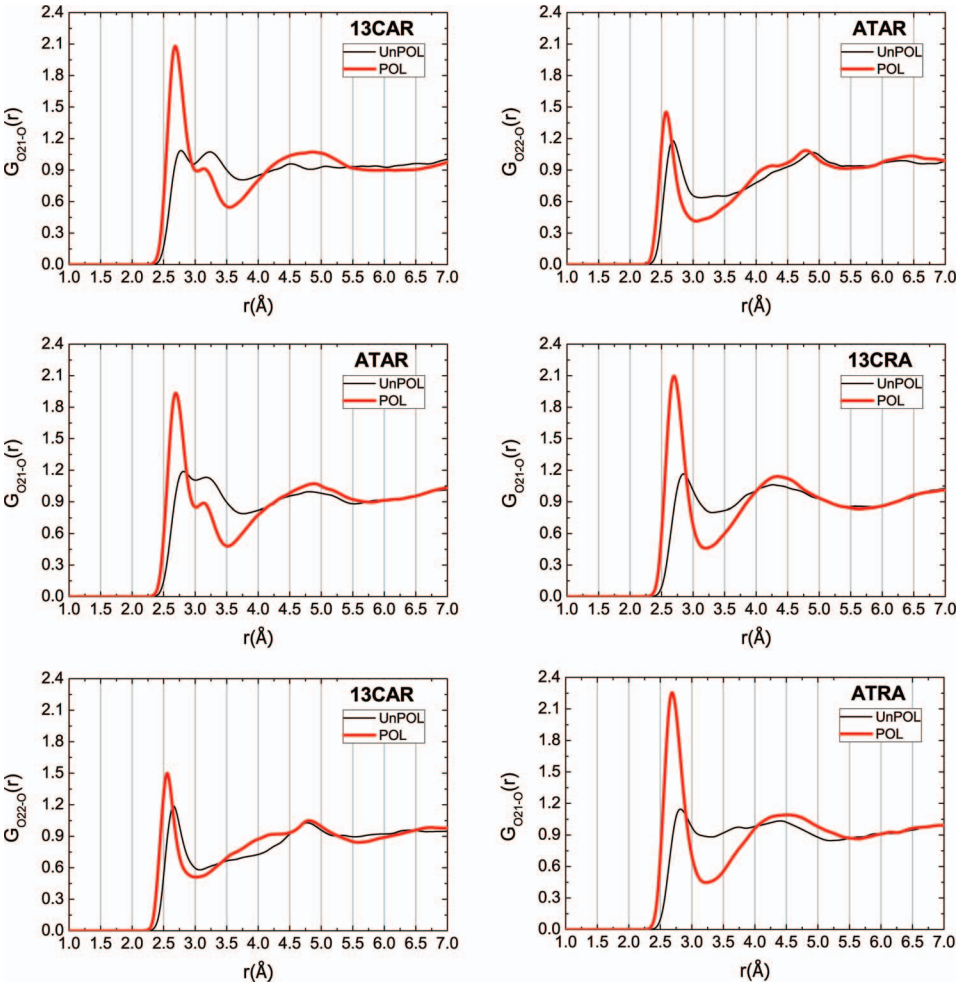

FIG. 3. Radial distribution functions between the oxygen atom of isomers 13CAR, ATAR, 13CRA, and ATRA and the oxygen atom of water, obtained with the polarized and unpolarized solute models.

using the average solvent electrostatic configuration. PCM results are also presented for comparison.

1. Solvent effects on $\sigma(^{13}C)$

A comparison between the gas-phase and in-water polarized shielding constants obtained at the GIAO-B3LYP/6-311++G(2d,2p) level for the isomers 13CAR, ATAR, 13CRA, and ATRA is presented in Table V. For a better discussion of the results, the carbon atoms are grouped according to the values of $\sigma(^{13}C)$. A group could be represented by the carbons of the β-ionone ring (C1-C4) and carbons of the methyl groups (C16-C20). For these carbons, the values of $\sigma(^{13}C)$ obtained in both water and gas-phase are between 139 and 169 ppm. An estimate of the solvent shift for the shielding constants can be obtained from the difference between the results obtained in solution and in gas-phase ($\Delta\sigma_{POL} = \sigma_{SOL} - \sigma_{GAS}$). For these carbon atoms, the $\Delta\sigma_{POL}(^{13}C)$ values are small, not exceeding 0.8 ppm.

Another group could be characterized by carbons of the polyene chain. The in-water [gas-phase] $\sigma(^{13}C)$ values of carbons C5-C12 are between 25 and 53 ppm [31 and 51 ppm]. For carbon atoms C13, C14, and C15 the corresponding σ values are between 9 and 18 ppm [22 and 24 ppm], 47 and 64 ppm [45 and 60 ppm], and −21 and 2 ppm [−14 and 8 ppm], respectively. Solvent effects for these $\sigma(^{13}C)$ values are more appreciable than those observed for the $\sigma(^{13}C)$ values of the β-ionone ring, being the solvent dependence of the odd-numbered carbons larger than the even-numbered ones (see Figure 4). One can see that significant changes occur for the odd-numbered carbons C13 and C15 with $\Delta\sigma_{POL}$ varying between −14 and −4 ppm and −7 and −6 ppm, respectively. For even-numbered carbons C12 and C14 the largest values of $\Delta\sigma_{POL}$ are between 0.2 and 2 ppm and 1 and 4 ppm. This alternating aspect has been noted before in the experimental works[6,7] and rationalized[7] as a consequence of the methyl substitution on the polyene chain. The gas-phase and solvent induced changes in the charges at the carbon sites also reveal an alternating pattern that is compatible with an alternating polarity of perturbed polyene chains.[36]

