Performance of Different Calculation Methods: Indications from the Study of Various Classes of Polyphenols

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***Abstract*—**The selection of the computational method that can be optimal for the molecule or class of molecules under study is a crucial issues in computational chemistry. When the molecules are not small, the search for an optimal balance between results accuracy and computational costs becomes a key aspect. Useful indications may be provided by the identification of patterns in the performance of different calculation methods. The present work compares the performance and the computational costs of three methods (HF, DFT/B3LYP and MP2), on the basis of the results of extensive studies of three classes of polyphenolic compounds (hydroxybenzenes, their carboxylic acids, and acylphloroglucinols). It is concluded that HF has considerably lower computational cost for middle-size molecules; that it can be considered a reasonable method, above all for studies aimed at trend identification; and that independent verification of its performance for any new class of molecules is to be recommended.

Keywords—Computational cost, Computational methods, Density Functional Theory, Hartree Fock, Møller Plesset Perturbation Theory.

I. Introduction

MOLECULAR calculations can be performed with different approaches and at different levels of theory. Electronic structure methods [1], based on quantum mechanics, are preferable whenever the size of molecules allow their use [2], because of their better descriptive abilities. Calculations become more expensive as the molecule size increases, as the basis set size increases, and as the algorithm of the level of theory becomes more demanding. On the other hand, the accuracy of the results increases as the basis set size increases, and as the level of theory is more sophisticated. For sufficiently small molecules, the most sophisticated levels of theory and large basis sets are easily affordable. However, as the size of the molecule increases, the affordability of large basis sets or of particularly demanding calculation methods decreases. Finding an optimal balance between results accuracy and computational affordability becomes a crucial issue, despite the continuous and fast growth of computers' power.

The nature of the molecules considered and the objectives of the study play a fundamental role in determining affordability, by determining the number of calculations needed for a given study. For instance, the study of a rather rigid molecule implies the calculation of a limited number of conformers; the study of a middle-size highly flexible molecule (a molecule with many rotatable bonds) implies the calculation of many conformers (from some dozens to few hundreds). A study considering many middle-size flexible molecules (e.g., the study of a class of related compounds) implies the calculation of a high total number of conformers (several hundreds, or even thousands) and the associated increase of the total computational time may exceed affordability in terms of overall computational effort for a single investigation.

The study of biologically active molecules provides significant examples of investigations involving many middle-size molecules. Such study aims at understanding as many relationships as possible between molecular properties and biological activities. It therefore benefits from the computational investigation of a considerable (as high as possible) number of compounds of the same class. Since biologically active molecules are often middle-size, the task implies considerable total computational costs. Furthermore, since the biological activity is exerted in a medium within a living organism, it is important to calculate the conformers of biologically active molecules not only *in vacuo*, but also in solution, selecting solvents with different polarities to cover the range of possible media in which a compound may preferably be present within an organism. When the molecules concerned have sites capable of forming hydrogen bonds, the solvents selected should preferably have also different H-bonding abilities, and the study in solution is ideally complemented by the study of adducts with explicit solvent molecules. This increases the computational costs enormously, as calculations in solutions are usually more expensive than calculations *in vacuo*, and the supermolecular structures of adducts with explicit solvent molecules have bigger size and greater flexibility than the isolated molecule. Being able to keep the costs within affordable limits while obtaining realistic results is thus particularly important for the study of large classes of biologically active compounds

In such cases, the choice of the level of theory and of the

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basis set becomes the key to optimize the balance between results accuracy and computational costs. It is therefore important to have indications about the performance of different levels of theory and different basis sets for the type of molecules and the research objectives considered.

The current work attempts to compare results reliability and computational costs of three commonly utilized calculation methods – Hartree Fock (HF), Density Functional Theory (DFT) and Møller Plesset Perturbation Theory (MP2) – on the basis of their performance within the study of three classes of related compounds, which were aimed at identifying trends/patterns for the geometry preferences, the characteristics and strength of intramolecular hydrogen bonds (IHB), and the solvent effects for each class.

Among the levels of theory considered, HF has the advantage of being an *ab initio* method and the disadvantage of considering electron correlation effects only indirectly (through an averaged potential) and of not including dispersion effects. In terms of computational demands, it is the less expensive among *ab initio* methods.

DFT is not an *ab initio* method. It utilizes functionals of the electron density. It includes part of the electron correlation. It is widely utilized, and a variety of functionals has been designed to attempt to take into account specific aspects that may be of more interest in the study of a given compound or a family of compounds.

MP2 includes both electron correlation and dispersion contributions, thus providing the best description of IHB and other non-covalent interactions and, therefore, also providing the best description of the molecular features whose characteristics depend on these interactions. It is the most sophisticated among the methods considered here and its results are therefore utilized as benchmarks to assess the quality of the results obtained from the other methods. It is also the most demanding in terms of computational costs, and its affordability decreases sharply as the number of atoms in a molecule increases.

