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## Lone-Pair Orientation Effect of an α-Oxygen Atom on ¹$J_{CC}$ NMR Spin−Spin Coupling Constants in *o*-Substituted Phenols. Experimental and DFT Study

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**Abstract:** The well-known N lone-pair orientation effect on ¹$J_{CC}$ spin−spin coupling constants (SSCCs) in oximes and their derivatives was used to study how negative hyperconjugative interactions of type $LP_1(O) \rightarrow \sigma^*_{CC}$ depend on ortho interactions involving the OH group. This study demanded the following analyses: (i) a qualitative estimation of how ¹$J_{CC}$ SSCCs are affected by hyperconjugative interactions, (ii) a study of similar stereochemical effects to those in oximes, but in ¹$J_{C_1C_2}$ and ¹$J_{C_1C_6}$ in a series of 2-substituted phenols, and (iii) a quantitative estimation, with the natural bond order approach, of some key electron delocalization interactions. A few unexpected results are quoted. $LP_1(O) \rightarrow \sigma^*_{CC}$ interactions are affected by proximity interactions as follows: (a) they are enhanced by hydrogen bonds transferring charge into the (O−H)* antibonding orbital; (b) they are enhanced by proximity interactions of type $LP_1(O)\cdots$ H−C; (c) they are inhibited by interactions of type $LP(O_1)\cdots$H−O. Consequences of these observations are discussed.

## 1. Introduction

Extensive experimental[1−8] and theoretical[9−15] studies of the ¹$J_{^{13}C^{13}C}$ (hereafter, ¹$J_{CC}$) spin−spin coupling constants, SSCCs, in oximes and their derivatives allowed determination of the stereospecificity of these couplings toward the orientation of the nitrogen lone pair. As an example, in Figure 1, the cis and trans ¹$J_{CC}$ couplings in the acetone oxime are shown;[3] it is observed that ¹$J_{trans} − $¹$J_{cis} = 7.9$ Hz. According



$J_{cis} = 49.3$ Hz     $J_{trans} = 41.4$ Hz
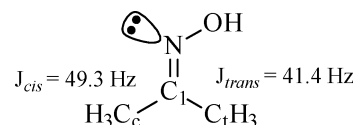
**Figure 1.** Experimental nitrogen lone-pair stereospecific effect on ¹$J_{CC}$ couplings in acetone oxime (taken from ref 3).

to Wray,[1] the respective SSCCs are 48.42 and 40.51 Hz, and their difference amounts to 7.91 Hz.

So far, the most detailed analysis of the lone-pair orientation effect on ¹$J_{CC}$ SSCCs in acetone oxime was presented by Barone et al.,[9] and it was based on the Natural *J* coupling, NJC,[16] dissection of SSCCs into localized molecular orbital, LMO, contributions. In short, the three main contributions discussed by Barone et al.[9] are (a) the nitrogen lone pair, (b) the carbon−carbon bonds containing the coupling carbon
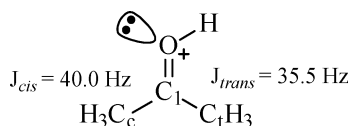
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**Figure 2.** Experimental oxygen lone-pair stereospecific effect on $^1J_{CC}$ couplings in protonated acetone (taken from ref 19). The difference $^1J_{cis} - ^1J_{trans}$ amounts to 4.5 Hz.

atoms, and (c) the carbon inner core orbitals.[17] This last contribution seems to be exaggerated within the NJC approach due to the localization procedure employed in the NJC dissection of SSCCs.[18]

A similar stereospecific effect of the oxygen lone pair with sp character in dicoordinated oxygen atoms in the α position to an sp$^2$ hybridized carbon atom was also studied.[5,8,19–21] It is interesting to compare values displayed in Figure 1 with the corresponding experimental couplings measured in protonated acetone,[19] which are displayed in Figure 2, where it is observed that the oxygen lone-pair effect is smaller than that corresponding to an N atom. Since the oxygen atom bears two nonbonding electron pairs, this stereoelectronic property cannot be used as straightforwardly as that of the N lone pair in oximes. However, its potential for studying structural problems is envisaged as excellent if a deeper insight into several aspects of this oxygen stereochemical behavior is obtained. The aim of this work is to achieve such a deeper insight. To this end, an adequate set of model compounds was sought, where $^1J_{CC}$ SSCCs could be measured at the $^{13}$C natural abundance and the orientation of both lone-pair oxygen atoms should be defined by intramolecular interactions. Following such criteria, in this work was chosen a set of nine 2-X-phenol derivatives (**1**, X = H; **2**, X = CH$_3$; **3**, X = CH$_2$CH$_3$; **4**, X = CN; **5**, CHO; **6**, X = F; **7**, X = Cl; **8**, X = Br; **9**, X = *t*-butyl). In these phenol derivatives, $^1J_{CC}$ SSCCs were measured and a series of calculations within the density functional theory (DFT) framework were carried out, considering in all cases two conformations for the O–H group, namely, the **a** conformation, defined as that where the O–H bond eclipses the $\sigma_{C_1C_2}$ bond, and the **b** conformation, defined by the O–H bond eclipsing the $\sigma_{C_1C_6}$ bond.

Calculations were carried out for different stable side-chain conformations including the dielectric solvent effect, which was taken into account using the polarization continuum model, PCM. The following two cases were considered: (i) an isolated molecule, that is, $\epsilon = 1$, and an infinitely diluted dimethylsulfoxide (DMSO) solution, that is, $\epsilon = 46.7$. To study the dielectric solvent influence on SSCCs, their calculations were carried out employing the respective optimized geometries. The results of this study are described in terms of a pictorial representation that is expected to be useful for many scientists interested in using these results in a qualitatively predictive way. For this reason, discussions are presented in terms of the NBO approach, and interactions that define the oxygen lone pairs' stereochemical behavior are presented in terms of hyperconjugative and conjugative interactions, as it is frequently found in the chemistry literature. However, SSCC calculations are calculated within the coupled perturbed density functional theory (CP–DFT)

approach as it is implemented in the Gaussian 03 package of programs. Following this line, it can be said that the main contributions[9] to the in-plane oxygen lone pair, hereafter LP$_1$-(O), orientation effect on $^1J_{C_1C_2}$ and $^1J_{C_1C_6}$ originate in the negative hyperconjugative interactions LP$_1$(O) → $\sigma^*_{CC}$, where $\sigma_{CC}$ is the σ-bond orbital involving the coupling nuclei. These interactions, among other factors, should depend on both the electron acceptor ability of the $\sigma^*_{CC}$ antibonding orbital and on the donor ability of the LP$_1$(O). This LP orientation effect should depend on, among other factors, the resonance interaction between both side chains and on the electrostatic interactions between them, or, more precisely, the proximity effects of both substituents placed ortho to each other. In this work, quantitative estimations of negative hyperconjugative as well as conjugative interactions were obtained using the Weinhold et al.'s natural bond orbital, NBO, approach.[22,23]

However, an important point to be taken into account when studying the in-plane LP$_1$(O) orientation effect in 2-X-phenols is the different substituent effects that affect the $^1J_{C_1C_2}$ and $^1J_{C_1C_6}$ SSCCs. In fact, while in compound **1** the difference between these two SSCCs can be attributed almost entirely to the LP$_1$(O) orientation effect, when a substituent is placed at ring position 2, different substituent effects are introduced on $^1J_{C_1C_2}$ and $^1J_{C_1C_6}$ SSCCs. It must be recalled that the influence of subtituents on $^1J_{CC}$ SSCCs in benzene derivatives was extensively studied,[5,7,24,25] and at present, it is accepted that the inductive effect is the main substituent interaction affecting such couplings. This effect decays rapidly when the $\sigma_{CC}$ bond containing the coupling nuclei departs from the ipso carbon atom bonded to the substituent. This suggests that the 2-X-inductive substituent effect on $^1J_{C_1C_2}$ is stronger than on $^1J_{C_1C_6}$. However, the OH inductive effect on both SSCCs is expected to be approximately the same.