The results show, in addition, that the shielding constant values for carbons C13, C14, and C15 are significantly affected by the presence of the functional group. For the C15 atom, in particular, the in-water σ values are around 2 ppm [−20 ppm] for isomers of retinoic acid [retinal], showing a large shielding constant variation between the retinal and retinoic acid isomers. Also, it is interesting to note that the

TABLE V. B3LYP/6-311++G(2d,2p) results for the ^{13}C isotropic magnetic shielding (in ppm) of the isomers 13CAR, ATAR, 13CRA, and ATRA in gas-phase and in water. The magnetic shieldings in water are calculated with ASEC solvation model and using 100 statistically uncorrelated configurations obtained by the MC simulations. HB + PC corresponds to the use of explicit hydrogen bonded solvent molecules embedded in the point charges of the remaining molecules. Uncertainty shown is the statistical error.

	13CAR				ATAR			
	Gas	UnPOL	POL	HB+PC	Gas	UnPOL	POL	HB+PC
C1	144.86	145.03	144.81	143.40 ± 0.05	144.38	144.31	144.30	144.14 ± 0.03
C2	139.57	140.18	140.06	139.19 ± 0.12	139.56	139.37	139.29	139.17 ± 0.11
C3	159.59	159.44	159.73	159.36 ± 0.07	160.04	160.09	160.45	160.32 ± 0.07
C4	144.90	144.77	144.64	145.03 ± 0.09	144.51	144.58	144.58	144.46 ± 0.07
C5	41.53	41.12	40.99	36.87 ± 0.30	43.15	42.55	40.25	39.85 ± 0.24
C6	33.69	34.23	33.61	33.60 ± 0.18	33.78	33.58	34.77	34.83 ± 0.15
C7	42.52	41.51	39.26	38.05 ± 0.33	42.70	41.94	40.48	39.67 ± 0.31
C8	35.00	35.18	35.59	35.72 ± 0.19	35.22	35.03	35.76	35.86 ± 0.17
C9	32.88	31.61	27.20	26.70 ± 0.32	34.15	32.58	32.09	31.48 ± 0.27
C10	44.31	44.66	45.69	45.58 ± 0.25	45.32	44.89	44.89	44.93 ± 0.21
C11	42.57	42.13	37.46	36.40 ± 0.23	43.96	42.87	41.76	40.52 ± 0.22
C12	45.90	45.75	48.01	47.81 ± 0.25	38.40	38.13	38.61	38.89 ± 0.22
C13	23.59	21.84	15.58	13.92 ± 0.20	22.42	20.61	18.06	16.88 ± 0.22
C14	60.21	59.44	64.03	64.97 ± 0.25	57.24	57.01	58.52	59.71 ± 0.21
C15	8.28	4.78	1.70	2.91 ± 0.16	7.64	3.74	1.11	2.20 ± 0.13
C16	158.38	158.37	158.31	158.30 ± 0.11	158.47	158.72	158.58	158.47 ± 0.10
C17	148.57	149.01	149.10	148.90 ± 0.14	148.52	149.07	148.92	148.81 ± 0.13
C18	154.36	154.54	154.79	155.05 ± 0.08	154.87	155.30	155.12	155.07 ± 0.09
C19	168.92	168.98	168.47	168.29 ± 0.07	168.91	168.91	168.96	168.86 ± 0.09
C20	158.87	159.00	158.42	157.90 ± 0.09	167.63	167.27	167.20	166.66 ± 0.09
	13CRA				ATRA			
	Gas	UnPOL	POL	HB+PC	Gas	UnPOL	POL	HB+PC
C1	144.68	144.56	144.44	144.33 ± 0.03	144.32	143.96	144.01	143.78 ± 0.03
C2	139.99	140.21	140.42	140.29 ± 0.12	139.35	139.50	139.54	139.39 ± 0.11
C3	159.74	159.86	159.87	159.80 ± 0.08	160.15	160.42	160.41	160.25 ± 0.07
C4	144.47	144.41	144.57	144.40 ± 0.08	144.61	144.53	144.62	144.46 ± 0.07
C5	41.95	40.43	39.25	38.64 ± 0.25	42.36	42.28	40.06	39.44 ± 0.26
C6	33.79	34.22	34.20	34.16 ± 0.17	33.89	32.80	33.98	34.01 ± 0.17
C7	41.77	40.58	37.68	36.58 ± 0.30	41.77	38.78	37.87	36.59 ± 0.32
C8	35.38	35.18	35.78	35.90 ± 0.16	35.34	35.72	35.45	35.55 ± 0.17
C9	32.01	30.08	26.55	25.75 ± 0.30	33.04	28.46	27.36	26.37 ± 0.27
C10	45.91	45.64	46.18	45.99 ± 0.26	45.34	46.02	44.83	44.84 ± 0.24
C11	43.27	40.61	36.49	35.47 ± 0.23	44.13	40.05	36.92	35.26 ± 0.23
C12	50.82	50.78	52.38	52.67 ± 0.23	39.30	40.44	40.67	40.78 ± 0.19
C13	22.87	16.09	9.91	8.54 ± 0.22	23.47	15.51	9.81	8.31 ± 0.24
C14	47.30	47.94	50.02	50.74 ± 0.20	45.20	46.06	46.84	47.69 ± 0.15
C15	−13.15	−19.00	−20.09	−17.47 ± 0.18	−14.16	−19.19	−20.87	−17.61 ± 0.20
C16	158.33	158.56	158.38	158.28 ± 0.10	158.48	158.83	158.44	158.32 ± 0.12
C17	148.67	148.82	148.97	148.85 ± 0.13	148.52	148.64	148.59	148.43 ± 0.14
C18	154.45	154.86	154.60	154.52 ± 0.10	154.88	155.10	155.19	155.14 ± 0.10
C19	168.92	168.98	168.80	168.70 ± 0.08	168.85	168.58	168.59	168.46 ± 0.07
C20	159.40	159.05	158.64	158.51 ± 0.08	169.33	168.64	168.27	168.12 ± 0.08