As already mentioned, HF is the less expensive among the *ab initio* electronic structure methods. Therefore, its use may be convenient when the results obtained are sufficiently reliable. The current work considers the following questions:

- a comparison of HF computational costs and affordability with those of DFT and MP2;
- the reliability of HF for the identification of trends within a given class of compounds;
- the options enabling the obtainment of a reasonable assessment of the performance of HF for the class of compounds of interest and for the research question of interest.

Although there have been qualitative mentions to the greater affordability of HF through the works here considered as references [3]–[11], there has not yet been a quantitative appreciation of it, nor has there been an investigation of the molecular size for which the greater affordability of HF becomes so significant as to extensively impact on the total computational effort, or even condition the very affordability, of a given study. The current work proposes to search for answers to these questions.

Although the calculations considered in this work were performed 2-4 years ago, and the computer power is increasing rapidly from year to year, the significance of the considerations reported here is not related to the absolute values of the time taken, but to the comparison among the times required by different methods. The increase in computer power pushes forward (toward a larger number of atoms) the limit for which the computational costs of different methods differ so extensively as to determine affordability; however, what could be considered the "relative computational demands" of the various methods maintain their effects. Therefore, the study reported here maintains its significance in terms of comparison among methods and their costs.

II. Outline of the Approach

The computational costs of HF, DFT and MP2 are compared for the study of three classes of polyphenolic compounds: acylphloroglucinols [3]–[8], hydroxybenzenes [9], [10] and the acids of some hydroxybenzenes [11]. The computational effort of each calculation is estimated in terms of the time taken to complete the calculation; therefore, the comparison of the computational efforts of the different methods considers the computational time taken for the calculation of a given conformer with different methods on the same personal computers (PC) or on PCs of comparable power.

The main basis set utilized in the calculations was 6-31G(d,p), which is able to account for the main features of geometry preferences, including those associated with the possibility of formation of IHB and the description of their characteristics [12]. The 6-31+G(d,p) basis set was also tested often and, for some cases, also the 6-31++G(d,p) basis set; their interest resides in the ability of the addition of diffuse functions to improve the description of IHB.

In all the cases considered, DFT calculations utilized the B3LYP functional [13]–[15], which is the most widely utilized functional [16].

All the calculations considered for the current comparison were performed with full optimization (fully relaxed geometry), to obtain better descriptions of the molecular geometries. The methods and basis sets tested for each molecule depended on the size of the molecule. HF/6-31G(d,p) calculations were performed for all the molecules, on inputs exploring all the possible viable geometries for the given molecule. The other calculations were usually performed on the HF-optimized geometries, thus being post-HF calculations (which by itself is expected to decrease the computational time of the other methods, because of more favorable inputs). Calculations with the addition of diffuse functions were performed on the geometries optimized with the same method, but without diffuse functions in the basis set.

The calculations in solution that are utilized for the current comparisons were performed with the Polarizable Continuum Model (PCM, [17]–[20]), with full reoptimization of the *in-vacuo* optimized geometry and at the same level of theory as the calculation *in vacuo*.

All the calculations were performed with Gaussian 03, revision D01 [21].

The computational efforts and other performance features will be analyzed individually for the different classes of compounds considered. For conciseness sake, the following acronyms are utilized to compact information about the method and the basis set: HF for HF/6-31G(d,p), HF+ for HF/6-31+G(d,p), HF++ for HF/6-31++G(d,p), MP for MP2/6-31G(d,p), MP+ for MP2/6-31+G(d,p), MP++ for MP2/6-31++G(d,p), DF for DFT/B3LYP/6-31G(d,p), DF+ for DFT/B3LYP/6-31+G(d,p) and DF++ for DFT/B3LYP/6-31++G(d,p).

III. Results

A. Comparisons for Acylphloroglucinols' Molecules

Acylphloroglucinols (ACPL) are derivatives of phloroglucinol (1,3,5-trihydroxibenzene) characterized by the presence of a COR group. Their general structure is shown in fig. 1, and two compounds that have been objects of specific case studies ([3], [22]–24]) are shown in fig. 2. In ACPL, the sp^2 O of the COR group can form an IHB with either of the two ortho OH (here termed "first IHB", [3]–[8]).

ACPL constitute the most important class of compounds among the ones utilized for the current comparisons, because of a variety of reasons:

- The high number of molecules that have been calculated (more than 180). This enables comparisons that have also some statistical significance.
- The variety of their molecular sizes (from 17 to more than 100 atoms). This enables an evaluation of the affordability of a given calculation method in relation to the size of the molecule.
- The high flexibility of the substituents in many of the calculated molecules. This implies a high number of conformers for each molecule and, therefore, increases the number of computational outputs/jobs available for comparisons.

The study of ACPL comprised the following research issues:

- the investigation of their conformational preferences in vacuo and in solution [4];
- the investigation of the characteristics of the first IHB in vacuo [5] and in solution [6];
- the study of the adducts of ACPL with explicit water molecules [25];
- the investigation of the influence of weaker IHB, such as C–H···O, on the conformational preferences of the molecules [7];
- the study of relevant features characterizing ACPL subsets, like the influence of the presence of additional IHB, besides the first IHB, if substituents in R or R′ enable it [8], or the influence of O–H···π IHB for ACPL whose molecules contain π bonds in positions suitable to interact with one of the phenol OH groups [7].

