INTRODUCTION

Flavans are natural products belonging to the flavonoid class. They are very important from the biological viewpoint, presenting anti-oxidant, antibacterial, antitumoral and anti-HIV activities. These substances are found in complex mixtures mainly because of the fact they condense with proteins and sugars. They suffer autocondensation or thermal decomposition, affording the formation of both oligomeric procyanidins and condensed and hydrolysable tannines. As a result, despite the extensive occurrence of flavans in the vegetal kingdom, their phytochemical isolation is currently difficult.

_Brosimum acutifolium_, a vegetal species found in the high lands of the Amazon region is largely used in folk medicine for the treatment of rheumatism. Its extracts present protein-quinase inhibitory activities. These substances are found in complex mixtures mainly because of the fact they condense with proteins and sugars. They suffer autocondensation or thermal decomposition, affording the formation of both oligomeric procyanidins and condensed and hydrolysable tannines. As a result, despite the extensive occurrence of flavans in the vegetal kingdom, their phytochemical isolation is currently difficult.

_NMR INVESTIGATION AND THEORETICAL CALCULATIONS OF THE EFFECT OF SOLVENT ON THE CONFORMATIONAL ANALYSIS OF 4',7-DI-HYDROXY-8-PRENYLFLAVAN._ The NMR conformational study of 4',7-di-hydroxy-8-prenylflavan 1 was carried out in acetone-d6, DMSO-d6 and CDCl3, which enabled the proposition of three conformations, namely 1a, 1b and 1c, differing in the position of the prenyl group. Geometry optimizations performed using AM1 method showed that 1a (∆Hf = -86.2 kcal/mol) is as stable as 1b (∆Hf = -85.1 kcal/mol) and 1c (∆Hf = -85.4 kcal/mol). When the solvent was included, the calculations showed that the solute-solvent interactions could be explained either in the light of the electronic intermolecular delocalization or the electrostatic character between solute and solvent. Theoretical calculations (HF/6-31G*, DFT/BLYP/6-31G*, and DFT/B3LYP/6-31G*) showed that the combination of these types of interactions present in each solute-solvent system, dependent on the chemical properties of the solvent, lead to different spatial arrangements of the prenyl group, which in turn determined the conformation of 1.

Keywords: _Brosimum acutifolium_; conformational analysis by NMR; theoretical calculations of di-hydroxyprenylflavan.

**EXPERIMENTAL PART**

1H and 13C NMR spectra, and NOESY contour maps were recorded on a Bruker DRX 400 AVANCE, in acetone-d6, DMSO-d6 and CDCl3, without sample degasification. The chemical shifts were recorded in ppm (δ units) in relation to TMS as an internal standard. Pulse conditions were as follows: for 1H NMR, dwell time (DW) 149.600 µs, acquisition time (AQ) 3.985 s, number of transients (NS) 16, recycle delay (RD) 1.000 s; for 13C NMR spectra, DW 31.400 µs, AQ 2.058 s, NS 1024, RD 2.000 s, decoupling multiple resonance method Waltz-16; and for the NOESY contour maps, DW 113.600 µs, AQ 0.233 s, NS 16, RD 2.000 s, mixing time 200 ms, time evolution 3 µs, TD 2048 (F1) and 512 (F2).

The methodology used in the isolation and determination of the physical and chemical data of 1, including NMR data for CDCl3 and DMSO-d6, was described elsewhere. For 1 in acetone-d6, 1H NMR (400 MHz) δ: 8.29 [s, HO(C-4')], 7.89 [s, HO(C-7)], 7.30 (d, J=8.36 Hz, H-2'/6'), 6.85 (d, J=8.36 Hz, H-3'/5'), 6.69 (dd, J=7.86 Hz, H-5), 5.27 (tqq, J=8.36 Hz, H-6), 4.97 (dd, J=7.86 Hz, H-2'), 3.34 (dd, J=7.43, 1.49 and 1.05 Hz, H-2').
The conformation to the C ring. In addition, the absence of correlations and B rings, the isobutylene part of the prenyl ramification is in were not observed. These results indicate that, in the plane of the A 1"a is closer to HO(C-7), while H-1"b is closer to H-2'/6'. In addition, the dihedral angle fixed.

