Determination of the Relative Stereochemistry of Flexible Organic Compounds by Ab Initio Methods: Conformational Analysis and Boltzmann-Averaged GIAO ^{13}C NMR Chemical Shifts**

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In memory of our colleague and long-time friend Professor Guido Sodano

Abstract: Ab initio calculations at the Hartree–Fock level with full-geometry optimization using the 6-31G(d) basis set, and GIAO (gauge including atomic orbitals) ^{13}C NMR chemical shifts, are presented here as a support in the study of the stereochemistry of low-polar organic compounds having an open-chain structure. Four linear stereoisomers, fragments of a natural product previously characterized by experimental ^{13}C NMR spectra, which possesses three stereogenic centers, 11 carbon atoms, and 38 atoms in total, were considered. Conformational searches, by empirical force-field molecular dynamics, pointed out the existence of 8–13 relevant conformers per stereoisomer. Thermochemical calculations at the ab initio level in the harmonic approximation of the vibrational modes, allowed the evaluation, at 298.15 K, of the standard Gibbs free energy of the conformers. The ^{13}C NMR chemical shift of a given carbon atom in each stereoisomer was considered as the average chemical shift value of the same atom in the different conformers. The averages were obtained by the Boltzmann distribution, using the relative standard free energies as weighting factors. Computed parameters related to linear correlation plots of experimental ^{13}C chemical shifts versus the corresponding computed average data allowed us to distinguish among the four stereoisomers.

Keywords: ab initio calculations · configuration determination · GIAO method · natural products · NMR spectroscopy

Introduction

In the preceeding paper[1] we have shown that Hartree–Fock (HF) calculations of NMR ^{13}C chemical shift (CS) of low-polar compounds can provide valid support in interpreting experimental ^{13}C NMR data of unknown species, and hence in resolving structural controversies.

NMR spectroscopy has been efficiently employed in the analysis of the relative stereochemistry of rigid[2, 3] and flexible organic compounds.[4] Recently, our research group has been involved in the assignment, by NMR spectroscopy, of the absolute and relative configuration of flexible systems, such as polysubstituted open chains and/or macrocyclic compounds.[5, 6] Empirical methods can be efficiently applied to determine the configuration of organic molecules, provided that a large set of experimental data is available.[5, 6] These are essentially based on the analysis of the NMR heteronuclear and homonuclear coupling constants, and of the distances between the NMR nuclei,[2–4] and permit confident predictions in the presence of a limited number of stereotopic centers. On the other hand, the increasing calculation power and low cost of modern computers suggest, as complementary and supporting approaches for conformation and configuration analysis, the use of quantum-chemical methods. Indeed, the determination of the absolute configuration of a flexible organic compound, containing one stereogenic center, was recently afforded by a successful combination of calculated and experimental optical rotatory dispersion (ORD) spectra.[7]

Following the encouraging results obtained in the preceding paper concerning the validation of NMR structures by ab initio calculation of NMR ^{13}C chemical shift (CS) values,[1] we

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[**] GIAO = gauge including atomic orbitals.

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have considered here the possibility of applying such a method to the determination or validation of the relative stereochemistry of flexible organic compounds. This task, to our knowledge, has been dealt with only by calculating the ^{13}C NMR spectra of compounds where the preponderance of a preferential conformation was out of the question,[8–10] for example, molecules with a relatively rigid skeleton.

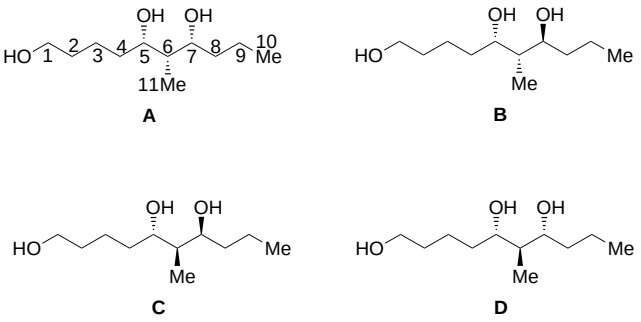
To get accurate results, the determination of ^{13}C chemical shift values and the geometry optimization of a given structure should be performed at the same level of calculation.[1] For flexible systems, further difficulties arise from the coexistence of conformational states in dynamic equilibrium, especially in solution and at room temperature. In fact, the energy differences among the conformers can usually be overcome by the thermal energy contributions, and consequently the NMR signals are influenced by the particular energy population distribution. Hence reliable calculations of NMR parameters should consider all conformers present in significant proportion at the NMR-recording temperature. This consideration is even more important when the right relative stereochemistry has to be attributed to flexible open-chain natural products possessing stereogenic centers.