Given the importance of keeping track of relevant geometry features both across the conformers of each compound and across all the compounds investigated, a set of symbols was introduced to denote individual features, [3]–[8]. The symbols

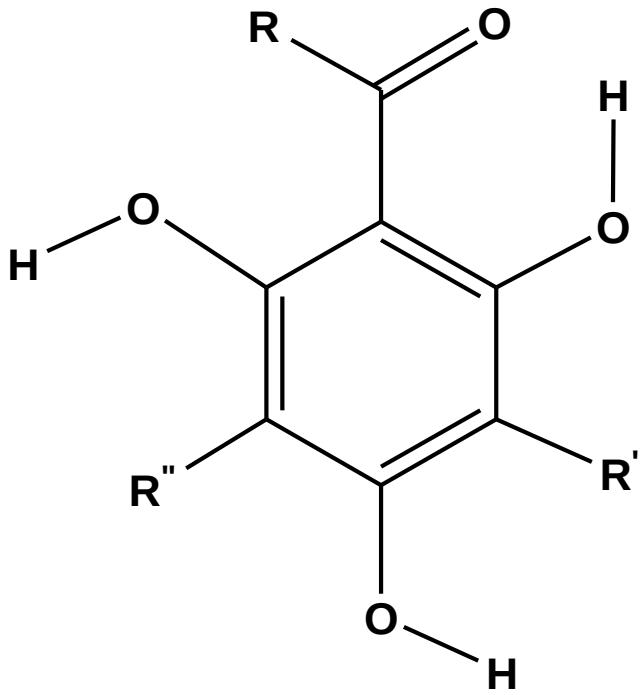


Fig. 1. General structure of acylphloroglucinols.

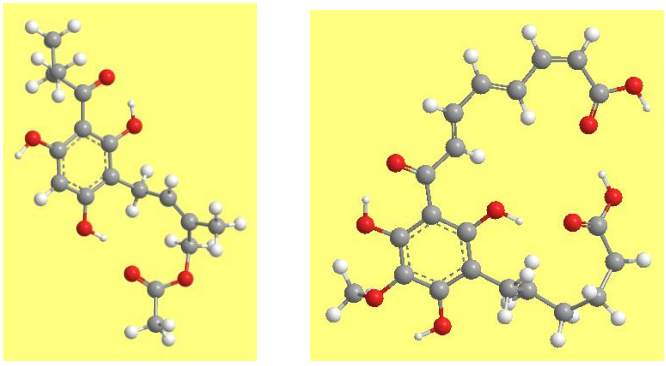


Fig. 2. Examples of acylphloroglucinols with a flexible R′ chain: caespitate (left, [3], [22]) and nodifloridin B (right, [23], [24]).

that appear in the names of conformers in the tables of data reported here are shown in table 1.

The quality of the results of different calculation methods can be summarized as follows [3]–[8]:

- The identification of trends/patterns is consistent with all the methods. These comprise conformational preferences and relative energy sequences, the influence of IHB on conformational preferences, and the changes in the transition from in vacuo to solutions of different solvents.
- HF gives results closer to those of MP2 for several aspects, including the characteristics of the first IHB, the extent of the energy increase when the first IHB is removed, the off-plane rotation of the sp^2 O of COR (and, consequently, of the whole COR) to smooth the O↔O repulsion ensuing when the first IHB is removed, and the solvent effect.

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

S	geometrical feature	S	geometrical feature
d	The first IHB is present. If R′≠H, it forms on the same side as R′.	s	If R′≠H, the first IHB forms on the other side with respect to R′.
r	The H of the OH in para to the acyl chain is oriented toward R′.	w	The H of the OH in para to the acyl chain is oriented away from R′.
u	The H of the OH in ortho to the acyl chain and not engages in the IHB is oriented toward R.		

- DFT gives shorter IHB lengths and greater IHB strengths than HF or MP2 (the overestimation of H-bond strength being a known tendency of DFT). Moreover, DF results (DFT results without the presence of diffuse functions in the basis set) appear rather poor, making the presence of diffuse functions (DF+) a necessity. For instance, the deviation of the IHB parameters from the MP2 results is considerably greater in DF results and decreases in DF+ results. The presence of diffuse functions increases the computational time significantly when the size of the molecule increases.

As already mentioned, the computational time is determined by the molecule's size and flexibility. For ACPL (fig. 1), the rotatable bonds whose rotation can bring geometry changes include the three C–O bonds of the phenol OH, the C–C bond connecting COR to the ring, all the C–C bonds in R, R′ or R″, and other rotatable bonds that may be present in the R, R′ or R″ of some molecules (e.g., C–O bonds of additional OH or other groups, fig 2).