**1.1. Qualitative Theoretical Analysis of Hyperconjugative Effects on $^1J_{CC}$ SSCCs.** In a recent paper,[26] it was shown how the CLOPPA method (Contribution from Localized Orbitals within the Polarization Propagator Approach)[27] can provide a qualitative prediction of how hyperconjugative interactions affect $^1J_{CH}$ SSCCs. Those considerations can easily be extended to get a qualitative estimation of how such interactions are expected to affect $^1J_{CC}$ SSCCs. An approach of this type is expected to be useful for rationalizing the stereospecific oxygen lone-pair effect on $^1J_{CC}$ SSCCs in the phenol derivatives studied in this work. In previous papers,[9] it was observed that, of the four Ramsey terms of $^1J_{CC}$ SSCCs, Fermi contact (FC), paramagnetic spin–orbit (PSO), spin-dipolar (SD), and diamagnetic spin–orbit (DSO), only the first one determines the orientation effect of the N lone pair on $^1J_{CC}$ SSCCs. For this reason, this qualitative description is based only on the FC term, which can be written as a sum of contributions from LMOs, eq 1

$$^1J_{CC}^{FC} = \sum_{ia,jb} {}^1J_{ia,jb}(C_mC_n) \qquad (1)$$

where $i$ and $j$ are occupied LMOs, while $a$ and $b$ are vacant LMOs. As shown previously, the LMO contributions to the

FC term can be written as in eq 2.

$$^1J_{ia,jb}^{FC}(C_mC_n) = W_{ia,jb}[U_{ia}(C_m)\,U_{jb}(C_n) + U_{ia}(C_n)\,U_{jb}(C_m)]$$ (2)

where $U_{ia}(C_m)$ [$U_{jb}(C_n)$] are the "perturbators", that is, the matrix elements of the FC operator between the occupied $i$ ($j$) and vacant $a$ ($b$) LMOs evaluated at the $C_m$ ($C_n$) site of the coupling nuclei, and they give a measure of the strength of the $i \rightarrow a$ ($j \rightarrow b$) virtual excitation due to that operator; $W_{ia,jb}$ are the polarization propagator matrix elements, and they correspond to the response of the electronic molecular system to the presence of the magnetic electron-nucleus FC interaction, connecting two virtual excitations $i \rightarrow a$ and $j \rightarrow b$. These matrix elements decrease when increasing the $\epsilon_{i \rightarrow a}$ and $\epsilon_{j \rightarrow b}$ energy gaps between these occupied and vacant LMOs involved in each virtual excitation. For this reason, any hyperconjugative interaction that increases any of these energy gaps should decrease the corresponding term in eq 2. On the other hand, the sum in eq 2 is largely dominated by the following two different types of terms: (1) The first is when $i = j$ corresponds to the LMO localized on the $\sigma_{CC}$ bond involving the coupling nuclei, $C_m$ and $C_n$, and $a = b$ corresponds to the vacant LMO localized at that $\sigma_{CC}$ bond. The corresponding term in eq 2 is dubbed the "bond contribution", $J^b$. For this type of coupling, this contribution is always positive. (2) The second type of term is where either $i$ or $j$ corresponds to the occupied LMO on the $\sigma_{C_mC_n}$ bond containing the coupling nuclei, and $j$ or $i$ corresponds to an occupied LMO on either other $\sigma_{C_mX}$ or $\sigma_{C_nY}$ bonds involving either the $C_m$ or $C_n$ coupling nucleus, and $a = b$ corresponds to a localized vacant MO placed at that $\sigma_{C_mC_n}$ bond containing the coupling nuclei. The corresponding term in eq 2 is dubbed "other bond contribution", $J^{ob}$; for two sp³ hybridized carbon atoms, there are six of these contributions, and for two sp² hybridized carbon atoms, there are four of them, two for each coupling carbon atom. However, it should be stressed that the $J^{ob}$ terms involve also the $\sigma_{C_mC_n}$ bond and antibond containing the coupling nuclei. For this type of coupling, $^1J_{CC}$, these $J^{ob}$ contributions are negative, and their absolute values are notably smaller than that of the corresponding $J^b$ term.

It is stressed that here only a qualitative description of the effect of hyperconjugative interactions on $^1J_{C_1C_2}$ and on $^1J_{C_1C_6}$ SSCCs in *o*-substituted phenols is sought. Qualitatively, the effect of such interactions on both occupied and vacant LMOs, eq 1, can be described by the simple "perturbed molecular orbital theory".[28] Thus, hyperconjugative interactions from the $\sigma_{C_mC_n}$ bond yield a decrease on the FC term of the $^1J_{C_mC_n}$ SSCC. A similar effect produces a hyperconjugative interaction into the $\sigma^*_{C_mC_n}$ antibonding orbital since both types of hyperconjugative interactions increase the energy gap between the $\sigma_{C_mC_n}$ bond and its antibond, $\sigma^*_{C_mC_n}$. On the other hand, hyperconjugative interactions from "other bonds" increase the energy gap relevant for the $^1J^{ob}$ contributions since such interactions do not affect the antibonding $\sigma^*_{C_mC_n}$ orbital energy, while the "other bond" orbital energy is pushed down. As two different examples, the negative hyperconjugative interaction LP(X) $\rightarrow$ $\sigma^*_{C_mC_n}$ or the hyperconjugative interaction from nearby $\sigma$ bonds into $\sigma^*_{C_mC_n}$ can
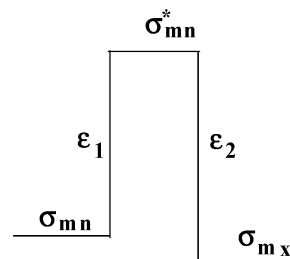


**Figure 3.** Schematic representation of LMOs involved in the $J^b$ and $J^{ob}$ contributions to $^1J_{C_mC_n}$ not perturbed by any hyperconjugative interaction. A $\sigma_{C_mC_n}$, hyperconjugative interaction from this bond into some antibonding orbital (not shown in this scheme, for instance $\sigma^*_{YZ}$) causes a lowering of its orbital energy, increasing the $\epsilon_1$ energy gap, and decreasing the $^1J^b$ contribution, while a hyperconjugative interaction into the $\sigma^*_{C_mC_n}$ antibonding orbital, like LP(X) $\rightarrow$ $\sigma^*_{C_mC_n}$, increases its energy, causing also an increase in the $\epsilon_1$ energy gap and concomitantly, producing also a decrease, in the absolute value of $^1J^b$ contribution.

be mentioned. These two types of interactions decrease the absolute value of $^1J^{ob}$, and therefore, since this contribution is negative, they cause the $^1J_{C_mC_n}$ SSCC to increase. The effects of hyperconjugative interactions on the relevant energy gaps is displayed schematically in Figure 3.
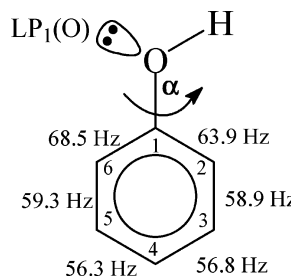
As an example, the above qualitative considerations can be applied to rationalize the difference between both $^1J_{CC}$ SSCCs in acetone oxime, Figure 1. For the $^1J_{C_1C_c}$ SSCC, the $\sigma_{C_1C_c}$ bond plays the role of "the bond contribution", $J^b$, while the $\sigma_{C_1C_t}$ bond plays the role of one of the "other bond" contributions, $J^{ob}$, while for $^1J_{C_1C_t}$, both roles are interchanged. The main hyperconjugative interaction defining the orientation of the N lone-pair stereospecific effect on $^1J_{CC}$ SSCCs is the LP(N) $\rightarrow$ $\sigma^*_{C_1C_t}$ negative hyperconjugation, which produces both a decrease in the $J^b$ contribution to the $^1J_{C_1C_t}$ SSCC and a decrease in the absolute value of the $J^{ob}$ contribution to $^1J_{C_1C_c}$. Therefore, such an interaction yields a decrease on the $^1J_{C_1C_c}$ SSCC and an increase on the $^1J_{C_1C_c}$ SSCC, both of them contributing to increase the $^1J_{C_1C_c}$ − $^1J_{C_1C_t}$ difference.

