Ab Initio and Density Functional Evaluations of the Molecular Conformations of *β*-Caryophyllene and 6-Hydroxycaryophyllene

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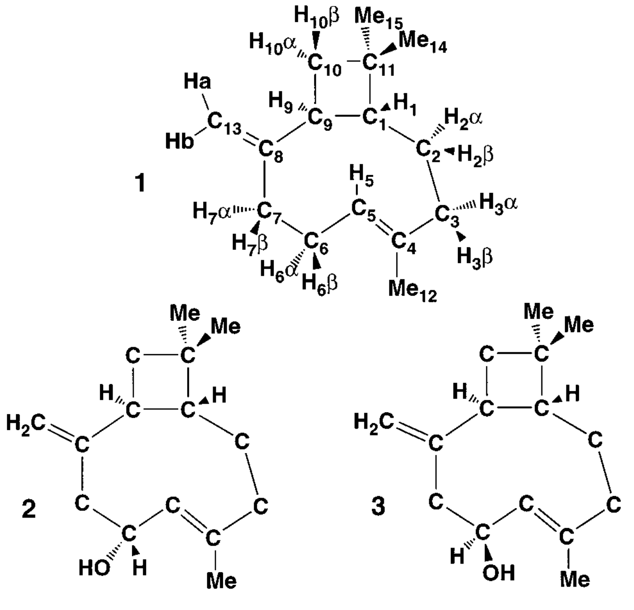
The four conformations of *β*-caryophyllene (αα, α*β*, *β*α, and *ββ*) were investigated ab initio at the 6-31G*/HF and MP2 levels and additionally with density functional methods (B3LYP/6-31G*), as it concerns their relative thermodynamic stabilities. The αα is predicted to be the most stable geometry, in agreement with low-temperature NMR measurements. In the case of 6-hydroxycaryophyllene, the αα is still the most stable conformation when the configuration at C-6 is *S*, but when the configuration is reversed to *R* the *ββ* geometry becomes the most stable one. This is again in agreement with NMR data. On the other hand, for both molecules the AM1 semiempirical model Hamiltonian fails to predict the αα as a low-energy geometry, mainly due to an incorrect description of the cyclobutane ring puckering. The interconversion paths among the different minima are also analyzed and discussed. The solvent effect (either chloroform or water) on the stability of the different conformers of *β*-caryophyllene and 6-hydroxycaryophyllene was studied in the polarizable continuum model framework.

Introduction

Notwithstanding a large body of theoretical investigations and experimental results, a conflicting interpretation still exists about the most stable conformations of *β*-caryophyllene.[1−6] This sesquiterpenic molecule, **1**, displayed in Scheme 1, is widespread in Nature, and also several oxygenated derivatives have been isolated.[7] It was long recognized that four different geometries were allowed in **1**, owing to the flexibility of the nine-membered ring. These conformations, αα, α*β*, *β*α, and *ββ*, are named following the relative orientations of the 8-13 exocyclic double bond and of the 5-4(-12) vinylic moiety, respectively, where α or *β* is the standard stereochemical descriptor (downward or upward the average molecular plane).

Scheme 1



From an experimental point of view, both chemical reactivity (formation of different products after protonation)[3,8] and NMR data (two sets of signals in the ^1H and ^{13}C spectra)[1] suggested that at least two conformers were equilibrating at room temperature (rt). Afterward it turned out that the conformers present at room temperature were actually three,[2] and only very recently Fitjer et al. published a detailed low-temperature NMR study,[6] that, after the inspection of the relative NOESY spectra, allowed a complete identification of the low-energy conformations. These were the αα (48%), *β*α (28%), and *ββ* (24%) conformations, in decreasing population order; the flip of the exocyclic double bond has a low activation

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energy, so that the $\alpha\alpha \rightarrow \beta\alpha$ conversion is fast on the NMR scale (one averaged set of signals at room temperature), while that of methyl 12 has a higher activation energy, and the $\beta\alpha \rightarrow \beta\beta$ conversion is therefore slow, allowing the NMR signals of the $\beta\beta$ conformation to be detected as a separate set at room temperature.

From a theoretical point of view, all of the investigations were carried out at a molecular mechanics (MM) level. Both MM1 and MM2 predicted the $\beta\beta$ and the $\beta\alpha$ as the two most stable geometries[1−2,5] (even if in a reversed order), while the $\alpha\alpha$ was calculated as a high energy one (3% estimated population at room temperature). On the other hand, an MM3 study by Fitjer et al.[3] indicated that $\alpha\alpha$ was the most stable geometry (44% at room temperature), followed by the $\beta\alpha$ (29%) and the $\beta\beta$ (26%), in close agreement with their successive experimental results.

In connection with our work on 6-hydroxycaryophyllene,[9] we investigated the molecular geometries of β-caryophyllene by the semiempirical AM1 method,[10] which has often produced molecular geometries in good agreement with the experiment and high level calculations,[11] when dealing with stable systems fully parametrized and without H-bonds. The results were again conflicting, as AM1 paralleled the MM1 and MM2 energy orders, predicting the $\beta\alpha$ and the $\beta\beta$ as the most stable conformations, while the $\alpha\alpha$ was found significantly higher in energy. The only result common to all calculation methods is that the $\alpha\beta$ geometry is high in energy and should therefore not contribute to the observed rt geometry, which is confirmed by the present ab initio study.

