15064 *J. Phys. Chem. A* **2009,** *113,* 15064–15077

A Computational Study of the Effects of Different Solvents on the Characteristics of the Intramolecular Hydrogen Bond in Acylphloroglucinols[†]

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Received: June 2, 2009; Revised Manuscript Received: September 1, 2009

Acylphloroglucinols are a broad class of compounds, derivatives from 1,3,5-trihydroxybenzene, and exhibiting a variety of biological activities. They are characterized by the presence of at least one COR group, whose sp^2 O can form an intramolecular hydrogen bond with a neighboring phenolic OH. This H-bond plays dominant roles in determining conformational preferences and energy, and is expected to play significant roles in biological activity mechanisms, which strongly motivates the study of its characteristics in solution. A computational study of a representative number of actual and model structures with different R was carried out in three solvents with different polarities and different types of interactions with solute molecules: water, acetonitrile, and chloroform, utilizing the PCM model. Calculations were mostly performed at the HF/6-31G(d,p) level because of affordability reasons in view of the size and number of the structures considered (the smallest structures were also calculated at MP2/6-31+G(d,p) level). Comparison with the results of a previous study in vacuo shows similar patterns within each medium, pointing to similarities in the influence of relevant geometry factors on the characteristics of the H-bond. The medium appears to have little influence on the parameters of the H-bond. Comparison across media of the energy increase on H-bond removal (an indication of the H-bond strength) is complicated by the greater solvent stabilization of the conformer resulting from H-bond removal, with respect to the one in which the H-bond is present. Several factors, however, would point to a strength not too different from that observed in vacuo.

1. Introduction

Intramolecular hydrogen bonds play important roles in determining conformational preferences and energy. They influence physicochemical properties like vibrational frequencies, chemical shifts, dielectric constants, density, surface tension, and vaporization enthalpy[1,2] and play relevant roles in important aspects of biological activity mechanisms like molecular recognition and selective binding and in specific activities (e.g., antitumor activity[3−5]).

The presence of a medium (solvent) influences molecular properties like bond lengths, electron populations on atoms,[6] energy level separations (and, consequently, electronic[7] and vibrational transitions[8]), relative stabilities of different conformers of a molecule or of different isomers,[6] dipole moments, polarizabilities, NMR and ESR parameters.[9,10] It influences aspects like reaction rates.[11,12] Its influence on important aspects of the mechanisms of biological activities, like molecular recognition[13,14] or the establishing of interactions with the receptor,[15] and the fact that biological activities are exerted in some medium within living organisms[16] provide strong motivations for the study of the effects of a solvent on the characteristics of biologically active molecules.

The current study investigates the influence of the presence of a medium on the characteristics of the intramolecular hydrogen bond (IHB) typical of acylphloroglucinols (Figure 1), a broad class of polyphenolic compounds, structural derivatives from 1,3,5-trihydroxybenzene (phloroglucinol) and characterized by the presence of at least one COR group (acyl chain), whose sp^2 O can form an IHB with a neighboring phenolic OH. The interest of acylphloroglucinols (many of which are found in natural sources) lies on the variety of their biological activities[17] and their potentialities as lead structures for drug development.[18] A previous study in vacuo[19] (considering more than 80 structures to make allowance for the great structural diversity of these compounds) had highlighted rather regular patterns for the characteristics of their IHB, its conformation-stabilizing effects, and the influences of specific geometry features of the rest of the molecule. The study in solution aims at verifying whether and to what extent those patterns remain valid, or new patterns emerge, under the influence of different types of solute−solvent interactions.

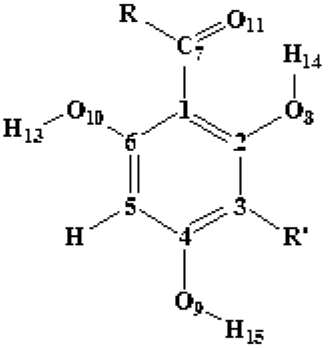

Figure 1. General structure of acylated phloroglucinols and atom-numbering utilized in this work. The first C atom of the R chain is numbered as C12.

Three solvents exerting different types of interactions with the solute molecules are selected: water (whose molecules are capable of forming intermolecular H-bonds with the solute, with both donor and acceptor roles, and also among themselves), acetonitrile (whose molecules can only form intermolecular

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[†] Part of the “Vincenzo Aquilanti Festschrift”.

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10.1021/jp905180c

H-bonds with the solute, with acceptor role), and chloroform (whose molecules cannot form H-bonds). Their different dielectric constants (78.39 for water, 36.64 for acetonitrile, 4.9 for chloroform) enable informative comparisons from the results of continuum model (PCM[20,21]) calculations. Their different polarities adequately cover the polarity range of possible media in which acylphloroglucinols molecules may be preferably present within a living organism, according to individual compounds' preferences for more or less polar solvents.

For the comparison with the results in vacuo to be significant, this study considers most of the model and actual structures already investigated in vacuo,[19] excluding only those with R chains not reported in the works/reviews on naturally occurring phloroglucinols utilized as major references[17,22−24] and the largest model structures with three identical acyl chains, because their information ability in solution is not expected to be significantly different from that in vacuo. Both structures with $R' = H$ and with $R' \neq H$ are considered for each R, because both types are widely spread. $R' \neq H$ is mostly mimicked by a methyl. The way this option proved viable for the study in vacuo[19,25] justifies its utilization for a study in solution focusing on the IHB, as it can be expected to be adequate for the identification of patterns like preferences and trends in the presence of $R' \neq H$, within a model viewing the solvent as a continuum (it would obviously not be adequate for the evaluation of the thermodynamic quantities of the solution process, because these depend on the actual complete structure of the molecule considered). The influence, on the IHB characteristics, of the other structural features that had been investigated in vacuo (the possibility of formation of a second IHB from donor/acceptor groups in R; the replacement of one or more phenolic OH by OCH_3 groups; the replacement of O7H15 by a keto group) is investigated also in solution, through the same sets of structures as in vacuo.

The fact that the PCM model does not take into specific account the possibility of formation of intermolecular H-bonds with the solvent molecules[26] is not expected to affect the identification of patterns in water or acetonitrile. Separate calculations of adducts of selected phloroglucinols with water molecules (e.g., caespitate[27]) show that the IHB does not break on competition with the possibility of formation of intermolecular H-bonds with water molecules (a similar result is obtained for the IHB involving the sp^2 O in the carboxylic acid of phloroglucinol[28]). Since this competition is stronger for water (a strong H-bond acceptor to phenol OH and H-bond donor to the sp^2 O), the extension of the result to acetonitrile (a weaker H-bond acceptor and no H-bond donor) is justified.

The results show that the trends within each solvent remain similar to those in vacuo: preference for the formation of the IHB on the same side of $R' \neq H$; scarce dependence on the nature of R, with exceptions for $R = H$ and for R containing a π bond or system conjugated to C7=O11; rather regular patterns for the dependence on the geometry features of the phloroglucinol moiety. Complications arise for cross-media comparisons of the IHB strength. For acylphloroglucinols, viable comparisons of the IHB energy in terms of energy increase on IHB removal are enabled within a given medium by the off-plane shift of O11 on IHB removal, minimizing the $O \leftrightarrow O$ repulsion[19,25,28] and occurring both in vacuo and in solution with similar extents. However, while in vacuo the energy increase on IHB removal is related solely to factors internal to the molecule (the IHB removal, the geometry deformation for the off-plane shift of O11), in solution it contains also the contribution from the higher solvent stabilization of the conformer resulting from IHB removal with respect to the one where the IHB is present, an effect that is different for different solvents. Therefore, it remains difficult to estimate the extent to which the decrease in the energy increase on IHB removal, as the solvent polarity and H-bond formation ability increase, can be ascribed to actual weakening of the IHB and the extent that should be ascribed to the solvent effect on the conformer without the IHB. The consideration of other features suggests the possibility that the IHB is not considerably weakened in solution, even in polar solvents.

2. Computational Details

Calculations in solution were performed with the polarizable continuum model (PCM[20,21]) as implemented in the Gaussian03 package,[38] with its default settings (Integral Equation Formalism model, IEF[30−32]), Gepol model[33−35] for building the cavity around the solute, with simple United Atom Topological Model (UAO) for the atomic radii (default values) and average tesserae area 0.200 Å^2). Calculations utilized the in-vacuo-optimized geometries as inputs, and performed reoptimization in solution at the same level of theory (reoptimization being the only option for the investigation of geometry-related characteristics like the parameters of the IHB, besides its general importance for the quality of the description of the solvation phenomenon[36]).

A satisfactory description of H-bonding would require a method taking into account electron correlation effects[37−46] and dispersion effects[47] and the inclusion of diffuse functions in the basis set,[48−55] which suggests MP2 calculations including diffuse orbitals as an optimal option.[52] However, the affordability of this option (already expensive in vacuo) is severely limited by the additional demands of PCM reoptimization in solution for structures that are not sufficiently small and by the fact that the current study involves a high number of structures, mostly not small. Therefore, all the structures were calculated at HF/6-31G(d,p) level, and only the smaller ones were calculated also at MP2/6-31+G(d,p) level in solution, to provide apt benchmarks for the IHB description, against which to compare the HF results. Despite its limitations for the investigation of H-bonding, the use of HF can be justified for discussing trends across a large family of related compounds (as in the current study), because then it can be expected that errors would be similar and therefore the trends, in general, reasonable.[19] This is further supported by the results of the study in vacuo[19] (where several more structures could be calculated at MP2/6-31+G(d,p) level, and DFT/B3LYP calculations were also performed): comparisons with the results of higher-level methods confirm the similarity of the identified trends. Moreover, the study in vacuo of acylphloroglucinols[19,25] and of another phloroglucinol derivative (the carboxylic acid[28]) had shown closer similarities between HF and MP2 results, than between DFT/B3LYP and MP2 results, for the off-plane shift of O11 on IHB removal; since this shift is crucial to prevent overestimation of the energy increase on IHB removal (and the effect of its inadequate consideration by DFT/B3LYP calculations would add to the general tendency of DFT to overestimate H-bond energies[56]), it appears that, for this class of compounds, the use of HF rather than DFT has additional motivations, besides computational economy (DFT calculations are more demanding for structures of this size).

