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Theoretical study of the stability of myrsinone in vacuo and in solution

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Abstract. The stability of various conformers of myrsinone (2,3-dihydroxy-5-undecyl-1,4-benzoquinone) and its tautomer [2,3-dihydroxy-5-(undec-1-ene)-cyclohex-2-ene-1,4-dione] has been studied in vacuo and in solution on model systems with the long alkyl side chains replaced with ethyl and eth-1-ene groups, respectively. Ab initio Hartree–Fock (HF) calculations in vacuo and free-energy calculations either in chloroform or in water solution, in the framework of the polarizable continuum model, have been carried out on the 6-31G* optimized geometries obtained in vacuo and in solution (water or chloroform). The nature of the stationary points found was investigated using normal mode analysis. The energy gap between the two tautomeric forms turns out to be about 1.3 kcal/mol in vacuo and becomes about 0.3 kcal/mol in chloroform solution, whereas in water the second tautomer is favored by about 1.2 kcal/mol. The effect of second-order Møller–Plesset (MP2) correlation corrections has been considered on both the energy and the geometry of the tautomers in vacuo, whereas in solution only their effect on the energy was taken into account. The contribution to the stability in the gas phase and in solution of the intramolecular hydrogen bonds between the hydroxy hydrogen and the quinonoid oxygen is larger at the MP2 level than at the HF one. The directionality of the hydrogen bonds between the hydroxy groups affects considerably only the stability of the isomer with the exocyclic double bond. The computed chemical shifts for the two tautomers were compared to the experimental ones. In addition the solvation properties of 2,5-dihydroxy-3-ethyl-1,4-benzoquinone and of an *ortho*-quinonoid system were considered in order to evaluate the effect of the repulsion between vicinal hydroxy or quinonoid groups.

Key words: Ab initio 6-31G* second-order Møller–Plesset calculation – Continuum solvent – Chemical shift – 2,3-Dihydroxy-5-ethyl-1,4-benzoquinone – 2,3-Dihydroxy-5-(eth-1-ene)-cyclohex-2-ene-1,4-dione

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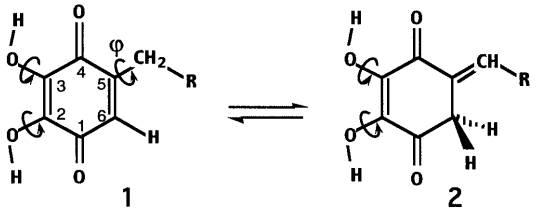
1 Introduction

The solvation properties of adjacent hydroxyl groups, as representatives of systems with "competing" hydrogen bonds in aqueous solution, have received our attention in the past both in saturated [1–4] and in aromatic compounds [5, 6], employing continuum models [3–5] as well as free-energy perturbation methods [1, 2, 6]. Others studied ethanediol water clusters with molecular dynamics [7] or employed the supermolecule approach [8] for ethanediol · H_2O. The supermolecule approach was also used for catechol · H_2O, allowing the interpretation of the torsional vibrations, which was supported by resonant two-photon ionization and dispersed florescence spectra [9]. In those systems, however, the nature of competing hydrogen bonds was fairly similar to that present within the aqueous solution, because even in protonated dopamine the charge distribution of the hydroxy groups on the catechol ring was not greatly affected by the charged side chain. Noticeably different behavior should be found in the presence of additional polar groups in a vicinal position with respect to the hydroxyl groups. The cooperative effect in solution of the carbonyl and hydroxy oxygen lone pairs versus that shown by the lone pairs of two hydroxy groups can be shown by studying myrsinone, a natural organic substance extracted from an African plant, whose structure was assigned on the basis of ^{1}H NMR measurements [10].

The stabilizing effect in vacuo or in solution produced by different types of intramolecular hydrogen bonds such as those which are present in a 2,3-hydroxy-1,4-benzoquinone structure is the topic of the present article. In order to elucidate their effect, the energy of the compound is compared to that of its isomer 2,5-dihydroxy-1,4-benzoquinone, a moiety belonging to known antitumor drugs [11] and HIV-1 inhibitors [12] and which exhibits several other interesting properties. The hydrogen bonds, though similar to those in ethanediol and dopamine, should behave in a different manner because they are probably stronger than in the

aforementioned compounds due to the peculiar bonding features of the quinonoid ring. As an interesting addition, myrsinone exhibits a rapid tautomeric equilibrium between its two forms [10], depicted in Scheme 1 (R=[CH_2]$_9$—CH_3), which gives rise to the so-called "fluxional behavior" [13].



Scheme 1.