This approach is applied in this work to rationalize the calculated and observed differences between $^1J_{C_1C_2}$ and $^1J_{C_1C_6}$ SSCCs in the chosen set of 2-substituted phenols mentioned above.

## 2. Results and Discussion

In compound **1**, employing the respective optimized geometries, $^1J_{CC}$ SSCCs were calculated for $\epsilon = 1$ and $\epsilon = 46.7$. For the latter dielectric constant, total $^1J_{CC}$ couplings are shown schematically in Figure 4, while in Table 1, the four contributions to all six $^1J_{CC}$ SSCCs in **1** are explicitly shown for $\epsilon = 1$ and $\epsilon = 46.7$, and they are compared with the experimental values obtained as part of this work. In Figure 4, it is observed that the difference between the calculated (for $\epsilon = 46.7$) $^1J_{C_1C_6}$ and $^1J_{C_1C_2}$ SSCCs is 4.6 Hz, a value quite close to the $^1J_{C_1C_c}$ − $^1J_{C_1C_t}$ difference measured in protonated acetone, Figure 2, that is, 4.5 Hz.[19] It is noted that, in the calculated values shown in Figure 4, a slight asymmetry is also observed for $^1J_{C_2C_3}$ and $^1J_{C_5C_6}$ and for $^1J_{C_3C_4}$

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**Figure 4.** In phenol, **1**, for $\epsilon = 46.7$ and using the optimized geometry obtained at the B3LYP-6-311G** level, $^1J_{CC}$ SSCCs were calculated at the B3LYP-EPR III level (in Hz). The difference $^1J_{C_1C_6} - {}^1J_{C_1C_2}$ amounts to 4.6 Hz, a value which is quite close to the corresponding experimental difference measured in protonated acetone.

**Table 1.** All Four Ramsey Contributions to the Six $^1J_{CC}$ SSCCs (in Hz) in **1** Calculated at the B3LYP/EPR-III Level Considering Both $\epsilon = 1$ and $\epsilon = 46.7^a$

| SSCC | $\epsilon$ | FC | SD | PSO | DSO | total | av. | exptl. |
|---|---|---|---|---|---|---|---|---|
| $^1J_{C_1C_2}$ | 1 | 70.7 | 1.4 | −6.8 | 0.3 | 65.5 | 67.8 | 65.4 |
| | 46.7 | 69.1 | 1.3 | −6.8 | 0.3 | 63.9 | 66.2 | |
| $^1J_{C_1C_6}$ | 1 | 75.3 | 1.4 | −6.8 | 0.3 | 70.2 | 67.8 | 65.4 |
| | 46.7 | 73.6 | 1.3 | −6.8 | 0.3 | 68.5 | 66.2 | |
| $^1J_{C_2C_3}$ | 1 | 66.2 | 1.3 | −7.1 | 0.2 | 60.6 | 60.8 | 58.0 |
| | 46.7 | 64.6 | 1.3 | −7.2 | 0.2 | 58.9 | 59.1 | |
| $^1J_{C_3C_4}$ | 1 | 64.4 | 1.3 | −7.2 | 0.2 | 58.7 | 58.4 | 56.5 |
| | 46.7 | 62.5 | 1.3 | −7.2 | 0.2 | 56.8 | 56.6 | |
| $^1J_{C_4C_5}$ | 1 | 63.6 | 1.3 | −7.1 | 0.2 | 58.0 | 58.4 | 56.5 |
| | 46.7 | 62.0 | 1.2 | −7.1 | 0.2 | 56.3 | 56.6 | |
| $^1J_{C_5C_6}$ | 1 | 66.7 | 1.4 | −7.3 | 0.2 | 61.0 | 60.8 | 58.0 |
| | 46.7 | 65.1 | 1.3 | −7.3 | 0.2 | 59.3 | 59.1 | |

$^a$ Since both planar conformers are equivalent, individual SSCCs are not amenable to measurement. Total couplings, properly averaged, are compared with the corresponding experimental values measured as part of this work.

and $^1J_{C_4C_5}$, respectively. Experimentally, these differences, as it also happens with $^1J_{C_1C_6}$ and $^1J_{C_1C_2}$ SSCCs, cannot be observed since, due to the equivalence of both planar rotamers of compound **1**, only the average of the respective values is amenable to measurement.

Trends of noncontact terms displayed in Table 1 are similar to those observed for other aromatic compounds;[21,29,30] the most important of them is the PSO term, although the SD term cannot be neglected. The "LP$_1$(O) orientation effect", that is, the $^1J_{C_1C_6} - {}^1J_{C_1C_2}$ difference is 4.7 Hz for $\epsilon = 1$, while it is 4.6 Hz for $\epsilon = 46.7$. In these results converge two different trends; that is, negative hyperconjugative interactions are slightly inhibited by a highly polar solvent[31] and the effect of electrostatic interactions of type $C_6-H_6\cdots$ $\cdots LP_1(O)$ and $C_2-H_2\cdots O-H$;[32] a highly polar solvent shields them.

For all $^1J_{CC}$ SSCCs in **1**, Table 1, the dielectric solvent effect causes a decrease within the range 1.6−1.8 Hz, which originates mainly in the respective FC contribution. Even though the inclusion of the dielectric solvent effect improves the agreement between total calculated and experimental SSCCs, their total calculated values are slightly overestimated in about 1 Hz. However, the experimental trends are correctly reproduced.

Two important questions to be answered for 2-X-phenols are these: how does the X side-chain affect the O−H conformation, and how much are the relative populations of the **a** and **b** conformations affected by a highly polar solvent? To answer these questions, the geometries of compounds **2−8** were optimized for different side-chain conformations (see Figure 5 for conformations considered when X is a nonlinear substituent). In Table 2 are shown the relative energies for the different conformers considered in this work. For X = CH$_3$, **2**; X = Et, **3**; and X = CN, **4**, **b** is the preferential conformation, even for $\epsilon = 1$. For a highly polar solvent in these three compounds, the **a** conformation is notably more destabilized. For conformation **a** of compound **4**, using the NBO method, a charge-transfer interaction $\pi_1$-(CN) → (O−H)* = 0.8 kcal/mol is calculated [$\pi_1$(CN) stands for the $\pi$ symmetry LMO with lowest energy]. For X = CHO, **5**, as expected, the preferential conformation for the OH group is **a** due to the strong intramolecular hydrogen bond that takes place between both side-chain groups. For a polar solvent, **a** is still the preferential conformation, although the energy of **5-(b-2)** is only 2.5 kcal/mol above that of the **a** conformation, see Figure 5. It is noted that for the **a** conformation the NBO analysis yields the H proton of the OH group as a separate unit. This is interpreted as being a very strong intramolecular hydrogen bond, but unfortunately, the magnitude of the LP$_1$(O) → $\sigma^*_{C_1C_2}$ interaction cannot be considered to be reliable.

