

# Computational Study of Nodifloridin-A and Nodifloridin-B, with Highlight on the Peculiarities of Acylated Phloroglucinol Derivatives

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**Abstract:** - Nodifloridin-A and nodifloridin-B are biologically active compounds of natural origin, whose comparison can highlight important differences between phloroglucinol derivatives and other phenolic derivatives. The study reported here analyses and compares conformational preferences in vacuo and in three solvents with different polarities. The role of intramolecular hydrogen bonding is given particular attention, because of its importance in influences conformational preferences and energies.

**Key-Words:** - 1,3,5-Trihydroxybenzene, Acetonitrile solutions, Acylphloroglucinols, Chloroform solutions, Intramolecular Hydrogen Bonding, Nodifloridin, Phenolic derivatives, Solute-Solvent Interactions, Water solutions.

## 1 Introduction

Nodifloridin-A and nodifloridin-B are compounds isolated from *Lippia nodiflora* [1], a plant utilized in Chinese traditional medicine to treat swellings and abscesses [2]. They are respectively denoted as Nod-A and Nod-B in this work. Fig.1 shows the two structures [3] and the atom numbering utilized here; only the atoms that are relevant for the analysis and discussion of results are given numbers; atoms in corresponding positions are given the same numbers in the two structures to facilitate comparisons.

Nod-A is a phenol derivative while Nod-B is a phloroglucinol (1,3,5-trihydroxybenzene) derivative [1]. The two structures have the same acyl chain,  $\text{CO}(\text{CH}_2)_6\text{COOH}$ , at C1 (with three conjugated  $\text{C}=\text{C}$  double bonds, also conjugated to the  $\text{C}_7=\text{O}_{14}$  and  $\text{C}_{23}=\text{O}_{24}$  double bonds) and an ether function ( $\text{OCH}_3$ ) at C5. The substituent at C3 (here termed R') differs for the presence of a methyl group at C9 and a double bond between C29 and C30 in Nod-A.

The  $\text{sp}^2$  O of the acyl chain and an OH *ortho* to it can form an intramolecular hydrogen bond (IHB) that will be termed "first IHB". Additional IHB are made possible by the H-bond donor/acceptor properties of the two COOH. In Nod-B, the presence of OH groups at C4 and C6 enables two possibilities for the formation of the IHB (with H15 or with H17) and the formation of IHB between H16 and/or H17 with O11. The study of IHB is particularly important because of their roles in determining conformational preferences and energies, as well as in the mechanisms of biological activities.

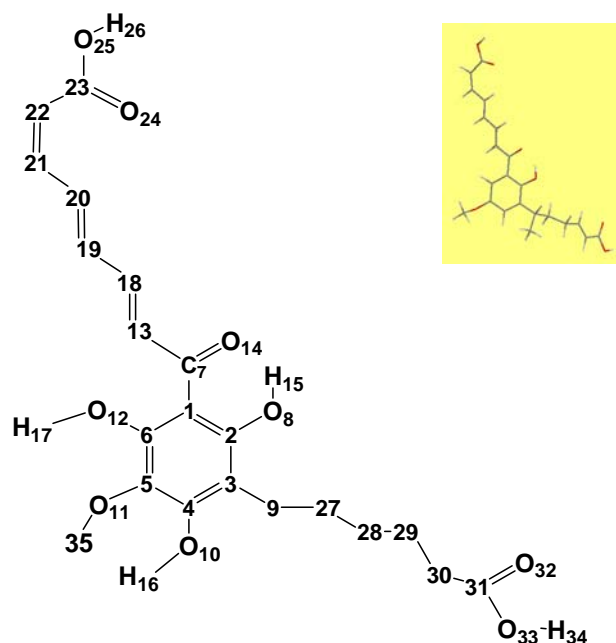


Fig.1. Structure of Nod-B, showing the atom numbering utilized in this work, and of Nod-A (higher left corner).