To estimate such contributions, we suggest that the ^{13}C chemical shift of each carbon atom, for a given stereoisomer, has to be expressed as the Boltzmann average of the ^{13}C chemical shift values of its conformers, the ab initio standard free energies being the weighting factors. In fact, such standard free energy of each conformer, calculated at the temperature of the experiment, should give a reliable estimate of the energy distribution among the conformational states.

Of course, the number of possible conformations in a molecular system increases with its size. In the present case of an open-chain saturated organic compound, the maximum number of conformers should in principle be given by 3^N, where N is the number of torsional angles and 3 is the number of different orientations assumed by the three bonds constituting the torsional angle. The enormous number of conformers to be considered, hence the number of calculations to be performed for a medium-sized flexible organic compound, would then make such an approach impractical for a routine application. This apparently-insurmountable computational problem nowadays can be easily overcome by performing the ab initio geometry optimization on only those energy-minimum structures resulting from a previous molecular dynamics conformational search. In fact, the empirical molecular mechanics algorithms have the advantage of being very fast and accurate enough to act as a filter for the majority of conformational states whose energy is significantly higher than that of the lowest energy minimum found. Moreover, the use of such methods helps to avoid subjective interferences and possible oversights in the conformational search performed "by hand". As it will be shown, this is a good choice, because the contribution of a given conformer to the Boltzmann-averaged NMR ^{13}C chemical shift decreases exponentially with the energy difference between the given conformer and the most stable species.

Boltzmann-average ORD spectra calculated for a set of conformers, whose geometry was determined by minimization algorithms based on empirical potentials, promisingly reproduced the experimental ORD spectra of flexible organic compounds.[7]

We applied this method to the analysis and determination of the relative configuration of the four linear stereoisomers shown in Scheme 1, previously characterized by experimental



Scheme 1. Structure of the four stereoisomers **A**–**D**.

^{13}C NMR spectra recorded, inter alia, in deuterated chloroform.[11] The ab initio GIAO (gauge including atomic orbitals) ^{13}C NMR chemical shift values were calculated on the in vacuo conformers, considering that for low-polar organic compounds the effects of the chloroform solvent should not significantly affect the ^{13}C chemical shift values.[1] A comparison of the Boltzmann-averaged ^{13}C chemical shift values with available experimental data, relative to that of compounds of known structures, allowed us to discriminate among the diastereoisomers.

Results and Discussion

In the present study we have chosen the low-polar compounds **A**–**D**, reported in Scheme 1.[11] They constitute 38 atoms, including 11 carbon atoms, three of which are stereogenic centers. These open-chain compounds are part of a NMR database. The ^{13}C NMR spectra of species **A**–**D** were recently compared to those of a fragment of oasomycin,[12] to determine its absolute configuration.[11] The choice of this class of compounds was mainly made by the availability of NMR spectra recorded in deuterated chloroform.[1] The related experimental ^{13}C chemical shift values were observed within the range $\delta = 0-70$ ppm, the region of the aliphatic carbon signals, where the HF-calculated ^{13}C chemical shift values followed the best linear trend with the experimental data.[1]

Each of the four stereoisomers **A**–**D** presents eight C–C and three C–O torsional angles. This would lead to a huge number, $3^{11} = 177147$, of possible conformers per stereoisomer. However, it is reasonable to assume that the biggest discrepancies in the observed NMR ^{13}C chemical shift among the four stereoisomers should mainly be due to the different disposition of atoms around the stereogenic centers C-5, C-6, and C-7 (Scheme 1). By further considering the two alkyl groups bound to C-5 and C-7 with completely staggered fixed conformation and neglecting the orientations of the OH groups, the maximum number of relevant conformers per