All the calculations were performed using GAUSSIAN 03, version D.01.[29]

All the energy values reported are in kcal/mol and all the distances are in angstroms. For conciseness sake, the media will be denoted with the following acronyms on reporting values: vac (vacuum), chlrf (chloroform), actn (acetonitrile), and aq (water).

TABLE 1: Letters Utilized To Denote the Different R Chains in the Calculated Structures

letter	R	letter	R	letter	R	letter	R
A	H	F1	$(CH_2)_3CH_3$	G3	$CH_2CH(CH_3)CH_2CH_3$	Q	$(CH)_6COOH$
B	CH_3	F2	$CH_2CH(CH_3)_2$	J	$(CH_2)_8CH_3$	W	CH_2OH
D	CH_2CH_3	F3	$CH(CH_3)CH_2CH_3$	K	$(CH_2)_{10}CH_3$		
E1	$CH_2CH_2CH_3$	G1	$(CH_2)_4CH_3$	L	$CH{=}CHCH_3$		
E2	$CH(CH_3)_2$	G2	$CH_2CH_2CH(CH_3)_2$	N	phenyl		

3. Calculations and Results

3.1. Naming of Structures and Conformers. The calculated structures are denoted with the system introduced for the study in vacuo.[19] The capital letter with which the name begins corresponds to a specific number of C atoms in the R chain (Table 1) and is utilized singly (A, B, ...) when R′ ≠ H and doubly (AA, BB, ...) when R′ = H. Isomeric R chains are distinguished by numbers after the initial letter, with number 1 assigned to the linear-chain isomer. The symbol ET informs that the OH attached to the C atom/s identified by the number/s following it has been replaced by an OCH_3 group. The letter P denotes a prenyl chain (a frequent substituent at C3 or C5). In this way, e.g., BB-ET4 denotes a structure in which R = CH_3, R′ = H, and the OH at C4 is replaced by OCH_3; B-P3-ET2 denotes a structure in which R = CH_3, R′ = prenyl, and the OH at C2 is replaced by OCH_3. Additional acyl chains, when present, are denoted by CO followed by the letter denoting their R and the number/s of the C atom/s to which they are attached; e.g., BB-COA3 denotes a structure, in whose longer acyl chain R = CH_3, and having a CHO group attached at C3.

The geometry features that are relevant for the analysis are denoted by lowercase letters after the letters identifying the structure (Figure 2), as in the system utilized for the study in vacuo.[19,25] The same atom numbering as for the study in vacuo (Figure 1) is utilized for all the structures, to facilitate comparisons.

Table 2 lists the calculated structures. The conformers calculated for each structure comprise all those whose relative energy in vacuo and in preliminary PCM single point calculations is below 4 kcal/mol (to ensure inclusion of all conformers that may be involved in biological activities, usually taken as those with relative energy ≤3.5), the conformers resulting from IHB removal (needed to estimate the IHB energy) and selected conformers that may be relevant for the identification/confirmation of trends (e.g., some u conformers).

TABLE 2: List of the Calculated Structures[n]

R	calculated structures
H	A, AA, A-COA35
CH_3	B, BB, BB-COA3, BB-COB3, BB-ET4, BB-ET24, B-ET2, B-ET24, B-ET4, B-ET46, B-ET6, B-B35-ET4, B-P3, B-P3-ET2, B-P3-ET6, B-COB35
CH_2CH_3	D, DD, KT1,[a] KTT1[b]
$CH_2CH_2CH_3$	E1, EE1, E1-ET4, EE1-ET4, KT2[c]
$CH(CH_3)_2$	E2, EE2, EE2-COA35, EE2-ET4, caespitate,[d] E2-B35, E2-D3, E2-P3, E2X′,[e] KT3,[f] KT3*[g] KT3**,[h] KT3#,[i] KT3##,[j] KTT3,[k] KT4[m]
$(CH_2)_3CH_3$	F1, FF1
$CH_2CH(CH_3)_2$	F2, FF2, FF2-COA35
$CH(CH_3)CH_2CH_3$	F3, FF3
$(CH_2)_4CH_3$	G1, GG1
$CH_2CH_2CH(CH_3)_2$	G2, GG2, G2-P3
$CH_2CH(CH_3)CH_2CH_3$	G3, GG3
$(CH_2)_8CH_3$	JJ
$(CH_2)_{10}CH_3$	KK
$CH{=}CHCH_3$	L, LL
phenyl	N, NN
$(CH)_6COOH$	Q
CH_2OH	W, W-ET46

[a] C=O at C6, two CH_3 at C3. [b] C=O at C6, two H at C3. [c] C=O at C6, two CH_3 at C3. [d] R′ = $CH_2CHC(CH_3)CH_2COOCH_3$.[25] [e] R′ = CH_2CHCH_2. [f] C=O at C6, two CH_3 at C3, CH_3 at C5. [g] C=O at C6, two CH_3 at C3, H at C5. [h] C=O at C6, CH_3 and H at C3, H at C5. [i] C=O at C6, CH_3 and H at C3, CH_3 at C5. [j] C=O at C6, two H at C3, CH_3 at C5. [k] C=O at C6, two H at C3, H at C5. [m] C=O at C6, CH_3 at C3, OH at C5. [n] For structures having characteristics not identified by the symbols listed in Table 1, additional information is given through notes. The letter P denotes a prenyl chain and the symbol ET denotes an OCH_3 group.

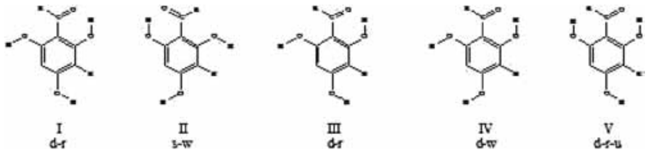


Figure 2. Symbols utilized to denote relevant geometry features of acylphloroglucinols. When R′ ≠ H, d informs that the H-bond is on the same side as R′ (I and V) and s informs that it is or on the other side (II). The letters r and w inform respectively that H15 is oriented toward the same side as R′ (I, V) or toward the other side (II). When R′ = H (III and IV), the letter d is used to denote that the H-bond is present, and the letters r and w inform respectively that H15 is oriented toward the same side as the H-bond (III) or toward the other side (IV). The letter u informs that the ortho OH not engaged in the H-bond is oriented toward the acyl chain (V). The structures also show that only the d-r and s-w conformers have uniform orientation of the three phenolic OH.

3.2. The Characteristics of the Intramolecular Hydrogen Bond. Like in vacuo, all the populated conformers in the three solvents contain the IHB and have the ortho OH not engaged in the IHB oriented away from the acyl chain (they are not u-type). When R′ ≠ H, the IHB prefers to form on the same side as R′, and this preference increases with increasing solvent polarity. The d/s population ratio of each structure, estimated over the four lowest energy conformers (d-r, d-w, s-r, and s-w) for all the structures for which these conformers are the only populated ones (with d comprising the total of d-r and d-w and s comprising the total of s-r and s-w) gives a clear indication of the increasing preference. The values for R′ = methyl (Table 3) show that s-type conformers are often scarcely populated in water. The ratio, however, depends considerably also on the nature of R′: e.g., when R′ = prenyl, the d population is 1.8_{vac}, $2.1-2.3_{\text{chlrf}}$, $\approx 4.5_{\text{actn}}$, and 50_{aq} times the s one; when R′ = propylene, the d population is 12.5_{vac}, 9.1_{chlrf}, 11.1_{actn}, and 100_{aq} times the s one.

Differently from in vacuo, d-w forms are preferred to d-r forms when R′ ≠ H: the lowest-energy conformers are d-w type in all solvents when R′ = CH_3, and in water and acetonitrile when R′ is a longer chain (d-r conformers remain preferred when R′ = H). This would point to a greater impact of steric effects between H15 and R′ in solution, parallel to the decrease of the stabilizing effect of the uniform orientation of the three phenolic

TABLE 3: Synoptic Comparison of Aspects Relevant to the Description of the IHB in vacuo and in the Three Solvents Considered[h]

aspect considered[a]	in vacuo	in chloroform	in acetonitrile	in water
preference for the IHB formation:				
(d-r + d-w)/(s-r + s-w) population ratio, $R' = CH_3$	mostly ≈2[b]	5−10	10−20	50−10
change in IHB length with respect to in vacuo[c]		0.000−0.015	0.000−0.013	0.001−0.046 mostly <0.022
s-r/d-r IHB length difference, $R' \neq H$	0.026−0.064	0.023−0.061	0.021−0.060	0.023−0.092
s-w/d-w IHB length difference, $R' \neq H$	0.012−0.036	0.011−0.038	0.011−0.042	0.012−0.073
d-w/d-r IHB length difference, $R' = H$	0.002−0.040	0.001−0.020 mostly <0.010	0.001−0.020 mostly <0.010	0.002−0.040
u/non-u IHB length difference, O11 not on plane:				
linear R	0.002−0.005	0.002−0.040	0.003−0.030	0.006−0.030
branched alkyl R	0.028−0.072	0.033−0.110	0.032−0.083	0.026−0.105
IHB length increase when the other *ortho* OH is replaced by OCH_3	0.031−0.055	0.043−0.053	0.026−0.052	0.035−0.059
IHB length shortening due to the presence of a second acyl chain	0.013−0.055	0.013−0.053	0.013−0.051	0.009−0.049
IHB length increase due to the formation of a second IHB from donor/acceptor in the R chain	0.024−0.026	0.026−0.029	0.020−0.031	023−0.028
u/non-u conformers O•••O distance increase				
linear R	0.000−0.027	0.000−0.027	0.000−0.027	0.000−0.033
branched alkyl R	0.019−0.055	0.024−0.055	0.025−0.063	0.019−0.078
donor O−H bond elongation on formation of the IHB	0.012−0.018	0.009−0.017	0.007−0.016	0.000−0.008
d/s difference for the energy increase on IHB removal	0.98−2.25	0.54−2.80	0.90−2.38	1.54−3.30
Additional stabilization, by the solvent, of the conformer resulting from IHB removal:				
$R \neq H$, $R' = H$		2.33−2.57	3.33−3.79	6.21−6.99
$R \neq H$, $R' \neq H$, w/d-w pairs[d]		1.52−2.22	2.22−3.08	4.50−5.88
$R \neq H$, $R' \neq H$, r/s-r pairs[e]		2.14−2.69	3.16−3.79	6.08−7.17
$R' = H$/ $R' \neq H$ for a given R[f]		0.49−0.62	0.68−0.99	1.44−1.58
r/w forms of same structure, $R' \neq H$		0.3−0.8	0.4−1.0	1.1−2.1
energy increase on IHB removal:				
d/s difference[g]	0.98−2.25	0.54−2.80	0.90−2.38	0.52−3.30
increase due to a second acyl chain: $R = H$	3.807	4.095	3.817	2.081
$R = CH_3$	3.371	2.150	1.316	1.161
increase when three acyl chains are present	4.89−7.17	4.95−5.54	4.50−5.72	2.29−2.84