## 2 Problem Formulation

The interest of a computational study of Nod-A and Nod-B goes beyond the obtainment of information on their individual conformational preferences and on relevant geometry characteristics like the parameters of their IHB. The results enable a range of comparisons, in turn expected to enable better insight on the molecular properties of APHLG and on how they compare with similar derivatives of

other phenols. The following issues are given particular attention in the analysis and discussion of computational results: • the effects, on the characteristics of the first IHB, of the presence of a conjugated  $\pi$  system in the acyl chain, and of the presence of a bulky chain at C3; • the effects of additional IHB, and the competition between the stabilizing effect of an IHB and the geometry constrains that may make the formation of some IHB energetically unfavourable; • comparison with the predictions from simpler model structures, to assess their predictive abilities, and comparison with the results of previous extensive studies of the characteristics of APHLG [4,5]; • comparison of conformational preferences in vacuo and in solution (results in solution being particularly important for biologically active molecules, because their activity within living organisms is exerted in a medium [6]); • comparison of the effects of the presence of three equally-spaced phenol OH in phloroglucinol derivatives, with respect to analogous derivatives of other phenolic compounds.

### 3 Problem Solution

#### 3.1 Computational details

Calculations were performed using the GAUSSIAN 03 package, version D.01 [7]. Given the size of the two molecules, and the additional demands of PCM calculations, all the calculations were performed at the HF/6-31G(d,p) level, because of affordability reasons. Previous comparisons of HF/6-31G(d,p) results with those of higher levels of theory (mostly using MP2/6-31++G(d,p) results as benchmarks, as the best for H-bonding description because of including correlation and dispersion effects and diffuse functions in the basis set [8]) had shown the reasonability of HF/6-31G(d,p) results, above all for the identification of trends, including conformers' relative energies, effects of molecular geometry features on the characteristics of the first IHB, geometry and energy effects of the IHB removal and stabilization patterns in solution [4,5].

Calculations in solution were performed with the polarisable continuum model (PCM [9,10]), with the default settings of Gaussian03, considering three solvents with different polarities and different H-bonding abilities (chloroform, acetonitrile and water) to cover the range of media that may be interesting for biological activity [5]. The *in-vacuo*-optimized geometries were utilized as inputs; re-optimization in solution (enabling better quality of the solvation phenomenon description) was performed for the lowest energy conformers; single-

point calculations were performed for all the conformers (a study of APHLG had shown that the trends identified from full re-optimization and from single-point calculations in solution are identical, and the energies differs by less than 1.00 kcal/mol.

All the energy values reported are in kcal/mol and all the distances are in angstrom ( $\text{\AA}$ ). For conciseness sake, the media are denoted with acronyms on reporting values: vac (*vacuum*), chlrf (chloroform), actn (acetonitrile) and aq (water).

### 3.2 Results of the calculations in vacuo

#### 3.2.1 Conformational preferences

Conformers are here named systematically. The names start with A for Nod-A and B for Nod-B. Relevant geometry features are denoted with symbols (table 1). For each structure, conformers with different geometries of the acyl chain and/or R' are numbered in order of increasing energy, and conformers that differ only by the features denoted by symbols (table 1) are given the same number.

Table 2 reports the relative energies of the best conformers of Nod-B (considering all the media) and Fig.2 shows the preferred geometries in vacuo (whose corresponding conformers, B-1-s-w-aj, B-1-s-w-aj-t, B-2-s-w-bfj, B-2-s-w-bfj-t, B-3-s-w-afj and B-3-s-w-afj-t, account for practically all the population in vacuo). These conformers combine the highest number of stabilizing effects: the presence of the first IHB; additional IHB involving the COOH, without excessive disruption of the planarity of the acyl chain (important for conjugation stabilization); the H16...O11 IHB and uniform orientation of the three phenolic OH [4,11]. In the absence of IHB involving the COOH functions (higher energy conformers), the possibility of two IHB with O11 makes d-w options preferred to other options.

The lowest energy conformer of Nod-A (A-1-d) corresponds to the geometry shown in fig.1, and the other populated conformers differ by features like the orientation of the ether methyl group or of R' or some torsion angles in R'.