We have recently isolated 6-hydroxycaryophyllene from a natural source.[9] For this molecule one set of NMR signals was detectable at room temperature; an *R* configuration at C-6 (**2**), i.e., with OH in place of H6α (see Scheme 1) and a $\beta\beta$ conformation was the only geometry that fits the observed interprotonic NOE contacts and the ^{1}H−^{1}H ^3J values. Moreover AM1 calculated the $\beta\beta$ geometry as the lowest energy one for **2**, while for the (6*S*) epimer **3**, with OH replacing H6β, the most stable conformation was the $\beta\alpha$ one, but this latter geometry (*S* configuration at C-6 and $\beta\alpha$ conformation) did not match our NMR results. Thus we felt that a theoretical calculation at a higher level was definitely needed to clarify the existing confusion, and we turned our attention to ab initio and DFT calculations, not yet applied to caryophyllenic systems.

Computational Details

AM1 Calculations. See ref 9.

Ab Initio Calculations. The ab initio calculations at the HF/6-31G*[12] level used the AM1 structures of the four rotamers as starting geometries in the energy minimizations. Single point calculations at the MP2/6-31G* level have been carried out on the HF/6-31G* geometries to estimate the incidence of electron correlation effects on the mutual stability of the conformers. To evaluate the correlation effects on the equilibrium geometries a more affordable method had to be employed; therefore they were considered within the DFT framework,[13] using a hybrid exchange-correlation functional, B3LYP,[14] at the 6-31G* level. Those optimized geometries were then used to compute the NMR properties at the HF/6-31G* level, predicting the isotropic chemical shift for carbons and hydrogens with respect to tetramethylsilane (TMS). This procedure was proposed and validated by Cheeseman et al.,[15] who recommend this combination as the minimum model chemistry able to give a reliable estimate of shielding constants. The NMR calculations have been carried out with the GIAO[16] method, as implemented in Gaussian98[17] (this system of programs was used for all the calculations, unless stated otherwise). The energy barriers related to the $\alpha\alpha \rightarrow \beta\alpha$ and $\beta\beta \rightarrow \beta\alpha$ interconversions were computed at the HF/6-31G* level, following each interconversion pathway in both directions with all the other parameters fully relaxed. The two geometries closest to the crossing point of the back and forth energy profiles were used as starting points for QST2 calculations.[18] The nature of the found structures was checked through a frequency calculation: all TS were first-order saddle points.

The relative stabilities of **2** and **3**, the 6-hydroxy-substituted compounds, were also considered, taking into account the torsional degree of freedom about the C−O bond in the flexible rotor approximation at the HF/6-31G* level. Energy barriers for the interconversions and chemical shifts of the OH-substituted compounds were computed as well. The solvent effect on the geometries optimized in vacuo was evaluated in two different solvents (water and chloroform) using the polarizable continuum model (PCM).[19]

Results and Discussion

1. β-Caryophyllene (1).

AM1 Calculations. The results of AM1 calculations are reported in Table 1, together with the relative Boltzmann populations at 298 K. As it can be seen, the $\beta\alpha$ and $\beta\beta$ conformations are predicted to be the lowest

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Table 1. Heats of Formation and Relative Energies (kcal/mol) of the Different Conformers of Caryophyllene 1, and of 6*R*- and 6*S*-hydroxycaryophyllene, 2 and 3, as Determined by AM1

	ΔH_f	ΔE	population,[a] %
1βα	5.71	0.	54.6
1ββ	5.82	0.11	45.3
1αα	9.83	4.12	<0.1
1αβ	9.86	4.15	<0.1
2ββ	−38.69	0.	86.0
2βα	−37.61	1.08	13.9
2αβ	−34.79	3.90	0.1
2αα	−33.35	5.34	<0.1
3βα	−39.57	0.	96.3
3ββ	−37.63	1.94	3.6
3αα	−34.98	4.59	<0.1
3αβ	−32.94	6.63	<0.1

[a] At 298 K.

Table 2. Relative Energies[a] (kcal/mol) of the Geometries Optimized at the HF and B3LYP Levels Using the 6-31G* Basis Set for Caryophyllene 1[b]

1	HF	μ	6−7−8−13	2−3−4−12	B3LYP	% HF	% B3LYP
αα	0.0	0.37	84.5	82.6	0.0	41.8	54.1
βα	0.149	0.57	−81.3	81.1	0.442	32.5	25.7
ββ	0.289	0.31	−91.5	−126.0	0.584	25.7	20.2
αβ	5.262	0.64	86.4	−129.5	4.975	≪0.1	≪0.1

[a] The reference values (in hartrees): $E^{HF} = -581.925945$; $E^{B3LYP} = -585.990218$. [b] The HF/6-31G* dipole moments (μ, Debyes) and the values of selected dihedral angles (degrees) are also reported.