For $\epsilon = 1$, 2-X-phenols (X = F, Cl, Br) **6**, **7**, and **8** show as preferential the **a** conformation, suggesting that an intramolecular hydrogen bond of type O−H$\cdots$X is operating. Such hydrogen bonds are expected to be mainly electrostatic in character.[33] It must be emphasized that in this work only the optimized geometries of a few obvious conformers were sought to study certain aspects of the stereospecificity of LP$_1$-(O) on the $^1J_{C_1C_6} - {}^1J_{C_1C_2}$ difference. Detailed studies of conformers of 2-substituted phenols were reported recently.[34] It is interesting to note that, according to the NBO approach, for the **6-(a)** conformation, the LP$_2$(F) → (O−H)* interaction is 0.8 kcal/mol (LP$_2$ stands for the in-plane F lone pair with important p character), which is of similar strength to that of the $\pi_1$(CN) → (O−H)* charge-transfer interaction calculated for **4-(a)**. For X = Cl and Br, the analogous charge-transfer interactions are weaker than 0.5 kcal/mol. In Table 3, the H$\cdots$X distances for the **a** conformation of compounds **6**, **7**, and **8** are compared for $\epsilon = 1$ and $\epsilon = 46.7$. In all three cases, an important increase of the H$\cdots$X distance is observed for $\epsilon = 46.7$. For a high polar solvent, all three of these compounds show as preferential the **b** conformation, although for X = F the **6-(a)** conformation is only 0.25 kcal/mol above the **6-(b)** conformation. Probably, in this case, the observed $^1J_{CC}$ SSCC shows a non-negligible contribution from conformation **6-(b)**. When calculating $^1J_{C_1C_6}$ and $^1J_{C_1C_2}$ SSCCs in these compounds, some caution should be exercised, since both ortho substituents contain an $\alpha$ electron-rich atom, and it is known that under such conditions DFT-calculated SSCCs could yield unreliable results for SSCCs.[17]

In Table 4, for different conformations of compounds **2−8** (see Table 2 and Figure 5), total calculated couplings for $\epsilon = 1$ and $\epsilon = 46.7$ are compared with the experimental values
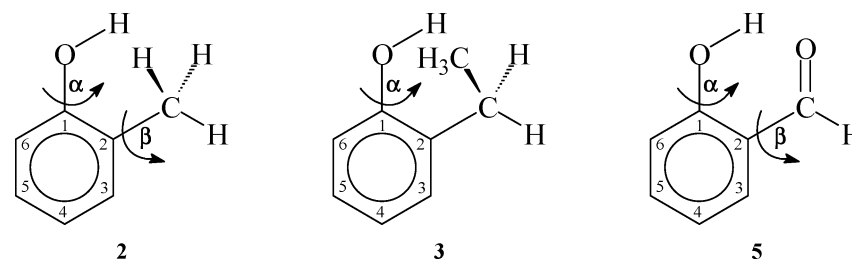
**Figure 5.** Conformations of compounds **2**, **3**, and **5**. For **2**, (**a-1**) $\alpha = 0°$, $\beta = 0°$; (**b-1**) $\alpha = 180°$, $\beta = 0°$; (**a-2**) $\alpha = 0°$, $\beta = 180°$; (**b-2**) $\alpha = 180°$, $\beta = 180°$. For **3**, (**a**) $\alpha = 0°$ and the dihedral angle $C_{Me}-C_{CH_2}-C_2-C_3 = 77.8°$; (**b**) $\alpha = 180°$ and the dihedral angle $C_{Me}-C_{CH_2}-C_2-C_3 = 78.3°$. For **5**, (**a**) $\alpha = 0°$, $\beta = 0°$; (**b-1**) $\alpha = 180°$, $\beta = 0°$; (**b-2**) $\alpha = 180°$, $\beta = 180°$.

**Table 2.** Relative Energies (kcal/mol) of Conformers **a** and **b** of Compounds **2**–**8**, 2-X-Phenols, Calculated at the B3LYP/6-311G** Level of Approximation Considering an Isolated Molecule, $\epsilon = 1$, and an Infinitely Diluted DMSO Solution, $\epsilon = 46.7^a$

|  | X | $\epsilon = 1$ | $\epsilon = 46.7$ |
|---|---|---|---|
| **2-(a-1)** | CH$_3$-(**a-1**) | 2.05 | 4.24 |
| **2-(b-1)** | CH$_3$-(**b-1**) | 0.89 | 0.97 |
| **2-(a-2)** | CH$_3$-(**a-2**) | 0.52 | 3.02 |
| **2-(b-2)** | CH$_3$-(**b-2**) | **0.0** | **0.0** |
| **3-(a)** | Et-(**a**) | 0.64 | 2.57 |
| **3-(b)** | Et-(**b**) | **0.0** | **0.0** |
| **4-(a)** | CN-(**a**) | 1.30 | 2.43 |
| **4-(b)** | CN-(**b**) | **0.0** | **0.0** |
| **5-(a)** | CHO-(**a**) | **0.0** | **0.0** |
| **5-(b)** | CHO-(**b**) | 11.60 | 4.25 |
| **5-(b-2)** | CHO-(**b-2**) | 8.62 | 2.52 |
| **6-(a)** | F-(**a**) | **0.0** | 0.25 |
| **6-(b)** | F-(**b**) | 3.02 | **0.0** |
| **7-(a)** | Cl-(**a**) | **0.0** | 1.41 |
| **7-(b)** | Cl-(**b**) | 3.06 | **0.0** |
| **8-(a)** | Br-(**a**) | **0.0** | 9.86 |
| **8-(b)** | Br-(**b**) | 3.12 | **0.0** |

$^a$ For the definition of the different conformations see Figure 5.

**Table 3.** The **a** Conformation of Compounds **6**–**8**, for Which the Optimized H–X Distances (in Å) for $\epsilon = 1$ and $\epsilon = 46.7$ Yield an Idea of the Electrostatic Character of These Interactions

| compound | H···X | $\epsilon = 1$ | $\epsilon = 46.7$ |
|---|---|---|---|
| **6** | H···F | 2.205 | 2.320 |
| **7** | H···Cl | 2.417 | 2.526 |
| **8** | H···Br | 2.511 | 2.617 |

measured as part of this work. For the sake of completeness, in the same table are shown also the experimental $^1J_{CC}$ SSCCs measured in 2-*t*-butyl-phenol as part of this work. No calculations were performed in this compound. In each case, the calculated preferential conformation is marked with an asterisk (*). It is observed that the best agreement between calculated and experimental values is obtained for the preferential conformation considering $\epsilon = 46.7$. Calculated SSCCs are overestimated in an amount somewhat above 1 Hz, except for X = F, Cl, and Br, that is, for compounds where the $\alpha$ atoms of both substituents are electron-rich atoms. In this case, DFT-B3LYP-calculated SSCCs are expected to be less reliable than in other types of compounds.

For compounds **2**–**6**, the difference $\Delta = {}^1J_{C_1C_6} - {}^1J_{C_1C_2}$ between these two SSCCs for the preferential conformation is also in better agreement with its experimental value. That difference $\Delta$ depends markedly on the side-chain conformations of both the OH and the X moieties. Since the inductive effect of both substituents is not expected to be sensitive to their conformation, the sensitivity of $\Delta$ to the side-chain conformations suggests that the negative hyperconjugative interactions $LP_1(O) \rightarrow \sigma^*_{C_1C_2}$ and $LP_1(O) \rightarrow \sigma^*_{C_1C_6}$ are sensitive to proximity interactions between both side chains.

In order to get a rationalization of how changes in the negative hyperconjugative interactions take place when changing the side-chain conformations, in Table 5 are displayed the aromatic $C_1=C_2$ and $C_1=C_6$ bond lengths as well as, for the OH group, the $LP_1(O) \rightarrow \sigma^*_{C_1C_2}$ and $LP_1(O) \rightarrow \sigma^*_{C_1C_6}$ negative hyperconjugative interactions and conjugative interactions of type $LP_2(O) \rightarrow \pi^*$, where $LP_2(O)$ stands for the oxygen lone pair of pure $\pi$ character. Values displayed in Table 5 correspond to calculations performed considering $\epsilon = 46.7$, since in this way experimental conditions are better reproduced. For compounds **2**, **3**, **4**, and **5**, the $C_1=C_2$ bond length is a bit longer than the $C_1=C_6$ bond, irrespective of the **a** or **b** conformation of the OH group. This suggests that the different strengths of the $LP_1(O) \rightarrow \sigma^*_{C_1C_2}$ interactions are not much affected by that bond length effect; indeed, when the corresponding bond lengths in compound **1** are compared, it is estimated that such interaction lengthens the antiperiplanar C=C bond with respect to $LP_1(O)$ only by about 0.001 Å. For compound **2**, it is observed that the strength of the $LP_1(O) \rightarrow \sigma^*_{CC}$ negative hyperconjugative interaction is notably enhanced for the **b** conformation. In fact, while for the **2-(a-1)** and **2-(a-2)** conformations they are, respectively, 7.6 and 7.4 kcal/mol (i.e., they are very close to the corresponding interaction in compound **1**, 7.4 kcal/mol), for the **2-(b-1)** and **2-(b-2)** conformations, they are 10.2 and 10.3 kcal/mol, respectively. It is evident that this marked difference between both types of hyperconjugative interactions is an important factor for determining as preferential the **b** conformation. At first sight, this marked difference for the negative hyperconjugative interaction involving the $LP_1(O)$ for the two planar conformations of the OH group seems to indicate that the $\sigma^*_{C_1C_6}$ antibonding orbital is a better acceptor than the $\sigma^*_{C_1C_2}$ antibonding orbital since the former corresponds to a bond shorter than the latter. However, in compound **4**, those bond lengths show a larger bond length difference than in