The results of both structures highlight the dominant stabilizing effect of the first IHB. In Nod-B, where the presence of O12H17 enables the formation of the first IHB on the left, the lowest energy conformers have both the first IHB and additional IHB engaging H15 and the two COOH. In Nod-A, where the formation of IHB involving H15 and the COOH would prevent the formation of the first IHB, the best conformers have only the first IHB (the relative energy of the lowest-energy conformer with IHB involving the COOH groups, A-6-fj, is 5.828, what makes it unpopulated).

S	IHB present <sup>1</sup>	S	geometrical feature
d	H15...O14	r	H16 is oriented toward R'
s	H17...O14	w	H16 is oriented toward the ether function
a	H15...O32	u	H15 or H16, not engaged in the first IHB, is oriented "upward" <sup>2</sup>
b	H15...O33		
c	H16...O32	p	when not engaged in IHB, O24 is oriented upward <sup>2</sup>
e	H16...O33		
f	H26...O32	q	when not engaged in IHB, O32 and O33H34 are oriented oppositely to the case without this symbol
g	H26...O33		
h	H26...O12		
j	H34...O24		
k	H34...O8	t	the methyl of the ether function is oriented "towards us" with respect to the plane of the benzene ring <sup>2,3</sup>
m	H34...O10		
n	H34...O25		

Table 1. Symbols (S) utilized to denote the main geometry features of the conformers.

<sup>1</sup> No symbol is introduced for the IHB with O11 in Nod-B, because their presence or absence is clear from other features: all w conformers have the H16...O11 IHB and all conformers that are not s-type or d-u-type have the H17...O11 IHB; <sup>2</sup> The way in which the structures are reported in fig. 1 is taken as reference; <sup>3</sup> If there is no indication in the name, the orientation is opposite to the one identified by this symbol.

conformer	relative energy			
	vac	chlrf	actn	aq
B-1-s-w-aj	0.0000	0.0000	0.0000	5.2831
B-2-s-w-bfj	0.4375	1.6503	2.2329	9.8423
B-2-s-w-afj	0.9351	2.0931	2.6913	10.3366
B-3-d-r-c	2.9672	1.0317	0.460	2.6972
B-5-d-w	4.3731	1.1762	0.0762	0.0000
B-3-d-r-cp	4.6921	2.4512	1.8315	3.9136
B-5-d-r	6.744	3.668	2.490	2.098
B-5-s-w	7.116	3.988	2.814	2.184

Table 2. Relative energies of selected conformers of Nod-B in different media. The results reported for the three solvents correspond to full re-optimization in solution.

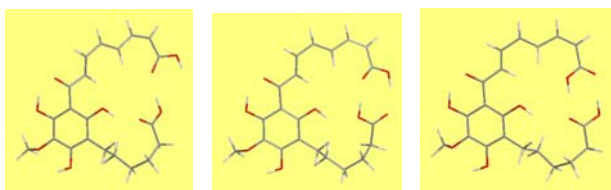


Fig. 2. Geometries of the lowest energy conformers of Nod-B in vacuo: from the left: B-1-s-w-aj, B-2-s-w-bfj and B-3-s-w-afj.

Not all the possible IHB have a stabilizing effect. This can be ascribed to a greater weight of the destabilization due to geometry strains with respect to the stabilization associated with the IHB, for certain IHB; the issue will be discussed more in detail on considering the IHB energy (section 3.2.3).

Other geometry features may have non-negligible influence on the conformers' energy. When not engaged in IHB, the COOH group of the acyl chain prefers an orientation like the one shown in fig.1, with the OH "up"; the reverse orientation (with the

OH "down") causes a 1.72–1.80 energy increase in Nod-B and 1.87–1.89 in Nod-A. The influence of the orientation of the COOH of R' (when not engaged in IHB) is considerably less; e.g., it is 0.76 for B-d-w-1 and 0.42 for A-d-1. The orientation of the methyl of the ether function with respect to the plane of the ring does not cause significant energy differences: 0.011–0.374 for Nod-B and 0.059–0.186 for Nod-A. The R and S conformations for the chiral C9 atom in Nod-A differ by 0.054–0.614.