5 degrees, geometry optimization was performed by using the semi-empirical method AM1, keeping only those atoms that determine the dihedral angle fixed.

The calculations of the atomic contributions of the occupied molecular orbitals (MO’s) of the optimized geometries were also performed at the DFT/BLYP/6-31G* and DFT/B3LYP/6-31G* levels, for the structures in the vapour phase state, after geometry optimization in the same level of calculation.

Geometry optimization calculations of the solute-solvent systems were performed using the semi-empirical method AM1. The enthalpies of the solute-solvent interactions were calculated by the combination of the formation enthalpies of each solute-solvent system characterized as true energy minima in PES through frequency calculations (when the frequencies are real, it corresponds to a structure of true minimal energy).

The rotational barriers of the C-8 – C-1", C-1" – C-2" and C-2 – C-1' bonds were calculated by varying the dihedral angles determined, respectively, by C-7,C-8,C-1",C-2" (α); by C-8,C-1",C-2",H-2" (β) and by C-3,C-2,C-1",C-2'. For each angular variation between 4 and 5 degrees, geometry optimization was performed by using the semi-empirical method AM1, keeping only those atoms that determine the dihedral angle fixed.

Calculations of solvent effects were also performed for HF/3-21G* fully optimized geometries, using the Polarizable Continuum Model (PCM) at the HF/6-31G** level16,25. In these cases, the electronic-nuclear (E_{elec-nuc}) and solvation (E_{solv}) energies were obtained.

RESULTS AND DISCUSSION

At first, the 1H NMR signals of the prenyl group of I were analyzed. Differently from that reported for spectra obtained in CDCl₃ and DMSO-d₆10,12, the magnetic non-equivalence of the two geminal hydrogens H-1" was made explicit in acetone-d₆. The signals at δ = 3.34 (H-1"a) and 3.29 (H-1"b), making up the AB portion of an ABX system with geminal coupling J_{H,H} = 13.53 Hz and the coupling of these two hydrogens with H-2", J_{H,H} = 7.43 Hz, were observed. NOESY data of I in acetone-d₆ presented in Table 1 show that, differently from that observed in the acetone-d₆ experiment, H-2'/6' correlates with H-5", but not with H-1". This observation indicates that the isobutylene portion of the prenyl ramification and the C ring must be syn in relation to the plane of the A and B rings (1b in Figure 3). The correlation of HO(C-7) with H-2", but not with H-1" is also observed in this table. This fact allows one to infer that the prenyl group of 1b suffers a rotation close to 180 degrees around the C-8 – C-1" bond, in relation to 1a. In contrast, H-2 presents equivalent correlations in the NOESY experiment both in DMSO-d₆ and acetone-d₆. This result indicates that 1a and 1b present the same conformation for the B ring, in which the C ring is in the equatorial position.

The correlation between H-2 and H-5” is observed in the NOESY data of I in DMSO-d₆ presented in Table 1. This correlation indicates that H-2 and the isobutylene portion of the prenyl ramification are on the same side of the plane of the A and B rings. Therefore, the prenyl ramification and the C ring are anti (1c in Figure 4) to each other. Considering the correlations of H-1" with H-2'/6' and H-2", it can be established that at least one of the H-1" hydrogens is close to the C ring. Furthermore, the absence of correlations of H-3_m (δ_H = 3.42 and 2.41 Hz, H-3ax), 1.93 (dd, J=3.42 and 2.41 Hz, H-3') to the C ring (1a in Figure 2).

Next, the hydrogen signals of the B and C rings of I in acetone-d₆ were analyzed. Table 1 presents the NOESY correlations of H-2 with H-4", H-3", and H-2'/6", indicating that H-2 must be in an axial position and, therefore, the C ring is in an equatorial position. The axial position of H-2 can be confirmed both by the NOESY correlation of H-2'/6" with H-3_m and by 1H NMR, through the J_{H,H} = 9.74 Hz and J_{H,H} = 2.41 Hz coupling constants, characteristic of diaxial relations between H-2 and H-3_m and axial-equatorial relations between H-2 and H-3_m, respectively.