Table 2 shows the computational time for representative conformers of representative ACPL molecules *in vacuo*, considering the methods tested for each of the reported conformers. The testing depended also on the molecular size or on the type of task considered. For instance, MP+ calculations were affordable only for molecules containing up to 26 atoms. In the case of $C_{20}H_{30}O_5$ (appearing at the bottom of table 2), only calculations with diffuse functions in the basis set were needed, because they were preliminary to calculation of corresponding ion-containing structures [26]; therefore, the table compares the time taken for HF+ and DF+ on selected conformers.

On comparing the time values, it has also to be taken into account that, while HF calculations were performed on tentative (guess) geometries, all the other calculations were performed on geometries that had already been optimized at the HF level, which by itself decreases the optimization computational effort. Random tests showed that the computational time of the other methods increases significantly when tentative (guess) inputs are utilized, instead of the HF optimized ones.

B. Comparisons for the Hydroxybenzenes' Molecules

There are only eleven different hydroxybenzenes molecules and, therefore, their structures are all shown in fig. 3. Their

Table 2. Comparison of the computational time with different methods for representative acylphloroglucinol molecules.
The molecules are described by giving the formula and the information on the nature of R and, R′; R″ is indicated only when it is ≠ H. The conformers are described through the symbols introduced in table 1, written in italics. The methods (meth) are indicated with the acronyms introduced in section 3.1. The time values indicate the number of hours (before the decimal point) and of minutes (after the decimal point).

molecule description and conformer description	meth	time (h.min)	meth	time (h.min)
$C_7H_6O_4$	HF	0.43	MP	1.25
R = H, R′ = H, *d-w*	DF+	1.45	MP+	4.27
$C_9H_{10}O_5$	HF	1.47	HF+	2.24
R = CH_2OH	DF	3.14	DF+	8.46
R′ = CH_3 , *d-r*	MP	5.16	MP+	13.45
$C_{10}H_{12}O_4$	HF	1.57	HF+	3.48
R = CH_2CH_3	DF	2.36	DF+	12.13
R′ = CH_3 , *d-w*	MP	11.25	MP+	34.38
$C_{10}H_{12}O_4$	HF	1.15	HF+	5.14
R = CH_3, R′ = CH_3	DF	2.12	DF+	10.48
OCH_3 in place of ortho OH *s-w*	MP	10.24	MP+	23.14
$C_{12}H_{16}O_4$	HF	3.22	HF+	7.09
R = $CH_2CH_2CH_2CH_3$	DF	4.39	DF+	20.04
R′ = CH_3 *d-r*	MP	22.51		
$C_{12}H_{16}O_4$	HF	2.44	HF+	4.23
R = $CH(CH_3)CH_2CH_3$	DF	5.43	DF+	12.6
R′ = CH_3 *s-w*	MP	16.58		
$C_{12}H_{16}O_4$	HF	1.14	HF+	4.4
R = $CH(CH_3)CH_2CH_3$	DF	3.34	DF+	6.14
R′ = CH_3 *d-r-u*	MP	16.4		
$C_{13}H_{10}O_4$	HF	2.17	HF+	11.23
R = phenyl	DF	5.58	DF+	12.48
R′ = H *d-r*				
$C_{13}H_{16}O_4$	HF	2.59	HF+	5.41
R = $CH(CH_3)_2$	DF	4.46	DF+	8.43
R′ = prenyl				
R″ = CH_3, *d-r*				
$C_{14}H_{18}O_4$	HF	1.52	HF+	4.59
R = CH_3, R′ = prenyl	DF	2.50	DF+	6.45
R″ = CH_3, *d-r*				
$C_{18}H_{18}O_8$ two phloroglucinol moieties	HF	10.40	DF+	33.08
$C_{19}H_{30}O_4$	HF	5.06		
R = $(CH_2)_{10}CH_3$,	DF	5.27		
R′ = CH_3 *d-r*				
$C_{22}H_{26}O_8$ two phloroglucinol moieties	HF	22.50	DF+	120.56
$C_{26}H_{24}O_{12}$ three phloroglucinol moieties	HF	15.51	DF+	95.53
HF+ and DF+ calculations for various conformers of $C_{20}H_{30}O_5$				
$C_{20}H_{30}O_5$	HF+	31.11	DF+	44.16
R = $CH(CH_3)_2$	HF+	33.47	DF+	38.01
R′ = CH_2CH_2OH	HF+	25.22	DF+	50.11
$(CH_3)CH_2CH_2CH$	HF+	26.06	DF+	46.16
$(CH_3)_2$	HF+	23.20	DF+	42.39