### 3.2.2 Characteristics of the IHB

Table 3 reports the parameters of the IHB present in the lowest energy conformers of Nod-B, and in other conformers representative of different IHB combinations (selecting the lowest energy one for each combination). The IHB engaging O11 (H16...O11 and H17...O11) are not included because their parameters vary in a rather small range, due to the constraints from the benzene ring.

The first IHB is always the shortest IHB present in a conformer. Its length shows trends similar to those identified for APHLG [4]: shorter when it forms on the same side as R' (1.670–1.706/d-w and 1.684–1.692/d-r) and longer when it forms on the other side (1.710–1.763/s-w and 1.726–1.767/s-r). Comparison of the lowest energy conformers of Nod-B without additional IHB (B-5-d-w) with the corresponding conformers of structure MB-1 (fig.3; an actual acylphloroglucinol [1] and a suitable model for Nod-B) shows no difference in the first IHB length for d-r and d-w cases, whereas the IHB is longer in Nod-B for s-r and s-w cases; this suggests that a methyl at C3 is a good model for the bulkier R' and for the combined effects of the acyl chain and R', while a COCH<sub>3</sub> group may not be adequate to model a longer acyl chain containing a conjugated  $\pi$  system (whose effect is the only effect on the IHB with H17). A model structure with the same acyl chain, a methyl at C3 and no ether function at C5 gives closer values (less than 0.004 difference) for the s-w and s-r first IHB, but not as close for the d-r and d-w cases.

The length of H16...O11 and H17...O11 depends on whether they are present simultaneously or singly. H16...O11 is 2.075–2.121 when it is alone (s-w) and 2.201–2.243 when H17...O11 is also present (d-w, w); H17...O11 is 2.057–2.149 when it is alone (d-r, r) and 2.154–2.262 when H16...O11 is also present (d-w, w). Comparison with a conformer of 1,2,3,5-trihydroxybenzene having bifurcated IHB (1,2,3,5-THB, fig.4) shows close values for the IHB lengths when H16...O11 and H17...O11 are present simultaneously.

conformer and IHB	H-bond parameters			$\Delta E$
	O...H Å	O...O Å	OHO	
B-1-s-w-aj	1.747	2.575	143.0	0.000
H15...O32	1.953	2.850	157.1	
H34...O24	1.882	2.823	166.9	
B-2-s-w-bfj	1.710	2.545	143.8	0.438
H15...O33	2.281	3.102	145.0	
H26...O32	1.968	2.894	161.8	
H34...O24	1.744	2.699	170.1	
B-2-s-w-afj	1.722	2.556	143.6	0.935
H15...O32	2.551	3.416	152.3	
H26...O32	1.850	2.793	167.1	
H34...O24	1.814	2.777	178.8	
B-3-d-r-c	1.684	2.531	145.3	2.967
H16...O32	1.991	2.888	157.3	
B-5-d-w	1.699	2.540	144.6	4.373
B-9-s-w-f	1.763	2.591	143.1	5.835
H26...O32	1.888	2.839	172.7	
B-10-d-w-m	1.700	2.541	144.7	6.130
H34...O10	2.460	3.100	124.7	
B-5-d-r	1.687	2.531	144.9	6.744
B-5-s-w	1.725	2.556	143.3	7.116
B-1-s-r-aj	1.767	2.591	142.7	7.509
H15...O32	1.942	2.851	159.9	
H34...O24	1.868	2.812	167.6	
B-12-s-w-agn	1.762	2.587	142.6	7.993
H15...O32	1.996	2.870	152.7	
H26...O33	2.545	2.958	106.4	
H34...O25	2.469	2.958	111.9	
B-14-s-w-bfn	1.760	2.585	142.6	8.373
H15...O33	2.371	3.111	135.1	
H26...O32	1.988	2.832	146.1	
H34...O25	2.503	3.333	145.8	
B-2-s-r-bfj	1.726	2.557	143.4	8.584
H15...O33	2.283	3.121	147.5	
H26...O32	1.979	2.905	162.0	
H34...O24	1.730	2.688	170.9	
B-11-d-r-e	1.691	2.534	144.9	8.801
H16...O33	2.627	3.221	121.3	
H34...O10	2.895	3.221	101.4	
B-10-s-w-m	1.731	2.561	143.1	9.212
H34...O10	2.409	3.088	128.4	
B-4-s-w-q	1.714	2.549	143.9	10.365
H15...O32	2.004	2.906	158.7	
B-15-d-w-k	1.670	2.521	145.6	11.371
H34...O8	2.285	3.157	152.8	
B-16-s-w-agq	1.739	2.568	143.1	11.640
H15...O32	2.076	2.970	157.0	
H26...O33	2.047	2.966	162.1	
B-3-s-r-c	1.745	2.573	143.2	11.996
H16...O32	1.989	2.895	159.7	
B-18-d-w-h-q	1.746	2.577	143.7	14.226
H17...O25	2.608	3.094	112.2	
H26...O12	2.926	3.094	91.2	
B-5-s-r	1.746	2.572	143.0	15.616