The NOESY data of 1 in DMSO-d₆ presented in Table 1 show that, differently from that observed in the acetone-d₆ experiment, H-2'/6' correlates with H-5", but not with H-1". This observation indicates that the isobutylene portion of the prenyl ramification and the C ring must be syn in relation to the plane of the A and B rings (1b in Figure 3). The correlation of HO(C-7) with H-2", but not with H-1" is also observed in this table. This fact allows one to infer that the prenyl group of 1b suffers a rotation close to 180 degrees around the C-8 – C-1" bond, in relation to 1a. In contrast, H-2 presents equivalent correlations in the NOESY experiment both in DMSO-d₆ and acetone-d₆. This result indicates that 1a and 1b present the same conformation for the B ring, in which the C ring is in the equatorial position.

The correlation between H-2 and H-5” is observed in the NOESY data of I in DMSO-d₆, presented in Table 1. This correlation indicates that H-2 and the isobutylene portion of the prenyl ramification are on the same side of the plane of the A and B rings. Therefore, the prenyl ramification and the C ring are anti (1c in Figure 4) to each other. Considering the correlations of H-1" with H-2'/6' and H-2", it can be established that at least one of the H-1" hydrogens is close to the C ring. Furthermore, the absence of correlations of H-3_m (δ_H = 3.42 and 2.41 Hz, H-3ax), 1.93 (dd, J=3.42 and 2.41 Hz, H-3') to the C ring (1a in Figure 2).
1.98) with either H-2 or H-4 (δ_H 2.91) confirms that these three hydrogens are in alternating axial positions in the B ring.

The NMR conformational analysis of 1 demonstrated a relationship between the solvent and the spatial position of the prenyl group. However, independently of the solvent used, the C ring is in an equatorial position in all the conformations. Nevertheless, the geometry optimization of 1a, 1b and 1c, presenting an equatorial C ring, as well as the respective conformations presenting an axial C ring were calculated (DFT/BLYP/6-31G*) for comparison purposes. The conformations with the equatorial C ring are about 0.6 kcal/mol more stable. Despite this small difference in energy, only conformers with an equatorial C ring are detected by NMR, signals indicative of conformational interconversion in the B ring not being observed. In contrast, calculations using the AM1 method show different rotational barriers of the interannular bond (C-2 – C-1'), being 2.9 kcal/mol when the C ring is axial, and 0.4 kcal/mol when it is equatorial. In the latter case, the smaller potential energy for the rotation of the interannular bond contributes to the thermodynamic stability of the conformation. It should be noted that the AM1 barriers have to be looked at with care30, and the rotational barriers discussed above should be viewed as estimates.

In the vapour phase and no considering intermolecular interactions, the enthalpies of formation of conformers 1a, 1b and 1c were calculated (AM1) to obtain Δ_H_f = -86.2, -85.1 and -85.4 kcal/mol, respectively. Considering that these values are close, three conformations for each solvent could occur, but were not observed by NMR. This fact suggests the possibility of contribution of the solute-solvent interaction, that favors a particular conformation and a high energy barrier for conformational interconversion31. According to literature, under the experimental conditions of the 1H NMR, the energy barrier for the coalescence of the signals should be superior to 10 kcal/mol32. Taking this fact into account, the rotational barriers involving C-8 – C-1” and C-1” – C-2” of the prenyl group were calculated by the AM1 method to give the results presented in Figure 5.

