Conformational Behavior of *cis*-2-Methoxy, *cis*-2-Methylthio, and *cis*-2-Methylselenocyclohexanol: A Theoretical and Experimental Investigation

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Studies on the conformational equilibria of 2-methoxy, 2-methylthio, and 2-methylselenocyclohexanol are reported. Dynamic NMR spectroscopy experiments at 203−210 K were performed, which provided the percentages of each conformer in equilibrium. Theoretical calculations using the B3LYP method and aug-cc-pvdz basis set were applied to determine the differences in energy between the conformers. The analysis of the potential energy surface of each conformer showed the presence of two rotamers. Natural bond orbital analysis provided an explanation of which factors are driving the rotamer and conformer preferences.

1. Introduction

The term "conformational analysis" is a broad one, but two of its aspects shall receive special consideration here: the determination of the molecular geometric structures, including the relative energies of the conformers, and the attempts to determine the major forces controlling the relative conformational stabilities. In this field, the conformation of the six-membered rings, which have two substituents in either the axial or the equatorial positions, is important, mainly as useful models to rationalize factors governing conformational equilibria. One of the most reliable methods to measure conformational equilibrium constants is the determination of the ratio of integral intensities of the NMR signals of individual conformers under "conformational inflexible" conditions. This occurs at temperatures around −80 °C, when the inversion of the ring in substituted cyclohexanes becomes sufficiently slow on the NMR spectroscopy time scale. Zefirov et al.[1] calculated the conformational equilibrium constants for a series of *trans*-1,2-disubstituted cyclohexanes by using this methodology through low-temperature ^{13}C NMR spectroscopy experiments. Because of an increase in computational chemistry power (computational calculations), a large variety of studies have been published in this area. The focus is mainly on the classical effects (steric and electrostatic) present in these systems. The *trans*-1,2-disubstituted cyclohexane isomer has been extensively studied[2−4] as a model in an attempt to clarify these effects. Some researchers have investigated the conformational preferences of *trans*-2-halocyclohexanols and their methyl ethers.[3−7] They verified that in halohydrins intra- and/or intermolecular hydrogen bonds lead the conformational equilibria toward the equatorial−equatorial (eq−eq) conformer,[3−6] while, for their methyl ethers, the eq−eq population is not as large as for the alcohols, the equilibrium is governed by steric and dipolar factors as well as the "gauche effect".[4,7,8] Abraham et al.[9] demonstrated, through NMR spectroscopy and theoretical data, the strong bonding between the hydroxyl group and the fluorine atom in *trans*-2-fluorocyclohexanol, which is responsible for the predominance of the eq−eq conformation of this molecule. Freitas et al.[3] demonstrated that, besides hydrogen bonding, the gauche effect and steric interactions are also present for chlorine, bromine, and iodine derivatives. By use of ab initio and force field calculations, Jansen and co-workers[10] accomplished a detailed investigation of the possible orientations of the hydroxyl group in cyclohexanol. They found four isomers and ab initio results showed that the difference in energy between the three most stable isomers is quite small.

Up to now, most reviews have focused on the effects (steric and electrostatic) involved in the conformational equilibrium only in *trans*-disubstituted cyclohexanes, even though the cis isomer is the major one from the reduction of 2-substituted cyclohexanones with $LiAlH_4$.[11]

In this paper, we carried out a detailed conformational investigation of *cis*-2-methoxy (**1**), *cis*-2-methylthio (**2**), and *cis*-2-methylselenocyclohexanol (**3**). NMR experiments, along with theoretical calculations, were used to clarify the main factors involved in this equilibrium.

2. Experimental

2.1. Compounds. Compounds **1** and **2** were synthesized through stereoselective reduction of the corresponding ketones with potassium tri-*sec*-butylborohydride (k-selectride)[12,13] in THF at −60 °C (ethanol/N_2(l)). Compound (**3**) was obtained through the reduction of the corresponding ketone with $LiAlH_4$ in THF at room temperature.