[a] When no indication is given, non-u conformers are considered. [b] Occasionally higher, like 7.7 for structure A. [c] Somewhat higher differences appear for the (unpopulated) u conformers. [d] Exceptions: structures A (higher than the shown range) and B-ET6 (lower than the shown range). [e] Exception: structure B-ET2 (lower than the shown range). [f] It is higher than these ranges for the F3/FF3 pair. [g] For caespitate (the structure with the bulkiest R′ among those investigated) the differences are 2.50_{vac},[25] 2.53_{chlrf}, 2.40_{actn}, and 3.42_{aq}. [h] Differences are indicated in the order as they are taken (e.g., s-r/d-r means that the difference is taken as "value corresponding to s-r minus value corresponding to d-r").

OH (Figure 2) with increasing solvent polarity ($\approx 1_{vac}$,[25,57] $0.4{-}0.6_{chlrf}$, $0.2{-}0.3_{actn}$, $0.0{-}0.2_{aq}$) and likely related to the greater accessibility of H15 for the formation of intermolecular H-bonds with solvent molecules, when it is oriented to the other side with respect to R′. On the other hand, this aspect does not influence the analysis of the characteristics and energy of the IHB, since its parameters are very close for r/w pairs and the evaluation of the energy increase on IHB removal is always carried out on d-w and s-r forms to prevent interferences by the shift from uniform to non-uniform orientation of the OH.

Table 3 shows a synoptic comparison of the most significant IHB-related features in the four media. Like in vacuo, the H-bond parameters (H•••O bond length, O•••O distance and $O\hat{H}O$ angle) are fairly similar for the same conformer-types across all structures, showing low influence from the nature of R. Greater influences appear when $R = H$ (what can be considered part of an overall different behavior of the CHO group) and for structures N and NN, containing an aromatic π system conjugated to C7═O11. Differently from in vacuo, structures L and LL, containing one π bond conjugated to C7═O11, and structure Q, containing a three-π-bonds linear system conjugated to C7═O11, do not differ significantly from the other structures in the three solvents.

The IHB length differs only slightly in vacuo and in the three solvents. It is often shorter in chloroform and acetonitrile than in water. The differences for different media are considerably smaller than the IHB length differences determined by geometry factors within each medium, like the d/s difference. Figure 3 shows the trends for the lowest-energy conformers of each type (d-r, d-w, s-r, and s-w when $R' \neq H$, d-r and d-w when $R' = H$).

The trends within each solvent appear similar to those observed in vacuo. When $R' \neq H$, the IHB on the same side as R′ is slightly shorter. When $R' = H$, the IHB length is close to that of the IHB forming on the other side with respect to R′ (s conformer) in the structure with the same R and $R' \neq H$. When two identical substituents are present at C3 and C5, the IHB length is often intermediate between the corresponding cases with $R' = H$ and $R' \neq H$ (e.g., for B-B35-ET4 and B-B35). Structures with $R' = H$ enable the isolation of the effect of the H15 orientation, making the IHB slightly shorter when oriented toward the same side.

The two O atoms and the H atom engaged in the IHB lie on the plane of the benzene ring for all non-u conformers of structures with linear R, in all the media. When R is branched, O11 is off-plane both in vacuo and in the three solvents, with greater deviations when the branching is at C12. For a given R, the greatest deviations correspond to structures with $R' \neq H$ and to s-r conformers. In the structures with R = isopropyl, O11 is 7.1−10.6°/EE2 and 9.7−23.1°/E2 off-plane, but despite this deviation, the IHB length is comparable to the corresponding structures with linear R (EE1 and E1 respectively) and may sometimes be shorter. For other branched R, deviations from

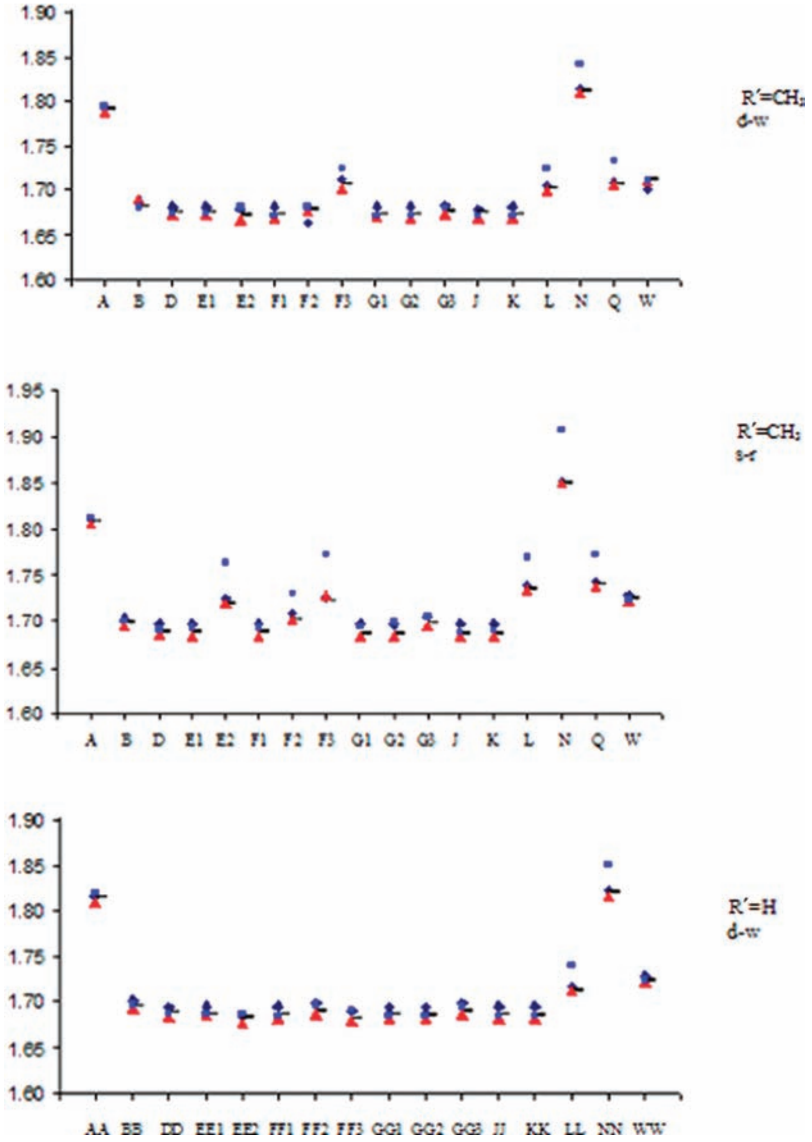


Figure 3. Comparison of the H-bond length in vacuo (diamond), in chloroform (bar), in acetonitrile (triangle), and in water (box) for d-w and s-r conformers of structures with R′ = CH_3 and for d-w conformers of structures with R′ = H. HF /6-31G(d,p) results.

planarity are associated with longer IHB. For R = isobutyl, the O11 off-plane deviation is greatest (7.4−11.6°/FF3 and 19.2−24.2°/F3) and the IHB lengths are the longest among the calculated structures with alkyl R′ ≠ H. Deviations are considerable also when R contains a π bond or π system conjugated to C7═O11 (17.0−23.2°/L and 29.6−35.1°/N). For a given structure, the O11 off-plane deviation is practically the same in vacuo, chloroform, and acetonitrile; it is greater in water for bulkier R, bulkier R′, or when an OCH_3 replaces the OH at C2 or C6.

The optimization of u-type inputs always yields u-type conformers in vacuo, whereas, in several cases in solution, the OH not engaged in the H-bond rotates “downwards” (away from the acyl chain) yielding the corresponding non-u conformer. Although u conformers are in any case scarcely populated, the consideration of their trends may contribute to the understanding of some steric influences. Deviations from planarity of the atoms forming the IHB appear, with similar values in all the media, in the u-conformers of structures with branched R (15.1−30.5° for O11) and in most s-type conformers of structures with linear R (12.0−18.3° for O11); they are greater when R contains a π bond or π system conjugated to C7═O11 (22.2−26.0°/L,LL and 25.1−33.7°/N,NN). While in vacuo the IHB length of a u conformer is always longer than the corresponding non-u one for R ≠ H (although by <0.010 for linear R), in solution it is often shorter for those cases when O11 does not deviate from planarity (D-d-r-$u_{chlrf,actn}$; D-d-w-u_{actn}, DD-r-$u_{chlrf,actn,aq}$, DD-d-w-$u_{chlrf,actn,aq}$, E1-d-w-$u_{chlrf,actn}$, EE1-d-r-$u_{chlrf,actn,aq}$, EE1-d-w-u_{chlrf}, F1-d-r-u_{chlrf}, F1-d-w-$u_{chlrf,actn}$, F1-s-w-u_{chlrf}, FF1-d-r-$u_{chlrf,actn,aq}$, FF1-d-w-$u_{chlrf,actn,aq}$, G1-d-r-u_{chlrf}, G1-d-w-$u_{chlrf,actn,aq}$, G1-s-w-u_{actn}, GG1-d-r-$u_{chlrf,actn}$, and GG1-d-w-$u_{chlrf,aq}$). When O11 deviates from planarity, the IHB length of the u conformer is longer than the corresponding non-u one. When R contains an aromatic system conjugated to C7═O11, the u conformer has a shorter IHB length than the non-u one in all the media, including vacuo (by 0.012−0.033).