Rotational barriers equal to 7.8 and 7.5 kcal/mol were calculated for C-8 – C-1” bonds, respectively, with α_dihedral angles determined for C-7,C-8,C-1”,C-2” around 0 and 180 degrees. These energy values indicate restrictions for the free rotation of this bond33. The α values calculated for the optimized structures are 101.1 degrees in 1a, 268.3 degrees in 1b, and 76.7 degrees in 1c. As the analysis of Figure 5 suggests, these values of α indicate that 1a and 1c are in different intervals of the minimal energy regions in relation to 1b. Taking into

Table 1. NOESY data of 1 in acetone-d6, DMSO-d6 and CDCl3, it is not decreed correlations between geminal hydrogens

<table>
<thead>
<tr>
<th>Hydrogen</th>
<th>acetone-d6</th>
<th>DMSO-d6</th>
<th>CDCl3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3eq; 4eq; 2’/6’</td>
<td>3eq; 4eq; 2’/6’</td>
<td>5eq; 3eq; 4eq; 4eq; 1eq; 2’/6’</td>
</tr>
<tr>
<td>3eq</td>
<td>3eq; 4eq; 4eq; 2’/6’</td>
<td>3eq; 4eq; 4eq; 2’/6’</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4eq; 4eq; 2’/6’</td>
<td>4eq; 4eq; 2’/6’</td>
<td></td>
</tr>
<tr>
<td>4eq</td>
<td>4eq; 5; 2; 3’/5’</td>
<td>3eq; 3eq; 5; 5</td>
<td>3eq; 4eq; 5; 2; 5</td>
</tr>
<tr>
<td>5</td>
<td>4eq; 4eq; 6</td>
<td>4eq; 4eq; 6</td>
<td>4eq; 4eq; 6</td>
</tr>
<tr>
<td>6</td>
<td>5; HO(C-7)</td>
<td>5; HO(C-7)</td>
<td></td>
</tr>
<tr>
<td>2’/6’</td>
<td>3eq; 1eq; 2; 3’/5’</td>
<td>3eq; 3eq; 1eq; 2; 3’/5’</td>
<td>3eq; 3eq; 1eq; 2; 3’/5’</td>
</tr>
<tr>
<td>3’/5’</td>
<td>2’/6’; HO(C-4’); HO(C-4’); HO(C-4’); HO(C-4’))</td>
<td>5eq; 2’/6’; 2’/6’; 2’/6’</td>
<td>2’/6’</td>
</tr>
<tr>
<td>1’a</td>
<td>5eq; HO(C-7)</td>
<td>5eq; 2’/6’</td>
<td>5eq; 2; 2’/6’</td>
</tr>
<tr>
<td>1’b</td>
<td>2eq; 2’/6’</td>
<td>2eq; 2’/6’</td>
<td></td>
</tr>
<tr>
<td>2”</td>
<td>4eq; 1”</td>
<td>4eq; 1”</td>
<td>4eq; 1”</td>
</tr>
<tr>
<td>4”</td>
<td>2”</td>
<td>2”</td>
<td></td>
</tr>
<tr>
<td>5”</td>
<td>1”</td>
<td>1”; 3’/5’</td>
<td>2’/6’</td>
</tr>
<tr>
<td>HO(C-7)</td>
<td>1eq; 6</td>
<td>2eq; 6</td>
<td></td>
</tr>
<tr>
<td>HO(C-4’)</td>
<td>3’/5’</td>
<td>3’/5’</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Conformer 1b, geometry optimization (BLYP/6-31G*) from conformational analysis by NMR of 1 in DMSO-d6 (hydrogen in yellow, carbon in grey and oxygen in red)

Figure 4. Conformer 1c, geometry optimization (BLYP/6-31G*) from conformational analysis by NMR of 1 in CDCl3 (hydrogen in yellow, carbon in grey and oxygen in red)
account only the results of these calculations, energy restriction for the interconversion between 1a and 1c, considering only the pseudo-rotations of bond C-8 – C-1", would not be expected. However, the same cannot be proposed for the interconversions of these conformers in 1b, which is in the other minimal region of the potential energy curve.

The calculation of the rotational barrier of bond C-1" – C-2" results in only one energy maximum of 12.4 kcal/mol for the β dihedral angles, determined for C-8-C-1",C-2",H-2" equal to 182.6 degrees. This energy barrier does not favor the free rotation of the bond. The β values calculated for the optimized structures of 1 in different solvents are 66.3 degrees for 1a, 61.6 degrees for 1b, and 295.1 degrees for 1c. Independently of these values, the existence of only one energy maximum for β indicates that there would be no restriction for the interconversion of these three conformers.