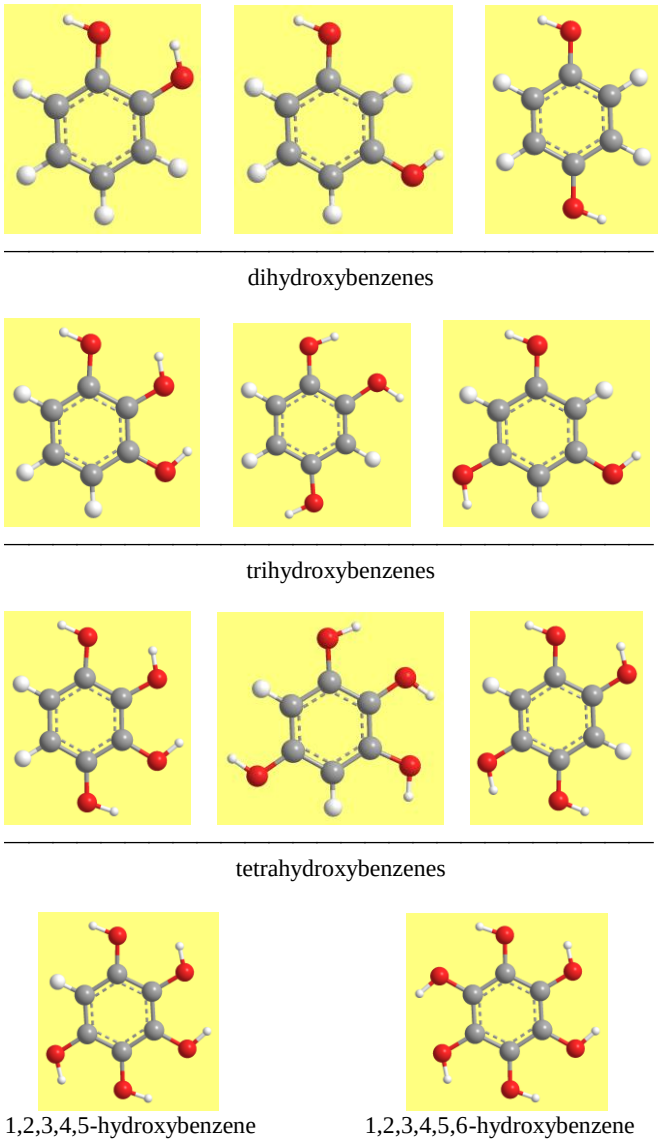


Fig. 3. Molecular structures of hydroxybenzenes.
For each molecule, the lowest energy conformer is shown (for the molecules capable of forming intramolecular hydrogen bonds, this corresponds to the conformer with the highest number of IHB).

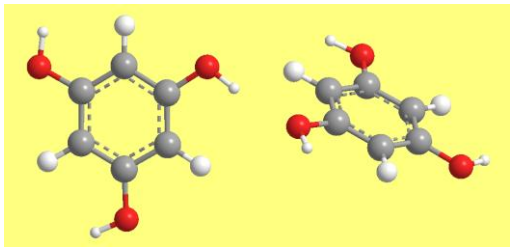
flexibility degree is limited. The only rotatable bonds are the C–O bonds of the phenol OH. Since it is known [27] that isolated OH prefer to lie on the plane identified by the benzene ring, it is easy to prepare inputs with geometries close to the optimized ones. Some geometry adjustments on optimization occur in the case of neighboring OH, because of the search for the best geometry of the IHB in low-energy conformers, or for the best geometry compatible with the stress caused by the O↔O repulsion in the high-energy conformers in which one or more IHB are removed. The size of these molecules is sufficiently small to enable the use of all the calculations methods listed in section 3.1, including MP++; therefore, MP++ results are selected as benchmarks to assess the performance of the other methods.

- A comparison of the quality of the results from different calculation methods can be summarized as follows [9]:
- The trend identification is the same with all the methods for the conformers' relative energies, for the parameters of the IHB and for the solvent effect. The only significant discrepancy concerns the lowest energy isomer of trihydroxybenzenes, identified as 1,3,5-trihydroxybenzene (phloroglucinol) by MP, MP++, DF and DF++ and as1,2,3-trihydroxybenzene by HF and HF++.
- HF results are closer to MP++ results than the DFT ones for the solvent effect and for the energy increase on IHB removal.

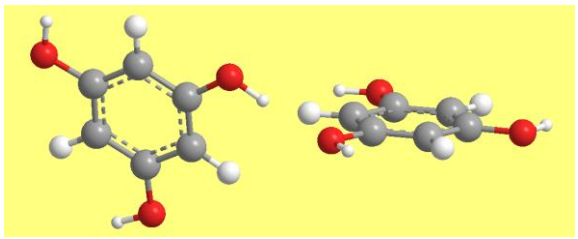
Table 3. Computational time with different methods and in different media for representative hydroxybenzene molecules.
The molecules are described by indicating the positions of the OH present. The calculation methods are indicated with the acronyms introduced in section 3.1. The time values indicate the number of hours (before the decimal point) and the minutes (after the decimal point).