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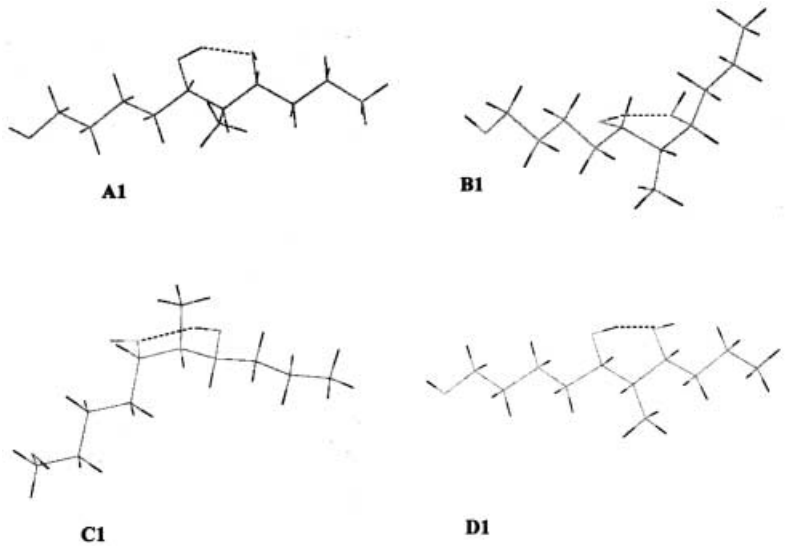
stereoisomer should be $3^4 = 81$, where the four torsional angles are defined by the atoms C-4, C-5, C-6, C-7, and C-8 (Scheme 1). On the other hand, by imposing such constraints, the relevant energy minima selected by the molecular dynamics conformational search, and successively optimized at the ab initio level, were just 8–13.

In the lowest energy conformers relative to the stereoisomers **A**–**D**, **A1**–**D1** in Scheme 2, the intramolecular hydrogen bond involving the two hydroxy groups on C-5 and C-7 provided a strong conformational stabilization. In fact, the most stable structures always presented this feature, whose stabilizing contribution was apparently more effective than the one related to the occurrence of the fully staggered conformation (present in **A1** and **D1** conformers, see Scheme 2). The standard free energy values of the most stable conformers for each stereoisomer are reported in Table 1, while the ^{13}C chemical shift values calculated for all the species investigated, and their Boltzmann-average values relative to the stereoisomers **A**–**D**, are shown in Tables 2–5.



Scheme 2. Optimized geometry of the most stable conformers, **A1**–**D1**, of the four stereoisomers **A**–**D**.

Table 1. Relative Gibbs standard free energy values (ΔG° [kJ mol^{-1}]) calculated for the conformers of stereoisomers **A**–**D** shown in Scheme 1.

	A	B	C	D
1[a]	0	0	0	0
2	0.3833	3.2556	5.9126	1.0554
3	7.0521	4.29532	7.5903	2.7594
4	13.2299	5.8207	8.6116	4.0301
5	14.5768	7.7898	8.8348	5.8549
6	15.5640	9.1577	9.0816	6.0334
7	17.9480	9.6933	10.4364	7.2175
8	19.7044	12.9516	11.9591	13.3113
9	–	–	15.5403	14.4639
10	–	–	16.9896	16.6430
11	–	–	19.9013	–
12	–	–	23.2488	–
13	–	–	24.4880	–

[a] The free energy values of the most stable conformers of the **A**, **B**, **C**, and **D** isomers shown in Scheme 2, were, −654.76430, −654.76408, −654.76405, and −654.76139 a.u., respectively.

As an example, we can evaluate the effect of the conformer energy on the Boltzmann weighting factors for stereoisomer **A**. The free energy of conformer **A2** is about 0.4 kJ mol^{-1} higher than that of **A1**. For this small energy difference, the contribution to the Boltzmann-average value of the chemical shift, was about 52 and 44% for conformers **A1** and **A2**, respectively. Approximately 2.5% was the weight of the isomer **A3** and the higher energy conformers **A4**–**A8** contributed the remaining 1.5%. Therefore, looking at Table 1, it is observed that at room temperature, conformational species destabilized by about 10 kJ mol^{-1} with respect to the most stable conformer, have weights of about 1% in the average chemical shift value. Hence, the higher energy conformers should play a negligible role in reproducing the NMR spectra of **A**. Similar remarks can be made for stereoisomers **B**–**D**.

The correlation plots of the experimental versus the corresponding Boltzmann-averaged GIAO calculated ^{13}C chemical shift are shown in Figure 1. The associated least-squares linear fit parameters, (intercept, slope and correlation coefficient) are reported in Tables 6, 7, and 8.

The correlation plots are relative to ^{13}C chemical shift data in the high-field region of the NMR spectrum. In this region, a higher linear correlation coefficient was observed at HF level, compared to the average value relative to the full ^{13}C NMR range.[1] Analysis of Tables 6–8 confirms these considerations.