The mixture of conformations derived from the interconversions inferred from theoretical calculations of the rotational barriers in relation to α and β was not detected by NMR. Since these calculations do not take the participation of the solvent into account, one can conclude that the solute-solvent interactions have a significant contribution to the restriction of the conformational intervention. Unfortunately, the quantum chemical calculation of the rotational potential energy curve with the explicit inclusion of the solvent is not a feasible computational task.

To analyze the effect of the solvent on a given conformation, geometry optimizations were performed taking the interactions of each conformer 1a, 1b, and 1c with each of the three solvents – acetone, DMSO and CHCl₃ – into account. Table 2 presents the results obtained by the AM1 method for formation (∆Hᵢ) and interaction (∆Hᵢ) enthalpies calculated for each of these solute-solvent systems. In these calculations, the geometry of each conformer was frozen so that only the effect of the solvent in its interactions with a certain conformation of 1 to ∆Hᵢ already calculated could be considered. In addition, the solvents were explicitly located close to the A ring and to the prenyl group. This choice of location of the solvent was made because the difference between the conformers 1a, 1b, and 1c involves fundamentally the spatial disposition of the prenyl group.

From the data in Table 2, it can be observed that in general the interaction enthalpy of each conformer with each of the three solvents is different, and also that the interactions are more thermodynamically favored for 1a with acetone (∆Hᵢ = -2.8 kcal/mol), 1b with DMSO (∆Hᵢ = -1.7 kcal/mol) and 1c with CHCl₃ (∆Hᵢ = -2.7 kcal/mol). These results confirm the existence of a preference for a given conformation for each solvent. This observation is in agreement with NMR experimental observations.

Calculations (DFT/BLYP/6-31G* and DFT/B3LYP/6-31G*) of the atomic contributions related to MO’s of conformers 1a, 1b, and 1c were realized with the objective of investigating the nature of the solute-solvent interaction. By DFT/BLYP/6-31G*, the electronic density (c², where c is the contribution of the atomic orbital to a given MO) of orbitals of carbons of the A ring to HOMO is 0.392 in 1a, 0.359 in 1b and 0.408 in 1c. By DFT/B3LYP/6-31G*, the values of c² are 0.609, 0.465, and 0.598, respectively. In both calculations, similar behaviors were observed in which the carbons of the A ring contribute predominately to the HOMO of the three conformers, as well as a smaller contribution relative to the carbons of this ring in 1b.

Consider that the HOMO must be the most relevant for the intermolecular interactions, ring A of 1 was initially chosen as a reference for the study of the solute-solvent interaction. Thus, AM1 optimization of the conformers were performed with frozen geometries, explicitly locating the solvent close to the A ring and on the side opposite to the prenyl group to dismiss effects other than the interaction of the solvent with this ring. For the optimized geometries (AM1) of the 1a-acetone, 1b-DMSO and 1c-CHCl₃, systems with solvent explicitly close to the A ring, the formation enthalpies were -136.5, -125.5 and -114.3 kcal/mol, respectively. From these results, the enthalpy of the solute-solvent interaction (∆Hᵢ) could be estimated to be equal to -2.5, -1.4, and -1.0 kcal/mol, respectively. These results show that the A ring and solvent interactions are thermodynamically more favored in 1a-acetone than in 1b-DMSO, wich, in turn, is more favored than in 1c-CHCl₃.

Calculations (DFT/BLYP/6-31G* and DFT/B3LYP/6-31G*) of the atomic contributions for MO’s of these systems were performed to study the kind of interactions of the A ring of each conformer with the corresponding solvent. In general, the comparison to those contributions obtained for conformers treated in isolation, in all solute-solvent systems studied reveals that the carbons of ring A have a

---

**Table 2. Formation (∆Hᵢ) and interaction (∆Hᵢ) enthalpies calculated (AM1) for solute-solvent systems with frozen geometries of 1a, 1b and 1c and the solvents were explicitly located close to A ring and to the prenyl group.**