The effects of important changes in the phloroglucinol moiety (different sizes of R′, replacement of an OH by an OCH_3 group, presence of more than one substituent) are similar to those observed in vacuo. They are illustrated in Figure 4 for structures with R = methyl and in Figure 5 for structures with R = isopropyl. When the size of R′ is greater than the model R′ = methyl, the IHB length decreases, both in vacuo and in the three solvents; however, the trends across different conformer-types

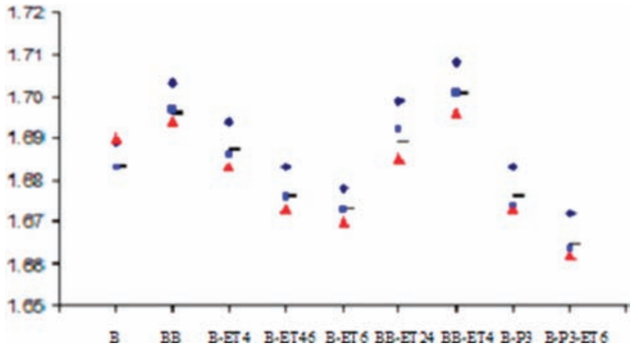


Figure 4. Comparison of the H-bond length in vacuo (diamond), in chloroform (bar), in acetonitrile (triangle), and in water (box) for the d-w conformers of structures with R = methyl and different R′. HF/6-31G(d,p) results.

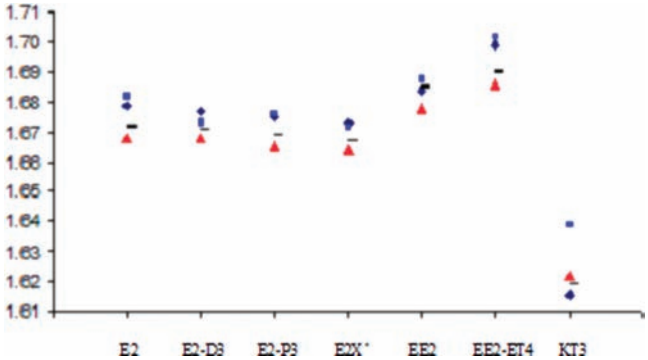


Figure 5. Comparison of the H-bond length in vacuo (diamond), in chloroform (bar), in acetonitrile (triangle), and in water (box) for the d-w conformers of structures with R = isopropyl and different R′. HF/6-31G(d,p) results.

of the same structure remain close to those identified through the mimicking methyl.

The effects of the replacement of a phenolic OH by an OCH_3 group are similar in all the media: IHB-length increase for replacement at C2 (with only H13 available for IHB); IHB-length decrease (mostly by ≤0.02) for replacement at C6 (with only H14 available for IHB); weaker effect for replacement at C4 (slight length increase when R′ ≠ H and slight decrease when R′ = H, mostly by <0.010).

The presence of additional acyl chains causes a shortening of the IHB with respect to the lowest energy conformer, in which the given chain is alone and the IHB has closest molecular-environment features. The shortening depends more on the size of the acyl chains and on the geometrical environment of the IHB and less on the medium, being very close in vacuo and in the three solvents for a given R chain and similar molecular environments. For a given conformer, the smallest shortening always pertains to water medium. In the same molecule, the shortening is greater for the acyl chain with smaller R. It is also greater when the IHB forms in the region between the two acyl chains; e.g., in BB-B3, where the two acyl chains are identical, it is considerably greater for the d-r case (0.053_{vac}, 0.051_{chlrf}, 0.050_{actn}, 0.047_{aq}) than for the s-w case (0.026_{vac}, 0.021_{chlrf}, 0.019_{actn}, and 0.016_{aq}). The presence of two additional acyl chains causes greater shortening: e.g., for A-COA35, the shortening with respect to A is 0.028_{vac}, 0.024_{chlrf}, 0.018_{actn}, and 0.012_{aq}; for B-COB35, the shortening with respect to B is 0.081_{vac}, 0.074_{chlrf}, 0.071_{actn}, and 0.066_{aq}.

The slight lengthening of the first IHB caused by the formation of a second IHB engaging donor/acceptor groups present in the R chain is very similar in all the media.

Differences in the O···O distance, with respect to in vacuo, are often considerably smaller than for the IHB length in the same conformer, mostly remaining below 0.012_{chlrf} and below $0.010_{actn,aq}$. Thus, the O···O distance remains close to 2.5 Å for all the structures and in all the media considered, except when R = H and for structures N and NN, where it is comprised between 2.6 and 2.7 in all the media. For u conformers, the O···O distance is slightly greater than for corresponding non-u ones when R ≠ H (with comparable increases across media) and smaller when R = H (by $0.006-0.028_{vac,chlrf,actn,aq}$) and when R contains an aromatic system conjugated to C7=O11 (by $0.010-0.025_{vac,chlrf,actn,aq}$).

The IHB angle does not change significantly in solution with respect to in vacuo; the difference does not exceed 1° (is slightly greater only for some u conformers).

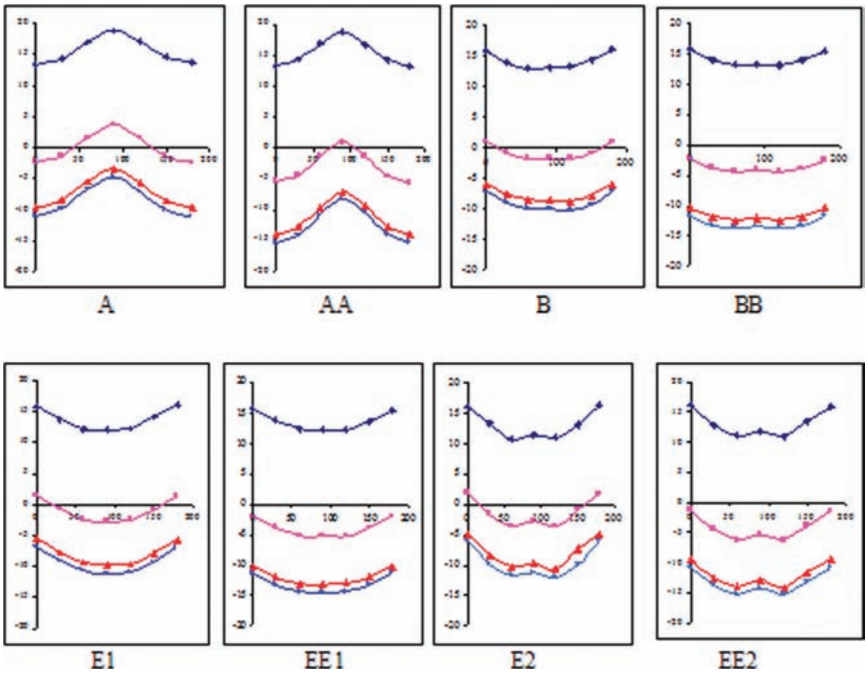
The presence of a keto group at C6 shows the same influences as in vacuo on conformational preferences and on the IHB parameters. The enhanced preference for d-w over d-r conformers leaves d-r conformers practically unpopulated in all the media (less than 0.3% population). The IHB length and O···O distance are considerably shorter than in fully enol structures. When R′ ≠ H (what, for these structures may imply one or two substituents at C3), the IHB length is 0.032−0.064/w and 0.013−0.045/r shorter in all the media (shown for KT3 in Figure 5), and the O···O distance 0.018−0.047 shorter. Structures in which all the substituents at C3 and C5 are removed show an increase in the IHB length, which, however, remains considerably shorter than those for fully enol structures with the same R and R′ = H. The atoms forming the IHB lie exactly on the plane in all the media, except for KT3, where O11 is slightly off-plane (3.4°/vac, 4.7°chlrf, 5.4°/actn, and 7.2°/aq for the lowest energy conformer).

The bond length of the donor O−H remains practically constant in all the media for a given structure when the IHB is present, while it increases slightly with the increase of the solvent polarity when the IHB is absent. The donor O−H bond elongation on formation of the IHB is greatest in vacuo and decreases as the polarity of the solvent increases; in two cases in water solution (AA and L), the O−H bond length decreases upon IHB formation.

3.3. The Strength of the Intramolecular Hydrogen Bond.

The estimation of the energy of intramolecular H-bonds is a challenging issue: the reference should be a conformer in which the IHB is removed, but the removal alters important energy-influencing features: even when it does not bring relevant changes in the rest of the molecule, it brings a sharp increase in the repulsion of the lone pairs of the two O atoms concerned.[58,59] In the case of phloroglucinol derivatives with an sp^2 O, the task is somehow facilitated by the behavior, on IHB removal, of the function containing the acceptor sp^2 O. The group rotates off-plane (with the only exception of the CHO group) until O11 reaches an orientation likely corresponding to optimal balance between the tendency to decrease the O ↔ O lone pair repulsion and the tendency to contain geometry-deformation energy.[19,28] The resulting smoothing of the O8 ↔ O11 or O10 ↔ O11 lone pair repulsion (and of the overall Coulomb repulsion between the partial negative charges of the two atoms) offers a viable option for comparing the IHB energy across different conformers and across different structures, in terms of energy increase on IHB removal ($\Delta E_{IHB\text{-}removal}$, the energy difference between the conformer resulting from IHB removal (no-IHB) and the starting conformer having the IHB).