Myrsinone is not a particularly flexible molecule, because in both tautomers (**1** and **2**) there are just two rotatable single bonds besides those of the aliphatic side chain. All possible conformers, with the only exception being those with the hydroxy hydrogens pointing towards each other, were considered and optimized in vacuo with the 6-31G* basis set at the Hartree–Fock (HF) and second-order Møller–Plesset (MP2) levels on the model system with R=CH_3. The free energy of solvation was then computed in chloroform and in aqueous solution within the polarizable continuum model (PCM) framework [14, 15] at both levels, including cavitation, repulsion and dispersion effects estimated using approximate formulas [16] which depend on the surface of the cavity formed around the solute inside the dielectric medium of given permittivity. Self-consistent-field (SCF)/6-31G* geometry optimizations in aqueous and chloroform solution were also carried out to evaluate the solvent effect on the solute structure.

2 Brief outline of the method

Exhaustive descriptions of the PCM method can be found in its source articles [14, 15] and in a related review [17], but a few modifications recently introduced in the algorithms need to be mentioned in order to explain the meaning of the computed quantities. Reference is made to the original articles for more details. The V_σ interaction between solute (M) and solvent appears in the Hamiltonian of the system with the unperturbed solute term, H_M°:

$$(H_M^\circ + V_\sigma)\psi_M = E_M\psi_M \quad . \tag{1}$$

The solute, surrounded by a cavity [18, 19] in the dielectric medium (of dielectric constant ε) shaped in the form of the solute, induces on the cavity surface an apparent charge distribution, σ, depending on the total charge distribution, Γ, of the solute (electrons and nuclei) as well as on σ itself. The apparent polarization charges (corrected for their mutual polarization and for the charge escaped outside the cavity), used to polarize the solute charge distribution, consist in the present version of the PCM of two sets which depend on the solute electrons and nuclei, respectively, and are computed by exploiting linear equations in matrix form [20]. The charges that should develop in the bulk of the dielectric medium as a reaction to the escaped electronic tails [21] are replaced by additional charges located on the cavity surface, according to the solute electronic density in each point, and this procedure is adopted to normalize the polarization charges as well. However, during geometry optimization, an alternative procedure is adopted: the charges are just scaled by a constant factor. The main novelty in the solvation code with respect to the PCM method already embodied in Gaussian94 [22] is the use of the united atom topological model for HF calculations for the definition of the cavity [19], which optimizes the van der Waals radii for atoms and atomic groups, allowing very accurate electrostatic solvation free energies, G_{el}, to be obtained, especially in the case of neutral systems [6]:

$$G_{el}^X = E_{tot}^X - \tfrac{1}{2}\int \Gamma_M^X(\mathbf{r})V_\sigma(\mathbf{r})d\mathbf{r} \quad , \tag{2}$$

(with $E_{tot}^X = E_M^X + E^{nuc}$) [15], where X stands for HF or MP2 (superscript not shown in tables and figures: the level is reported in legends only). The solvent field is kept in its HF description to obtain the MP2 free energy in solution [23].

Other terms (namely cavitation, dispersion and repulsion), which do not affect the solute wavefunction because they do not enter into the Hamiltonian, are, however, necessary to obtain the total molecular free energy in solution:

$$G_{tot}^X = G_{el}^X + G_{cav} + G_{dis} + G_{rep} \quad . \tag{3}$$

The solvent effect at each level is defined as

$$G_X^{sol} = G_{tot}^X - E_X^\circ \quad , \tag{4}$$

where E_X° is the energy of the solute in vacuo at the X level.

If not otherwise specified, the total values of the free-energy differences between the generic conformer and the reference one [$\Delta G_{tot} = G_{tot}(Conf) - G_{tot}(Ref)$] are displayed throughout.

3 Computational details

The geometries were fully optimized in vacuo using the 6-31G* [24] basis set with Gaussian94 and Gaussian98 [25] at the SCF and MP2 [26] levels. The PCM cavity was built with the united atom topological model. After geometry optimization in solution was complete, a single-point calculation was performed on the final configuration with the SCF convergence threshold lowered to 10^{-8} hartrees and with additional effective charges placed on the cavity surface according to the solute electronic density in each of its points in order to normalize the polarization charge to the value predicted by Gauss' law, mimicking the charges which should develop in the bulk of the dielectric medium as a reaction to escaped electronic tails. Single-point calculations in solution were carried out on the MP2/6-31G* optimized geometries obtained in the gas phase. The calculations were performed on an SGI Origin 2000 computer at H.H. Wills Physics Laboratory and on Digital and SGI Indigo^2 workstations at ICQEM-CNR. NMR shielding tensors were computed in the gauge including atomic orbital (GIAO) [27] framework as implemented in Gaussian98.