<table>
<thead>
<tr>
<th>System</th>
<th>∆Hᵢ (kcal/mol)</th>
<th>∆Hᵢ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a-acetone</td>
<td>-136.2</td>
<td>-2.9</td>
</tr>
<tr>
<td>1a-DMSO</td>
<td>-125.4</td>
<td>-1.2</td>
</tr>
<tr>
<td>1a-CHCl₃</td>
<td>-113.7</td>
<td>-0.1</td>
</tr>
<tr>
<td>1b-acetone</td>
<td>-133.6</td>
<td>-1.1</td>
</tr>
<tr>
<td>1b-DMSO</td>
<td>-126.5</td>
<td>-1.7</td>
</tr>
<tr>
<td>1b-CHCl₃</td>
<td>-113.3</td>
<td>-1.2</td>
</tr>
<tr>
<td>1c-acetone</td>
<td>-134.4</td>
<td>-0.9</td>
</tr>
<tr>
<td>1c-DMSO</td>
<td>-124.9</td>
<td>-1.2</td>
</tr>
<tr>
<td>1c-CHCl₃</td>
<td>-116.0</td>
<td>-2.7</td>
</tr>
</tbody>
</table>

---

**Figure 5. Potential energy calculation (AM1) of rotation of the C-8 – C-1" (α, continuous line, determined by C-7,C-8,C-1",C-2") and C-1" – C-2" (β, dashed line, determined by C-8,C-1",C-2",H-2") bonds in flavan 1.**
larger number of occupied MO’s and consequently, smaller electronic density (c^2) values per orbital. In the 1a-acetone system, the most significant contributions of the carbons of ring A are in HOMO, HOMO-1, HOMO-2, HOMO-3, and HOMO-4; in 1b-DMSO system, the contributions are in HOMO-1, HOMO-2, HOMO-3, and HOMO-4; and in 1c-CHCl3 system, in HOMO, HOMO-1, HOMO-3, and HOMO-4. These results show the electronic changes when the contributions of the carbons in ring A for occupied frontier MO’s of conformers treated in isolation are compared to the same conformers in systems also containing the solvent. Thus, the interactions of the solute A ring with the solvent significantly influence the electronic properties of conformer 1.

Furthermore, these calculations show that HOMO and HOMO-1 present concomitant contributions of solute and solvent atoms in the 1a-acetone system, as shown in Figure 6. This fact indicates that the intermolecular interactions involve electronic delocalization with the joint participation of atoms of the solute and solvent in these systems. Similar results were observed for the 1b-DMSO system. However, in this case, concomitant contribution of atoms of 1b and solvent only for HOMO-4 of the 1b-DMSO system is observed. The observation that this orbital is significantly more stable than those MO’s of the 1a-acetone system which present electronic delocalization between solute and solvent suggests that the interactions of the A ring of 1 with the solvent are relatively less intense in the 1b-DMSO system. In contrast, none of the occupied MO’s studied in the 1c-CHCl3 system presented concomitant contributions of solvent and solute atoms. Therefore, the interactions of the solvent with ring A have a predominantly electrostatic character in the 1c-CHCl3 system.

AM1 calculations demonstrate that the dipole moment of 1c (µ = 2.88 D) is larger than that of 1a (µ = 1.32 D), and of 1b (µ = 2.49 D). This factor could be contributing to favor an electrostatic interaction with CHCl3. However, the calculated DFT (B3LYP/6-31G*) dipole moments are somehow different from the AM1 ones being 1a (µ = 3.10 D), 1b (µ = 2.48 D) and 1c (µ = 2.73 D). From these results the effect of the dipole moment on the electrostatic solute-solvent interactions can not be established (the acetone would be a candidate due to the higher dipole moment value of 1a at the DFT level).

Calculations using a continuum model, PCM, were also carried out. Table 3 gives the PCM solvation energies (E_{solv}) for the three conformers of compound 1 in acetone, DMSO and CHCl3. For all solvents E_{solv} is negative indicating the solvent effect of stabilizing each conformer. This effect is more pronounced in acetone, where, E_{solv} = -5.3, -4.6 and -5.2 kcal/mol, respectively for 1a, 1b and 1c. The results alone do not explain the NMR data, which show a conformational preference of 1a, 1b and 1c in acetone, DMSO and CHCl3, respectively. Therefore, besides solute-solvent electrostatic interactions and dielectric constant of the solvent, regioespecificity must be considered to describe the solute-solvent interactions in order to explain the stability of the systems 1a-acetone, 1b-DMSO and 1c-CHCl3.