OH positions	method	time (h.min)			
		vac	chlrf	actn	aq
1,2	HF	0.06	0.08	0.09	0.13
	HF++	0.09	0.16	0.17	0.24
	DF	0.08	0.14	0.15	0.14
	DF++	0.27	0.27	0.27	0.26
	MP	0.26	0.17	0.18	0.28
	MP++	5.16	1.06	2.11	1.31
1,2,3	HF	0.11	0.11	0.11	0.13
	HF++	0.26	0.26	0.25	0.33
	DF	0.10	0.18	0.18	0.17
	DF++	0.47	0.37	0.36	0.35
	MP	0.49	0.25	0.24	0.23
	MP++	1.48	0.58	0.58	0.57
1,2,3,4	HF	0.13	0.14	0.27	0.22
	HF++	0.22	0.29	1.00	0.50
	DF	0.17	0.22	0.22	0.21
	DF++	0.37	0.45	0.45	0.44
	MP	1.02	1.03	1.04	1.02
	MP++	5.13	4.02	4.26	7.04
1,2,3,4,5	HF	0.25	0.17	1.27	0.21
	HF++	0.22	0.42	0.50	1.11
	DF	0.15	0.27	0.27	0.34
	DF++	0.31	0.56	0.57	1.39
	MP	0.40	1.25	1.24	1.53
	MP++	4.28	1.45	1.45	3.50
1,2,3,4,5,6	HF	0.30	0.20	0.20	0.25
	HF++	0.28	0.49	0.51	1.04
	DF	0.16	0.30	0.40	0.31
	DF++	0.37	1.28	1.23	1.31
	MP	0.51	1.52	2.18	8.46
	MP++	2.23	9.34	10.20	10.42

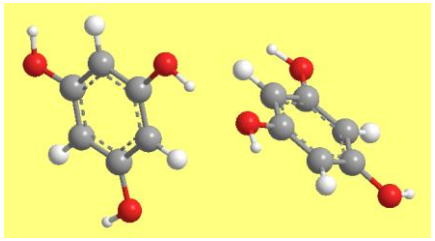
Table 3 shows the computational time for the lowest energy conformer of selected hydroxybenzenes in different media. Given the comparatively small size and the limited flexibility of the hydroxybenzenes molecules, the computational time remains small in all the media (with occasional increases for MP++ in solution); this is in line with the affordability of sophisticated methods and large basis sets for sufficiently



HF/6-31G(d,p)

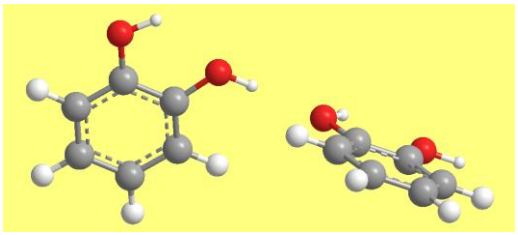


DFT/B3LYP/6-31++G(d,p)

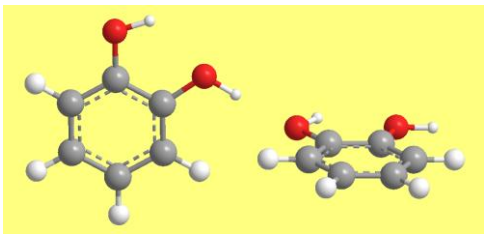


MP2/6-31G(d,p)

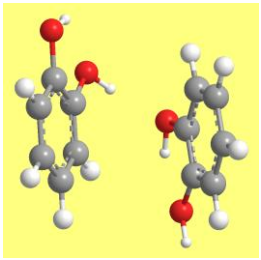
Fig. 4. An example of dimer geometry in which the results of different calculation methods differ by the angle between the planes of the rings of the two monomers.
The calculation method is reported below the dimer structure or to its right.



HF/6-31G(d,p)



DFT/B3LYP/6-31++G(d,p)



MP2/6-31G(d,p)

Fig. 5. An example of dimer geometry in which the results of MP2 calculations differ considerably from the other, likely because of the ability of MP2 to take into account the interactions between the aromatic rings.
The calculation method is reported below the dimer structure or to its right.

small molecules.

C. Comparisons for Hydroxybenzenes' Dimers

Hydroxybenzenes can form dimers through hydrogen bonds (H-bonds) between the OH of two monomers, often complemented by other types of interactions. Dimers were calculated for dihydroxybenzenes and trihydroxybenzenes, trying to include all the possible combinations of different conformers of the same molecule and all the possible dimer's geometry types [10]. Different calculations methods whose affordability was compatible with the dimer's size were utilized. The identification of trends was consistent for most features [10]. However, DFT (even at the DF++ level) showed some discrepancies with respect to MP2 and HF, which suggest some inadequacies in the way in which DFT takes into account the interactions between two hydroxybenzene monomers.

Optimized geometries often differ more significantly, in the results of different methods, than they differ for monomeric hydroxybenzenes, or for the case of ACPL. Fig. 4 shows a case in which the geometries differ by the mutual orientation of the two planes (with HF results closer to MP that the DF++ results).