Table 3. Parameters of the IHB in Nod-B, in vacuo. The values in the row with the name of the conformer correspond to the first IHB. The other IHB present in the given conformer are listed below its name. The conformer relative energy ( $\Delta E$ ) is included as reference for the stabilizing effect of each set of IHB.

The IHB involving one or both COOH groups shows a variety of ranges, and their length appears to depend considerably on the molecular context.

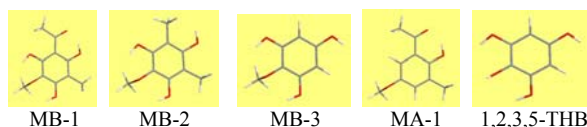


Fig. 3. Main structures utilized as models or for comparisons.

E.g., H15...O32 (IHB between a phenol OH and a carboxyl  $sp^2$  O) is shortest in B-1-s-r-aj and longest in B-12-s-w-agn, with an even longer value in B-2-s-w-afj, where O32 is engaged in a bifurcated IHB. Of the IHB between COOH groups, the shortest are (predictably) those between the OH of one group and the  $sp^2$  O of the other, whereas IHB engaging the O of the carboxyl OH are comparatively long.

The length of the first IHB in Nod-A (1.739–1.766) is closer to the first IHB of Nod-B engaging H17 than to that engaging H15. The lengths of the other IHB (appearing only in high energy conformers) fall within the ranges observed for nod-B; e.g., the range for H26...O32 is 1.923–1.964. For both structures, the IHB parameters are not influenced significantly by the orientation of the ether methyl with respect to the plane of the ring.

### 3.2.3 The strength of the IHB

The evaluation of IHB energy is a difficult task, because there is no suitable reference [12]. The removal of an IHB by  $180^\circ$  rotation of the donor group leaves the lone pairs of the two O atoms exposed to mutual repulsion and may cause geometry changes in the rest of the molecule; both factors (geometry changes and  $O \leftrightarrow O$  repulsion) contribute to the energy difference between the conformers with and without the IHB, preventing the isolation of the effect of the IHB removal.

For the first IHB in APHLG, the  $O \leftrightarrow O$  repulsion is partially smoothed by the off-plane shift of the acyl group on IHB removal [4,5] and there are no other relevant geometry changes; therefore, the energy difference between the conformers with and without the IHB can be viewed as a reasonable indication of the IHB energy. The shift occurs also in Nod-B, bringing O14  $51\text{--}54^\circ$  off-plane ( $63\text{--}74^\circ$  in APHLG with no  $\pi$  systems in the acyl chain conjugated to  $C7=O14$ ). In all APHLG with  $R' \neq H$ , the IHB on the same side as  $R'$  is stronger than when it forms on the other side [4]. The energy increase on its removal from d-r or d-w Nod-B conformers (11.56–13.43) is comparable with that of the other APHLG (8.72–12.10). For the first IHB engaging H17, an independent evaluation is impossible, as its removal implies the formation of the H17...O11 IHB; the IHB length suggests that H17...O14 is

somewhat weaker than H15...O14, consistently with the results for all other APLHG with  $R' \neq H$ .