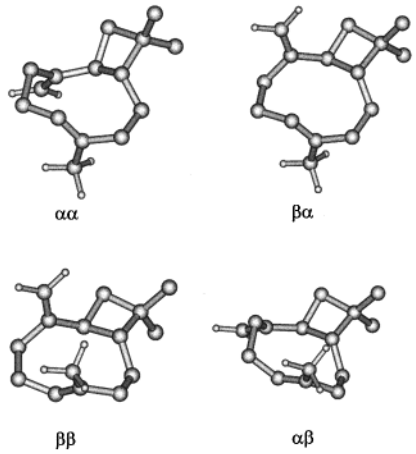

Figure 1. Structures of the four conformers considered of β-caryophyllene, **1**. For the sake of clarity, all the hydrogens but those belonging to carbon atoms 12 and 13 have been removed.

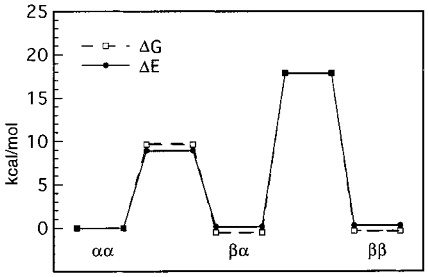

Figure 2. Relative internal energies (solid line) and free energies (dashed line) at the HF/6-31G* level along the paths for the αα → βα and βα → ββ interconversions of β-caryophyllene, **1**.

energy ones, being almost degenerate. The αα geometry is found much higher in energy (ca. 4 kcal/mol), and this is a common feature of AM1 calculations also in the case of the 6-hydroxy derivatives **2** and **3** (see Table 1).

Ab Initio Calculations. The relative energies of the four rotamers computed at the HF/6-31G* level after geometry optimization, using as starting structures those obtained with AM1, are reported in Table 2 together with the relevant dipole moments, two dihedral angles, the corresponding populations, and the reference energy. The αα conformer is the most stable one, while βα and ββ are close to each other (and to αα at the HF level) with populations of 42%, 32%, and 26%, respectively.

The inclusion of correlation effects at the MP2 level[20] on the HF/6-31G* geometries widens the gap between αα and the others (for βα and ββ by about 1 kcal/mol, while for αβ only by ~0.3 kcal/mol): the relevant populations become 80% (αα), 11% (ββ), and 9% (βα), with a negligible amount of αβ.

Geometry optimizations carried out at the B3LYP/6-31G* level, using the AM1 starting structures as before, do not produce any appreciable changes in the final structures which closely resemble the HF/6-31G* one, displayed in Figure 1. Therefore, when discussing the structures, 6-31G* stands for HF or B3LYP without distinction, since either one can well be mentioned. The highest root-mean-square deviation (rms), in fact, is 0.05 Å for αβ, while the lowest one is 0.02 Å for ββ, with those for αα and βα equal to 0.03 Å, rms due mainly to the H atoms. The energies, however, also reported in Table 2, of βα and ββ are 0.3 kcal/mol less favorable than αα with respect to HF, while αβ is less unfavorable by about the same amount, without any effect, however, on its negligible population. The other populations turn out to be 54%, 26%, and 20% for αα, βα, and ββ, respectively.

To estimate the effect of structural changes, though very limited, between HF and B3LYP, the energy of the HF/6-31G* optimized structures was computed at the B3LYP/6-31G* level, indicated with B3LYP/6-31G*//HF/6-31G*. The reference value of αα raised by ~2.2 kcal/mol because of the structure deformation, but the stability order remained unchanged with respect to the HF calculations, with populations of 44%, 33% and 23% for αα, βα and ββ, respectively, fairly close to the HF/6-31G* ones.

Due to the limited effect of the calculation level on the structures, the interconversion of the various forms was studied at the HF/6-31G* level. As displayed in Figure 2, the activation internal energy for the flip of the exocyclic double bond turns out to be ~8.9 kcal/mol at the torsion 6-7-8-13 = 182.3° (its values for αα and βα were ~84° and ~−81.3°, respectively), while that of the C12 methyl group is ~17.9 kcal/mol at the torsion 2-3-4-12 = 158.2° (with 81° for βα and −126° for ββ). The βα → ββ conversion is therefore slower than the αα → βα conversion, and the results obtained are in satisfactory agreement with the activation parameters, computed as free energies, reported in ref 6. To allow a more consistent comparison with them, the relative free energy in the gas-phase ΔG(gas) at $T = 298$ K and $p = 1$ atm, was calculated in the rigid-rotor, harmonic oscillator ap-

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Table 3. Puckering Coordinate (in Å) of the Four-membered Ring of Caryophyllene 1 for the Geometries Optimized at the AM1 and B3LYP Levels