Table 8 shows the linear correlation coefficients obtained from the least-squares fit of the plots in Figure 1. It can be seen that the calculated ^{13}C chemical shift values of stereoisomers **A** and **D** fit the experimental data very well, following the highest diagonal values of linear correlation coefficient. Conversely, stereoisomers **B** and **C** are, as Table 8 shows, less unequivocally determined by considering least-squares linear correlation coefficients. A further comment concerns the structure assignment based on correlation coefficients differing in the third decimal digit. For instance, it has been shown[1] that any alternative to the correct structure usually shows a large set of reasonable chemical shift assignments, producing small differences in the linear correlation with the available experimental data. Hence, the difference between a wrong and the right structure is restricted to just few atom positions in the molecule.[1] In cases of stereoisomerism of open-chain flexible compounds, the problem becomes even more complex because the structural differences are restricted to the combination of stereogenic centers, undergoing fast interconversion among the available conformational states. In this context, the present study actually represents a good benchmark to verify the performance of ab initio methods in reproducing experimental ^{13}C NMR chemical shift data.

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Table 2. Stereoisomer **A**: values of GIAO chemical shift [ppm] relative to TMS for the conformers **1**–**8** and their Boltzmann average.

^{13}C atom	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	Average
1	57.1	56.8	56.3	56.9	56.1	56.9	56.8	56.8	57.0
2	29.9	29.6	31.0	29.7	32.2	29.7	32.7	32.7	29.8
3	21.8	21.6	20.8	21.8	22.4	21.8	19.8	19.2	21.7
4	33.7	34.6	33.2	34.5	34.8	34.1	33.3	34.4	34.1
5	67.7	69.8	68.8	62.4	62.9	61.9	61.3	61.8	68.6
6	39.2	39.3	35.2	42.9	41.4	38.0	36.8	33.0	39.1
7	69.8	67.8	67.5	64.9	63.9	65.9	65.4	63.1	68.8
8	35.7	34.8	35.0	33.9	34.3	31.3	33.4	33.5	35.3
9	19.5	19.7	19.7	19.2	19.6	19.8	18.8	14.5	19.6
10	15.2	15.5	15.5	15.4	15.4	15.4	15.5	15.5	15.4
11	6.8	6.7	5.9	10.6	9.9	11.0	10.0	10.3	6.7

Table 3. Stereoisomer **B**: values of GIAO chemical [ppm] relative to TMS for the conformers **1**–**8** and their Boltzmann average.

^{13}C atom	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	Average
1	57.2	56.8	56.0	56.5	56.0	56.8	57.0	57.0	56.9
2	29.9	29.6	32.1	31.1	31.9	32.4	29.8	29.9	30.2
3	21.6	21.6	22.3	22.4	22.3	21.6	21.7	21.7	21.7
4	34.0	34.6	34.7	29.9	28.5	34.6	34.3	34.4	33.8
5	61.1	63.7	63.6	67.8	69.9	62.9	62.0	61.8	62.5
6	38.8	38.3	38.4	38.5	37.3	34.0	40.6	37.1	38.6
7	69.8	67.2	67.3	67.0	62.9	66.6	63.4	61.5	68.6
8	34.7	35.7	35.7	34.7	34.9	34.2	34.3	33.7	34.9
9	19.2	19.9	19.9	18.3	18.6	18.1	18.9	14.0	19.3
10	15.3	15.5	15.5	15.2	15.6	15.6	15.5	15.4	15.4
11	14.8	12.3	12.4	15.8	15.1	12.2	9.8	9.7	14.1

Table 4. Stereoisomer **C**: values of GIAO chemical shift [ppm] relative to TMS for the conformers **1**–**13** and their Boltzmann average.