effect of functional group leads to the carbon C15 shielded in retinoic acids but is unshielded in retinals. For the atoms C13 and C14, the shielding constant variations are around −7 ppm and −13 ppm, respectively.

2. Solvent effects on $\sigma(^{17}O)$

In Table VI we present a comparison between the gas-phase and in-solution $\sigma(^{17}O)$ polarized shielding constants, computed with the GIAO-B3LYP/6-311++G(2d,2p) method for the isomers 13CAR, ATAR, 13CRA, and ATRA. For the retinoic acid isomers, the results show, in addition, that the $\sigma(^{17}O)$ values present different solvent dependence: σ(O21) values increase with increasing solvent polarity whereas σ(O22) values are almost not affected. For discussion, we consider the values obtained for the molecule ATAR but similar conclusions are also obtained for the other isomers. In comparison with the gas-phase result of −113 ppm, the

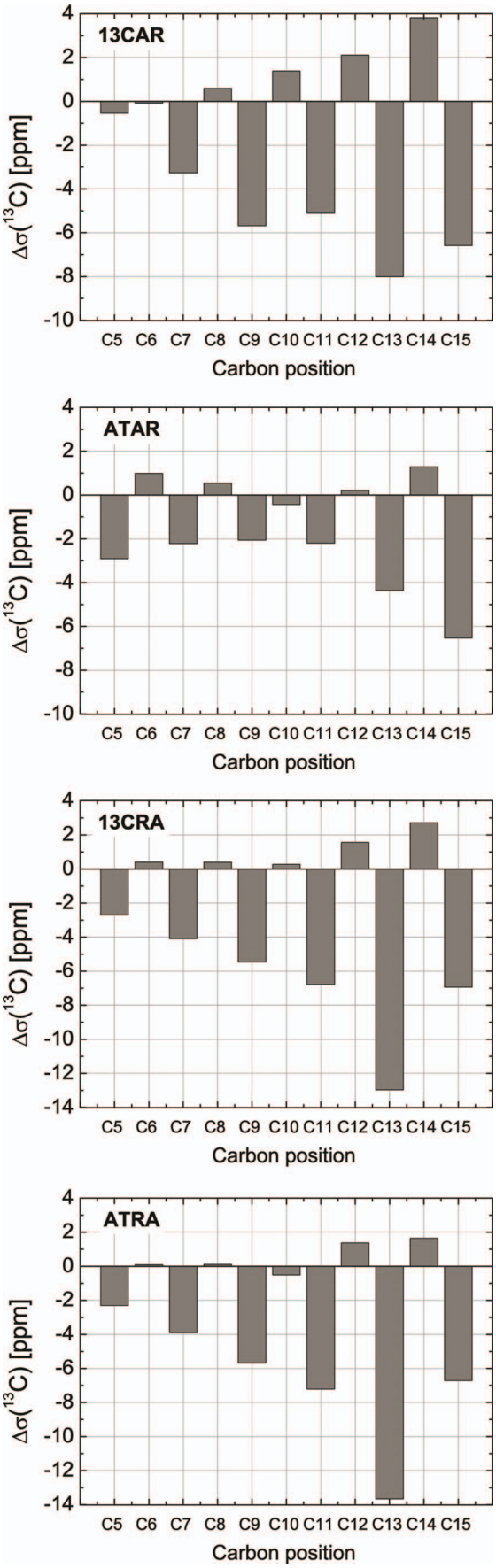

FIG. 4. Solvent shift for the ^{13}C shielding constants along the polyene chain computed as the difference between the results obtained in water and in gas-phase.

values of σ(O21) in chloroform, acetonitrile, methanol, and water increase to −87, −83, −45, and −16 ppm, respectively. For comparison, the corresponding PCM results (not listed in the table) are of −73, −59, −70, and −70 ppm, quite different from those obtained with the POL model. This leads to the corresponding $\Delta\sigma_{POL}$ [$\Delta\sigma_{PCM}$] values of 26, 30, 68, and 96 [40, 54, 43, and 43] ppm, with marked solvent shifts in protic solvents. For the atom O22, the $\Delta\sigma_{POL}$ [$\Delta\sigma_{PCM}$] values are of −4, −2, −5, and 0.4 [−2, −5, −6, and −6] ppm in chloroform, acetonitrile, methanol, and water, indicating that solvent effects have a small impact on σ for this atom.