4 Results and discussion

4.1 HF gas-phase results

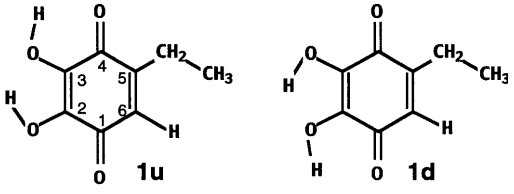
The geometries of the conformers of the two tautomeric forms (**1** and **2**) of myrsinone (with R=CH_3, still called myrsinone) were optimized at the HF level in vacuo using the 6-31G* basis set. The relative energies of their stable conformers with respect to the lowest energy conformer in vacuo are reported in Table 1. The reference conformer, **1o**, has two intramolecular hydrogen bonds between the hydroxy hydrogens and the facing quinonoid oxygen lone pair; therefore, its hydroxy groups are pointing in almost opposite directions

Table 1. 6-31G* relative energies and free energies (kcal/mol) in water (*wat*) and in chloroform (*chl*) of the two tautomeric forms (**1** and **2**) of myrsinone, at the Hartree–Fock (*HF*) and second-order Møller–Plesset (*MP2*) levels, with respect to **1o** (reference energies of the geometries optimized in vacuo at each level: $E^{HF} = -607.0280132$ hartrees and $E^{MP2} = -608.748906$ hartrees), the minimum energy conformer in vacuo. The solvent effect is also displayed

HF[a]	**1o**	**1u**	**1d**	**2o**	**2u**	**2d**
ΔE	0	1.95	1.79	1.28	3.47	4.27
ThCor[b]	0	−0.24	−0.27	−0.77	−0.97	−0.60
$\Delta\mathscr{G}^{c}_{vac}$	0	1.71	1.52	0.51	2.50	3.67
ΔG_{tot} (wat)	0	0.90	0.85	−1.24	0.31	0.74
G^{sol} (wat)	−11.15	−12.40	−12.21	−13.80	−14.75	−15.07
ΔG_{tot} (chl)	0	1.50	1.49	0.31	2.28	2.89
G^{sol} (chl)	−2.89	−3.39	−3.21	−3.90	−4.18	−4.37
MP2[d]	**1o**	**1u**	**1d**	**2o**	**2u**	**2d**
ΔE	0	2.76	2.64	1.20	4.13	5.08
ΔG_{tot} (wat)	0	1.59	1.70	−0.28	1.34	1.98
G^{sol} (wat)	−7.86	−9.03	−8.80	−9.34	−10.65	−10.95
ΔG_{tot} (chl)	0	2.29	2.32	0.61	3.22	3.98
G^{sol} (chl)	−1.74	−2.21	−2.06	−2.33	−2.65	−2.84

[a] Geometries optimized at the HF/6-31G* level in each environment
[b] Calculated in the rigid rotor, harmonic oscillator approximation [25] as $0.9 \cdot \Delta$zero-point energy $+ \Delta\Delta H(0-T) - T\Delta\Delta S(0-T)$. The reference value of the zero-point energy (scaled by 0.9 for the 6-31G* known overestimate of vibrational frequencies) and thermal corrections is 0.110446 hartrees. $T = 298.15$ K. The terms $\Delta\Delta H(0-T)$ and $\Delta\Delta S(0-T)$ stand for the relative (with respect to **1o**) changes in enthalpy and entropy from 0 to 298.15 K
[c] The free-energy change in the gas phase (vac) with respect to **1o**, given by ΔE + ThCor
[d] Geometries optimized at the MP2/6-31G* level in the gas phase

(**o**). The corresponding conformer of **2**, **2o**, is only 1.28 kcal/mol less favorable than **1o**. The other two possible arrangements, displayed in Scheme 2, are



Scheme 2.

named up (**u**) or down (**d**) according to the orientation of both hydroxy groups, which can point in the same direction (either toward the quinonoid carbonyl 4 or 1). These structures still have two intramolecular hydrogen bonds, one between a hydroxy hydrogen and a quinonoid oxygen lone pair, as in the most stable conformer, and the other between the isooriented hydroxy groups.

The **1u** conformer is almost equal in energy to the **1d** (the energy difference is less than 0.2 kcal/mol), thus indicating that the aliphatic side chain position does not affect much the stability of benzoquinones, and both are less stable than **2o** by about half a kcal/mol (see also Fig. 1a). Their energy gaps with respect to **1o** are 1.95 and 1.79 kcal/mol for the **u** and **d** forms, respectively, so the effect associated with the presence of either an ethyl group or a hydrogen atom on the carbon atom vicinal to a hydrogen bond acceptor carbonyl group is almost negligible. In contrast, the energy gaps are much larger in **2**, where the **2u** and **2d** forms are 2.2 and 3.0 kcal/mol, respectively, less favorable than **2o**. The presence of the exocyclic double bond syn with respect to the C=O group gives an additional destabilizing contribution to the internal energy, especially when the CO group is not involved in an intramolecular hydrogen bond.