1	AM1	B3LYP
αα	0.055	0.288
βα	0.028	0.215
ββ	0.060	0.250
αβ	0.013	0.297

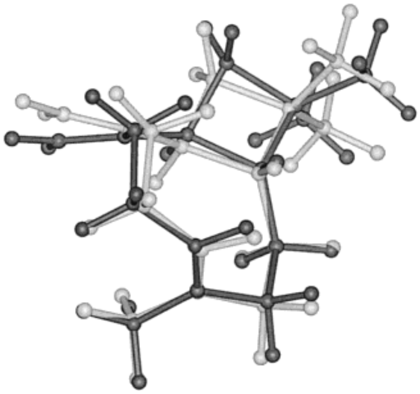

Figure 3. The best match of the AM1 (light gray) and B3LYP/6-31G* (dark gray) structures for the αα conformer (rms = 0.52 Å).

proximation[21] as $\Delta E(0) + 0.9\ \Delta ZPE + \Delta\Delta H(0\text{-}T) - T\Delta\Delta S(0\text{-}T)$, where $\Delta E(0)$ is the quantum mechanical energy difference, a scaling factor of 0.9 is applied to the change in vibrational energy at 0 K (ZPE) because of the known overestimate of vibrational frequencies at the HF/6-31G* level, and the last two terms stand for the relative changes in enthalpy and entropy from 0 to 298 K. The activation free energies, also shown in Figure 2, are somewhat less favorable than the activation internal energies: for the flip of the methyl group (12) the barrier becomes 18.4 or 18.2 kcal/mol, depending on the path direction (βα → ββ or *vice-versa*), while for the exocyclic double bond it becomes 9.6 (αα → βα) or 10.1 kcal/mol. Interestingly enough the free energy slightly favors βα and ββ over αα.

Comparison among the AM1 and 6-31G* Results. The AM1 geometries are sensitively different from the 6-31G* ones, for changes concerning both cycles. By using the AM1 Hamiltonian, the four-membered ring turns out to be in general flat, whereas at the 6-31G*/HF (or B3LYP) level the pucker is noticeable. The puckering coordinate, pc, computed according to the Cremer & Pople's definition[22] and reported in Table 3, turns out to be in the range 0.013 Å for αβ to 0.060 Å for ββ, while it is much larger with B3LYP (0.215 Å ≤ pc ≤ 0.297 Å). Also the dihedral angles in the nine-membered ring assume different values at the AM1 and 6-31G* levels. For the αβ conformer, for instance, whose rms is 0.72 Å when comparing the AM1 structure to the B3LYP one (0.69 Å with respect to HF), the 10-9-8-13 dihedral angle is 43° (AM1) vs 95° (6-31G*). The rms for βα, ββ, and αα are, however, remarkably lower (0.45, 0.46, and 0.52 Å, respectively). The structures obtained with AM1 and HF for the αα conformer are shown superimposed in Figure 3.

In this system, even the relative stabilities computed with AM1 do not coincide with the energy gaps found using B3LYP/6-31G*//AM1 (i.e., single point B3LYP/6-31G* calculations carried out on the AM1-optimized structures): βα is found to be the most stable conformer (93%), followed by ββ (6%) and αα (1%). Similarly, the AM1//B3LYP/6-31G* relative stabilities (i.e., the B3LYP-optimized geometries are evaluated using the AM1 model Hamiltonian) suffer the same drawback, with αα less stable than βα and ββ by 4.3 and 4 kcal/mol, respectively. The only common feature is the unfavorable energy of αβ, which is predicted to be the less stable conformer at all levels.

Table 4. Relative Energies[a] (in kcal/mol) of the Geometries Optimized Employing ONIOM (HF/6-31G*:AM1) on Two Different Partitions (see text) of Caryophyllene 1, in Comparison with the Full HF/6-31G* and AM1 Results

	AM1	a	b	HF
1αα	4.12	2.349	0.334	0.0
1βα	0.	0.977	0.709	0.149
1ββ	0.11	0.	0.	0.289
1αβ	4.15	3.667	2.801	5.262

[a] The reference values (in hartrees): $E^{\mathrm{ONIOM}} = -156.0886224$ (partition a) and -232.9954196 (partition b) for **1**ββ.

As an additional check of the quality of semiempirical descriptions we used the PM3 Hamiltonian,[23] which was parametrized to avoid some of the inconveniences found for AM1. However, for this molecular system, the quality of the descriptions obtained using these semiempirical models is similar both under the point of view of structure and energetics. The rms between the various structures is in fact in the range 0.10 Å (for αα) − 0.26 Å (for αβ, with 0.13 and 0.16 Å for ββ and βα, respectively). As far as the energies are concerned, their ordering is conserved as in the AM1 description, but while the AM1 energy seems to mostly depend on the conformation assumed by the $C{=}CH_2$ group and almost insensitive to the $C{=}C{-}CH_3$ arrangement, with PM3 the destabilizing effect of the $C{=}C{-}CH_3$ group β position with respect to the ring amounts to about 0.7 or 1.2 kcal/mol when $C{=}CH_2$ is β or α, respectively.