On removing the first IHB from Nod-A, the  $O \leftrightarrow O$  repulsion can disappear completely through a simultaneous  $180^\circ$  rotation of H15 and O14. The estimated IHB energy is 3.105–4.978 smaller than for nod-B H15...O14, due to the combined effects of greater IHB length in Nod-A and absence of overestimations related to  $O \leftrightarrow O$  repulsion. Fig.4 highlights the different patterns for APLHG and for acylated phenol derivatives, through the scans of the rotations of relevant bonds in model structures: MB-1 for Nod-B and MA-1 for Nod-A. The scan of H15 shows the barrier for IHB removal ( $180^\circ$  rotation of the donor); the MB-1 pattern is consistent with that of other APLHG; e.g., the barrier is 12.975 (11.400–13.491 for APLHG) and O14 moves steadily away from O8, reaching  $65^\circ$  off-plane; the MA-1 pattern differs for a partial “return” of O14 towards O8 (returning to  $54^\circ$  in the last steps after reaching  $61^\circ$  off-plane for  $150^\circ$  torsion angle of H15). The scan of O14 in conformers without IHB shows the low-energy orientations of O14 when not engaged in the IHB: two minima, at  $60^\circ$  off-plane from O8 or O12, for MB-1 (balancing the tendency to lower  $O \leftrightarrow O$  repulsion and the tendency to avoid perpendicular orientation, like the other APLHG [4]) and on the other side with respect to O8 for MA-1, with disappearance of the  $O \leftrightarrow O$  repulsion and additional stabilisation from an unconventional H-bond with the H at C6.

Estimating the energy of the IHB involving atoms of the COOH groups is practically impossible, because of the dramatic geometry changes on removing such IHB. Comparisons of pairs of conformers in which one of these IHB is respectively present and absent (table 3) highlight the great weight of geometry factors: in a number of cases, the conformer without the IHB has better energy than the conformer with the IHB, showing that the energy-increasing effects of the geometry strains in one or both chains overcome the stabilizing effect of the IHB. Because of the impossibility of separating the two types of effects, it is considered that the best option for a first-approximation comparison of the IHB strength is by comparing their lengths (the IHB length being a fair indicator of its strength).

The energy of H16...O11 in Nod-B can be estimated from comparison of w-r pairs. Using a rough  $\sim 1.0$  estimation [4,11] for the stabilization associated with uniform orientation of the three phenol OH in d-r and s-w forms, its energy is 6.5–7.1 when it is on the same side as the first IHB

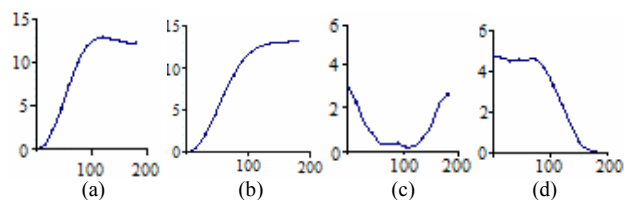


Fig.4. Scans of the rotation of H15 (energy versus C1C2O8H15 torsion angle, removing the IHB) for MB-1 (a) and MA-1 (b), and scans of the rotation of O14 (energy versus C2C1C7O14 torsion angle, in absence of IHB) for MB-1 (c) and MA-1 (d).