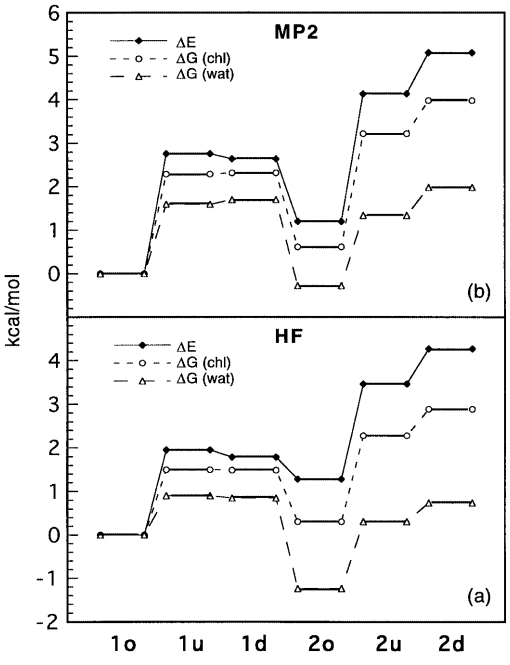


Fig. 1. 6-31G* internal energy differences in vacuo (ΔE) and free-energy differences in chloroform (*chl*) and water (*wat*) solution with respect to **1o**, taken as zero, of the conformers of myrsinone considered at the **a** Hartree–Fock (*HF*) and **b** second-order Møller–Plesset (MP2) levels. The differential solvent effect can be estimated by the separation between the gas-phase and solution values for the individual conformers

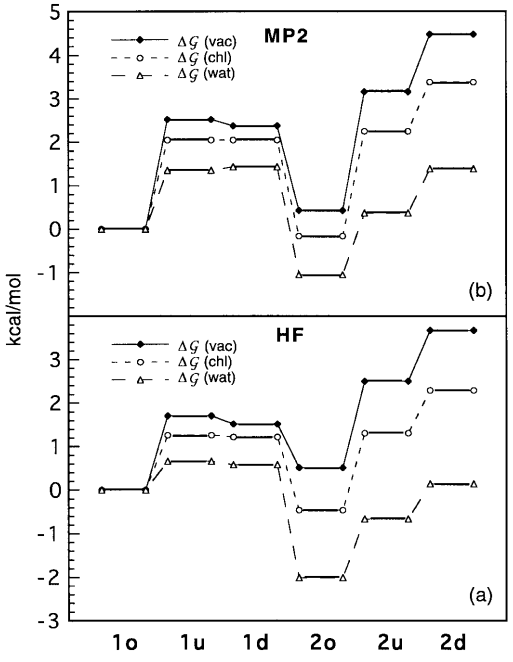


Fig. 2. 6-31G* free energy differences in vacuo, in chloroform and in water solution, including $\mathscr{G}_{vac}$, with respect to **1o**, taken as zero, of the conformers of myrsinone considered at the **a** HF and **b** MP2 levels. For an estimate of the differential solvent effect see the caption to Fig. 1

When considering, in place of the internal energy, the free energy in vacuo, $\mathscr{G}_{vac}$, also reported in Table 1, the gaps are slightly reduced in **1**, while the conformers of **2** are all sensitively stabilized with respect to **1**, because the thermal corrections (including the zero-point energy) sensitively favor the second tautomer. The relevant mutual free energy levels are displayed graphically in Fig. 2a.

It is worth noting that the aliphatic side chain in **1o** is rotated about φ by 75.96° at the HF level and by 73.95° at the MP2 level, though this arrangement is only slightly more stable (by 0.22 and 0.50 kcal/mol at the HF and MP2 levels, respectively) than the $\varphi = 180°$ one (displayed in Scheme 1). The results obtained by imposing this constraint are reported in Table 2. It is apparent that the energy and free-energy pictures do not change because of the small rearrangements in these values with respect to the fully optimized structures.