To evaluate the incidence of the four-membered ring pucker on the overall quality of the AM1 results, a few sets of ONIOM[24] calculations were performed. In Table 4 we report the results obtained for just two of them, as compared to the AM1 and HF/6-31G* energy gaps. In the first (a), only the four-membered ring (four CH_2 including the link atoms) is described at the HF/6-31G* level, while in the second (b) the ab initio part is extended to comprise the exocyclic vinyl group, in both cases with all the remaining atoms described with AM1. The correct description of the four-membered ring sharply stabilizes αα with respect to the other conformers and, moving the vinyl group into the ab initio section, αα is found to be the second most stable conformer, disfavored by only ~0.3 kcal/mol with respect to ββ. Small differences between the ab initio and ONIOM structures are found in the C12 methyl group rotation and in the nine-membered ring pucker: each additional part moved to the ab initio section, of course, makes the ONIOM results converge to the HF/6-31G* ones.

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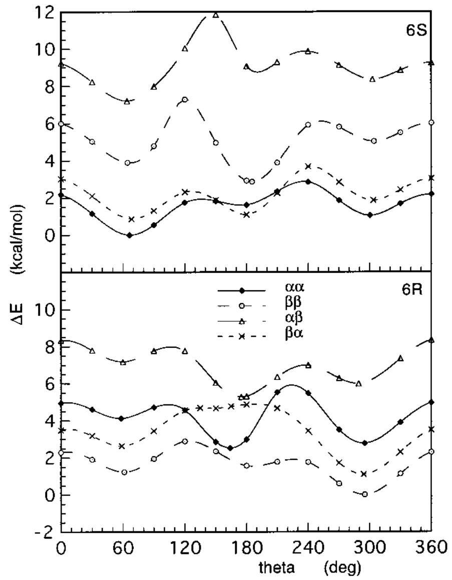

Figure 4. Dependence of the HF/6-31G* relative energies of the four conformers of the 6-hydroxycaryophyllene stereoisomers **2** (6*R*) and **3** (6*S*) upon the torsion about θ = H—O—C— H.

Table 5. Relative Energies[a] (kcal/mol) of the Geometries Optimized at the HF and B3LYP Levels Using the 6-31G* Basis Set for (6*R*) 2 and (6*S*) 3 OH-caryophyllene[b]

	HF	μ	B3LYP	% HF	% B3LYP
2ββ	0.	2.07	0.	85.4	49.5
2βα	1.096	1.52	0.444	13.4	23.4
2αα	2.522	2.38	0.358	1.2	27.1
2αβ	5.284	2.53	3.891	$\ll$0.1	<0.1
3αα	0.	1.90	0.	80.7	63.8
3βα	0.869	2.05	0.446	18.6	30.0
3ββ	2.866	2.07	1.385	0.6	6.2
3αβ	7.210	1.50	6.260	$\ll$0.1	$\ll$0.1

[a] The reference values (in hartrees): $E^{HF} = -656.7787022$; $E^{B3LYP} = -661.2001989$ for **3**αα OH-caryophyllene and $E^{HF} = -656.7780409$; $E^{B3LYP} = -661.1991585$ for **2**ββ OH-caryophyllene. [b] The HF/6-31G* dipole moments (μ, Debyes) are also reported.

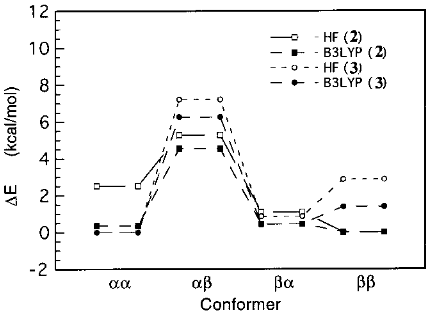

Figure 5. Relative energies of the lowest energy conformers of the 6-hydroxycaryophyllene stereoisomers **2** (6*R*) and **3** (6*S*) at the HF and B3LYP/6-31G* levels.

Concerning the results obtained by molecular mechanics, it should be noted that one of the major implementations of the MM3 method,[25] compared to MM2 and MM1, is the new set of bending parameters for the cyclobutane ring, which allows it to assume a more puckered conformation, approaching thus the experimentally observed geometry. This accounts for the correct prediction obtained for the conformations of **1** by Fitjer et al.[3], who used the MM3 force-field, and for the incorrect prediction obtained when MM1 or MM2 were used.[1,2–5]

2. 6-Hydroxycaryophyllene (2, 3).

AM1 Calculations. The results have been reported elsewhere[9] and are summarized in Table 1 for both the 6*R* stereoisomer **2** and the 6*S* stereoisomer **3**.

Ab Initio Calculations. The relative energies, computed at the HF/6-31G* level, for the four conformers of stereoisomers **2** and **3**, with their dependence upon the torsion about θ = H—O—C—H, are reported in Figure 4. There are in general three local minima at $\theta \approx 60°$, 180°, or −60° (*gauche, trans*, or *gauche′*) for each curve, whereas the lowest minimum can be either *gauche′* for **2**ββ and **2**βα, *trans* for **2**αα and **2**αβ, or always *gauche* for **3**, with the only exception of **3**ββ which is *trans*. To discriminate between the minima whose energies are very similar, geometry optimizations carried out in their regions at the B3LYP/6-31G* level confirmed the HF/6-31G* assignments reported above in all the cases but for **3**βα, which turned out *trans*: the energy gap between the *trans* and *gauche* conformers, however, is less than 0.2 kcal/mol. The relative energies obtained for the lowest energy conformers of **2** and **3** optimized at the HF/6-31G* and B3LYP/6-31G* levels, reported in Table 5 together with the dipole moments, are displayed in Figure 5. Dipole moments do not provide any rationale for the stability order. Even energy partitioning techniques, such as NPA and NBO,[26] are almost independent of the conformation: changes in the relevant values occur at the third decimal digit. The related outputs are available from the authors upon request.