^{13}C atom	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	Average
1	56.0	56.8	57.2	56.3	57.1	56.8	57.1	57.1	57.1	56.0	57.3	56.6	56.9	56.2
2	31.9	29.6	30.0	31.1	29.8	32.6	27.2	32.7	29.7	29.7	27.3	30.9	29.7	31.5
3	22.1	20.5	20.8	20.4	21.4	15.9	18.9	16.1	21.7	22.0	19.0	23.1	18.3	21.7
4	33.6	33.7	33.8	31.0	33.5	33.5	32.4	31.4	30.4	28.4	28.4	34.2	26.5	33.5
5	69.6	67.0	62.8	69.0	63.6	64.7	62.3	61.8	67.7	62.3	63.6	67.9	58.1	68.8
6	39.0	38.6	37.4	34.5	43.4	34.6	40.5	33.8	40.5	40.6	40.3	38.1	40.4	38.8
7	61.1	67.8	70.0	60.6	61.4	67.4	68.2	69.6	64.8	65.2	64.3	68.3	65.0	62.2
8	35.1	31.1	29.5	34.8	34.7	31.0	30.7	29.5	36.4	32.9	36.4	31.5	32.9	34.4
9	19.5	19.6	19.4	19.6	19.5	19.6	19.7	19.5	19.4	19.2	19.3	20.0	19.1	19.5
10	15.5	15.7	15.3	15.5	15.5	15.6	15.5	15.3	15.3	15.4	15.3	15.5	15.4	15.5
11	14.8	15.8	15.0	12.6	10.9	15.4	15.6	14.8	6.9	11.0	6.7	18.0	10.7	14.7

Table 5. Stereoisomer **D**: values of GIAO chemical shift [ppm] relative to TMS for the conformers **1**–**10** and their Boltzmann average.

^{13}C atom	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	Average
1	56.9	56.0	57.3	56.8	56.8	57.0	56.9	57.8	56.8	55.8	56.9
2	29.6	32.1	29.9	29.6	29.8	29.7	32.7	28.9	32.1	28.0	30.1
3	21.2	21.9	21.2	21.2	22.2	21.2	21.4	23.6	21.0	21.2	21.2
4	35.2	35.4	32.4	34.1	35.3	34.5	29.0	34.1	35.1	27.1	33.5
5	66.3	66.2	64.5	70.1	65.8	64.8	62.2	68.7	69.1	61.5	66.4
6	39.9	40.0	40.1	40.1	43.4	41.8	41.5	37.4	34.9	40.5	40.1
7	67.6	67.6	70.0	64.6	62.1	62.1	64.9	70.4	63.3	65.8	67.4
8	39.0	39.0	35.2	33.5	32.1	30.0	35.6	36.1	31.7	33.7	35.3
9	19.7	19.7	19.0	19.1	19.7	19.2	19.1	19.6	14.4	19.4	19.1
10	15.4	15.4	15.3	15.6	15.4	15.4	15.3	15.2	15.5	15.3	15.4
11	18.8	18.8	14.6	14.6	12.9	11.0	11.0	21.0	18.8	10.9	15.3

It is important to point out that, besides the theoretical approach proposed here, a careful analysis focusing on the NMR values observed in the so-called topic centers, must always be carried out. In fact, as a comparison, Table 9 reports the matrix of the linear correlation coefficients obtained from the experimental ^{13}C chemical shift values.[11] It may be seen that the linear correlation coefficients relative to the plots of chemical shift values of the conformers also differ in the third digit from 1.000.

To rule out this inconvenience, and hence get more reliable structure assignments, in the preceding paper[1] we have employed a parameter ($\Delta\delta$) defined as the difference between the scaled-calculated and the experimental ^{13}C chemical shift values.[1] Using $\Delta\delta$, it is possible to determine the departure of fit for any single ^{13}C chemical shift for the different trial structures considered.

In Table 10 we report the sum of $|\Delta\delta|$, the absolute value of $\Delta\delta$, for **A**, **B**, **C**, and **D**. Conversely, Table 11 shows the sum of $|\Delta\delta|$ relative to the experimental ^{13}C chemical shift data[11] of the four stereoisomers. By comparing Tables 10 and 11 we observe that the values obtained from incorrect assignments have the same order of magnitude both in theoretical-experimental as well as in experimental–experimental correlation plots. Moreover, the theoretical–experimental diagrams point out the correct assignments, including **B** and **C** stereoisomers. It has to be stressed that in increasing the level of the calculation, and hence the computational-time expense, the difference between the values reported in Tables 10 and 11 should be reduced.[1]

These results allow us to conclude that the present computational method can provide