The effect produced by the alkyl and vinyl side chain positions on the stability of the compounds was taken into account at the HF/6-31G* level. For **1** the trans–cis interconversion path was followed; the resulting profiles are shown in Fig. 3. The trans rotamer is nearly as stable as the gauche ones, as stated previously, while the cis rotamer (about 6 kcal/mol less favorable) coincides with the maximum along the energy profile. This result may indicate that myrsinone itself shows a good mobility of the benzoquinone head, which can easily span the gauche, trans and gauche' positions with respect to its long tail. From now on, however, only the gauche isomer is considered for **1**, unless otherwise specified. For **2** the trans and cis isomers with respect to the vinyl bond are considered: the isomer presenting the methyl group trans

Table 2. 6-31G* relative energies and free energies (in kcal/mol) in water and in chloroform of form **1′** ($\varphi = 180°$) of myrsinone at the HF and MP2 levels, with respect to **1o**, the minimum energy conformer in vacuo. The solvent effect is also displayed

HF	**1′o**	**1′u**	**1′d**
ΔE	0.22	2.21	2.08
ThCor	−0.03	−0.28	−0.29
$\Delta\mathscr{G}_{vac}$	0.19	1.93	1.79
ΔG_{tot} (wat)	−0.17	0.64	0.72
G^{sol} (wat)	−11.45	−12.79	−12.61
ΔG_{tot} (chl)	−0.11	1.40	1.44
G^{sol} (chl)	−3.23	−3.75	−3.52
MP2	**1′o**	**1′u**	**1′d**
ΔE	0.50	3.28	3.21
ΔG_{tot} (wat)	0.11	1.44	1.60
G^{sol} (wat)	−8.24	−9.70	−9.47
ΔG_{tot} (chl)	0.17	2.53	2.57
G^{sol} (chl)	−2.07	−2.50	−2.38

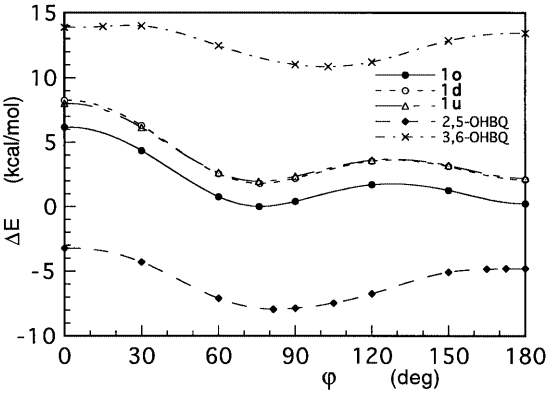


Fig. 3. Relative energy profiles for the rotation about φ of the aliphatic side chain in **1o**, **1u**, **1d**, 2,5-dihydroxy-3-ethyl-1,4-benzoquinone (*2,5-OHBQ*) and 3,6-dihydroxy-4-ethyl-1,2-benzoquinone (*3,6-OHBQ*) with respect to **1o** (*solid line*), taken as zero

with respect to C_4 (as displayed in Scheme 1) was found to be 2.10 kcal/mol more favorable than the cis one.

The structures with the hydroxy hydrogens pointing towards each other were not considered in this study because of their steric hindrance and unfavorable electrostatic interaction. Moreover structures with the hydroxy groups behaving both as proton donor and proton acceptor are not local minima and evolve to either the up or down arrangement. This may be due to the presence of the adjacent quinonoid oxygens and mainly of the COH═COH double bond, which keeps the C—O bonds in the same plane. These kinds of structures were in fact found previously by us only for the gauche arrangement of the O—C—C—O dihedral of ethanediol, namely g'Gg' [1, 3].

4.2 MP2 gas-phase results

The effect of the correlation corrections at the MP2 level on the geometries was also taken into account. The

comparison of the main geometric parameters optimized in vacuo at the HF/6-31G* and MP2/6-31G* levels, performed for tautomers **1** and **2**, reveals a limited change in the structures: the double bonds (C3C6, C11C12, O1C2 and C9O10, see the values in Table 3 and the relevant schemes) at the MP2 level are longer than at the HF one; the bond distances within the COH groups are somewhat longer as well, causing the O4O7 separation to increase. All these features are also found for **2o** in all the bonds which are conserved; in contrast, C11C13 in **1o** and C11C12 in **2o** as single bonds are slightly shorter than at the HF level. The bond angles are almost insensitive to correlation corrections (on average the changes are less than 0.5°), while the dihedrals are affected by about 10° only in **2o**; in **1o** the change is limited to about 5°.

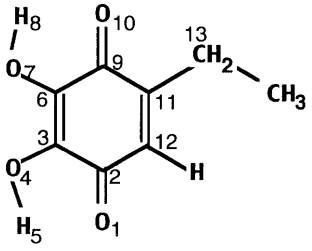
The relative energies and free energies of the structures optimized at the MP2 level turn out to be in line with those obtained at the HF level (Table 1, Figs. 1, 2). The **u** and **d** forms are 0.7–0.8 kcal/mol less favorable than at the HF level, whereas **2o** is slightly more stable (1.20 versus 1.28 and 0.43 versus 0.51 kcal/mol for ΔE and $\Delta \mathscr{G}$, respectively).