The correlation effect, evaluated at the MP2/6-31G* level on the HF/6-31G* structures, is nonnegligible and reduces the gap of the various conformers among themselves and with respect to the minimum energy one, but do not alter the picture obtained at the HF level. There could be some spurious effect, however, because neither αα nor ββ are in the MP2 global minimum. An optimization at the MP2 level, presently beyond our computer capabilities, could clarify the matter.

The αα → βα and βα → ββ interconversions for **2** and **3**, left apart because extremely computer intensive and because in our opinion the hydroxy substitution would not largely affect the barriers, were also studied upon request of the referees. As displayed in Figure 6, the activation internal energy for the flip of the exocyclic double bond turns out to be ~10 kcal/mol for both **2** and **3** at the torsion 6−7−8−13 = ~180° (**2**) and ~184° (**3**) (its values are about 86° (**2**) and 84° (**3**) in αα, −81° (**2**) and −83° (**3**) in βα), while that of the C12 methyl group is about 20 (**2**) and 16 (**3**) kcal/mol at the torsion 2−3−4−12 = 158.4° (**2**) and 156.3 (**3**) (about 81° in βα for both **2** and **3**, −125° (**2**) and −143° (**3**) in ββ). The trend of the conversions is therefore similar to that found for **1**, with limited changes even after the inclusion of the free energy contributions, as can be seen by examining Figure 6 and comparing it to Figure 2.

Most of the discussion related to the comparison of the AM1 vs 6-31G* results holds for the 6-hydroxy-substi-

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(25) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J. *J. Am. Chem. Soc.* **1989**, *111*, 8551. (b) Aped, P.; Allinger, N. L. *J. Am. Chem. Soc.* **1992**, *114*, 1.

(26) (a) NBO, Version 3.1, Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

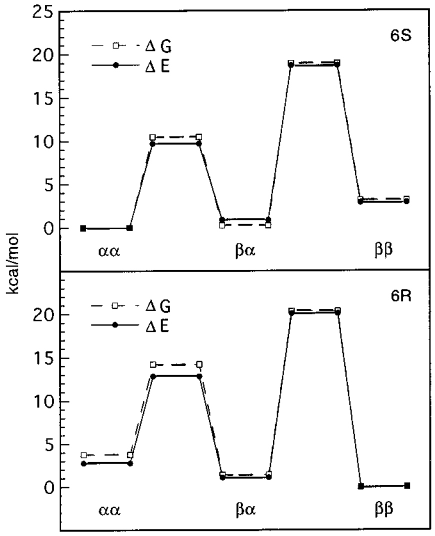

Figure 6. Relative internal energies (solid line) and free energies (dashed line) at the HF/6-31G* level along the paths for the αα → βα and βα → ββ interconversions of 6*R* (**2**, lower part) and 6*S* (**3**, upper part) hydroxycaryophyllene.

Table 6. Chemical Shifts (in ppm) with Respect to TMS Computed at the HF/6-31G*//B3LYP/6-31G* Level for the Four Conformers of β-Caryophyllene 1[a]

	1ββ		**1**αα		**1**βα		**1**αβ	
atom	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
C1/H1	48.16	1.48	41.41	1.71	49.36	1.62	41.82	1.47
C2/H2α	29.51	1.57	26.03	1.27	28.16	1.44	27.25	1.42
H2β	–	1.35	–	1.33	–	1.26	–	1.46
C3/H3α	30.67	2.33	35.08	1.86	35.67	1.83	30.14	2.27
H3β	–	1.36	–	1.83	–	1.96	–	1.37
C4	135.65	–	134.01	–	133.42	–	134.04	–
C5/H5	124.15	5.41	124.54	5.39	125.12	5.56	128.28	5.44
C6/H6α	27.97	1.91	29.41	2.24	25.40	2.19	28.96	1.87
H6β	–	2.30	–	1.93	–	1.81	–	2.37
C7/H7α	37.12	2.30	29.58	2.07	35.91	1.54	30.59	2.12
H7β	–	1.69	–	1.80	–	2.26	–	1.84
C8	151.98	–	149.68	–	151.45	–	149.00	–
C9/H9	43.40	1.89	44.20	2.41	41.94	1.87	43.68	2.55
C10/ H10α	37.46	1.69	35.45	1.42	35.48	1.62	36.18	1.57
H10β	–	1.65	–	1.52	–	1.81	–	1.33
C11	27.40	–	29.15	–	26.81	–	29.73	–
Me12	21.52	1.52	17.36	1.47	15.83	1.62	20.25	1.61
C13/H_a	112.40	5.10	115.25	5.00	112.50	5.24	113.49	5.03
H_b	–	5.14	–	4.86	–	5.17	–	4.94
Me14	27.97	1.00	28.09	1.14	28.10	1.04	28.45	0.97
Me15	21.43	0.97	21.05	1.02	22.50	0.97	21.26	1.03

[a] For the atom names, refer to Scheme 1.

tuted compounds as well. The B3LYP puckering coordinate is almost insensitive to the OH (either R or S) substitution with the values for **2** slightly lower than those for **3** (0.213 Å ≤ pc ≤ 0.291 Å and 0.229 Å ≤ pc ≤ 0.299 Å, respectively).