(s forms) and 3.0–3.4 when it is on the other side (d forms). Estimating the energy of H17...O11 is complicated by the fact that its removal results in u-type conformers, with considerable energy increase from steric effects [4]. Estimations on the simplest phloroglucinol with an ether function (MB-3) give 2.7 for the removal of one IHB and 7.2 for the simultaneous removal of both. Estimations on model structure MB-2, mimicking the steric effects at C1 and C3 by two methyls (to remove the complications of u-type geometries with a carbonyl) give 4.6 for the removal of one IHB and 9.9 for the simultaneous removal of both. These values may be slightly overestimated, since they are very close to those for the bifurcated IHB in 1,2,3,5-THB, while an ether O is a somewhat weaker H-bond acceptor than the hydroxide O; on the other hand, the rigidity of the benzene ring might increase the similarity of IHB with an ether O and with a hydroxide O.

### 3.4 Results of the calculations in solution

The results in solution show different patterns for different solvents. The solvent polarity and its ability to form intermolecular H-bonds with the solute molecules play major roles in determining the solute conformational preferences. Although PCM does not take solute-solvent H-bonds into explicit account, the relative energies resulting from the bulk consideration of solute-solvent interactions indicate preferences for the presence or absence of a certain IHB in solution, thus suggesting which IHB would likely break in a given solvent.

The polarity influence is particularly evident in the case of Nod-B, where conformers with several IHB are preferred in vacuo, in chloroform and in acetonitrile (table 2; the lowest energy conformer is the same in vac, chlrf and actn and the relative energy pattern of the other conformers is the same in chlrf and actn), while the lowest energy conformers in water solution have only the first IHB, leaving the two COOH functions available for intermolecular H-bonds. This is consistent with the results for APLHG (showing that the first IHB does not break

in aq solution on competition with the possibility of formation of intermolecular H-bonds), and with the results for caespitate [13], showing that the weaker IHB between a phenol OH and an ester  $sp^2$  O in R' breaks on such competition. The fact that the IHB between the two COOH in Nod-B (stronger than an IHB with an ester O) break in aq solution supports the hypothesis that only the first IHB of APHLG does not break in aq solution.

The IHB parameters are also influenced by the solvent polarity. The length of the first IHB, and of H16...O11 and H17...O11, increases with increase in solvent polarity, while that of H16...O32 decreases. The changes in the length of the IHB between the two COOH are different for H26...O32 or H34...O24 and depend on the accessibility of the IHB to the solvent molecules and on the solvent polarity. The estimation of IHB strength in solution is complicated by the greater stabilization, by the solvent, of conformers without IHB with respect to those with the IHB, preventing the possibility of considering their energy difference as an approximation to the IHB energy [5]; the IHB length remains a reasonable indicator of the IHB strength.

The solvent effect (free energy of solvation,  $\Delta G_{\text{solv}}$ ) is always negative for aq, always positive for actn, and mostly negative for chlrf. The values of  $\Delta G_{\text{solv}}$  have the largest range in aq solution, with clear correspondence to the number of free H-bond donor-acceptor sites. For Nod-B (considering  $\Delta G_{\text{solv}}$  absolute values and single-point results): ~2.4 with no site available (e.g., B-2-s-w-bfj); ~6–7 with one site of a COOH available (e.g., B-1-s-w-aj); ~14–15 with one COOH completely available and the other partially available (e.g., B-3-d-r-c); ~17–19 with both COOH completely available (e.g., B-5-d-w) and ~20–25 for conformers with no IHB. For Nod-A: ~5 with no site available (e.g., A-6-fj), ~8 with one site of a COOH available (e.g., A-7-f), ~16 with both COOH completely available and ~18 for conformers with no IHB (some absolute values being greater for Nod-B than for Nod-A, because of the higher number of H-bond donor/acceptor sites).

## 4 Conclusion

The results of the calculations of Nod-B and Nod-A show determining influence of the hydroxybenzene moiety on conformational preferences and energies. The three equally-spaced OH of the phloroglucinol moiety in Nod-B enable a number of stabilizing features: the possibility of the H17...O14 option for the first IHB leaves the “right-hand” part available

for other IHB, having a stabilizing effect in vacuo and in solvents with low or intermediate polarity; additional IHB can be formed with the ether O. The results support the hypothesis that the phloroglucinol moiety has optimal stabilizing features among hydroxybenzenes derivatives.

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