The off-plane shift of O11 on IHB removal occurs also in solution and the similarity in its extent points to a similarity of



A AA B BB

E1 EE1 E2 EE2

Figure 6. Energy versus orientation of O11 in the absence of intramolecular H-bond, for selected structures. The rotations scan the C2C1C7O11 torsion angle from 0° to 180° in vacuo (diamond), in chloroform (box), in acetonitrile (triangle), and in water (circle). For each diagram, all the energy values are referred to the lowest energy conformer of the given structure, in vacuo. HF/6-31G(d,p) results.

the O ↔ O lone pair repulsion in vacuo and in the three solvents considered. For most structures, the angle of O11 with the plane does not differ by more than 4.0° in the four media. An additional confirmation of the similarities is offered by the scan of the rotation of the C1−C7 bond in the absence of the IHB (Figure 6), showing similar trends across structures with R ≠ H and close energy differences between maxima and minima for a given structure in all the media. The energy lowering for the off-plane orientation of O11 increases with the size/bulk of R. The diagrams also highlight the different behavior of the CHO group, having minima for planar orientation of O11 and a considerable barrier at 90°, whose height increases with the solvent polarity. Comparison of the O11 ↔ O8 Coulomb repulsion in structures A and B, and in structures AA and BB (i.e., the structures with R = H and the simplest structures with R ≠ H), based on the Mulliken charges on the O atoms, also highlights the energy-lowering effect of the off-plane shift of O11 in B and BB, decreasing the repulsion by 2.55_{vac}, 2.65_{chlrf}, 3.21_{actn}, and 4.18_{aq} for the B/A pair and by 0.96_{vac}, 5.54_{chlrf}, 2.56_{actn}, and 3.17_{aq} for the BB/AA pair.

To exclude the risk that conformers with off-plane O11 would result merely from the use of in-vacuo-optimized geometries as inputs for PCM calculations, separate calculations independently implying IHB removal in solution (calculations, in whose inputs O11 was on the plane and H13 or H14 oriented "downwards" to remove the IHB) were performed for selected structures. Out of 21 structures tested in this way (with both r and w conformers considered for each structure), O11 rotates off plane in all the cases in water solution, and in most cases in acetonitrile and chloroform; the few exceptions correspond all to w forms and linear R (B-w, D-w, FF1-w in acetonitrile, B-w, BB-w, D-w, EE1-w and F1-w in chloroform). These exceptions were utilized to evaluate the overestimation of the energy increase on IHB removal, if referred to conformers in which O11 is not shifted off-plane (by comparison with the estimations referred to the conformers resulting from full in-solution reoptimization of in-vacuo-optimized geometries without the IHB and with O11 off-plane). The overestimation is $3.0-4.1_{\text{actn}}$ and $2.5-4.0_{\text{chlrf}}$ and is comparable to the $2.6-5.2_{\text{vac}}$[19] that had been evaluated on geometries with O11 frozen at the same angle as when it is engaged in the H-bond. Since the overestimation is related to the O ↔ O lone pair repulsion, the similarity of its ranges further confirms the similarity of the effects of the O ↔ O lone pair repulsion in vacuo and in the three solvents considered.

An important difference between in vacuo and in solution appears for the meaning of $\Delta E_{\text{IHB-removal}}$. The values in vacuo can be considered the best approximation to the IHB energy attainable from computational results (although it is not easy to evaluate how close they might be to the true IHB energy), because no external factors interfere with the energy difference between the two conformers (with and without the IHB) considered for the evaluation. In solution, the stabilization by the solvent is greater for the no-IHB conformer than for the conformer with the IHB;[26] therefore, the difference between the energies of the two conformers is due not only to factors "inner" to the molecule (IHB removal, geometry change on the off-plane shift of O11, O ↔ O lone pair repulsion) but also to an "external" factor (the solvent stabilization) that is different for the two conformers. While the "inner" factors appear to have similar weights in all the media (as highlighted also by the similarities in the O11 off-plane shift), the external factor is different for different media.

The values of the additional stabilization, by the solvent, of the no-IHB conformers (coinciding with the decrease of $\Delta E_{\text{IHB-removal}}$ in each solvent with respect to in vacuo) are reported in Tables 4 and 5. The additional stabilization increases with increasing solvent polarity and with the solvent ability to form stronger intermolecular H-bonds with the solute molecule (because the removal of the IHB makes the OH available for intermolecular H-bond[19,27,28]). For individual structures, it is 0.7−1.2 greater in acetonitrile than in chloroform, and 2.8−3.7/w and 3.1−4.6/r greater in water than in chloroform. Its dependence on the molecule's structural and geometry features in the

TABLE 4: Additional Solvent Stabilization ($\Delta E_{\text{solv-stab}}$) of the Conformer Resulting from Intramolecular H-Bond Removal, for Structures with $R' = H$, HF/6-31G(d,p) Results[a]

	$\Delta E_{\text{solv-stab}}$		
structure	in chloroform	in acetonitrile	in water
AA	2.756	4.106	6.998
BB	2.405	3.404	6.244
BB-ET24	2.268	3.343	6.584
BB-ET4	2.345	3.420	6.308
DD	2.433	3.459	6.264
EE1	2.463	3.475	6.375
EE1-ET4	2.404	3.474	6.419
EE2	2.297	3.398	6.302
EE2-ET4	2.401	3.487	6.439
FF1	2.435	3.464	6.319
FF2	2.331	3.332	6.209
FF3	2.335	3.498	6.431
GG1	2.426	3.445	6.334
GG2	2.476	3.481	6.359
GG3	2.382	3.376	6.259
JJ	2.470	3.511	6.390
KK	2.438	3.452	6.328
LL	2.524	3.794	6.895
NN	2.574	3.579	6.340
KTT3	4.712	6.728	10.769

[a] $\Delta E_{\text{solv-stab}}$ is evaluated as the difference between the solvent stabilization of the conformer resulting from IHB removal and the solvent stabilization of the corresponding conformer with the IHB (lowest energy d-w conformer of each structure).

TABLE 5: Additional Solvent Stabilization ($\Delta E_{\text{solv-stab}}$) of the Conformer Resulting from Intramolecular H-Bond Removal, for Structures with $R' \neq H$, HF/6-31G(d,p) Results[a]

	$\Delta E_{\text{solv-stab}}$ in chloroform		$\Delta E_{\text{solv-stab}}$ in acetonitrile		$\Delta E_{\text{solv-stab}}$ in water	
structure	w/d-w	r/s-r	w/d-w	r/s-r	w/d-w	r/s-r
A	3.245	2.820	4.300	4.133	6.291	7.017
B	1.869	2.515	2.723	3.434	4.805	6.637
B-ET2		1.287		1.933		4.343
B-ET4	1.912		2.681		4.823	
B-ET46	1.524		2.336		4.742	
B-ET6	0.475		0.823		2.716	
B-P3	2.055	2.621	2.822	3.581	5.566	6.723
B-P3-ET2		2.137		3.240		6.081
B-P3-ET6	1.860		2.522		5.442	
B-B35-ET4	2.241		3.066		5.876	
D	1.874	2.498	2.754	3.549	4.814	6.951
E1	1.882	2.266	2.728	3.253	4.859	6.584
E1-ET4	1.893		2.707		4.944	
E2	1.854	2.308	2.735	3.280	4.846	6.341
E2-D3	1.848	2.236	2.715	3.273	5.441	6.562
E2-P3	1.938	2.556	3.083	3.651	5.711	6.810
E2X′	2.218	2.432	2.988	3.505	5.879	5.673
E2-B35	1.798		2.553		5.260	
F1	1.891	2.285	2.745	3.250	4.834	6.530
F2	1.808	2.255	2.653	3.220	4.707	6.350
F3	1.705	2.216	2.512	3.158	4.497	6.151
G1	1.882	2.182	2.726	3.308	4.885	6.579
G2	1.863	2.279	2.718	3.246	4.894	6.552
G3	1.805	2.173	2.654	3.067	4.700	6.349
J	1.881	2.512	2.745	3.627	4.864	6.970
K	1.882	2.277	2.754	3.274	4.849	6.523
L	2.060	2.595	3.114	3.790	5.412	7.169
N	2.050	2.685	2.900	3.674	4.757	6.219
Q	1.906	2.534	2.893	3.689	5.099	6.893
W	1.683	2.361	2.354	3.401	5.056	6.840
W-ET46	1.540		2.220		5.170	
KT1	3.872		5.770		9.047	
KT2	3.937		5.777		9.061	
KT3	3.861		5.509		9.157	
KT4	2.894		4.084		7.162	

[a] $\Delta E_{\text{solv-stab}}$ is evaluated as the difference between the solvent stabilization of the conformer resulting from IHB removal and the solvent stabilization of the corresponding conformer with the IHB (lowest energy d-w and s-r conformers of each structure).

two polar solvents can also be related to the possibility of formation of solute−solvent intermolecular H-bond. It is higher for $R = H$, presumably because of the greater overall accessibility of the sites capable of forming intermolecular H-bond with solvent molecules in the absence of the hydrophobic zone corresponding to $R \neq H$. It is higher for $R' = H$ than for $R' \neq H$ (with the exception of $CHO_{\text{chlrf,actn}}$), because of the greater accessibility of H15 and the free H14 when $R' = H$. When $R' \neq H$, it is higher for w/d-w pairs than for r/s-r pairs, presumably because of the better stabilization of the d-w conformer with respect to the s-r conformer, in view of the greater accessibility of free H13 (in d) than free H14 (in s), when $R' \neq H$.

Despite these complications depending on solvent effects and solvent stabilization, the trends identified within each medium are similar to those identified in vacuo,[19] nearly suggesting a considerable "medium-independence" of the IHB. Within each medium, the values of $\Delta E_{\text{IHB-removal}}$ are fairly close for most R, showing a comparatively scarce dependence on the nature of R (with the usual exceptions for $R = H$ and for R containing a π bond or π system conjugated to C7=O11). When $R' \neq H$, $\Delta E_{\text{IHB-removal}}$ is greater for the IHB forming on the same side as R′, and the difference is greater for greater/bulkier R′. When $R' = H$, it is close to the s-type of the structure with the same R and $R' = CH_3$. When two identical substituents are present at C3 and C5, it is intermediate between the values of the structures with $R' = H$ and $R' = CH_3$ and the same R.