For the isomers of retinal, the values for σ(O21), that forms a double bond with a carbon atom, are more deshielded (see Table VI). The values of σ(O21) of the retinal isomers increase with increasing solvent polarity, being the increments even more relevant than those observed for σ(O21) of the retinoic acid isomers. As an example, for ATRA, the results for σ(O21) increase to −303, −291, −217, and −130 ppm in chloroform, acetonitrile, methanol, and water, respectively, as compared with the gas-phase results of −357 ppm. The corresponding PCM values are of −278, −249, −265, and −263 ppm. As a consequence, the $\Delta\sigma_{POL}$ [$\Delta\sigma_{PCM}$] values are estimated to be 54, 66, 141, and 227 [79, 108, 92, and 95] ppm. These findings show that the solvent shifts for the shielding constants of the atom O21 of the retinal isomers are essentially two times larger than the counterparts in retinoic acid isomers.

3. Polarization effects on σ

We have analyzed the effects of solvent polarization on the magnetic shielding constants by comparing the POL and UnPOL results reported in Tables V and VI. An inspection of the σ(^{13}C) results quoted in Table V shows that the solute polarization affects the σ(C9), σ(C13), and σ(C15) values of retinoic acid isomers and the σ(C11) and σ(C13) values of retinal isomers. For instance, the differences between POL and UnPOL results for σ(C13) [σ(C15)] of 13CAR and ATAR in water are of −6 and −3 [−3 and −3] ppm, respectively. Similarly, for σ(C13) of 13CRA and ATRA the corresponding differences are −6 ppm. For the remaining carbon atoms in both isomers, the polarization effects are small.

The σ(^{17}O) results obtained for all isomers show clearly that the effects of polarization have a marked impact on the σ(O21) values, especially in protic solvents (see Table VI). For the 13CAR [ATAR], the differences between POL and UnPOL results of σ(O21) are estimated to be 0, 6, 30, and 53 [7, 3, 32, 38] ppm, respectively for chloroform, acetonitrile, methanol, and water. In the same manner, the corresponding differences between POL and UnPOL results for σ(O21) of 13CRA [ATRA] are 15, 15, 36, and 96 [15, 11, 57, and 105] ppm. Thus, even in a low-polarity solvent such as chloroform, the later results show that a reliable description of σ(O21) requires the use of a polarized solute model. The variations between the results obtained with the POL and UnPOL models for σ(O22) of the retinoic acid isomers are in general small but, in the case of protic solvents, they could be experimentally detected.

TABLE VI. B3LYP/6-311++G(2d,2p) results for the ^{17}O isotropic magnetic shielding (in ppm) of the isomers 13CAR, ATAR, 13CRA, and ATRA in gas-phase and in aprotic and protic solvents. The magnetic shieldings for each type of solution are calculated with ASEC solvation model and, additionally, in water using 100 statistically uncorrelated configurations obtained by the MC simulations. Uncertainty shown is the statistical error.

		$CHCl_3$		CH_3CN		CH_3OH		H_2O		
Atoms	Gas-phase	UnPOL	POL	UnPOL	POL	UnPOL	POL	UnPOL	POL	HB + PC
					13 CAR					
O21	− 108.14	− 87.81	− 87.59	− 87.73	− 81.32	− 74.00	− 44.26	− 58.55	− 5.34	− 14.74 ± 1.31
O22	112.63	111.34	111.75	114.99	114.27	114.53	112.22	114.86	115.90	111.95 ± 0.62
					ATAR					
O21	− 112.62	− 94.37	− 86.99	− 85.50	− 82.51	− 76.43	− 44.71	− 54.02	− 16.49	− 23.39 ± 1.24
O22	113.94	111.32	110.29	111.69	111.70	113.77	108.97	117.19	114.37	111.61 ± 0.26
					13CRA					
O21	− 353.48	− 312.87	− 297.70	− 303.92	− 289.13	− 278.37	− 242.47	− 248.94	− 153.29	− 149.07 ± 2.41
					ATRA					
O21	− 357.04	− 317.46	− 302.62	− 301.63	− 290.83	− 273.53	− 216.52	− 235.02	− 130.05	− 127.34 ± 2.27

E. Hydrogen bond effects on σ

To examine the influence of hydrogen bonds on the magnetic shielding constants in aqueous solution, we consider supermolecular structures obtained from the MC simulations with the explicit inclusion of some hydrogen-bonded water molecules. With the objective of obtaining statistically converged results for σ we selected 100 statistically uncorrelated supermolecular structures. In addition, these configurations were electrostatically embedded by a solvation shell composed by 400 outer water molecules, treated as point charges (TIP3 model). The statistically converged average results obtained with these embedded configurations are referred to as HB + PC in Tables V and VI.