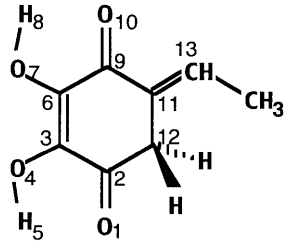
4.3 Results in solution

The free-energy differences in water and chloroform solution for the structures optimized in each environment at the HF/6-31G* level are also displayed in the upper part of Table 1 and in Figs. 1a and 2a, together with the relevant solvent effect. The solvent effect is feeble as expected for chloroform due to its low dielectric constant, which is close to the gas-phase one; however there is a solvent preferential stabilization for the **u** and **d** forms, and mainly for **2** over **1**. This produces an overall decrease in the free-energy gaps, and **2o** turns out to be just 0.3 kcal/mol less stable than **1o**. This trend is also maintained in aqueous solution, though the solvent effect is about 4 times larger in water than in chloroform: **2o** turns out to be the most stable tautomer, more favorable by about 1.2 kcal/mol than **1o**. Notice that **2u** and **2d** follow in the order, immediately before **1d** and **1u**, which are less stable than **2o** by more than 2 kcal/mol.

The solvent effect on the internal geometries is very limited for these systems, as can be seen from Table 3, where a number of geometrical values are reported for

Table 3. Selected 6-31G* geometrical parameters (distances in Angstroms, angles in degrees) of forms **1o** and **2o** optimized at the MP2 level in vacuo and at the HF level in vacuo, in water and in chloroform





	1o				**2o**			
	MP2	HF_{vac}	HF_{wat}	HF_{chl}	MP2	HF_{vac}	HF_{wat}	HF_{chl}
C2C3	1.472	1.484	1.481	1.482	1.463	1.475	1.475	1.475
C3C6	1.361	1.328	1.327	1.327	1.366	1.334	1.332	1.332
C6C9	1.470	1.484	1.484	1.484	1.471	1.485	1.483	1.483
C9C11	1.490	1.500	1.498	1.498	1.481	1.485	1.478	1.480
C11C12	1.353	1.325	1.325	1.325	1.507	1.513	1.511	1.513
C2C12	1.473	1.482	1.478	1.480	1.509	1.509	1.502	1.506
O1C2	1.244	1.198	1.201	1.199	1.240	1.199	1.202	1.200
C9O10	1.245	1.198	1.198	1.198	1.245	1.202	1.207	1.204
C3O4	1.350	1.334	1.338	1.335	1.349	1.334	1.339	1.336
O4H5	0.984	0.953	0.962	0.954	0.985	0.953	0.961	0.954
C6O7	1.352	1.336	1.338	1.336	1.346	1.331	1.336	1.333
O7H8	0.984	0.952	0.963	0.953	0.987	0.954	0.964	0.955
C11C13	1.498	1.507	1.505	1.506	1.349	1.328	1.329	1.328
O1C2C3	118.26	118.93	118.83	118.80	118.29	118.49	118.32	118.01
C2C3O4	116.70	116.30	117.14	116.57	116.56	115.95	116.94	116.11
C9C6O7	116.66	116.03	116.73	116.27	115.98	115.39	116.10	115.59
C6C9O10	117.97	118.49	118.45	118.40	116.83	117.03	116.67	116.73
C3C2C12C11	4.55	−0.40	−0.46	−0.37	25.99	15.62	−10.57	5.16
C9C11C12C2	−3.03	1.01	0.83	0.89	−28.86	−17.06	12.50	−5.25
O10C9C11C13	−2.36	−1.81	−1.38	−1.64	12.85	7.37	−5.94	1.94
O4O7	2.844	2.803	2.773	2.792	2.799	2.756	2.723	2.744