2.2. Theoretical Calculations. All the calculations were performed with the Gaussian 03 package.[14] The stable conformers of compounds **1**−**3** (Scheme 1) were obtained by calculating the potential energy surface (PES) through the HF/6-31G level of theory. The geometries for the most stable conformers were optimized by density functional theory (DFT) calculations with the B3LYP hybrid functional, which consists of the nonlocal

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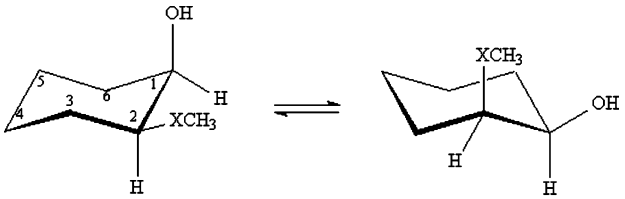
SCHEME 1: Conformational equilibrium of the investigated compounds



exchange functional of Becke's three-parameter set[15] and the nonlocal correlation functional of Lee et al.[16] Dunning's basis set (aug-cc-pVDZ) was used to carry out these calculations. It is defined as a correlation consistent basis set that contains all the correlating functions that lower the correlation energies by similar amounts as well as all correlation functions that lower the energy by large amounts.[17] These sets are compact, converge systematically to the CBS limit, and well defined with respect to the increase in both size and accuracy.[18] Stationary points were fully optimized and characterized by vibrational frequency calculations, which also provided zero-point vibrational energies (ZPE). Natural bond orbital (NBO) calculations were performed by using B3LYP/6-31G(d,p).[19,20]

2.3. NMR Spectroscopy Experiments. All the compounds were characterized through ^{1}H, ^{13}C, and 2D NMR spectroscopy. The spectra were obtained on a Varian Mercury Plus 300 operating at 300.06 MHz for ^{1}H and 75.46 MHz for ^{13}C. Spectra were obtained with ca. 20 mg cm^{-3} solutions with a probe temperature of 298 K referenced to Me_4Si under typical conditions for ^{1}H (spectral width 4000 Hz with 32K data points and zero filled to 128 K to give a digital resolution of 0.03 Hz).

The chemical shifts of the compounds studied are presented below and the key to atom numbering is shown in Scheme 1.

2.3.1. cis-2-Methoxycyclohexanol. ^{1}H NMR ($CDCl_3$, 300.06 MHz; δ in ppm): δ 3.84 (1H, m, H_1); 3.40 (3H, s, CH_3) 3.27 (1H, m, H_2); 2.40 (1H, dd, OH); 1.78 (2H, m, H_{3eq} and H_{6eq}); 1.60 (4H, m, H_{3ax}, H_{4eq}, H_{5eq}, H_{6ax}); 1.35 (1H, m, H_{5ax}); 1.28 (1H, m, H_{4ax}). ^{13}C NMR ($CDCl_3$, 75.46 MHz, δ in ppm): δ 21.0 (C_5); 22.0 (C_4); 25.9 (C_3); 30.0 (C_6); 56.1 (CH_3); 68.2 (C_1) and 80.0 (C_2).

2.3.2. cis-2-Methylthiocyclohexanol. ^{1}H NMR ($CDCl_3$, 300.06 MHz; δ in ppm): δ 3.87 (1H, m, H_1); 2.80 (1H, m, H_2); 2.24 (1H, dd, OH); 2.10 (3H, s, CH_3); 1.87 (1H, m, H_{6eq}); 1.65 (4H, m, H_{3ax}, H_{3eq} H_{4eq} and H_{5eq}); 1.50 (1H, m, H_{6ax}); 1.35 (2H, m, H_{4ax} and H_{5ax}). ^{13}C NMR ($CDCl_3$, 75.46 MHz, δ in ppm): δ 14.0 (CH_3); 20.1 (C_5); 24.7 (C_4); 27.4 (C_3); 31.3 (C_6); 52.1 (C_2); 66.1 (C_1).

2.3.3. cis-2-Methylselenocyclohexanol. ^{1}H NMR ($CDCl_3$, 300.06 MHz; δ in ppm): 3.77 (1H, m, H_1); 3.11 (1H, m, H_2); 2.56 (1H, dd, OH); 2.00 (3H, s, CH_3); 1.45−1.28 (8H, m). ^{13}C NMR ($CDCl_3$, 75.46 MHz, δ in ppm): δ 4.0 (CH_3); 21.0 (C_5); 24.8 (C_4); 28.7 (C_3); 32.2 (C_6); 50.0 (C_2); 68.0 (C_1).

The low-temperature ^{13}C NMR spectra were obtained on Bruker DPX 300 operating at 75.47 MHz for ^{13}C in acetone-d_6 at 200−210 K. The chemical shifts are compiled in Table 1.