One can see from the results of Table V that, in general, the presence of explicit water molecules that form hydrogen bonds does not affect much the $\sigma(^{13}C)$ values. The HB + PC model gives converged $\sigma(^{13}C)$ values that are also essentially equivalent to those obtained with the ASEC. There is, however, a small impact on $\sigma(^{13}C)$ only for the carbon atoms C13 and C15. For the molecule 13CAR [ATAR], the HB + PC model gives for these atoms the converged values that lead to small differences of 1.66 [1.18] and 1.21 [1.09] ppm, as compared with the corresponding values obtained with

TABLE VII. B3LYP/6-311++G(2d,2p) results for the ^{13}C chemical shift differences relative to ATRA (in ppm) of polarized retinal isomers in gas-phase and in aprotic and protic solvents. The chemical shifts in solution were calculated with ASEC solvation model.

	11CRA							13CRA						
	GIAO-B3LYP/6-311++G(2d,2p)					Expt.[a]		GIAO-B3LYP/6-311++G(2d,2p)					Expt.[a]	
Carbon	Gas-phase	$CHCl_3$	CH_3CN	CH_3OH	H_2O	C_6H_{12}	C_3H_6O	Gas-phase	$CHCl_3$	CH_3CN	CH_3OH	H_2O	C_6H_{12}	C_3H_6O
C1	0.56	0.35	0.30	0.30	0.50	0.06	− 0.01	− 0.36	− 0.37	− 0.33	− 0.35	− 0.42	0.02	− 0.03
C2	− 0.22	− 0.12	− 0.64	− 0.53	− 0.43	− 0.05	0.50	− 0.64	− 0.26	− 0.77	− 0.84	− 0.87	− 0.01	− 0.03
C3	0.58	0.49	0.76	0.56	0.67	0.04	0.02	0.41	0.31	0.41	0.36	0.56	0.02	− 0.03
C4	− 0.65	− 0.56	− 0.15	− 0.13	− 0.10	− 0.04	− 0.03	0.14	0.14	0.35	0.12	0.06	0.03	− 0.03
C5	0.70	1.21	0.30	0.40	− 0.02	− 0.21	− 0.07	0.41	0.34	0.21	0.00	0.82	0.03	− 0.02
C6	0.55	0.11	0.36	0.10	0.97	0.06	0.03	0.10	− 0.04	0.19	0.14	− 0.22	− 0.08	− 0.05
C7	0.73	1.18	0.31	− 0.05	2.78	0.05	0.10	0.00	0.01	− 0.13	− 0.74	0.21	− 0.02	− 0.06
C8	0.60	0.19	0.25	0.28	− 0.75	0.37	0.27	− 0.04	− 0.08	0.19	0.06	− 0.36	0.00	− 0.05
C9	1.65	1.58	0.10	− 0.12	2.33	0.54	0.37	1.03	1.08	1.11	0.19	0.76	0.39	0.12
C10	− 4.61	− 4.87	− 2.30	− 2.69	− 3.74	− 3.70	− 3.75	− 0.57	− 0.63	− 0.47	− 0.39	− 1.35	0.21	0.07
C11	1.76	1.27	0.44	0.31	1.93	− 1.03	− 1.51	0.86	0.97	0.98	0.15	0.41	1.29	0.87
C12	− 3.95	− 4.04	− 3.71	− 3.57	− 5.31	− 4.44	− 4.18	− 11.52	− 11.68	− 11.59	− 11.11	− 11.74	− 7.88	− 7.97
C13	2.82	2.54	2.22	0.93	2.24	1.03	0.85	0.60	0.92	0.36	− 1.03	− 0.15	0.23	− 0.42
C14	1.96	1.78	1.54	1.90	0.64	0.78	0.90	− 2.10	− 2.29	− 2.24	− 2.25	− 3.13	− 1.33	− 1.22
C15	− 0.03	− 0.06	0.80	− 0.12	0.24	0.08	0.09	− 1.01	− 0.88	− 0.88	− 2.09	− 0.79	− 0.55	− 1.18
C16	− 0.05	0.04	− 0.15	− 0.09	− 0.35	0.04	− 0.07	0.15	0.11	0.23	0.13	0.05	0.07	− 0.04
C17	− 0.22	− 0.10	− 0.38	− 0.55	− 0.87	0.03	− 0.04	− 0.15	− 0.07	− 0.19	− 0.28	− 0.38	0.05	− 0.04
C18	0.09	− 0.01	0.26	0.07	0.17	0.03	− 0.04	0.43	0.46	0.38	0.55	0.57	0.05	− 0.04
C19	− 1.22	− 1.20	− 0.72	− 0.60	− 0.22	− 0.51	− 0.60	− 0.07	− 0.02	− 0.06	− 0.11	− 0.20	0.02	− 0.08
C20	4.38	4.46	5.25	4.88	5.05	4.98	4.90	9.93	9.89	9.87	9.48	9.56	8.06	7.94

[a]Experimental ^{13}C chemical shift differences (in ppm) were obtained from Ref. 6.

ASEC. Similarly, for the 13CRA [ATRA] molecule the corresponding converged values differ from those obtained with the ASEC by 1.37 [1.50] and 2.62 [3.26] ppm.