As far as the influence of "inner" factors is concerned, the interference, on $\Delta E_{\text{IHB-removal}}$ evaluation, by changes in known geometry-related factors is prevented through apt conformers' selection.[19] The interference by shifts from uniform to non-uniform orientation of the phenolic OH on IHB removal is prevented by selecting starting conformers with non-uniform orientation (d-w and s-r); this also improves the viability of across media trends-comparisons, as it removes a factor whose influence is different in different media (greater in vacuo and decreasing as the polarity of the solvent increases). When $R' \neq H$, the interference by removal of a C−H···O non-classical H-bond,[60] simultaneously to the IHB removal, is prevented by selecting d-w conformers having the non-classical H-bond with O9 (not with O8).

Figure 7 highlights the trends of $\Delta E_{\text{IHB-removal}}$ when the IHB is removed from the lowest energy d-w and s-r conformers of structures with $R' \neq H$ and from the lowest energy d-w conformers of structures with $R' = H$. The values for structures A and AA have been included in the diagram to show the changes in the three solvents with respect to in vacuo; however, they cannot be compared with the values of the other structures, because of the overestimation due to the inclusion of $O \leftrightarrow O$ lone pairs repulsion, inherent to the fact that O11 does not shift off-plane on IHB removal when $R = H$; the actual energy of the IHB for $R = H$ is weaker than for alkyl $R \neq H$,[61] as indicated also by its greater length. An attempt to evaluate the overestimation specifically for $R = H$ considered the two possible no-IHB conformers of 2-hydroxybenzaldehyde (Figure 8), ascribing all their energy difference to the presence (conformer c) or absence (conformer b) of the $O \leftrightarrow O$ repulsion. The energy

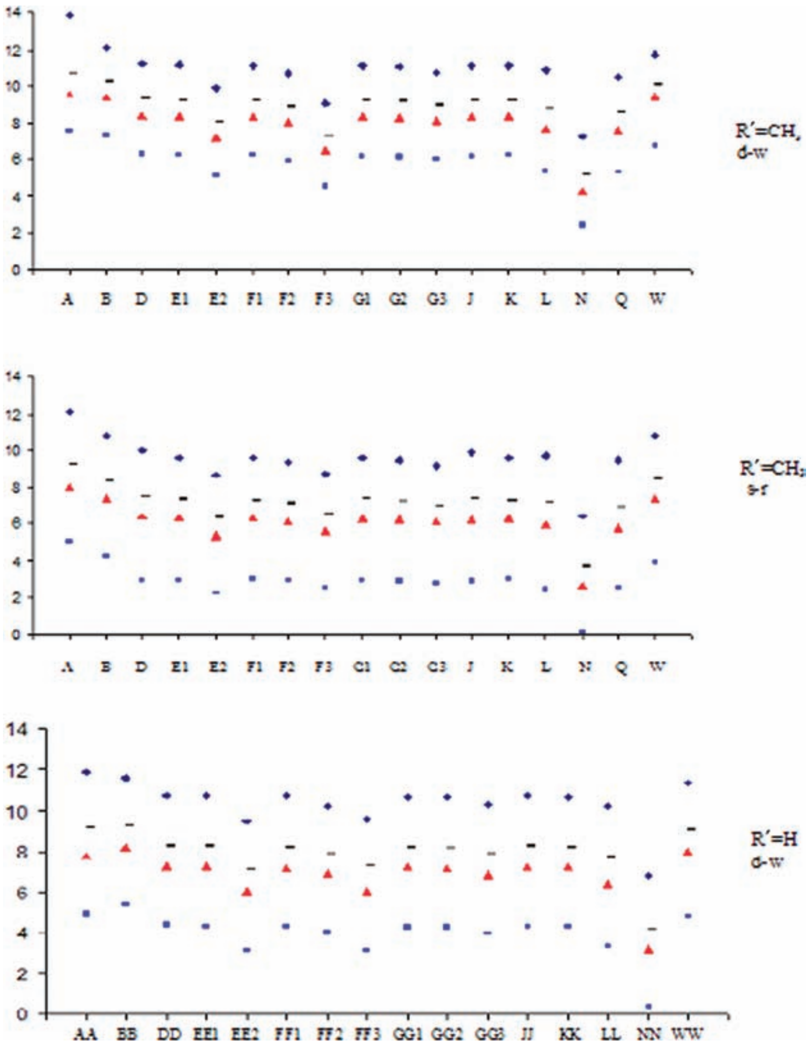


Figure 7. Comparison of the energy increase on intramolecular H-bond removal in vacuo (diamond), in chloroform (bar), in acetonitrile (triangle), and in water (box), for d-w and s-r conformers of structures with R′ = CH_3 and for d-w conformers of structures with R′ = H. HF/6-31G(d,p) results. The values for structures A and AA are included to show the effect of the media; however, they cannot be compared with the values of the other structures because of the overestimation due to the permanence of O11 on the plane.

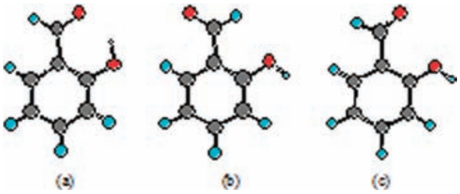


Figure 8. The three conformers of 2-hydroxybenzaldehyde. Of the two conformers without the IHB, the O ↔ O lone pair repulsion is removed in (b) and is maximum in (c).

difference is 4.29_{vac}, 3.40_{chlrf}, 2.97_{actn}, and 2.39_{aq} from HF/6-31G(d,p) results, 2.97_{vac}, 2.31_{chlrf}, 1.98_{actn}, and 1.41_{aq} from MP2/6-31+G(d,p) results, and 2.84_{vac}, 2.20_{chlrf}, 1.89_{actn}, and 1.32_{aq} from B3LYP/6-31++G(d,p) results. The enthalpy difference (calculated to compare with the 2.7_{vac} IHB enthalpy overestimation reported from a B3LYP/6-31G(d,p) study in vacuo[56]) is 4.21_{vac}, 3.37_{chlrf}, 2.96_{actn}, and 2.41_{aq} from HF/6-31G(d,p) results, and 2.80_{vac}, 2.19_{chlrf}, 1.90_{actn}, 1.35_{aq} from B3LYP/6-31++G(d,p) results. Although the overestimation for structures A and AA cannot be the same as for 2-hydroxybenzaldehyde, because of the effect of the second OH in ortho to the CHO group, these values (that are also comparable with the ranges found for R ≠ H) can be considered the best attainable approximation to it (a similar comparison for structures A and AA would not be possible, because the presence of the OH at C6 prevents the possibility of a no-IHB conformer like b).

The heights of the rotational barriers for the removal of the IHB trough 180° rotation of the donor group (Figure 9) highlight trends fairly similar to those of $\Delta E_{\text{IHB-removal}}$. In vacuo and in water, the height of the barrier is greater than $\Delta E_{\text{IHB-removal}}$ and the values of the two quantities are significantly closer for R′ ≠ H ($0.3-1.4_{\text{vac}}$, $0.1-1.8_{\text{aq}}$ difference) than for R′ = H ($1.9-3.4_{\text{vac}}$, $2.3-3.2_{\text{aq}}$ difference). In chloroform and acetonitrile, the height of the barrier may be greater or smaller than $\Delta E_{\text{IHB-removal}}$ (differing by $0.0-1.4_{\text{chlrf}}$, $0.2-1.6_{\text{actn}}$).

The part of the rotational curves after the barrier shows a difference in the energy aspects after IHB removal between structures with R′ = H and with R′ = CH_3. For R′ = H, a new minimum is attained when H14 lies on the plane, completing the 180° rotation for IHB removal. For R′ ≠ H, H14 prefers an off-plane orientation (≈30°, greater in water), probably because of steric interferences with R′; this, however, does not correspond to optimal energy for the orientation of phenolic OH, that prefer to lie on the plane,[57] as shown by the scan of the rotation of the OH in the parent compound (Figure 10); the effect on the no-IHB conformer energy (an energy-raising contribution related to geometry features) might affect the evaluation of $\Delta E_{\text{IHB-removal}}$, toward overestimation. When R′ =

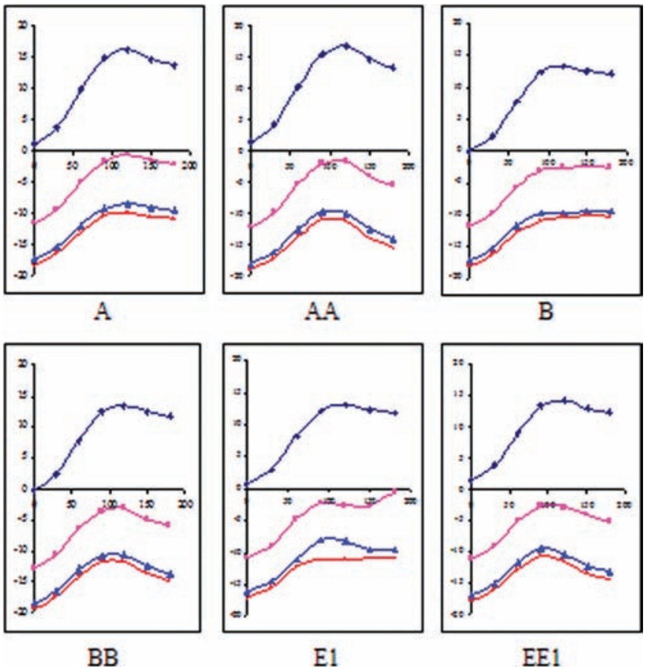


Figure 9. Energy barriers for the rotation of H14 in vacuo and in the three solvents, removing the intramolecular H-bond from selected structures. HF /6-31G(d,p) results. The rotations scan the C1C2O8H14 torsion angle from 0° (when H14 is engaged in the H-bond) to 180° in vacuo (diamond), in water (bar), in chloroform (box) and in acetonitrile (triangle). For each diagram, all the energy values are referred to the lowest energy conformer of the given structure, in vacuo.