3. Results and Discussion

3.1. Theoretical Results. The conformational equilibrium of the compounds is shown in Scheme 1. The conformational structures of conformers **I** and **II** were obtained through a PES calculation considering the rotation of the two dihedral angles C_6-C_1-O-H and $C_3-C_2-X-CH_3$.

TABLE 1: ^{13}C Chemical Shifts (ppm) of Compounds 1, 2, and 3 at Room Temperature and at Low Temperature

	1			2			3		
	I−II[a]	**I**[b]	**II**[b]	**I−II**[a]	**I**[b]	**II**[b]	**I−II**[a]	**I**[b]	**II**[b]
C_1	68.5	64.9	71.7	66.1	66.0	72.6	68.1	68.6	72.3
C_2	80.2	81.4	79.6	52.1	50.9	53.1	49.7	46.1	50.3
C_3	26.1	25.9	27.0	27.4	27.0	29.5	29.1	28.6	29.2
C_4	22.1	24.7	24.9	24.7	26.7	25.0	25.1	28.7	27.6
C_5	21.3	19.6	19.4	20.1	19.5	20.7	21.1	19.5	21.7
C_6	30.5	31.1	30.0	31.3	33.1	30.8	32.2	36.3	36.4
CH_3	56.1	55.1	56.4	13.9	13.4	16.5	3.80	2.60	4.90

[a] 298 K in $CDCl_3$ from TMS. [b] 203−210 K in acetone-d_6 from TMS.

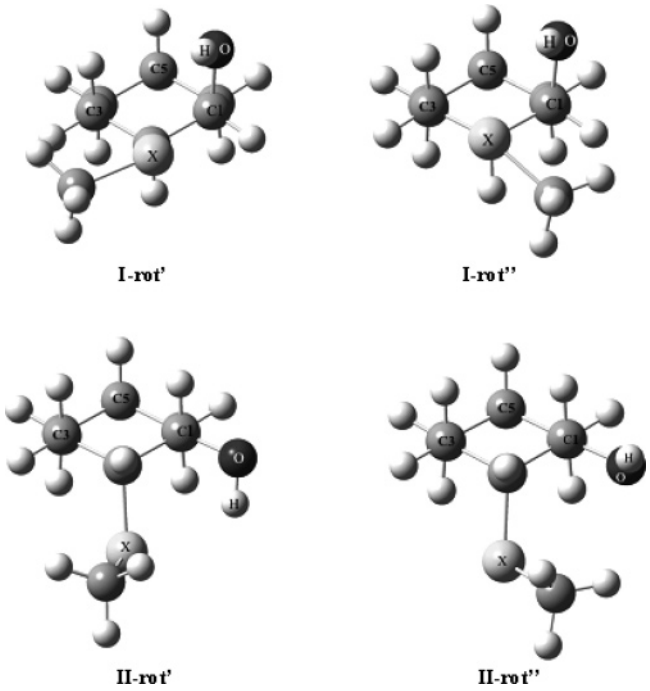


Figure 1. Structures optimized through the B3LYP/aug-ccpvdz level of theory, considering the conformational and rotational equilibrium present in this system (X = O, S, and Se).

Two minima (**rot′** and **rot″**) were localized for each conformer (Figure 1) and then fully optimized, yielding the energies presented in Table 2. According to Table 2, conformer **I** showed **rot″** as the most stable rotamer (about 2.00 kcal/mol) for both compounds **2** and **3**, while for **1**, the small difference in energy between **rot′** and **rot″** (0.07 kcal/mol) suggested a rotamer mixture. By taking the most stable rotamer of each conformer, it was possible to determine the conformational energy differences between conformers **I** and **II** as 0.05, 1.18, and 0.92 kcal/mol for **1**, **2**, and **3**, respectively, conformer **I** being the most stable in all compounds. In eq 1, N is the mole fractions of **I** and **II**, $N_I + N_{II} = 1$, and ΔE is the conformational energy difference previously determined

$$N_I/N_{II} = e^{-\Delta E/RT} \quad (1)$$

By analysis of the spatial geometry of the compounds, we note that there is a hydrogen bond between the hydroxylic hydrogen and the heteroatom of the substituent in both **rot′** and **rot″** of **I**. This interaction was also observed in **II**, but only for **rot′**, since in **rot″** the electron lone pair is turned away from the hydroxylic hydrogen. The hydrogen bond provides a five-membered ring formation that contributes to system stabilization. The same interaction was reported for *trans*-2-halocyclohexanols.[3−7]