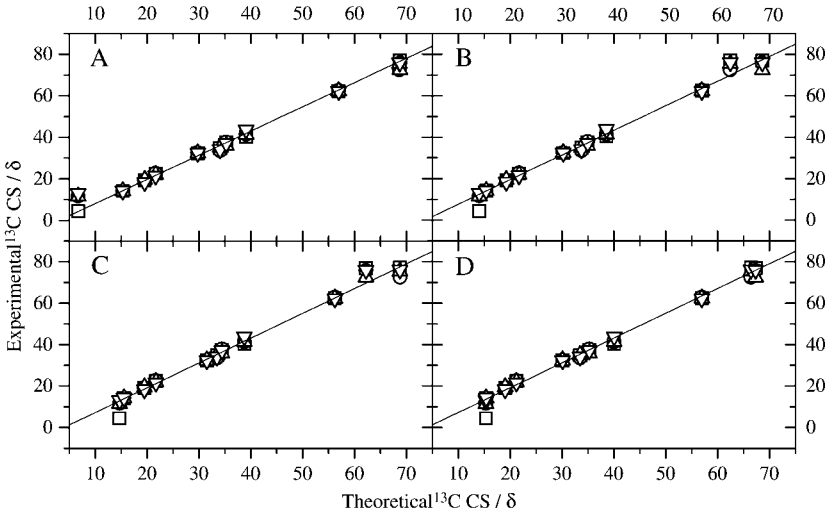

Figure 1. Correlation plots of experimental versus theoretical ^{13}C NMR chemical shift (CS) values for the species represented in Scheme 1. In any frame A – D, the experimental data[11] of the species **A** (□), **B** (○), **C** (△), and **D** (▼) are plotted against the corresponding average theoretical data (Tables 2 – 5) of A – D, respectively. Solid lines show the corresponding linear fits.

Table 6. Slopes of least-squares linear fits of the theoretical versus experimental isomer-shift correlation plots shown in Figure 1.

	$\mathbf{A}_{calcd}$	$\mathbf{B}_{calcd}$	$\mathbf{C}_{calcd}$	$\mathbf{D}_{calcd}$
$\mathbf{A}_{exp}$	1.166	1.272	1.286	1.251
$\mathbf{B}_{exp}$	1.077	1.188	1.195	1.167
$\mathbf{C}_{exp}$	1.072	1.177	1.195	1.161
$\mathbf{D}_{exp}$	1.101	1.212	1.226	1.196

Table 7. Intercepts of least-squares linear fits of the theoretical versus experimental isomer-shift correlation plots shown in Figure 1.

	$\mathbf{A}_{calcd}$	$\mathbf{B}_{calcd}$	$\mathbf{C}_{calcd}$	$\mathbf{D}_{calcd}$
$\mathbf{A}_{exp}$	– 3.627	– 7.446	– 8.058	– 7.222
$\mathbf{B}_{exp}$	– 0.253	– 4.220	– 4.580	– 3.995
$\mathbf{C}_{exp}$	– 0.222	– 3.975	– 4.739	– 3.911
$\mathbf{D}_{exp}$	– 0.764	– 4.775	– 5.386	– 4.698

Table 8. Correlation coefficients of least-squares linear fits of the theoretical versus experimental isomer shift correlation plots shown in Figure 1.

	$\mathbf{A}_{calcd}$	$\mathbf{B}_{calcd}$	$\mathbf{C}_{calcd}$	$\mathbf{D}_{calcd}$
$\mathbf{A}_{exp}$	0.999(4)	0.992(0)	0.991(5)	0.992(3)
$\mathbf{B}_{exp}$	0.995(5)	0.998(3)	0.993(0)	0.998(2)
$\mathbf{C}_{exp}$	0.996(0)	0.994(3)	0.998(4)	0.998(0)
$\mathbf{D}_{exp}$	0.994(0)	0.995(9)	0.996(0)	0.999(3)

Table 9. Correlation coefficients matrix of least-squares linear fits of the experimental isomer shift data[11].

	$\mathbf{A}_{exp}$	$\mathbf{B}_{exp}$	$\mathbf{C}_{exp}$	$\mathbf{D}_{exp}$
$\mathbf{A}_{exp}$	1.000	0.995(8)	0.996(1)	0.993(8)
$\mathbf{B}_{exp}$	0.995(8)	1.000	0.997(5)	0.998(3)
$\mathbf{C}_{exp}$	0.996(1)	0.997(5)	1.000	0.998(5)
$\mathbf{D}_{exp}$	0.993(8)	0.998(3)	0.998(5)	1.000

a valid support in the routine analysis of ^{13}C NMR spectra in solution to determine the relative stereochemistry of low-polar open-chain organic compounds.