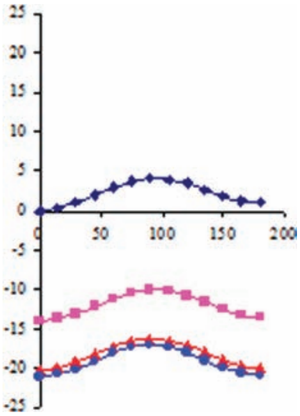


Figure 10. Energy versus orientation of a phenolic OH with respect to the plane of the benzene ring in the C_{3h} conformer of 1,3,5-trihydroxybenzene, in vacuo (diamond), in chloroform (box), in acetonitrile (triangle), and in water (circle). HF/6-31G(d,p) results. The rotations scan the torsion angle of the OH from 0° to 180°.

H, the difference between the maximum of the barrier and the minimum corresponding to no-IHB increases with the polarity of the solvent and appears to depend also on the size of R (e.g., it is 3.411_{vac}, 3.816_{chlrf}, 4.249_{actn}, and 4.383_{aq} for AA, 1.765_{vac}, 2.675_{chlrf}, 2.992_{actn}, and 3.116_{aq} for BB, 1.804_{vac}, 2.430_{chlrf}, 3.813_{actn}, and 3.913_{aq} for EE1); since the barriers for the parent compound are very close in all the media (4.126_{vac}, 3.933_{chlrf}, 3.917_{actn}, and 3.988_{aq}), the different pattern of acylphloroglucinols can be ascribed to the presence of the COR group.

While the heights of the barriers for the IHB removal by 180° rotation of the donor group are considered informative about the IHB energy,[62] the removal of the IHB through 180° rotation of the acceptor group can be more complicated. In the case of acylphloroglucinols, it is often impossible to isolate the rotation of the acceptor group, because of the simultaneous “downward” rotation of the donor OH, as O11 “moves away” from the engagement in the IHB.

Influences by relevant features of the phloroglucinol moiety are better identified on different structures with the same R: Figure 11 compares $\Delta E_{\mathrm{IHB\text{-}removal}}$ for different structures with R = methyl and Figure 12 for different structures with R = isopropyl. Both the size/bulk and the geometry of R′ appear to influence $\Delta E_{\mathrm{IHB\text{-}removal}}$. There is no immediate correspondence between the size of R′ and its influence, likely because of a variety of factors, from simultaneous influences of geometry and steric factors to the impossibility of the IHB length to vary largely, because of the constraints from the aromatic ring.

$\Delta E_{\mathrm{IHB\text{-}removal}}$ increases if additional acyl chains, also forming an IHB, are present, and additional chain contributes to further increase. For structure A-COA35 (the only structure with three acyl chains from which the three IHB can be removed simultaneously, because of the on-plane permanence of O11), the overall energy increase on simultaneous removal of the three identical IHB is 50.397_{vac},[19] 43.10_{chlrf}, 39.98_{actn}, and 29.86_{aq}, yielding 16.80_{vac}, 14.37_{chlrf}, 13.33_{actn}, and 9.95_{aq} contribution for each IHB. These values are respectively 2.93_{vac}, 3.74_{chlrf}, 3.76_{actn}, and 2.37_{aq} higher than the corresponding values when the CHO group is alone in structure A. The assignment of these differences solely to IHB energy increase, within each medium, is justified by the absence of changes in other potentially influencing factors, on IHB removal, and by the fact that the overestimation due to the permanence of the sp^2 O on the plane (corresponding to highest O ↔ O lone pair repulsion) can be considered the same for each of the three IHB in A-COA35 and for the IHB in A. The shorter IHB lengths in A-COA35 with respect to A also support the interpretation.

The replacement of an ortho phenolic OH by an OCH_3 group may influence $\Delta E_{\mathrm{IHB\text{-}removal}}$ significantly. For structures B-ET2 and B-ET6, the values in solution are closer to those in vacuo than for the other structures, respectively remaining 1.049_{chlrf}, 1.397_{actn}, 1.992_{aq} higher than the upper range for the d-w cases of other structures and 0.85_{chlrf}, 1.134_{actn}, 1.738_{aq} higher than the upper range for the s-r cases of other structures. This may be associated with the smaller additional stabilization by the solvent of the no-IHB conformer (Table 4), probably due to steric effects affecting accessibility by solvent molecules, including lesser accessibility of an ether O than a hydroxyl O, and to the weaker ability of the ether O to make intermolecular H-bonds with solvent molecules.

The formation of a second H-bond from the R chain does not influence $\Delta E_{\mathrm{IHB\text{-}removal}}$ for the first IHB significantly, in any medium.

For the selected structures with a keto group at C6, the IHB is stronger than when the phloroglucinol moiety has full enol form; however, $\Delta E_{\mathrm{IHB\text{-}removal}}$ decreases faster than for fully enol forms, as the solvent polarity increases: e.g., it is 16.753_{vac}, 12.880_{chlrf}, 10.983_{actn}, and 7.706_{aq} for KT3 and 18.730_{vac}, 15.252_{chlrf}, 13.380_{actn}, and 10.602_{aq} for KT4-r.

PCM calculations at MP2/6-31+G(d,p) level were performed only for A, AA, B, BB, D, DD, and EE2 (being unaffordable for bigger structures). The addition of the diffuse orbitals in the basis set responds to their importance for the quality of H-bonding description. The MP2/6-31+G(d,p) results give shorter IHB length (1.585−1.641 in all the media, except for structures A and AA where it is 1.707−1.737) and smaller $\Delta E_{\mathrm{IHB\text{-}removal}}$, which suggests an overestimation by HF (by

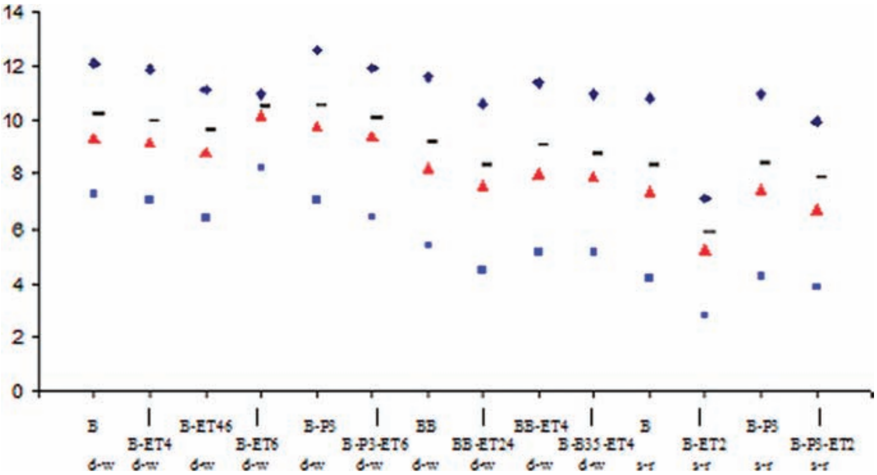


Figure 11. Comparison of the energy increase on intramolecular H-bond removal for structures with R = methyl and different R′, in vacuo (diamond), in chloroform (bar), in acetonitrile (triangle), and in water (box). HF/6-31G(d,p) results. The type of conformer from which the H-bond is removed is indicated under the symbol of each structure.

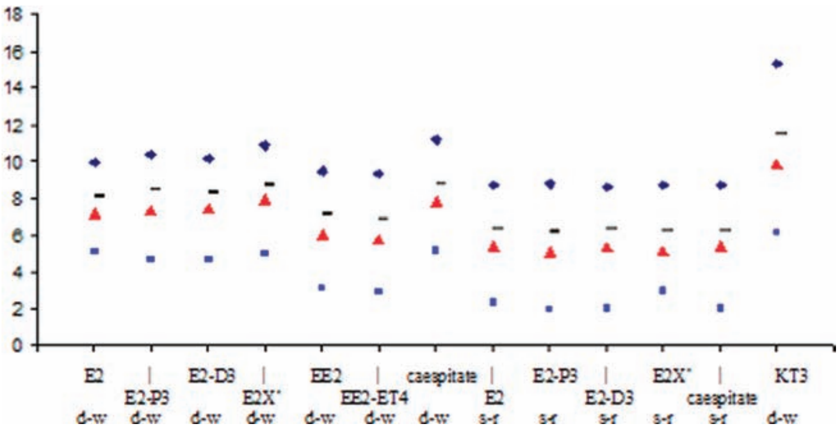


Figure 12. Comparison of the energy increase on intramolecular H-bond removal for structures with R = isopropyl and different R′, in vacuo (diamond), in chloroform (bar), in acetonitrile (triangle), and in water (box). HF/6-31G(d,p) results. The type of conformer from which the H-bond is removed is indicated under the symbol of the structure.

$1.536-2.075_{\text{vac}}$, $1.496-2.485_{\text{chlrf}}$, $1.259-1.954_{\text{actn}}$, and $1.351-2.367_{\text{aq}}$) except for AA, where the difference is negligible, and for A_{actn}, where $\Delta E_{\text{IHB-removal}}$ from MP2/6-31+G(d,p) is slightly higher than that from HF/6-31G(d,p)). The trends remain fairly similar, both across different conformers-types and across media.

A test comparison was also carried out for 2-hydroxybenzaldehyde in the same four media: the results of the two methods are very close for the relative energy of conformer *c*, whereas the relative energy of conformer *b* is 0.9−1.2 higher in the MP2/6-31+G(d,p) results, maintaining, however, fairly similar trends across the media.