TABLE 2: Rotamer Energies (*E*) and Rotational Energy Difference (ΔE) of the Studied Compounds

	E (hartrees)				ΔE (kcal/mol)	
	I		**II**		**rot″−rot′**	
compounds	**rot′**	**rot″**	**rot′**	**rot″**	**I**	**II**
2-methoxycyclohexanol	−425.46434 7	−425.464236	−425.46427 1	−425.45963 1	0.07	2.91
2-methylthiocyclohexanol	−748.45531 3	−748.458434	−748.45655 8	−748.45226 3	−1.96	2.70
2-methylselenocyclohexanol	−2751.8047 41	−2751.80806 5	−2751.8065 92	−2751.8021 81	−2.08	2.76

TABLE 3: Interaction Energy Orbital Obtained through NBO Analysis[a] of the Compounds

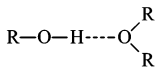
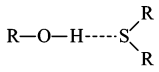
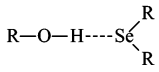
		E (kcal/mol)		
NBO donator	NBO acceptor	**1**	**2**	**3**
	I rot′			
LP_x	σ^*_{C2-C3}	7.70	3.94	2.11
LP_x	σ^*_{C1-C2}	1.14	0.15	0.47
LP_x	σ^*_{C2-Hax}	6.28	4.17	2.63
LP_x	σ^*_{C1-C6}	0.63	0.32	
LP_x	σ^*_{C3-C4}	0.66	0.45	0.22
LP_x	σ^*_{O-H}	1.38	3.14	4.56
	I rot″			
LP_x	σ^*_{C2-C3}	1.65	0.14	
LP_x	σ^*_{C1-C2}	7.25	4.69	3.46
LP_x	σ^*_{C2-Hax}	5.41	2.96	1.64
LP_x	σ^*_{C1-C6}	0.81	0.79	0.71
LP_x	σ^*_{O-H}	1.83	5.13	5.04
	II rot′			
LP_x	σ^*_{C3-Hax}	0.65	0.81	0.64
LP_x	σ^*_{C1-C2}	1.52	1.83	2.19
LP_x	σ^*_{C2-Heq}	5.09	0.87	0.37
LP_x	σ^*_{O-H}	2.05	4.75	4.74
LP_x	σ^*_{C2-C3}	7.52	3.82	2.05
	II rot″			
LP_x	σ^*_{C1-Hax}	0.61	0.63	0.55
LP_x	σ^*_{C1-C2}	8.67	5.82	3.99
LP_x	σ^*_{C2-Heq}	5.62	2.28	1.09
LP_x	σ^*_{O-H}			
LP_x	σ^*_{C2-C3}	1.89	0.44	0.24

[a] Threshold = 0.1 kcal/mol.

To evaluate the interactions in both rotamers from each conformer, we performed a detailed NBO analysis on all of them. Table 3 shows the main orbital interactions between the electron lone pair (LP_x) of the substituent and the antibonding sigma (σ^*) to adjacent bonds. The main hyperconjugatives interactions observed in both rotamers of **I** (Figure 1) are $LP_x \rightarrow \sigma^*_{C1-C2}$, $LP_x \rightarrow \sigma^*_{C2-C3}$, and $LP_x \rightarrow \sigma^*_{C2-Hax}$. One inversion between the energy value interactions of $LP_x \rightarrow \sigma^*_{C1-C2}$ and $LP_x \rightarrow \sigma^*_{C2-C3}$ is observed when going from **rot′** to **rot″** (rotation of the dihedral angle $C_3-C_2-X-CH_3$). This fact is due to the electron lone pair position, clearly depicted in Figure 1 (**I-rot′** and **I-rot″**).