***Table 4.*** Comparison between Calculated (for $\epsilon = 1$ and $\epsilon = 46.7$) and Experimental $^1J_{CC}$ SSCCs (Hz) in 2-X-Phenols Studied in This Work[a]

| X | | $^1J_{C_1C_2}$ | $^1J_{C_1C_6}$ | $\Delta^b$ | $^1J_{C_2C_3}$ | $^1J_{C_3C_4}$ | $^1J_{C_4C_5}$ | $^1J_{C_5C_6}$ |
|---|---|---|---|---|---|---|---|---|
| CH₃-(**a-1**) | 1 | 66.2 | 71.6 | 5.4 | 61.9 | 60.0 | 57.2 | 61.3 |
| | 46.7 | 70.5 | 66.9 | −3.6 | 61.4 | 59.3 | 57.9 | 61.1 |
| CH₃-(**b-1**) | 1 | 70.5 | 66.9 | −3.6 | 61.4 | 59.3 | 57.9 | 61.1 |
| | 46.7 | 69.1 | 65.0 | −4.1 | 60.3 | 57.6 | 56.1 | 59.4 |
| CH₃-(**a-2**) | 1 | 64.3 | 71.9 | 6.6 | 62.9 | 59.2 | 57.8 | 61.0 |
| | 46.7 | 63.8 | 70.6 | 6.8 | 61.2 | 57.3 | 56.0 | 59.3 |
| CH₃-(**b-2**)(*) | 1 | 68.8 | 67.3 | −1.5 | 62.4 | 58.5 | 58.6 | 60.7 |
| | 46.7 | 67.4 | 65.5 | −1.9 | 61.3 | 56.8 | 56.7 | 59.0 |
| | **exptl.** | **66.1** | **64.3** | **−1.8** | **59.3** | **56.4** | **56.0** | **57.5** |
| Et-(**a**) | 1 | 64.4 | 71.7 | 7.3 | 62.2 | 59.2 | 57.7 | 61.0 |
| | 46.7 | 64.2 | 70.3 | 6.1 | 60.1 | 57.3 | 55.9 | 58.8 |
| Et-(**b**)(*) | 1 | 69.0 | 67.1 | −1.9 | 61.9 | 58.5 | 58.4 | 60.7 |
| | 46.7 | 67.6 | 65.2 | −2.4 | 60.7 | 56.9 | 56.6 | 59.0 |
| | **exptl.** | **66.5** | **65.7** | **−0.8** | **59.3** | **56.6** | **56.0** | **57.6** |
| CN-(**a**) | 1 | 66.4 | 71.1 | 4.7 | 64.2 | 60.2 | 56.7 | 60.9 |
| | 46.7 | 68.3 | 69.9 | 1.6 | 61.5 | 58.9 | 54.5 | 59.4 |
| CN-(**b**)(*) | 1 | 74.1 | 66.4 | -7.7 | 63.5 | 59.3 | 57.4 | 60.6 |
| | 46.7 | 72.9 | 64.8 | -8.1 | 62.4 | 58.2 | 55.2 | 58.9 |
| | **exptl.** | **71.1** | **63.5** | **−7.6** | **61.1** | **57.2** | **55.0** | **57.2** |
| CHO-(**a**)(*) | 1 | 60.4 | 68.2 | 5.8 | 61.5 | 60.6 | 55.9 | 61.2 |
| | 46.7 | 60.4 | 67.7 | 7.3 | 60.1 | 58.6 | 54.2 | 59.4 |
| CHO-(**b-1**) | 1 | 69.7 | 64.3 | −5.4 | 62.1 | 59.4 | 57.0 | 61.0 |
| | 46.7 | 68.1 | 62.9 | −5.2 | 60.5 | 57.9 | 54.7 | 59.2 |
| CHO-(**b-2**) | 1 | 69.6 | 65.2 | −4.4 | 61.2 | 59.4 | 56.9 | 61.1 |
| | 46.7 | 68.5 | 63.0 | −5.5 | 60.1 | 58.5 | 54.5 | 59.4 |
| | **exptl.** | **61.3** | **66.7** | **5.4.** | **59.0** | **57.9** | **54.5** | **58.3** |
| F-(**a**)(*) | 1 | 76.5 | 72.4 | −4.1 | 77.5 | 59.7 | 58.7 | 61.2 |
| | 46.7 | 76.9 | 70. 9 | −6.0 | 76.1 | 58.2 | 56.7 | 59.7 |
| F-(**b**) | 1 | 82.4 | 67.3 | −15.1 | 76.6 | 59.5 | 58.9 | 60.9 |
| | 46.7 | 81.2 | 65.8 | −15.4 | 75.8 | 57.9 | 57.0 | 59.3 |
| | **exptl.** | **76.7** | **68.2** | **−8.5** | **73.6** | **57.5** | **56.7** | **58.4** |
| Cl-(**a**) | 1 | 72.3 | 71.4 | −0.9 | 71.4 | 59.0 | 57.9 | 61.7 |
| | 46.7 | 72.7 | 70.0 | −2.7 | 69.9 | 57.4 | 56.0 | 60.2 |
| Cl-(**b**)(*) | 1 | 79.2 | 66.7 | −12.5 | 70.8 | 58.5 | 58.3 | 61.3 |
| | 46.7 | 78.3 | 64.9 | −13.4 | 70.1 | 56.9 | 56.5 | 59.7 |
| | **exptl.** | **72.5** | **67.3** | **−5.2** | **67.4** | **56.5** | **56.0** | **58.4** |
| Br-(**a**) | 1 | 70.4 | 70.9 | 0.5 | 68.9 | 58.4 | 57.9 | 61.9 |
| | 46.7 | 70.7 | 69.6 | −1.1 | 67.3 | 56.7 | 56.0 | 60.3 |
| Br-(**b**)(*) | 1 | 77.9 | 66.3 | −11.6 | 68.4 | 57.8 | 58.5 | 61.4 |
| | 46.7 | 76.6 | 64.4 | −12.2 | 67.5 | 56.2 | 56.5 | 59.9 |
| | **exptl.** | **71.5** | **67.0** | **−4.5** | **65.8** | **56.0** | **56.0** | **58.5** |
| *t*-Bu | **exptl.** | **67.3** | **64.7** | **−2.6** | **59.7** | **56.6** | **55.6** | **57.5** |

[a] An asterisk denotes the preferential conformation (see Table 2). [b] $\Delta = {}^1J_{C_1C_6} - {}^1J_{C_1C_2}$.

compound **2**, and the corresponding LP₁(O) negative hyperconjugative interactions do not show such a difference. Therefore, it is thought that the above-mentioned differences originate mainly in proximate interactions between the LP₁-(O) and the methyl group; a similar assertion holds for compound **3**. The dielectric solvent effect on such differences is worth noting. For the four conformations of compound **2** shown in Figure 5, the negative hyperconjugative interactions, LP₁(O) → σ*₍CC₎, and the conjugative interactions, LP₂-(O) → π*, are displayed in Table 6 as calculated for $\epsilon = 1$ and $\epsilon = 46.7$. In the same Table 6, the corresponding interactions in **1** are also shown for reference purposes. To rationalize adequately the data displayed in Table 6, it is important to recall that in a previous paper[35] it was studied

how electrostatic interactions can inhibit or enhance electron delocalization interactions.[26] Keeping these trends in mind, it is expected that in Table 6 there is not a general trend for the influence of the dielectric solvent on the displayed interactions. While a polar solvent enhances the LP₁(O) → σ*₍CC₎ interaction for the **a** conformation, an important inhibition for the **b-1** conformation is observed. This suggests that, for the **a** conformation, interactions of type O−H⋯H−C, which are mainly electrostatic, slightly inhibit the LP₁-(O) → σ*₍C₁C₂₎ interactions. A polar solvent shields the O−H⋯H−C interaction (Figure 6), and therefore the negative hyperconjugative interaction LP₁(O) → σ*₍C₁C₂₎ tends to recover its original strength, that is, for $\epsilon = 1$. For the **b** conformations, an important increase in LP₁(O) → σ*₍CC₎ is