When comparing the AM1 and ab initio minimum energy conformations of **2**ββ, a minor difference is the orientation of the OH group (H–O–C6–H6 dihedral), which is calculated to be ≈ −60° (6-31G*) and ≈ −170° (AM1). In Figure 4 it is possible to see that the AM1 value corresponds to a relative minimum in the ab initio potential energy surface.

Notwithstanding the differences between the two structures, the AM1 distances that we have used to interpret the NOESY experiment[9] show only little changes in the ab initio geometry: the largest difference in **2**ββ is for the H5–H9 distance (2.32 vs 2.69 Å for AM1 and 6-31G*, respectively), the other ones being much lower than this. So we can say that the present ab initio geometry of **2** in the ββ conformation is not in contrast with our configurational assignment of 6-hydroxycaryophyllene.[27] Given the high energy barrier required for the flip of methyl, and the absence of a second set of NMR signals, it seems that no significant contribution from the βα and αα conformations is present in the room temperature NMR spectrum of **2**.

3. NMR Calculations. We computed both the ^{1}H and the ^{13}C NMR chemical shifts using the gauge-including atomic orbital method (GIAO), which achieves gauge invariance with basis functions that have an explicit magnetic field dependence.[16] The results for the β-caryophyllene (**1**) conformers are reported in Table 6: the computed chemical shifts are in general at higher fields than those measured at −87.2 °C.[6] According to our calculations, the experimental assignments[6] to the 14 and 15 methyl groups might be interchanged.

The ^{13}C and ^{1}H computed shifts for the 6*R* and 6*S* hydroxy derivatives, **2** and **3**, are reported in Tables 7 and 8 together with the corresponding experimental values, obtained in $CDCl_3$. Again the calculation seems to produce chemical shifts values which are in majority moved upfield when compared to experiment. When considering this limitation of the calculation method, it can be seen that better agreement is found between the experimental data and the values calculated for the ββ conformation of stereoisomer **2**; this is mainly visible in the proton chemical shifts.

4. Continuum Solvent Effect. The solvent (either water or chloroform) effect on **1** is very limited and almost independent of the conformation, because the system has a very low dipole moment (see Table 2). G_{sol} is about 1.5–1.8 kcal/mol in chloroform, as a result of an electrostatic contribution of ∼−0.45 kcal/mol more than counterbalanced by the non electrostatic terms (cavitation, dispersion and repulsion), which sum to 1.9–2.3 kcal/mol. In water the values are slightly stronger because of the higher dielectric constant of the medium: G_{sol} is about 2.7–3.2 kcal/mol, with an electrostatic term of about −2 kcal/mol overwhelmed by the non electrostatic contributions, which sum to 4.7–5.2 kcal/mol. Thus the system behaves as a hydrocarbon. In addition, it should be noted that the differential solvation results are below the precision limit of the method.

When the hydroxy group is present, the dipole moment of the molecule increases (see Table 5), but the non eletrostatic positive terms still prevail in chloroform (G_{sol} is about 0.3–0.9 kcal/mol), whereas in water a feeble stabilization (G_{sol} ranges from −0.4 to −1.9 kcal/mol) due to the electrostatic solvent effect is found, regardless the stereochemistry at C6, in both solvents. Even though these effects stabilize somewhat the βα conformation, the stability order of the conformers does not change with respect to the vacuum either for **1**, **2** or **3**. In chloroform solution, however, **2**ββ gains a little extra stability with respect to **2**βα and **2**αα.

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(27) In light of the present ab initio results, the other configurational assignment, viz. that natural 6-hydroxycaryophyllene can be 6*S*, should now be confronted not only with a **3**βα geometry (as done previously), but with a mixture of **3**αα and **3**βα rapidly exchanging. After examining all the interprotonic distances <3.5 Å of the above two geometries, this possibility can be safely ruled out given the absence of an NOE correlation between H1 and H5.