Table 3. Electronic plus nuclear repulsion energy in gas phase (E_{ele-nuc}), HF/3-21G* fully optimized geometry value, and solvation energy (E_{solv}), HF/6-31G** single point value, for 1a, 1b and 1c in acetone, DMSO and CHCl3, using the Polarizable Continuum Model (PCM)

<table>
<thead>
<tr>
<th>Conformer</th>
<th>E_{ele-nuc} (in hartree)</th>
<th>Acetone^a</th>
<th>E_{solv} (in kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>-994.788851</td>
<td>-5.3</td>
<td>-3.5</td>
</tr>
<tr>
<td>1b</td>
<td>-994.784292</td>
<td>-4.6</td>
<td>-2.7</td>
</tr>
<tr>
<td>1c</td>
<td>-994.784811</td>
<td>-5.2</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

Table 3. Electronic plus nuclear repulsion energy in gas phase (E_{ele-nuc}), HF/3-21G* fully optimized geometry value, and solvation energy (E_{solv}), HF/6-31G** single point value, for 1a, 1b and 1c in acetone, DMSO and CHCl3, using the Polarizable Continuum Model (PCM)

<table>
<thead>
<tr>
<th>Conformer</th>
<th>E_{ele-nuc} (in hartree)</th>
<th>Acetone^a</th>
<th>E_{solv} (in kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>-994.788851</td>
<td>-5.3</td>
<td>-3.5</td>
</tr>
<tr>
<td>1b</td>
<td>-994.784292</td>
<td>-4.6</td>
<td>-2.7</td>
</tr>
<tr>
<td>1c</td>
<td>-994.784811</td>
<td>-5.2</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

Considering that conformers 1a, 1b and 1c differ from each other in the spatial arrangement of the prenyl group in relation to the plane of the A ring (Figures 2 to 4), geometry AM1 optimizations were also carried out for the systems containing conformers with non-frozen geometries, locating explicitly the solvent close to the prenyl group and of the solvent were not observed. Therefore, one can
propose that the interactions of this group with the solvent involve electronic delocalization only in the 1b-DMSO system, while in the two other systems, the interactions of the prenyl group with the solvents involve electrostatic interactions.

The solute-solvent interaction sites discussed above treated the A ring or prenyl group separately. Another geometry optimization calculation (AM1) was performed considering the possibilities for interaction of the solvent concomitantly with the prenyl group and the carbons and oxygen of ring A of each of the three conformers of 1. The results of these calculations showed that, for the 1a-acetone, 1b-DMSO, and 1c-CHCl₃ systems, the enthalpies are -136.6, -128.0, and -114.8 kcal/mol, respectively, permitting estimation of the carbons and oxygen of ring A of each of the three conformers of 1. The results of these calculations showed that, for the 1a-acetone, 1b-DMSO, and 1c-CHCl₃ systems, the enthalpies are -136.6, -128.0, and -114.8 kcal/mol, respectively, permitting estimation of $\Delta H$ as -3.2, -3.8, and -1.5 kcal/mol, respectively. According to these results, the solute-solvent interaction is more favored thermodynamically in the 1b-DMSO system. Furthermore, differently from the 1a-acetone and 1c-CHCl₃ systems, the calculations (DFT/BLYP/6-31G* and DFT/B3LYP/6-31G*) of the MO’s of 1b-DMSO demonstrate concomitant contributions of atoms of the solvent and of 1b (the prenyl group and hydroxyl group and carbons of the A ring) to HOMO, HOMO-1, and HOMO-2, as shown in Figure 7.