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**Table 5.** $C_1=C_2$ and $C_1=C_6$ Bond Lengths, $d_{C_1C_2}$ and $d_{C_1C_6}$, Respectively (in Å); Negative Hyperconjugative Interactions, of Types $HI_{1,2} = LP_1(O) \rightarrow \sigma^*_{C_1C_2}$ and $HI_{1,6} = LP_1(O) \rightarrow \sigma^*_{C_1C_6}$; and Conjugative Interactions, CI, of Types $CI_{1,2} = LP_2(O) \rightarrow \pi^*_{C_1C_2}$ and $CI_{1,6} = LP_2(O) \rightarrow \sigma^*_{C_1C_6}$ [a]
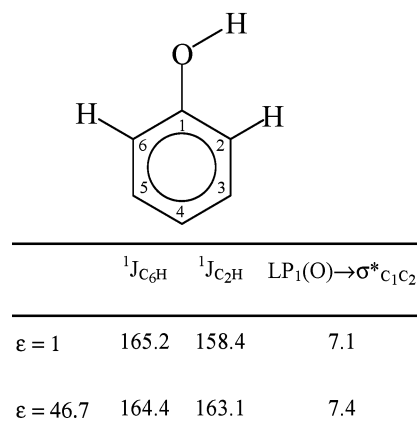
| X | $d_{C_1C_2}$ | $d_{C_1C_6}$ | $HI_{1,2}$ | $HI_{1,6}$ | $CI_{1,2}$ | $CI_{1,6}$ |
|---|---|---|---|---|---|---|
| H | 1.400 | 1.399 | <0.5 | 7.4 | 28.9 | <0.5 |
| $CH_3$-(**a-1**) | 1.405 | 1.401 | 7.6 | <0.5 | 27.2 | <0.5 |
| $CH_3$-(**b-1**) | 1.406 | 1.400 | <0.5 | 10.2 | <0.5 | 26.9 |
| $CH_3$-(**a-2**) | 1.406 | 1.397 | 7.4 | <0.5 | 26.9 | <0.5 |
| $CH_3$-(**b-2**) | 1.408 | 1.397 | <0.5 | 10.3 | <0.5 | 28.2 |
| Et-(**a**) | 1.407 | 1.397 | 7.6 | <0.5 | 20.9 | 1.4 |
| Et-(**b**) | 1.408 | 1.397 | <0.5 | 10.3 | <0.5 | 28.1 |
| CN-(**a**) | 1.412 | 1.400 | 8.9 | <0.5 | 34.5 | <0.5 |
| CN-(**b**) | 1.412 | 1.398 | 0.9 | 7.6 | 34.1 | <0.5 |
| CHO-(**a**)[b] | 1.419 | 1.399 | 7.8 | <0.5 | 36.1 | <0.5 |
| CHO-(**b-1**) | 1.417 | 1.400 | 0.7 | 7.1 | <0.5 | 33.8 |
| CHO-(**b-2**) | 1.413 | 1.401 | 0.9 | 6.8 | <0.5 | 32.7 |
| F-(**a**) | 1.396 | 1.397 | 10.1 | <0.5 | <0.5 | 27.9 |
| F-(**b**) | 1.400 | 1.397 | <0.5 | 10.9 | 29.0 | <0.5 |
| Cl-(**a**) | 1.401 | 1.401 | 8.1 | <0.5 | 32.4 | <0.5 |
| Cl-(**b**) | 1.402 | 1.400 | 0.7 | 7.6 | 32.2 | <0.5 |
| Br-(**a**) | 1.401 | 1.402 | 8.5 | 0.6 | 32.2 | <0.5 |
| Br-(**b**) | 1.402 | 1.401 | <0.5 | 7.5 | 32.1 | <0.5 |

[a] All of these interactions are given in kilocalories per mole. [b] For the **a** conformation, the NBO parameters are not reliable since the NBO approach yields the OH proton as a separated unit.

**Table 6.** Dielectric Solvent Influence on the $LP_1(O) \rightarrow \sigma^*_{CC}$ and $LP_2(O) \rightarrow \pi^*_{CC}$ Interactions (in kcal/mol) for Conformations **a-1**, **b-1**, **a-2**, and **b-2** of Compound **2**

| conformer | interaction | $\epsilon = 1$ | $\epsilon = 46.7$ |
|---|---|---|---|
| X = H | $LP_1(O) \rightarrow \sigma^*_{CC}$ | 7.1 | 7.4 |
| | $LP_2(O) \rightarrow \pi^*_{CC}$ | 28.2 | 28.9 |
| **a-1** | $LP_1(O) \rightarrow \sigma^*_{CC}$ | 7.1 | 7.6 |
| | $LP_2(O) \rightarrow \pi^*_{CC}$ | 27.5 | 27.3 |
| **b-1** | $LP_1(O) \rightarrow \sigma^*_{CC}$ | 12.2 | 10.2 |
| | $LP_2(O) \rightarrow \pi^*_{CC}$ | 25.7 | 26.9 |
| **a-2** | $LP_1(O) \rightarrow \sigma^*_{CC}$ | 6.9 | 7.4 |
| | $LP_2(O) \rightarrow \pi^*_{CC}$ | 27.1 | 26.9 |
| **b-2** | $LP_1(O) \rightarrow \sigma^*_{CC}$ | 10.0 | 10.3 |
| | $LP_2(O) \rightarrow \pi^*_{CC}$ | 27.0 | 28.2 |

observed. For **b-1** and $\epsilon = 1$, it amounts to 12.2 kcal/mol, and that decreases to 10.2 kcal/mol for $\epsilon = 46.7$. This suggests that the proximity between the $LP_1(O)$ and the methyl C—H bonds, that is, interactions of type $LP_1(O)\cdots$ H—C, enhances notably negative hyperconjugative interactions of type $LP_1(O) \rightarrow \sigma^*_{CC}$. A polar solvent should shield the former, and therefore the $LP_1(O) \rightarrow \sigma^*_{CC}$ interaction should recover in part its original value; for example, for **b-1**, it goes from 12.2 to 10.2 kcal/mol. It is interesting to observe the opposite behavior for the **b-2** conformation, where a methyl C—H bond points directly to $LP_1(O)$. It is stressed that, in compound **2-(b-2)**, the difference $\Delta = {}^1J_{C_1C_6} - {}^1J_{C_1C_2} = 65.5 - 67.4$ Hz $= -1.9$ Hz is in excellent agreement with the experimental difference, $-1.8$ Hz. This difference is smaller, in absolute value, than for any other conformation. This trend seems to originate in the small value for the ${}^1J_{C_1C_2}$ SSCC, which is affected by the $(C_{Me}-H) \rightarrow \sigma^*_{C_1C_2} = 2.5$ kcal/mol $\sigma$-hyperconjugative interaction since



| | ${}^1J_{C_6H}$ | ${}^1J_{C_2H}$ | $LP_1(O) \rightarrow \sigma^*_{C_1C_2}$ |
|---|---|---|---|
| $\epsilon = 1$ | 165.2 | 158.4 | 7.1 |
| $\epsilon = 46.7$ | 164.4 | 163.1 | 7.4 |