The issue of the IHB strength in the four media requires deeper analysis. As noted earlier, the different solvent effects on the two conformers (with and without the IHB) utilized for the evaluation of $\Delta E_{\text{IHB-removal}}$ prevent the possibility of considering it as a realistic approximation to the IHB energy in solution. The greater stabilization of the no-IHB conformer suggests that the IHB energy may be greater than $\Delta E_{\text{IHB-removal}}$. However, it is not easy to find criteria enabling a reasonable approximation to the IHB energy in solution, and experimental techniques are also absent.[56] Quantities that are normally viewed as informative on H-bonds strengths, like the H-bond length[63] or the red shift,[63] may also require deeper analysis when considered in solution.

Although the IHB length variability in acylphloroglucinols is somewhat restrained by the rigidity of the benzene ring, the results in vacuo show fair correlation between weaker IHB (like for the case of the CHO group, or structures containing π bonds or systems conjugated to C7═O11) and longer IHB length. On the basis of the IHB lengths alone (Figures 3, 4, and 5), the IHB strength in solution would not appear very different from that in vacuo. There are no identifiable relationships between the IHB length changes in solution and the $\Delta E_{\text{IHB-removal}}$ changes: actually, the IHB length often decreases in solution, but $\Delta E_{\text{IHB-removal}}$ is always considerably smaller in solution than in vacuo. All this confirms that the major factor influencing $\Delta E_{\text{IHB-removal}}$ is "external" (due to the different solvent stabilization of the conformers with and without the IHB).

A similar phenomenon occurs with the IR frequencies lowering of the donor O−H, usually termed red shift and calculated as difference with the frequency of a free O−H (taken as O9−H15 in the current study). The red shifts in vacuo are fairly correlated to $\Delta E_{\text{IHB-removal}}$; e.g., they are smaller for R = H than for R ≠ H and considerably greater when the OH at C6 is replaced by a keto group, with respect to the fully enol structures. Calculating the red shift with respect to the frequency of the same reference O−H in solution leads to considerable smaller values, with greater decreases as the solvent polarity increases ($6.5-9.3_{\mathrm{vac}}$, $4.6-8.9_{\mathrm{chlrf}}$, $3.7-8.7_{\mathrm{actn}}$, $0.7-6.3_{\mathrm{aq}}$). However, what is considerably lowered in solution is the reference itself (the frequency of the free O−H). The consideration of the actual lowering of the IR frequency of the O−H engaged in the IHB, with respect to in vacuo, shows that the solvent effect on it is much weaker than those on the free O−H: $0.00-0.58_{\mathrm{chlrf}}$, $0.03-1.04_{\mathrm{actn}}$, $0.23-1.03_{\mathrm{aq}}$.

The similarity of the two phenomena is obvious: in both cases, the estimation of a difference shows considerable decreases in solution because of the solvent effect on the reference: the greater stabilization of the no-IHB conformer utilized as reference for the evaluation of $\Delta E_{\mathrm{IHB\text{-}removal}}$ and the greater lowering of the IR frequency of the free O−H utilized as reference for the red shift evaluation. It may therefore be worthy to ascribe more importance, as IHB-strength indicator, to a quantity that is not evaluated as difference, e.g., the IHB length. Since a potentially IHB-weakening factor is the competition with the possibility of formation of intermolecular H-bonds with the solvent molecules, the results of calculations of adducts with explicit water molecules were considered for selected acylphloroglucinols (caespitate,[27] some preliminary results of an ongoing separate study, and also the carboxylic acid of phloroglucinol[28]), because of their explicitly taking into account the competition by water molecules: these results show that the IHB length does not increase significantly in the adduct (actually, it is often shorter in the adduct than in vacuo), which points to no weakening of the IHB by the solvent; moreover, they show that the region of the IHB is hydrophobic; i.e., water molecules do not approach the area of the IHB and thus do not compete for the H atom tightly embedded between the carbonyl and the hydroxyl O atoms in these compounds (while they "open" weaker IHB like the second IHB in caespitate[27] or the weak IHB denoted as ξ in the study of the acid[28]).

Another quantity that is not evaluated as difference (and, therefore, does not depend on different solvent effects on the evaluation reference) is the charge on the atoms engaged in the IHB. Their significance is related to the largely electrostatic nature of H-bonding. The calculated Mulliken charges do not decrease in solution, suggesting that at least the electrostatic component of the IHB interaction does not decrease in solution. Other computed properties also point to a lower effect by the solvent on the IHB region than on the other parts of the molecule, e.g., the lower effect on the bond length of the O−H engaged in the IHB than on that of the free O−H, mentioned in section 3.2.

These considerations cannot be generalized to all types of IHB (as clearly shown by the recalled cases of weaker IHB that break in solution to enable the formation of intermolecular H-bonds with solvent molecules). It appears however reasonable to suggest the possibility (or even probability) that the IHB characterizing acylphloroglucinols (and other phloroglucinol derivatives with an sp^2 O, like the carboxylic acid) may not be particularly weakened in solution, including in polar and H-bond donor/acceptor solvents like water. The suggestion is here limited to phloroglucinol derivatives because some of the factors supporting it appear to be closely associated with their structural characteristics; e.g., the hydrophobicity of the IHB region is probably associated with (or enhanced by) the sequence and proximity of H-bond donor/acceptor sites in their molecules, enabling arrangements of water molecules that leave the IHB region undisturbed[28]).

4. Discussion and Conclusions

PCM calculations, in chloroform, acetonitrile, and water, of a representative number of model and actual structures, covering the most frequent types of R in the COR group and considering different structural and geometry features for the phloroglucinol moiety, show only limited influence, by the solvent, on the characteristics of the IHB characterizing acylphloroglucinols. The main trends identified in vacuo[19] are confirmed in all three solvents considered: the fundamental role of the IHB in determining conformational preferences and energy, and its presence in all populated conformers; the low influence on its characteristics and energy by the nature and geometry of R (significant difference appearing when R = H or when R contains a π bond or system conjugated to C7=O11); the preference for the H-bond to form on the same side of a substituent R′ in meta to COR; the off-plane shift of O11 on H-bond removal, minimizing the O ↔ O lone pair repulsion; a considerable increase in the H-bond strength when the other ortho OH is replaced by a keto function. The geometry parameters of the IHB are not significantly affected by the solvent: the changes due to the different solvents are smaller than those due to geometry changes in the molecule (e.g., changes in the orientation of the free OH groups, or presence or absence of a substituent at C3).

Differences in the behavior of the CHO group (longer and weaker IHB; no off-plane shift of O11 on IHB removal) appear in all the media. It is worthy noting it because the CHO group is present in many acylphloroglucinols as a second or third acyl chain adding to a chain with a longer R. Calculations of larger structures in which it is present as additional acyl chain show that its behavior remains the same and, therefore, its peculiarities can be considered general for a CHO group attached to a phloroglucinol moiety.

The estimation of the IHB strength/energy is complicated by the greater solvent stabilization of the no-IHB conformer with respect to the conformer with the IHB, determining a decrease in the energy gap between the two conformers in solution that is not directly related to the IHB. This prevents the consideration of the energy gap in solution as a realistic approximation of the IHB energy (although its trends may still be considered representative of the trends of the IHB energy) because its values are differences between terms that are differently affected by the solvent. Similarly, conventional evaluation of the red shift in solution cannot be related to the IHB energy, because of the greater solvent effect on the frequency of the free O−H utilized as reference. The consideration of quantities (like the IHB length) that are not evaluated as differences and are, therefore, independent of the solvent effect on the reference, suggests that, for this class of compounds, the IHB might not be significantly weakened in solution. The results of calculations of adducts with explicit water molecules support this suggestion, showing a broad hydrophobic region around the IHB (implying that the solvent molecules do not approach the IHB), whose extent is likely related to the distribution of H-bond donor/acceptor sites in acylphloroglucinols molecules. Although the hypothesis cannot be extended to other classes of compounds without specific investigation, it might be viable for classes of compounds for which analogous phenomena are observed (e.g., both the decrease, in solution, of the energy gap between the conformers with and without the IHB[64] and the lack of any correlation, in solution, between IHB lengths and the IHB enthalpies evaluated as differences between the enthalpies of the conformers with and without the IHB, have been reported[56] for 2-substituted phenols capable of forming IHB). It is also suggested that, in general, the consideration of adducts with explicit molecules of a solvent capable of competing for H-bond formation may contribute interesting information on the situation of an IHB in that solvent.

Despite selecting the smallest existing structures with a given R and using CH_3 to mimic long substituent chains attached to the phloroglucinol moiety, the calculated structures are generally medium size, which imposes careful attention to computational affordability. Calculations were carried out at HF/6-31G(d,p) level, as the more affordable option for a large number of non-small structures and with the additional demands of PCM reoptimization in solution. Calculations of the smaller structures at MP2/6-31+G(d,p) show fair similarities between trends for the two levels of theory, supporting the reliability of the identification of trends from HF/6-31G(d,p) results (which also suggests that the cancellation of errors in HF/6-31G(d,p) calculations may be particularly fortunate for this class of compounds).

Acknowledgment. The authors wish to express their gratitude to Professor Maurizio Persico, of the Department of Chemistry and Industrial Chemistry of the University of Pisa (Italy), for his fundamental technical assistance and to Dr. Caterina Ghio and Dr. Giuliano Alagona, of the Institute for Physico-Chemical Processes - Molecular Modelling Lab (Pisa), for a number of fruitful interactions. L. Mammino is grateful to the South African National Research Foundation (NRF) for a research grant. Mwadham M. Kabanda is grateful to NRF for a 2007−2009 PhD African Scholarship Bursary enabling him to participate in this work.

Supporting Information Available: Tables with all the numerical values of the relevant quantities (parameters of the IHB, elongation of the O−H bond engaged in the IHB, charges on the atoms forming the IHB, energy increase on IHB removal, calculated IR frequencies, comparison of MP2/6-31+G(d,p) and HF/6-31G(d,p) results for the structures for which MP2/6-31+G(d,p) calculations were affordable, results for the calculations of 2-hydroxybenzaldehyde) and tables of relevant differences, meant to facilitate quick comparisons and analysis, a diagram expanding the comparison of the IHB length with respect to the text, and a diagram highlighting trends for the O···O distance. This information is available free of charge via the Internet at http://pubs.acs.org.

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JP905180C