As in compound **1** the hydrogen bond is possible for both rotamers (**rot′** and **rot″**), the orbital interactions should explain the rotational preference. The interaction energies for **rot′** and **rot″** are very similar, while in **rot′** there is one more interaction ($LP_O \rightarrow \sigma^*_{C3-C4}$/0.66 kcal/mol) than in **rot″**. Indeed, by comparison of the sum of interaction energies presented in Table 3 from **rot′** against the ones in **rot″**, the former is 0.85 kcal/mol larger, in accordance to the rotamer preference. By analysis of the interaction energies (Table 3) for the conformer **I**, in compounds **1**, **2**, and **3**, we observed the preference for **rot″** only for **2** and **3** by 1.54 and 0.86 kcal/mol, respectively. This preference is attributed to interactions $LP_x \rightarrow \sigma^*_{C1-C2}$ and $LP_x \rightarrow \sigma^*_{C1-C6}$ that are more effective in **rot″**, as well as the interaction $LP_x \rightarrow \sigma^*_{O-H}$, that becomes larger in **rot″** than in **rot′**.

TABLE 4: PNBO Overlap Integrals for Attractive $LP_x \rightarrow \sigma^*_{O-H}$ ($I_{n\sigma^*}$) and Repulsive $LP_x \rightarrow \sigma_{O-H}$ ($I_{n\sigma}$) Interactions

Complex	$I_{n\sigma^*}$	$I_{n\sigma}$	$(I_{n\sigma^*}/I_{n\sigma})^2$
	0.104	0.066	2.48
	-0.184	-0.127	2.10
	-0.189	-0.140	1.82

[a] Pre-orthogonal localized orbitals.

As $LP_x \rightarrow \sigma^*_{C1-C2}$ and $LP_x \rightarrow \sigma^*_{C2-C3}$ are through bond interactions, the energy decreases in the order O > S > Se; therefore, the oxygen lone pair will interact more effectively than those of sulfur and selenium.

Another important interaction observed in **rot′** and **rot″** is $LP_x \rightarrow \sigma^*_{O-H}$. In contrast to the results previously discussed, this one is a through-space interaction, increasing in the order O < S < Se (Table 3). This interaction is intrinsically correlated with hydrogen bond formation and the charge transfer is in turn strongly correlated with the overlap $I_n\sigma^*$ of LP_x and σ^*_{O-H} orbitals. We compared the values of the attractive donor−aceptor ($I_n\sigma^*$) and repulsive donor−donor $I_n\sigma$ ($LP_x \rightarrow \sigma_{O-H}$) overlaps for the most stable conformer (**I**) for all compounds (Table 4). The ratio $(I_n\sigma^*/I_n\sigma)^2$, gives a measure of the energetic balance between attractive and repulsive terms in the equilibrium geometry. When both $I_n\sigma^*$ and $(I_n\sigma^*/I_n\sigma)^2$ are favorable, the shortest and strongest H-bond results.[21] Thus, as only for compound **1** is this value favorable, a stronger H-bonding is observed than for compounds **2** and **3**. The high energy observed for this interaction, in S and Se derivatives, is due to the diffuse lone pair ($LP_{S/Se}$) when compared with the O derivative (most polar hydride antibond σ^*_{O-H}).

Conformer II exhibits essentially the same behavior as **I**, except for the absence of $LP_x \rightarrow \sigma^*_{O-H}$ in **rot″**. It is clear that this interaction, together with the interaction $LP_x \rightarrow \sigma^*_{C2-C3}$, is responsible for the lowest system energy that increases around 2.80 kcal/mol when these interactions are not possible or not effective, as in **II**-rot″, Figure 1.

To evaluate how important is the hyperconjugative interaction to conformer stabilization, we calculated the electronic delocalization energy for the most stable rotamers in each conformer from compounds **1**, **2**, and **3**.

To perform this calculation we deleted all hyperconjugative interactions in order to obtain just the localized contribution (natural Lewis structure). The difference of the original energy (full) minus the localized one provide the stabilizing effect of the delocalization contribution. Thus, conformer **II** shows the electronic delocalization energies 1.75, 1.85, and 3.04 kcal/mol higher than conformer **I**, for compounds **1**, **2**, and **3**, respectively. These results are presented in Table 5 and indicate an inversion

TABLE 5: Electronic Delocalization Energy ($\Delta\Delta E$) for Compounds 1, 2, and 3

	1		2		3	
	I	**II**	**I**	**II**	**I**	**II**
total energy (E_t)[a]	−425.48890 8801	−425.488517169	−748.470313444	−748.468554519	−2749.485259765	−2749.485530261
deletion energy (E_d)[a]	−424.98725 5207	−424.984072424	−748.002715350	−747.998005507	−2749.010376426	−2749.005798883
$\Delta E^b = E_t - E_d$	314.793	316.544	293.422	295.274	297.994	301.036
$\Delta\Delta E^b$		1.75		1.85		3.04

[a] In hartrees. [b] In kcal/mol.