1o and **2o** as representatives of their other conformers. The values in chloroform are generally closer to those in vacuo than the values in water as expected, but the parameters seem to be more sensitive to the level (either HF or MP2) than to the presence of the solvent polarizing field, even though the solvent is polar. The very limited solvent effect on the geometries of these compounds can be shown by solvating their in vacuo optimized geometries. The results obtained (not shown) are very close to those reported in Tables 1 and 2 because the solvent effect is on average 94% of the values displayed in the tables, with very small oscillations ($\pm 4\%$) about the mean; therefore, the thermal corrections to the internal energy computed for the structures optimized in vacuo may be applied with confidence to the structures optimized in solution. The relative free energy values in solution, $\Delta\mathscr{G}$, calculated using the free energy in vacuo, are displayed in Fig. 2. Since the geometry optimization in solution at the MP2 level has not yet been implemented, and in any case would be at present beyond our computer resources, we preferred to compute the correlation corrected free energies in solution on the structures optimized in vacuo at the MP2 level rather than on the geometries obtained in solution, but at the HF level. The relevant results, reported in the lower parts of Tables 1 and 2 and in Figs. 1b and 2b, are fairly consistent with the HF ones. The slight damping effect of correlation corrections on the energy gaps observed in other systems [28] is not as evident here. The solvent effect turns out to be weaker, especially for **2**, though the solvent field is kept frozen in its HF description as stressed in the method outline. Thus, the mutual stability of the various conformers of the two tautomers is not noticeably affected by MP2 correlation corrections, with the only exception being the **2d** form, which turns out to be the least stable form in water as in the other environments (Fig. 1b); by including $\mathscr{G}_{vac}$, however, its stability turns out to be within **1u** and **1d** (Fig. 2b).

4.4 Competing hydrogen bonds

It is apparent from the results obtained that two hydrogen bonds with the quinonoid carbonyl are more stable than one, the second being substituted by a hydrogen bond between the hydroxyl groups. In order to avoid the artificial stabilization due to the presence of hydrogen atoms along some oxygen lone pairs, we computed the relative energies in vacuo by adding to each structure two ghost hydrogens (i.e., only their basis functions) centered on the positions occupied by the real hydrogens in the other conformers. This produced a very limited stabilization (about 0.2 kcal/mol) of the **u** and **d** forms over **o**.

The stabilization of tautomer **2** over tautomer **1** seems to be due to the peculiar electronic features of these compounds. Considering in fact 5-methyl-1,4-benzoquinone and its tautomer 5-methene-cyclohex-2-ene-1,4-dione there is an energy gap of 7.2 kcal/mol favoring the quinonoid form. Interestingly this gap becomes just 3.9 kcal/mol by substituting the methyl group with an ethyl group, as in the model of myrsinone used in this work. This seems to indicate a contribution to the stabilization due to the length of the aliphatic side chain. By substituting an OH group for the hydrogen atom in position 2 (2-hydroxy-5-ethyl-1,4-benzoquinone) the energy gap remains about 4 kcal/mol, while when the OH group is moved onto the other carbon, the 3-hydroxy-5-(eth-1-ene)-cyclohex-2-ene-1,4-dione form is only 2.3 kcal/mol less favored than its 3-hydroxy-5-ethyl-1,4-benzoquinone tautomer. The presence of both OH groups lowers the gap to 1.28 kcal/mol, as described previously, when their hydrogens point towards the quinonoid oxygens, producing two strong intramolecular hydrogen bonds. At least part of the **2o** stabilization seems to be due to a relief of the repulsion between the hydroxy oxygen lone pairs, caused by the formation of the exocyclic double bond. In an attempt to evaluate this repulsion, the 2,5-dihydroxy-3-ethyl-1,4-benzoquinone isomer (2,5-OHBQ) was considered. This compound still has two intramolecular hydrogen bonds with the quinonoid oxygens but that repulsion is impossible, because the OH groups are located on diametrically opposed ring atoms, not on adjacent atoms. In contrast to **1**, 2,5-OHBQ does not allow tautomerism, though the fluxional behavior observed is linked to the proton transfer from the hydroxy to the quinonoid groups, giving exactly the same compound. The 3,6-dihydroxy-4-ethyl-1,2-benzoquinone isomer (3,6-OHBQ) was also considered to evaluate the repulsion between the quinonoid oxygen lone pairs. Their different arrangement with respect to myrsinone produces a single perpendicular minimum for the rotation about the aliphatic chain (Fig. 3). The results concerning these two isomers are reported in Table 4. 2,5-OHBQ is the most stable isomer in the series, being about 8 kcal/mol more stable than **1o** in vacuo, whereas the *ortho*-quinone (3,6-OHBQ) is less favorable than **1o** in vacuo by 9–11 kcal/mol, depending on the level. The solvent effect in aqueous solution is practically equal for both com-

Table 4. 6-31G* relative energies and free energies (kcal/mol) in water and in chloroform of 2,5-dihydroxy-3-ethyl-1,4-benzoquinone (*2,5-OHBQ*) and 3,6-dihydroxy-4-ethyl-1,2-benzoquinone (*3,6-OHBQ*) at the HF and MP2 levels, with respect to **1o**. The solvent effect is also displayed