Furthermore, the task (investigation of the interactions between two hydroxybenzene monomers) is a typical task in which higher method-sophistication is needed because of the inadequacies of both HF and DFT to take into account the interactions between the two benzene rings (stacking interactions), which may significantly influence the dimer's geometry. The example in fig. 5 shows a case in which the MP2 optimization, on the same starting geometry as the other

Table 4. Calculation time for some dimers of hydroxybenzenes.
The acronyms DHB and THB are utilized in place of dihydroxybenzene and trihydroxybenzene respectively. The calculation methods are indicated with the acronyms introduced in section 3.1.

dimer	method	time (h.min)	method	time (h.min)
dimer of 1,2-DHB	HF	4.04	MP	18.08
	DF++	16.56	MP++	198.51
dimer of 1,3-DHB	HF	12.57	MP	45.03
	DF++	44.29	MP+	62.07
dimer of 1,3,5-THB	HF	4.47	MP	54.16
	DF++	29.55		

two, brings the two aromatic rings into a position suggesting mutual interactions.

The calculation time differs with different methods, with remarkable increase as the method sophistication increases. The difference is related not only to the size (total number of atoms) of the dimer, but also to the different ways in which each method takes into account the interactions between the two monomers, leading to substantial geometry changes during the optimization process and to different output geometries for the same dimer.

D. Comparisons for the Acids of Hydroxybenzenes

The carboxylic acid of phloroglucinol was investigated to compare the effects of the presence of a carboxylic group on a phloroglucinol moiety with that of the COR group in ACPL [11]. A number of carboxylic acids of hydroxybenzenes were also investigated to compare them with that of phloroglucinol [11]; their structures are shown in fig. 6.

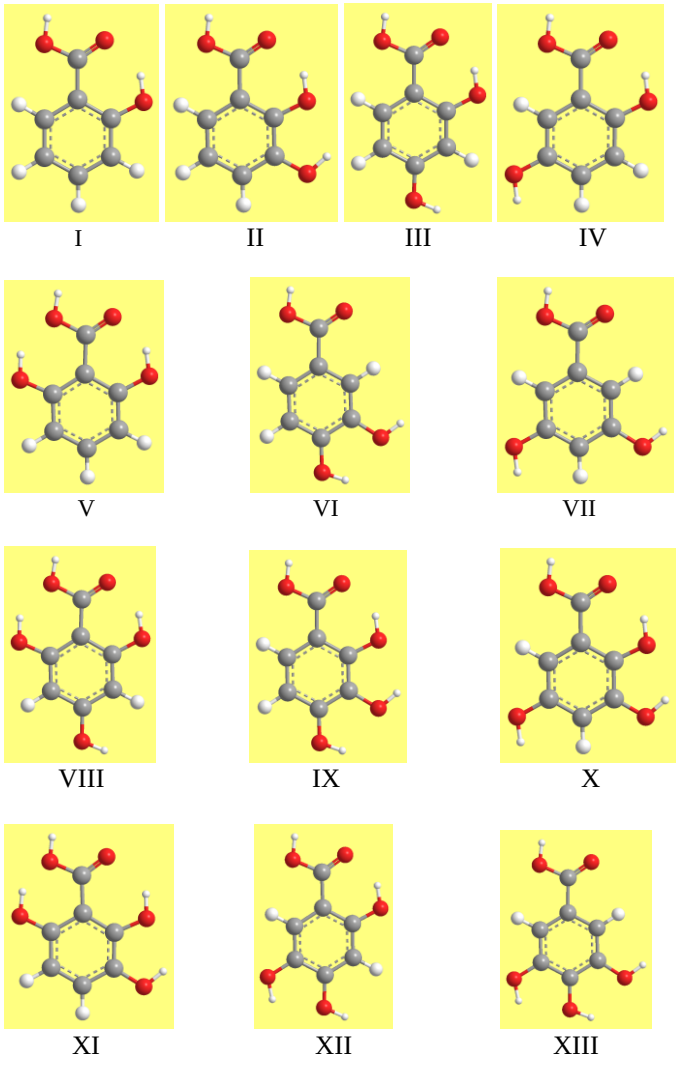


Fig. 6. Calculated acids of hydroxybenzenes.
The acids are denoted by numbers, to be used as references in the first column of table 5.

Table 5. Calculation time (in vacuo) for selected conformers of the carboxylic dimers of hydroxybenzenes.
The acids are denoted with the numbers introduced in fig. 6. The calculation methods are denoted with the acronyms introduced in section 3.1.

acid	method	time (h.min)	method	time (h.min)
I	HF	0.16	MP	1.07
	DF+	1.38	MP++	2.17
II	HF	0.18	MP	1.09
	DF+	1.51	MP++	2.34
III	HF	0.18	MP	1.17
	DF+	1.51	MP++	2.57
IV	HF	0.17	MP	1.24
	DF+	1.41	MP++	2.34
V	HF	0.20	MP	1.10
	DF+	2.16	MP++	2.10
VI	HF	0.17	MP	0.54
	DF+	1.08	MP++	2.05
VII	HF	0.16	MP	0.56
	DF+	1.30	MP++	2.05
VIII	HF	0.39	MP	1.43
	HF++	0.50	DF+	2.26
	DF	0.48	DF++	1.50
IX	HF	0.40	MP	1.58
	DF+	2.02	MP++	19.48
X	HF	0.34	MP	1.59
	DF+	2.05	MP++	4.09
XI	HF	0.40	MP	1.36
	DF+	2.48	MP++	4.00
XII	HF	0.31	MP	1.58
	DF+	2.08	MP++	16.47
XIII	HF	0.24	MP	1.19
	DF+	1.25	MP++	2.53

Like for hydroxybenzenes, the molecules of their carboxylic acids are sufficiently small to enable the use of all the calculation methods listed in section 3.1. The trends-identification is consistent with all the methods for features like the parameters and energy of the IHB, the relative energies *in vacuo* and in water solution, and the solvent effect.