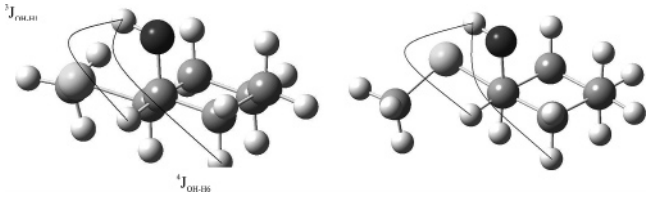


Figure 2. Couplings $^3J_{OH-H1}$ and $^4J_{OH-H6}$ observed in the **I** rotamers of compounds **1**, **2**, and **3**.

of the conformer preferences (**II** more stable than **I**), that is opposed to those previously determined.

Indeed, when we deleted only the main interactions, described in Table 3, the same behavior was observed, in other words, according to these results the hyperconjugative interactions, mainly the ones in Table 3, are driving the conformer preference, rather than steric effects.

3.2. Experimental Results. Compounds **1** and **2** were synthesized through stereoselective reduction from the parent ketone, while compound **3** was prepared by reduction with a metallic hydride ($LiAlH_4$), which produced a mixture of cis and trans isomers. Because of the difficulty in obtaining pure cis isomer for **3**, all the NMR spectra were run with the mixture, as the cis isomer represents more than 85% of this mixture.

By use of the ^{13}C spectrum run at low temperature (showing two conformers) together with 2D NMR spectroscopy techniques (COSY and HMQC), obtained at room temperature, we assigned each conformer (**I** and **II**, Scheme 1) to the cis isomer (at 203−210 K) of **1**, **2**, and **3** through correlation with the trans isomers, once the latter has the same substituent effect on the ^{13}C chemical shifts of the conformer **II** of each compound.

All these chemical shifts are presented in Table 1. The experimental percentages determined for the more stable conformer **I** for **1**, **2**, and **3** are 63.0, 80.8, and 72.4%, respectively.

These results are in agreement with expectations since, despite the size of the methylseleno derivative, it shows only a little more contribution of **II** (Se in the axial position) than that of the methylthio derivative. As the heteroatom becomes larger (O < S < Se), the C−X bonds get longer and more distant from the synaxial hydrogens.[22] The theoretically calculated (vacuum) conformer percentages are in agreement with the values determined from dynamic NMR spectroscopy (DNMR). The difference observed is probably due to the absence of the solvent effect in the calculations.

In the ^1H NMR spectra of compounds **1**, **2**, and **3** in $CDCl_3$ at room temperature, the hydroxylic hydrogen splits as a double duplet (dd) with coupling constants 4.80 and 0.60 Hz for **1**, 3.57 and 1.50 Hz for **2**, and 5.10 and 1.05 Hz for **3**. The major coupling is attributed (COSY) to $^3J_{OH-H1}$, while the minor one is a long-range coupling due to a planar W arrangement between O−H and the axial hydrogen attached to carbon C_6 ($^4J_{OH-H6}$). The W coupling shows typical values next to 1.1 Hz in the analogue systems.[23] Figure 2 clearly shows the existence of this coupling in the optimized structures.

As the $^4J_{OH-H6}$ coupling is possible only for conformer **I**, the variation observed in these values can be explained in terms of the conformer population (Scheme 1). Thus, the $^4J_{OH-H6}$ values approach typical ones as the population of **I** becomes larger. The observed coupling reinforces the existence of the interaction between the hydroxylic hydrogen and the heteroatoms (O, S, Se).

4. Conclusion

The conformational equilibrium of compounds **1**, **2**, and **3** was investigated through theoretical and experimental methods. The percentages of conformers determined through DNMR spectroscopy is in agreement with the ones determined through theoretical calculations. Conformer **I** is the most stable for all compounds investigated. The interactions $LP_x \rightarrow \sigma^*$, through-bond or through-space, are shown to be the most important ones to explain the conformer preferences. Indeed, the interactions $LP_x \rightarrow \sigma^*_{O-H}$ and $LP_x \rightarrow \sigma_{O-H}$ contributed to evaluate the energetic balance between attractive and repulsive terms in the equilibrium geometry.

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