Table 7. ^{13}**C Chemical Shifts (in ppm) with Respect to TMS Computed at the HF/6-31G*//B3LYP/6-31G* Level for the Four Conformers of (6*R*)- and (6*S*)-OH-*β*-caryophyllene[a], 2 and 3, in Comparison to the Experimental Value**

atom	**2**ββ	**3**ββ	**2**αα	**3**αα	**2**βα	**3**βα	**2**αβ	**3**αβ	exptl[b]
C1	47.76	49.42	42.12	41.14	49.15	48.53	41.92	40.48	55.7
C2	29.37	28.04	26.57	26.03	27.92	28.03	27.54	27.65	31.4
C3	30.85	32.67	36.86	35.15	36.30	35.40	30.09	30.21	34.9
C4	138.25	134.65	133.30	135.55	141.09	130.34	131.97	142.33	137.1
C5	127.41	127.43	127.37	128.70	125.80	131.58	132.68	127.86	128.0
C6	63.57	63.03	61.51	65.48	64.37	59.50	59.72	68.25	70.9
C7	43.39	45.16	35.75	36.00	43.07	43.16	37.68	37.65	49.4
C8	149.23	150.22	148.45	146.07	149.31	150.02	148.12	146.28	150.2
C9	43.15	43.83	43.88	43.62	41.31	42.07	43.38	43.71	49.1
C10	37.33	36.42	36.21	35.29	35.15	34.65	36.62	36.30	42.4
C11	27.46	27.61	28.99	29.20	26.87	26.87	29.52	29.82	32.9
Me12	21.99	19.33	16.04	17.87	16.17	16.65	20.70	21.37	23.1
C13	113.47	112.50	114.66	116.44	113.63	112.37	113.17	115.12	112.6
Me14	27.94	27.86	27.98	27.98	28.12	28.01	28.35	28.38	30.0
Me15	21.36	21.40	21.03	21.04	22.51	22.23	21.18	21.02	22.0

[a] For the atom names refer to Scheme 1; [b]$CDCl_3$ solution.

Table 8. ^{1}**H Chemical Shifts (in ppm) with Respect to TMS Computed at the HF/6-31G*//B3LYP/6-31G* Level for the Four Conformers of (6*R*)- and (6*S*)-OH-*β*-caryophyllene[a], 2 and 3, in Comparison to the Experimental Value**

atom	**2**ββ	**3**ββ	**2**αα	**3**αα	**2**βα	**3**βα	**2**αβ	**3**αβ	exptl[b]
H1	1.38	1.32	1.62	1.76	1.55	1.53	1.33	1.56	1.42
H2α	1.58	1.34	1.24	1.35	1.48	1.27	1.45	1.49	1.67
H2β	1.36	1.56	1.31	1.22	1.27	1.40	1.39	1.34	1.60
H3α	2.33	1.34	1.78	1.83	1.83	1.91	2.28	1.38	2.53
H3β	1.33	2.29	1.85	1.81	1.89	1.81	1.35	2.25	1.53
H5	5.46	4.90	5.06	5.38	5.26	5.15	5.05	5.13	5.26
H6α/H6β	4.26	4.28	4.08	4.15	3.91	4.24	4.31	3.95	4.60
H7α	1.88	1.86	2.21	2.02	1.85	2.47	2.33	2.18	1.94
H7β	2.73	2.73	2.07	2.51	2.75	1.69	2.02	2.59	2.78
H9	1.96	1.94	2.49	2.30	1.97	1.89	2.54	2.45	2.27
H10α	1.72	1.71	1.61	1.50	1.64	1.82	1.64	1.41	1.78
H10β	1.64	1.69	1.46	1.55	1.80	1.59	1.37	1.60	1.60
Me12	1.52	1.76	1.66	1.45	1.95	1.57	1.62	1.98	1.62
H_a	5.10	5.12	5.06	5.03	5.22	5.14	5.01	5.05	5.00
H_b	5.16	5.08	4.76	4.92	5.15	5.10	4.89	4.98	4.89
Me14	1.00	1.00	1.01	1.03	1.03	1.03	0.96	1.01	0.97
Me15	0.98	0.98	1.03	1.02	0.99	0.97	1.01	1.02	0.96
hydroxy H	0.66	1.45	1.93	0.70	0.79	1.45	1.65	0.81	-

[a] For the atom names, refer to Scheme 1. [b] $CDCl_3$ solution.

Conclusions

This paper is aimed at solving the problem of the relative stabilities of the four conformers of β-caryophyllene **1**, which has been long subjected to different interpretations. Sesquiterpenes bearing the molecular skeleton of **1** are common and widespread in Nature, therefore a good knowledge of their conformational behavior is important to gain a better understanding of their configurations and reactivities.

After the present calculations with two different approaches at the 6-31G* level which can be considered among the most refined calculation methods now affordable for systems of this size, a complete agreement with recent NMR data can be reached. It is clear that previous erroneous results were due either to misinterpretations of experimental results or to calculation methods that gave incorrect structures. In fact, while past calculations had only focused on the cyclononane ring conformations, we here demonstrate that in **1** a correct description of the cyclobutane ring puckering is indispensable to predict the αα as the minimum energy geometry.

In the case of the 6-hydroxy derivative, the present work confirms the configuration assignment previously obtained from NMR and AM1 calculations. Here, in the 6R stereoisomer **2**, the ββ conformation is predicted as the lowest energy one by all calculation methods, even if when electron correlation is taken into account (at the B3LYP level), the energy difference of the αα and βα geometries is small. Note however that solvation stabilizes the ββ conformation over the other two. From an experimental point of view, NMR data tend to exclude a remarkable presence of the αα and βα structures at room temperature.

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