HF	2,5-OHBQ	3,6-OHBQ
ΔE	−7.94	10.86
ThCor	0.47	−0.50
$\Delta\mathscr{G}_{vac}$	−7.47	10.36
ΔG_{tot} (wat)	−8.91	10.84
G^{sol} (wat)	−11.45	−11.43
ΔG_{tot} (chl)	−6.78	11.10
G^{sol} (chl)	−1.74	−2.67
MP2	2,5-OHBQ	3,6-OHBQ
ΔE	−8.87	9.14
ΔG_{tot} (wat)	−6.34	9.35
G^{sol} (wat)	−5.33	−7.65
ΔG_{tot} (chl)	−7.76	9.45
G^{sol} (chl)	−0.63	−1.42

Table 5. 6-31G* chemical shifts (ppm) for **1o** and **2o** and experimental values (**1**;**2**). Atom numbering as in the header of Table 3

Position	**1o**		**2o**		**1**;**2**	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C[a]	^{1}H[a]
13	23.3	2.00/2.59	142.8	7.79	31.1	2.39(m);4.25(t)
12	128.3	6.49	32.0	2.98/3.36	114.9	5.3(t); –
11	147.1	–	118.7	–	116.1	–
6	129.0	4.52	135.4	5.12	–	7.8(b)
3	129.2	4.58	133.3	4.81	–	7.8(b)

[a] Ref. [10]

pounds, whereas in chloroform it is feeble, especially in the case of 2,5-OHBQ.

4.5 Chemical shift

The chemical shifts (δ), computed with the GIAO method and referred to tetramethylsilane [isotropic magnetic shielding tensor (σ_{ref}) of 201.6982 and 32.9008 ppm for C and H, respectively] optimized at the 6-31G* level were obtained by using the formula

$$\delta = \sigma_{ref} - \sigma$$

and were compared to the experimental ones [10] in order to examine their structure dependence and to possibly evaluate the solution population. The theoretical and experimental values are reported in Table 5 (the atom numbering is shown in the header of Table 3). The values of C11 and C13 support either **2o** or **1o**, respectively. As far as the chemical shifts of the hydrogen(s) connected to C13 are concerned, 2.39 supports **1o** as well, while the computed value for **2o** is larger than the experimental one related to **2o**, 4.25 [10]; consider however that there could be some uncertainty in the experimental assignments. As far as the hydroxyl groups are concerned the experimental broad bands could be due to the acidity of those protons and to the relative mobility of the OH groups, in that the **u** and **d** forms especially for **1** are likely to be present in solution.

5 Conclusions

The structural features of the conformers of myrsinone (with a drastically shortened aliphatic side chain) examined at the HF/6-31G* level are characterized by a sensitive stabilization of the **o** arrangement, showing two almost equivalent hydrogen bonds between the hydroxy hydrogens and the quinonoid oxygens, with respect to the **u** and **d** ones, where one of the hydrogen bonds is formed between the OH groups themselves. All the conformers have a gauche aliphatic side chain, though the energy difference with respect to the trans arrangement is very small (about 0.2 kcal/mol), with a barrier not exceeding 1.7 kcal/mol, suggesting a good mobility of the benzoquinone head. The formation of an exocyclic double bond due to the release of a proton to the adjacent ring carbon produces an experimentally observed tautomeric equilibrium between **1** and **2**, which is shifted towards **1** or **2** depending on the level and the nature of the environment (either the gas phase or solvents of different dielectric constants). The trans form of **2** is about 2 kcal/mol more favorable than the cis form. MP2 correlation corrections in vacuo do not alter the energy difference between **1o** and **2o**, whereas the **d** and **u** forms are less favorable than at the HF level. The geometry, fully relaxed at the MP2 level in vacuo, underwent limited changes, though these were larger than those produced by the polar solvent. This justifies the use of the gas-phase MP2 geometry to compute the free energy of solution at the MP2 level. The free energies in vacuo and in solution favor tautomer **2** over tautomer **1**, though tautomer **1o** remains the most stable in vacuo. Due to the very limited solvent effect on the internal geometry, the HF free energy of solvation is close to that computed using the geometry optimized in vacuo. By placing the hydroxy groups at diametrically opposite locations on the ring there is an energy gain of about 8 kcal/mol, because the repulsion between the hydroxy oxygen lone pairs is prevented. In any case the repulsion between the quinonoid oxygens is larger by 9–11 kcal/mol, as can be appreciated by considering the corresponding *ortho*-quinone. In both these latter compounds, however, only a perpendicular position of the aliphatic side chain with respect to the ring is favorable. The chemical shifts computed in the GIAO framework can contribute to the interpretation of the experimentally observed values of δ.

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