**Figure 6.** Interplay between electrostatic and negative hyperconjugative interactions in phenol. SSCCs are in hertz, and negative hyperconjugative interactions are in kilocalories per mole. The $C_6-H\cdots LP_1(O)$ interaction inhibits in part the negative hyperconjugative interaction $LP_1(O) \rightarrow \sigma^*_{C_1C_2}$. This effect yields an algebraic increase of the $\sigma_{C_1C_2}$ "other bond contribution" to ${}^1J_{C_2H}$, decreasing its total value. The proximity between the $C_6-H$ bond and the $LP_1(O)$ lone pair causes an increase in the ${}^1J_{C_6H}$ SSCC. These values are taken from ref 32.

the in-plane $C_{Me}-H$ bond is placed in an anti-periplanar configuration with respect to the $C_1=C_2$ bond. This same effect seems to be present for the **2-(a-2)** conformation affecting the difference ${}^1J_{C_1C_6} - {}^1J_{C_1C_2} = 6.8$ Hz $= 70.6 - 63.8$ Hz, which is larger than usual (compare with compound **1**, Figure 4), suggesting that the ${}^1J_{C_1C_2}$ SSCC is reduced by the mentioned $\sigma$-hyperconjugative interaction. It is to be noted that in both cases such a reduction in the ${}^1J_{C_1C_2}$ SSCC is between 2.3 and 2.6 Hz. The enhancement of the negative hyperconjugative interaction $LP_1(O) \rightarrow \sigma^*_{CC}$ due to the proximity effects between $LP_1(O)$ and the methyl group seems to play a key role in defining as more preferential the **b** conformation with respect to the **a** conformation.
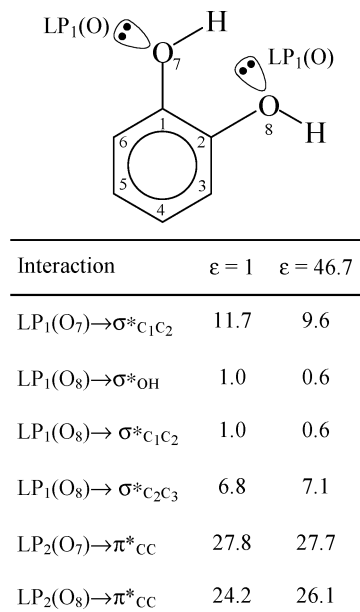
Another important point to note in Table 5 is that the conjugative $LP_2(O) \rightarrow \pi^*$ interaction depends on both the methyl and the hydroxyl groups conformations; that is, this interaction is also affected by proximity interactions between the $LP_2(O)$ and the methyl C—H bonds. Quite similar effects are also observed for the **a** and **b** conformations of compound **3**, although for the former conformation, a very strong inhibition of the conjugative effect takes place, probably due to the closeness between the $\pi$-type oxygen lone pair, $LP_2$-(O), and the methyl moiety of the ethyl group. It is important to note that for compound **3** only one conformation of the $CH_3$ moiety was considered. Comparing the conjugative interaction for **2-(b-1)** and **2-(b-2)**, it is suggested that the larger inhibition of the conjugative effect that takes place in the former defines the latter as the preferential conformation. While in **2-(b-1)** there are two out-of-plane C—H methyl bonds close to the $\pi$-oxygen lone pair, in **2-(b-2)**, there is only one in-plane C—H methyl bond that points to the node of that LMO representing the $LP_2(O)$ nonbonding electron pair.

In compound **4-(a)**, the $LP_1(O) \rightarrow \sigma^*_{CC}$ negative hyperconjugative interaction is stronger than that in the **4-(b)**

conformation. This seems to indicate that a charge-transfer interaction into the (O−H)* antibonding orbital enhances the corresponding negative hyperconjugative interaction $LP_1(O) \rightarrow \sigma^*_{CC}$. On the other hand, in **4-(b)**, the $LP_1(O) \rightarrow \sigma^*_{CC}$ interaction is close to that in **1**. The expected enhancement of the $LP_2(O) \rightarrow \pi^*$ resonance for the electron-donating O−H group when it is in a position ortho to an electron-withdrawing X substituent is observed in compounds **4** and **5**, although in the latter, this effect is partially inhibited for the **b** conformation of the OH group. On the other hand, in **4**, the important resonance enhancement, $LP_2(O) \rightarrow \pi^*$, due to the electron-donor OH group and the electron-withdrawing CN group depends only slightly on the O−H conformation. How much does the charge-transfer interactions into the (O−H)* antibond observed for the **a** conformations of compounds **4**, **6−8** affect the negative hyperconjugative interactions of type $LP_1(O) \rightarrow \sigma^*_{CC}$? In **4-(a)**, $LP_1(O) \rightarrow \sigma^*_{C_1C_2}$ amounts to 8.9 kcal/mol, while for the **4-(b)** conformation, $LP_1$-$(O) \rightarrow \sigma^*_{C_1C_6}$ amounts to 7.6 kcal/mol. This suggests that, when the (O−H)* antibond participates in an interaction like that in **4-(a)**, then the negative hyperconjugative interaction $LP_1(O) \rightarrow \sigma^*_{C_1C_2}$ is enhanced. It is observed that a similar effect seems to be operating for the **6-(a)** compound, where the O−H···F hydrogen bond shows also a strong electrostatic character. It is to be noted that in **6-(b)** there is also an important enhancement of the electron-donor ability of $LP_1$-(O) due to the proximity between $LP_1(O)$ and $LP_2(F)$. This interaction, as commented upon previously,[26] favors the $LP_1$-$(O) \rightarrow \sigma^*_{C_1C_6}$ charge-transfer interaction. In **7-(a)** and **8-(a)**, a similar effect to that in **6-(a)** can be appreciated, although it is a weaker effect, a fact that is consistent with a weaker electrostatic hydrogen bond involving Cl or Br rather than F (see the respective H···X distances in Table 3).

In order to verify the trends commented upon above for charge-transfer interactions in **4**, the geometry of the **a** conformer 2-OH-phenol was optimized at the same level as compounds **1−8**, and the relevant charge-transfer interactions were calculated; they are displayed in Figure 7. These results are compatible with these comments. (i) The $LP_1(O_7) \rightarrow \sigma^*_{C_1C_2}$ negative hyperconjugative interaction is enhanced due to the $LP_1(O_8) \rightarrow \sigma^*_{OH}$ hydrogen bond. (ii) The charge-transfer interaction involved in that hydrogen bond is weaker in 2-OH-phenol than those reported above in compounds **4** and **6**. (iii) The $LP_1(O_8) \rightarrow \sigma^*_{C_2C_3}$ negative hyperconjugative interaction is slightly weaker than the corresponding interaction in compound **1**. This comment is in line with results discussed previously[35] on the slight inhibition of a negative hyperconjugation when the corresponding lone pair is involved in a standard hydrogen bond. (iv) The conjugative interactions of both $LP_2(O)$'s show a slight inhibition typical of two-electron-donor substituents placed ortho to each other. However, this effect is more important for $LP_2(O_8)$ than for $LP_2(O_7)$, indicating that the hydrogen-bond acceptor shows a larger inhibition than the hydrogen-bond donor, which actually seems to be enhanced by the hydrogen-bond interaction. (v) It is interesting to observe the different solvent trends exhibited by the different interactions displayed in Figure 7. In general, they are compatible with observations i−iv, which tend to confirm the effects of proximate



| Interaction | $\varepsilon = 1$ | $\varepsilon = 46.7$ |
|---|---|---|
| $LP_1(O_7) \rightarrow \sigma^*_{C_1C_2}$ | 11.7 | 9.6 |
| $LP_1(O_8) \rightarrow \sigma^*_{OH}$ | 1.0 | 0.6 |
| $LP_1(O_8) \rightarrow \sigma^*_{C_1C_2}$ | 1.0 | 0.6 |
| $LP_1(O_8) \rightarrow \sigma^*_{C_2C_3}$ | 6.8 | 7.1 |
| $LP_2(O_7) \rightarrow \pi^*_{CC}$ | 27.8 | 27.7 |
| $LP_2(O_8) \rightarrow \pi^*_{CC}$ | 24.2 | 26.1 |

**Figure 7.** Negative hyperconjugative and conjugative interactions in 2-OH-phenol for the **a** conformation as calculated for $\epsilon = 1$ and $\epsilon = 46.7$.

interactions on negative hyperconjugative and conjugative interactions.