The results of Table VI show that the presence of explicit hydrogen bonds significantly affects the shielding constants of oxygen atoms. For the molecules 13CAR and ATAR, the HB + PC model gives for σ(O21) the converged values which differ from those obtained with the ASEC by −9.40 and −6.90 ppm, respectively. The corresponding differences for σ(O21) of 13CRA and ATRA are of 4.22 and 2.71 ppm, respectively. Despite these differences being significant one may note that they are numerically less important than the difference obtained with the inclusion of the polarization effect. Similarly, for σ(O22) of retinoic acid isomers, the corresponding differences between HB + PC and ASEC results are of −3.95 and −2.76 ppm. In this case, such differences are comparable to those caused by the polarization effect. We attribute the larger solvent effect in the carbonyl oxygen compared to the hydroxyl oxygen to the larger number of hydrogen bonds (see Sec. III C). For instance, in the 13CAR the number of hydrogen bonded water molecules is 2.4 for the carbonyl oxygen and only 0.7 for the hydroxyl oxygen.

IV. COMPARISON WITH EXPERIMENTAL RESULTS

The theoretical predictions for the ^{13}C chemical shifts in gas-phase and in solution are overestimated as compared with the experimental ones, as previously reported by Touw *et al.*[9] To make an appropriate comparison with experiment, we present in Table VII the ^{13}C chemical shift differences relative to ATRA ($\Delta\delta_{\text{CIS-TRANS}} = \delta_{\text{ISOMER}} - \delta_{\text{ATRA}}$) for the isomers 11CRA and 13CRA calculated in gas-phase and in solution, together with the corresponding experimental chemical shift differences measured in acetone and cyclohexane.[6] An overall look at Table VII shows that our theoretical predictions for $\Delta\delta_{\text{CIS-TRANS}}$ exhibit only a small solvent dependence, with a marked impact of isomeric changes for carbon atoms close to the structural modifications. Our ASEC-GIAO-DFT model predicts for C12 of 13CRA upfield shifts around 12 ppm in gas-phase and in solution, being overestimated in 4 ppm as compared with the experimental results. In both theoretical and experimental cases the $\Delta\delta_{\text{CIS-TRANS}}$ are essentially independent of the solvent presence. At the same time, our theoretical predictions for C10 and C12 of 11CRA give upfield shifts around 5 and 4 ppm, respectively, both in gas-phase and in chloroform. In this case, is found a better agreement with experiment, with theoretical results overestimated in less than 1 ppm. One can see that the $\Delta\delta_{\text{CIS-TRANS}}$ results for C12 are essentially independent of the solvent presence but for C10 the upfield shifts are slightly reduced in acetonitrile and methanol. The results also show that $\Delta\delta_{\text{CIS-TRANS}}$ values for C20 (far from the structural modifications) of both 11CRA and 13CRA are downfield shifts around 5 and 10 ppm, respectively, being the latter overestimated in 2 ppm in comparison with experiment. Another interesting aspect is the solvent dependence of the odd-numbered carbons, which can be compared to the experimental results taking the differences between the results obtained in different solvents, as illustrated in Figure 5 for the isomers 13CRA and ATRA.

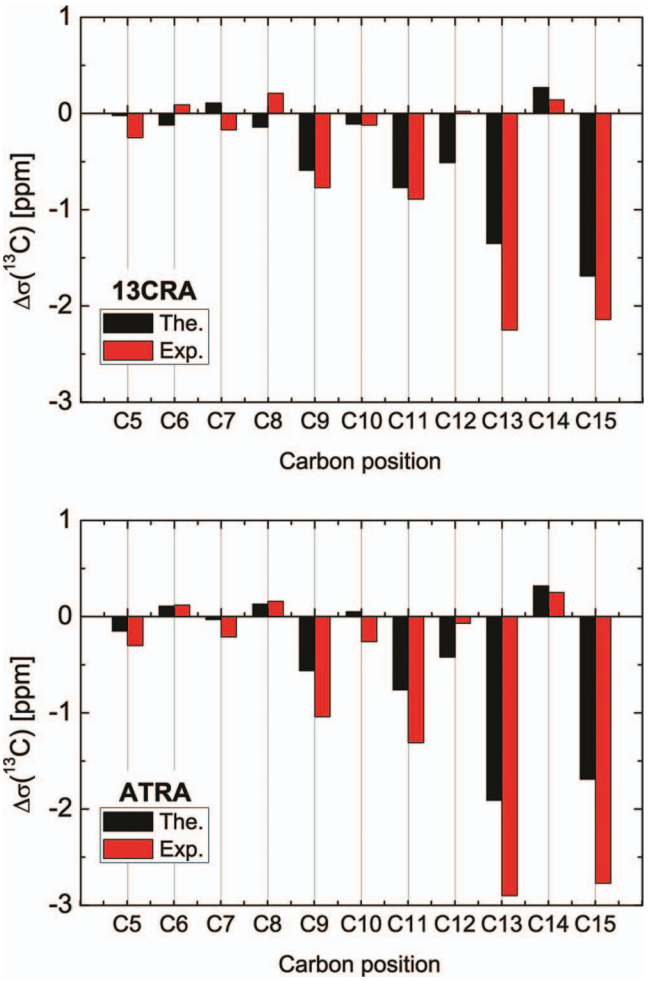

FIG. 5. Solvent shift differences for the ^{13}C shielding constants along the polyene chain computed as the difference between the results obtained in acetonitrile and in chloroform (Theory) and between acetone and cyclohexane (Expt.).[6]

Our computed solvent shift differences for C9, C11, C13, C15 in going from chloroform to acetonitrile are comparable to the measured differences in going from cyclohexane to acetone. Similar conclusions have been drawn for the $\Delta\delta_{\text{CIS-TRANS}}$ values of the retinoic acid isomers but there are no experimental results for comparison.