Conclusion

The ab initio HF method is proposed here to be a complementary computational tool in the determination of the relative stereochemistry of four low-polar linear stereoisomeric fragments of natural products by analyzing their ^{13}C NMR spectra. The theoretical ^{13}C chemical shift values, to be compared to the corresponding experimental ones, were determined by the Boltzmann average of the GIAO ^{13}C chemical shift values calculated for all the conformers. The weighting factors in the Boltzmann distribution were the relative values of the HF free energy of the conformers evaluated at the temperature of the experiment. The least-squared parameters of linear correlation plots, of experimental versus theoretical ^{13}C NMR data, allowed the correct structural assignment of the considered stereoisomers.

Computational Methods

Ab initio calculations were performed on the isomeric compounds, **A** – **D**, (Scheme 1), at the HF level, with the 6-31G(d) basis set, using the Gaussian98W package.[13] A preliminary conformational search on each of the four stereoisomers (Scheme 1) was performed by molecular dynamics, employing the CVFF force field[14] implemented in the INSIGHT II package.[15] The vacuum and the chloroform solution phases were

Table 10. Sum of $|\Delta\delta|$ values of theoretical-experimental[11] chemical shifts relative to the four stereoisomers **A** – **D**. The theoretical chemical shift data, reported in the last column of Tables 2 – 5,, were scaled[11] by using the corresponding slope and intercept values reported in Tables 6 and 7.

	$\mathbf{A}_{calcd}$	$\mathbf{B}_{calcd}$	$\mathbf{C}_{calcd}$	$\mathbf{D}_{calcd}$
$\mathbf{A}_{exp}$	6.77	17.95	17.29	19.98
$\mathbf{B}_{exp}$	26.68	10.91	15.89	16.08
$\mathbf{C}_{exp}$	26.50	18.47	9.93	15.10
$\mathbf{D}_{exp}$	23.42	12.42	12.68	7.96

Table 11. Sum of $|\Delta\delta|$ values of experimental-experimental[11] chemical shifts relative to the four stereoisomers **A** – **D**.

	$\mathbf{A}_{exp}$	$\mathbf{B}_{exp}$	$\mathbf{C}_{exp}$	$\mathbf{D}_{exp}$
$\mathbf{A}_{exp}$	0.00	16.52	16.95	17.97
$\mathbf{B}_{exp}$	16.52	0.00	11.43	11.08
$\mathbf{C}_{exp}$	16.95	11.43	0.00	11.68
$\mathbf{D}_{exp}$	17.97	11.08	11.68	0.00

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mimicked through the values of the corresponding dielectric constant. This led to the selection of a larger number of energy minima. The geometry of the conformers above, as well as that of tetramethylsilane (TMS), was fully optimized at the ab initio level. Thermochemical calculations, in the harmonic approximation of the vibration modes, allowed the determination of the standard Gibbs free energy values, at 298.15 °C, relative to the minimum energy geometries found. The NMR isotropic magnetic shielding (IMS) values were calculated by the GIAO method.[16–18] The ^{13}C chemical shift (CS) values of any carbon atom X in a given conformer *i* (CS_{Xi}) were obtained by subtracting its calculated ^{13}C IMS (IMS_{Xi}) from the average ^{13}C IMS of TMS ($IMS_{TMS} = 201.728$ ppm): $CS_{Xi} = IMS_{TMS} - IMS_{Xi}$. The theoretical ^{13}C chemical shift values of a given carbon atom X in one stereoisomer (CS_X) were obtained by the Boltzmann distribution function given in Equation (1), where *N* is the number of conformers found, for each

$$CS_X = \frac{\sum_{i=1}^{N}\left[CS_{Xi}\cdot\exp(-\Delta G_i^0/RT)\right]}{\sum_{i=1}^{N}\left[\exp(-\Delta G_i^0/RT)\right]} \quad (1)$$

of the four isomers **A**–**D**, *R* is the ideal gas constant, *T* the absolute temperature and ΔG_i^o the standard free energy value of the i^{th} conformer relative to the energy of the most stable conformer, **1** in Table 1. The CS_{Xi} and their average CS_X values are reported in Tables 2–5. To prevent errors in the Boltzmann-average value of the chemical shift by overestimating the contributions of particular conformations, in the ab initio structure refinement it was always checked that the convergence occurred towards different energy minima, and redundant minima were discarded. Linear fittings of correlation plots between experimental and theoretical chemical shift values were performed to quantify the reliability of the stereochemical assignments (see Figure 1 and Tables 6–8).

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