## 3. Experimental and Computational Details

**NMR Measurements.** Compounds studied in this work are commercially available, and their identities and purities were checked by taking their ${}^1H$ and ${}^{13}C$ NMR spectra. Such spectra were recorded using 5 mm sample tubes from DMSO−DMSO-$d_6$ solutions at 30 °C in concentrations of ca. 80% w/w and were run on a Bruker AM 500 spectrometer, operating at 125.76 MHz when observing ${}^{13}C$ signals. ${}^1J_{13c13c}$ coupling constants were measured at natural abundance using the INADEQUATE technique,[36] which was adjusted for ${}^1J_{13c13c} = 60$ Hz. ${}^{13}C$ signals were first assigned from the ${}^1H$-coupled ${}^{13}C$ spectra and then confirmed when performing the INADEQUATE experiments. According to the acquisition parameters used, the digital resolution was in the range of 0.07−0.21 Hz per point. All spectra were recorded at the LANAIS NMR-500 facility of the Department of Physics, FCEyN, University of Buenos Aires.

**Computational Details.** All DFT calculations carried out in this work were performed using the hybrid B3LYP functional of Lee et al.,[37] where the exchange part is treated according to Becke's three-parameter approach.[38] In all cases, the geometries of compounds **1−8** were fully optimized at the B3LYP/6-311G** level considering both an isolated molecule, $\epsilon = 1$, and a molecule in an infinitely diluted DMSO solution, $\epsilon = 46.7$. In each case, two different conformations of the hydroxyl group were considered, namely, **a**, with the O−H bond eclipsing the aromatic $C_1 = C_2$ bond, and **b**, with the O−H bond eclipsing the aromatic $C_1 = C_6$ bond. All conformations were verified to correspond to true minima on the potential surface.

Besides, for X = $CH_3$, two different conformations of the methyl group were considered yielding, therefore, four stable rotamers **a-1**, **a-2**, **b-1**, and **b-2**, see Figure 5. In compound

**5**, that is, with X = CHO, for the **b** conformation of the hydroxyl group, two different conformations of the CHO group were considered, namely, **b-1** with $\beta = 0°$ and **b-2** with $\beta = 180°$ (Figure 5). It is important to recall that samples were prepared using in general high solute concentrations, and therefore these solutions depart from the "infinitely diluted DMSO" solution model. Besides, in a previous paper, it was observed that dielectric solvent effects on aromatic $^1J_{CC}$ SSCCs show a saturation effect for $\epsilon$ slightly larger than 10.[29] For this reason, PCM calculations considering $\epsilon = 46.7$ are thought just to take into account a highly polar solution and not only an infinitely diluted DMSO solution.

For compounds **1−6**, all four isotropic terms of $^1J_{CC}$ SSCCs, that is, the FC, SD, PSO, and DSO, were calculated using the EPR-III basis set[39] which is of a triple-$\zeta$ quality and includes diffuse and polarization functions. The s part of this basis set is enhanced to better reproduce the electronic density in the nuclear region; this point is particularly important when calculating the FC term. It is to be stressed that coupling constants calculated at the B3LYP/EPR-III level are close to the basis-set converged values.[40] For Cl- or Br-containing compounds, inner-shell electrons were taken into account by using the LANL2DZ effective core potential. In these compounds, for all other atoms, the EPR-III basis set was used. The CP−DFT perturbative approach was used for calculating all three of the second-order terms of SSCCs, that is, FC, SD, and PSO. SSCC calculations were performed using the respective optimized geometry. Dielectric solvent effects were taken into account using the SCRF-PCM version of the PCM of Tomasi et al.[41] Calculations of SSCCs including dielectric solvent effects were performed using optimized geometries obtained within the SCRF-PCM model using the respective dielectric constant, for $\epsilon = 1$ and $\epsilon = 46.7$. All DFT calculations were carried out with the Gaussian 03 program.[42] Conjugative and hyperconjugative interactions were calculated using the NBO approach[22,43] as included in the Gaussian 03 suite of programs.[42]

## 4. Concluding Remarks

The aim of this work was to study in detail some stereochemical effects of oxygen nonbonding electron pairs on $^1J_{CC}$ SSCCs. It is expected that the results presented in this work will contribute to supporting the use $^1J_{CC}$ SSCCs as adequate probes for certain stereochemical studies in dicoordinated oxygen-containing aromatic compounds. This study was carried out on a series of nine 2-X-phenols where, for each compound, the six $^1J_{CC}$ SSCCs were measured. DFT calculations were carried out for different side-chain conformations in most of the nine 2-X-phenols, and stereochemical oxygen lone-pair effects were nicely verified, obtaining very good agreement between measured and calculated $^1J_{CC}$ couplings. This same study allowed a detailed analysis of some interesting features of ortho interactions and their effect on side-chain conformations. One of these unexpected results is this one: the OH mesomeric effect can be much affected by the ortho interaction with C−H bonds. The stereospecific properties of $^1J_{CC}$ SSCCs depend more strongly than expected on ortho interactions, and this calls for some caution when using these parameters as probes to study some stereochemical aspects.

It is important to recall that ortho interactions calculated in this work do not depend on any molecular orbital model employed in this analysis. However, since it is expected that within the readership of this journal there are many chemists familiar with concepts such as conjugative and hyperconjugative interactions, it is considered important to describe results obtained in this work in terms of a pictorial representation resorting to that type of interaction. In this way, a qualitative or semiquantitative model with interesting predictive character in terms of NBOs is used to discuss the main results obtained in this work.

Results presented above suggest that negative hyperconjugative and conjugative interactions involving a two-coordinated oxygen atom acting as the $\alpha$ atom of a substituent in an aromatic ring strongly depend on ortho interactions. Such effects present several subtleties that are worth mentioning in detail, indicating at the same time possible applications. They are as follows:

(1) $LP_1(O) \rightarrow \sigma^*_{CC}$ negative hyperconjugative interactions are enhanced up to a few kilocalories per mole (a) when $LP_1(O)$ is involved in a weak hydrogen bond of type $LP_1$-$(O)\cdots H$−C and (b) when O belongs to an OH group that is involved as a donor in a hydrogen-bond interaction of type O−H$\cdots$X, where X is an electronegative element.

(2) $LP_1(O) \rightarrow \sigma^*_{CC}$ negative hyperconjugative interactions are slightly inhibited when $LP_1(O)$ is involved in conventional hydrogen bonds of type $LP_1(O)\cdots H$−X, where X is an electronegative element. This point is worth highlighting: a conventional hydrogen bond shows an opposite effect of that of a weak hydrogen bond.

(3) $LP_2(O) \rightarrow \pi^*_{CC}$ conjugative interactions are easily inhibited by weak hydrogen-bond interactions of type $LP_2$-$(O)\cdots H$−C.

All of these effects depend upon the dielectric solvent. Apparently, in most cases, the dielectric solvent effects operate both by shielding proximate electrostatics interactions and by a slight inhibition of negative hyperconjugative interactions. In general, the latter are less important than the former.

One of the consequences of point 1 is this: the preferential conformation of an O−H group can be strongly defined by an O−H$\cdots$X interaction where there is only a modest charge-transfer interaction into the (O−H)* antibonding orbital, but it is reinforced by a notably enhanced $LP_1(O) \rightarrow \sigma^*_{CC}$ interaction (up to a few kilocalories per mole).

The lone-pair orientation effect on $^1J_{CC}$ coupling appears to be an adequate probe to study the interplay of the 1−3 effects commented upon above. It is also important to stress, as observed in previous papers, that in aromatic compounds $^1J_{CC}$ SSCCs can be adequately reproduced at the level of theory used in this work, B3LYP/6-311G**//B3LYP-EPRIII. However, it should be mentioned that this assertion could fail when there are two electron-rich atoms bonded directly to the C−C bond containing the coupling nuclei.

Lone-Pair Orientation Effect of an α-Oxygen Atom

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