V. CONCLUSION

We have reported the results of a theoretical investigation of the nuclear isotropic shielding constants σ(^{13}C) and σ(^{17}O) of isomers of retinoic acid and retinal in gas-phase and in chloroform, acetonitrile, methanol, and water solutions computed at the B3LYP level using the 6-311++G(2d,2p) basis sets. Solvent effects were investigated using a sequential quantum mechanics/molecular mechanics methodology. To properly account for the change in the equilibrium geometry, the nuclear magnetic properties were computed at the equilibrium geometry of the solute molecule obtained using the polarizable continuum model in each specific solvent. These geometries reflect in some average way the structures adopted by the molecule in the solvent environment. The solute

polarization by the solvent in aprotic and protic environments has been included by using an iterative procedure, and is found to be important for a reliable description of electronic properties. Using MP2/6-311+G(d,p) calculations, increments of 55%–100% are obtained for the in-water dipole moment of retinal derivatives as compared to the gas-phase situation. Although the oxygen shielding constants may be affected by the presence of explicit solvent molecules, the solute polarization effect plays a more crucial role for a quantitative description of $\sigma(^{17}O)$ of the oxygen atom of the carbonyl group but is mild for $\sigma(^{17}O)$ of the oxygen atom of the hydroxyl group. On the basis of the polarized solute model, there is a sizable increase in the magnitude of $\sigma(^{17}O)$ of the carbonyl oxygen with increasing solvent polarity, when compared with the results obtained in gas-phase. At the same time, the small solvent dependence observed for the $\sigma(^{17}O)$ of the hydroxyl oxygen, even in protic solvents, suggests that the NMR signature of oxygen atoms in functional groups could be detected in nuclear magnetic resonance experiments. It is found that solvent effects on carbon shielding constants are small but significant solvent shift differences for the $\sigma(^{13}C)$ values of the odd-numbered carbons of the polyene chain, in aprotic solvents, are comparable to the available experimental data. In addition, our in-solution GIAO-B3LYP results for isomers of retinal show that ^{13}C chemical shift differences allow probing structural distortions caused by the isomerization on the polyene chains, in agreement with NMR data measured in solution.