**Figure 7.** Optimized geometry (B3LYP/6-31G*) of 1b-DMSO system, considering interactions of prenyl group, oxygen of ring A with solvent (superior structure) and inferior structures, of left side to right side, HOMO, HOMO-1 and HOMO-2 of this system (hydrogen in yellow, carbon in grey and oxygen in red; positive phases in green and negative phases in blue)

CONCLUSIONS

From NMR conformation analysis of 4’,7-di-hydroxy-8-prenyllflavan 1 in acetone-d₆, DMSO-d₆, and CDCl₃, and geometry optimizations (AM1 and DFT/BLYP/6-31G*), the three conformers 1a, 1b, and 1c were proposed. In all these conformers, ring C is in an equatorial position; however, they differ with respect to the spatial position of the prenyl group. The rotational barriers calculated for the prenyl group shows that the conformational interconversion between 1a and 1c is thermodynamically favored. However, NMR data are rather characteristic, indicating the absence of interconversion between these conformers. Thus, an effect of the solvent on the stability of each conformer can be proposed. This observation is in agreement with geometry optimization calculations of the systems constituted by 1a, 1b, and 1c with each of the solvents. The results confirm the existence of a preference of a given conformation for a certain solvent, 1a with acetone, 1b with DMSO, and 1c with CHCl₃.

Theoretical calculations demonstrated that the type of solute-solvent interaction depends on the type of solvent used, considering three different sites of the solute molecule for the approximation of the solvent molecule, namely, the prenyl group, A ring, or both jointly.

The interaction of 1a with acetone depends on the molecular site considered. Electrostatic interactions are observed when only the prenyl group is involved. However, electronic delocalization with the concomitant participation of the solute and the solvent is observed when only ring A is involved. The calculations demonstrate that the interaction of the prenyl group is more favored thermodynamically ($\Delta H = -4.4$ kcal/mol) than that of the A ring ($\Delta H = -2.5$ kcal/mol), or when the prenyl group and A ring are considered simultaneously ($\Delta H = -3.2$ kcal/mol). These results suggest that electrostatic interaction in the 1a-acetone system is more important than electronic delocalization. Therefore, since even smaller steric restrictions are expected for the approximation of the acetone molecule to the prenyl group in conformation 1a, an agreement between theoretical and NMR experimental results of 1 in acetone is observed.

In the case of the interaction of 1b with DMSO, the theoretical calculations demonstrate that there is only electronic delocalization in the solute-solvent system, regardless of the site of approximation considered, and that the interaction involving the prenyl group and the hydroxyl group of ring A is more favored thermodynamically ($\Delta H = -3.7$ kcal/mol) than isolated interactions with the prenyl group ($\Delta H = -1.4$ kcal/mol), and with ring A only ($\Delta H = -2.0$ kcal/mol). These data are in agreement with the conformation deduced from NMR experiments for 1b, which presents a spatial arrangement that favors the simultaneous interaction of the prenyl group, the hydroxyl of the A ring, and the DMSO molecule.

For the interactions of 1c with CHCl₃, the calculations demonstrate that, for any approximation site considered, the interactions have a predominantly electrostatic character, the concomitant interactions with the prenyl group and A ring ($\Delta H = -1.5$ kcal/mol) being more favored than the interactions with ring A only ($\Delta H = -1.4$ kcal/mol) or with the prenyl group ($\Delta H = -1.1$ kcal/mol). These $\Delta H$ data are in agreement with the conformation of 1c deduced from NOESY experiments, since the spatial arrangement of the substituents in ring A favors the approximation of the CHCl₃ molecule concomitantly to this ring and the prenyl group.

Finally, as a result of the methodological sequence developed in this work, NMR analysis was shown to be a basic and very important instrument for the assessment the theoretical method of investigation of the chemical properties of flavan 1.

SUPPLEMENTARY MATERIAL

Tables with all optimized geometrical parameters and other results for all structures considered in the present work are available from the authors upon request.

ACKNOWLEDGEMENTS

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for financial support, and J. S. Lula and R. A. Machado for recording NMR spectra. The authors also thank the Prof. D. L. Nelson by the discussions about the text.
REFERENCES


30. Dos Santos, H. F.; De Almeida, W. B.; THEOCHEM 1995, 335, 129.