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[1]T. Yoshizawa and G. Wald, Nature (London) **197**, 1279 (1963); G. Wald, Science **162**, 230 (1968).
[2]R. R. Birge, Annu. Rev. Phys. Chem. **41**, 683 (1990); Biochem. Biophys. Acta **1016**, 293 (1990).
[3]R. W. Schoenlein, L. A. Peteanu, R. A. Mathies, and C. V. Shank, Science **254**, 412 (1991).
[4]G. Gröbner, I. J. Burnett, C. Glaubitz, G. Choi, A. J. Mason, and A. Watts, Nature (London) **405**, 810 (2000).
[5]J. Saam, E. Tajkhorshid, S. Hayashi, and K. Schulten, Biophys. J. **83**, 3097 (2002); V. Hornak, S. Ahuja, M. Eilers, J. A. Goncalves, M. Sheves, P. J. Reeves, and S. O. Smith, J. Mol. Biol. **396**, 510 (2010).
[6]R. Rowan and B. D. Sykes, J. Am. Chem. Soc. **96**, 7000 (1974).
[7]G. S. Harbison, P. P. J. Mulder, H. Pardoen, J. Lugtenburg, J. Herzfeld, and R. G. Griffin, J. Am. Chem. Soc. **107**, 4809 (1985).
[8]R. S. Becker, S. Berger, D. K. Dalling, D. M. Grant, and R. J. Pugmire, J. Am. Chem. Soc. **96**, 7008 (1974); S. O. Smith, I. Palings, M. E. Miley, J. Courtin, H. J. M. de Groot, J. Lugtenburg, R. A. Mathies, and R. G. Griffin, Biochemistry **29**, 8158 (1990); A. F. L. Creemers, S. Kiihne, P. H. M. Bovee-Geurts, W. J. DeGrip, J. Lugtenburg, and H. J. M. de Groot, Proc. Natl. Acad. Sci. U.S.A. **99**, 9101 (2002).
[9]S. I. E. Touw, H. J. M. de Groot, and F. Buda, J. Mol. Struct.: THEOCHEM **711**, 141 (2004).
[10]R. Ditchfield, Mol. Phys. **27**, 789 (1974); K. Wolinski, J. F. Hinton, and P. Pulay, J. Am. Chem. Soc. **112**, 8251 (1990).
[11]J. A. Gascón, E. M. Sproviero, and V. S. Batista, J. Chem. Theory Comput. **1**, 674 (2005); U. F. Röhrig and D. Sebastiani, J. Phys. Chem. B **112**, 1267 (2008).
[12]K. Coutinho and S. Canuto, Adv. Quantum Chem. **28**, 89 (1997); J. Chem. Phys. **113**, 9132 (2000); *ibid.* **112**, 7293 (2000).
[13]J. R. Cheeseman, G. W. Trucks, T. A. Keith, and M. J. Frisch, J. Chem. Phys. **104**, 5497 (1996).
[14]T. L. Fonseca, K. Coutinho, and S. Canuto, J. Chem. Phys. **129**, 034502 (2008).
[15]A. G. Bezerra, Jr., A. S. L. Gomes, D. A. da Silva-Filho, L. H. Acioli, C. B. de Araújo, and C. P. de Melo, J. Chem. Phys. **111**, 5102 (1999).
[16]H. M. Lee, J. Kim, C. J. Kim, and K. S. Kim, J. Chem. Phys. **116**, 6549 (2002).
[17]T. Hamanaka, T. Mitsui, T. Ashida, and M. Kakudo, Acta Crystallogr. B **28**, 214 (1972).
[18]R. D. Gilardi, I. L. Karle, and J. Karle, Acta Crystallogr. B **28**, 2605 (1972); C. J. Simmons, R. S. H. Liu, M. Denny, and K. Seff, *ibid.* **37**, 2197 (1981).
[19]S. Miertus, E. Scrocco, and J. Tomasi, Chem. Phys. **55**, 117 (1981); R. Cammi and J. Tomasi, J. Comput. Chem. **16**, 1449 (1995); J. Tomasi, B. Mennucci, and R. Cammi, Chem. Rev. **105**, 2999 (2005).
[20]M. J. Frisch, G. W. Trucks, H. B. Schlegel *et al.*, GAUSSIAN 03, Revision D.01, Gaussian, Inc., Wallingford, CT, 2004.
[21]K. Coutinho and S. Canuto, DICE: A Monte Carlo program for molecular liquid simulation, v. 2.8, University of São Paulo, São Paulo, 2003.
[22]W. L. Jorgensen, D. S. Maxwell, and J. Tirado-Rives, J. Am. Chem. Soc. **118**, 11225 (1996).
[23]C. M. Breneman and K. B. Wiberg, J. Comput. Chem. **11**, 361 (1990).
[24]N. A. McDonald, H. A. Carlson, and W. L. Jorgensen, J. Phys. Org. Chem. **10**, 563 (1997).
[25]H. J. Böhm, I. R. McDonald, and P. A. Madden, Mol. Phys. **49**, 347 (1983).
[26]W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, J. Chem. Phys. **79**, 926 (1983).
[27]R. M. Gester, H. C. Georg, T. L. Fonseca, P. F. Provasi, and S. Canuto, Theor. Chem. Acc. **131**, 1220 (2012); V. Manzoni, M. L. Lyra, R. M. Gester, K. Coutinho, and S. Canuto, Phys. Chem. Chem. Phys. **12**, 14023 (2010).
[28]H. C. Georg, K. Coutinho, and S. Canuto, Chem. Phys. Lett. **429**, 119 (2006).
[29]K. Aidas, A. Møgelhøj, H. Kjaer, C. B. Nielsen, K. V. Milkkelsen, K. Ruud, O. Christiansen, and J. Kongsted, J. Phys. Chem. A **111**, 4199 (2007).
[30]W. L. Jorgensen, J. Chem. Theory Comput. **3**(6), 1877–2145 (2007); E. E. Dahlke and D. G. Truhlar, *ibid.* **3**, 46 (2007); M. E. Martin, M. L. Sánchez, F. J. Olivares del Valle, and M. A. Aguilar, J. Chem. Phys. **113**, 6308 (2000); J. Gao and X. Xia, Science **258**, 631 (1992).
[31]K. Coutinho, H. C. Georg, T. L. Fonseca, V. Ludwig, and S. Canuto, Chem. Phys. Lett. **437**, 148 (2007).
[32]M. J. Frisch, G. W. Trucks, H. B. Schlegel *et al.*, GAUSSIAN 09, Revision A.02, Gaussian, Inc., Wallingford, CT, 2009.
[33]G. Colherinhas, T. L. Fonseca, H. C. Georg, and M. A. Castro, Int. J. Quantum Chem. **111**, 1616 (2011).
[34]T. L. Fonseca, H. C. Georg, K. Coutinho, and S. Canuto, J. Phys. Chem. A **113**, 5112 (2009).
[35]K. Coutinho and S. Canuto, J. Mol. Struct.: THEOCHEM **632**, 235 (2003); T. Malaspina, K. Coutinho, and S. Canuto, J. Chem. Phys. **117**, 1692 (2002); A. G. Kalinichev and J. D. Bass, J. Phys. Chem. **101**, 9720 (1997); M. Mezei and D. L. Beveridge, *ibid.* **74**, 622 (1981); D. C. Rapaport, Mol. Phys. **50**, 1151 (1983); A. Rahman and F. H. Stillinger, J. Chem. Phys. **55**, 3336 (1971).
[36]S. Canuto, J. L. Calais, and O. Goscinski, J. Phys. B **14**, 1409 (1981).