The DFT values are closer to the MP2 ones (although considerably smaller) for the IHB lengths, while the HF values are closer to the MP2 ones for the IHB strength and for the off-plane shift of COOH on IHB removal.

The computational time, although not long, differs for different methods more remarkably than in the case of hydroxybenzenes. Table 5 shows the time values for the lowest energy conformer of each of the acids considered.

IV. Discussion and Conclusions

The information considered in the previous sections prompts two trends of reflection: the relative affordability of the various computational methods and the suitability of utilizing only one computational method when investigating a molecule or a class of molecules.

A comparison of result quality and computational time

points to affordability advantages of HF, above all for the identification of trends within a family of related compounds when their molecules are middle-size and flexible, i.e., when the optimization is time-demanding and the use of other methods would imply several-fold increase of the computational effort. Among the cases considered here, this is the case of ACPL, whose molecules are middle-size and flexible. Furthermore, in the case of ACPL, DFT required the presence of diffuse functions on the heavy atoms (DF/6-31+G(d,p)) for its results to get somewhat closer to the (benchmark) MP2 results, while HF results were closer than the (DF/6-31+G(d,p) ones utilizing the 6-31G(d,p).

It is not easy to state whether the methods' performance observed for ACPL, and also for hydroxybenzenes and their acids, would be maintained for other classes of compounds, or whether the "good performance" of HF is related to some characteristics of ACPL (or of polyphenols in general) which might, e.g., favor cancellation of errors. For this reason, it may be important to re-assess HF performance for other classes of compounds, by comparing HF results against the results of more sophisticated methods (e.g., MP2) for molecules that are sufficiently small and, at the same time, sufficiently representative of the main characteristics of the given class. Should analogous performance-patterns be verified for other classes of compounds, then more extensive generalizations would be possible.

Similarly, it may be important to assess the performance of HF for the objectives of a given study. This would, e.g., include the verification that the class of compounds considered does not involve aspects that HF would not take into account adequately – at least at first approximation level – or that the focus of the study is not beyond HF capabilities (as might be, e.g., the study of stacking interactions between benzene rings).

The results of hydroxybenzenes and their acids confirm the affordability of more demanding methods when the molecules are sufficiently small and not too flexible. Furthermore, they confirm that HF mostly provides trends similar to the MP2 ones and that, when they differ, the HF trends coincide with the DFT ones; this may suggest that DFT would not offer significant advantages when a study is aimed at trends-identification.

The information presented here, as well as the information from several other studies, suggests that the sole utilization of DFT calculations may imply the risk of missing relevant aspects or getting information that is too distant from the experimental one. For instance, if only DFT had been utilized for the study of ACPL, there would have been a considerable overestimation of the IHB energies, and the off-plane rotation of the sp^2 O of the COR group would have been nearly unnoticed. Some authors have identified inadequacies of DFT to take into account some aspects relevant to specific studies, such as failing to recognize interactions between aromatic rings in some molecular recognition contexts [28], or the inadequate reliability [29] of the evaluation of energy gaps between frontier orbitals (HOMO, highest occupied molecular orbital, and LUMO, lowest unoccupied molecular orbital). Even a simple study of the dimer of acetic acid [30] shows considerable discrepancies (table 6): DFT overestimates the interaction energy between the two dimers, underestimates the BSSE correction, gives a value of the intermonomer H-bonds that is too short (thus overestimating the strength of the H-bonds), and gives a totally out-of-range value for the HOMO-LUMO difference (confirming the warning expressed in [29]). DFT gives less accurate results than HF for the structure and dynamics of liquid water [31] and HF proves fully adequate for the study of hydrogen bonding in liquid water [32]. HF performs better than DFT (gives results closer to the MP2 ones) for the characterization and prediction of the activity of μ-opioid compounds [33, 34] as well as for the potential energy surfaces of some alkaloids [35].

Table 6. A comparison of the results of different calculation methods for the dimer of acetic acid [29]. In the first column, the methods are denoted with the same acronyms introduced in section 3.1. .

calculation method	interaction energy (kcal/mol)	BSSE correction (kcal/mol)	HB length (H···O) (Å)	HOMO LUMO gap (kcal/mol)
HF	-13.231	2.262	1.819	397.860
DF+	-15.519	0.800	1.651	174.096
MP	-13.351	5.363	1.700	389.740

On the basis of all this, it appears reasonable to conclude that HF has good potentialities for trends-identification within a class of related compounds, and may give results closer to the experimental ones for a variety of issues. Therefore, it is important to test the HF performance in relation to the class of compounds of interest, or to the research question of interest. Whenever affordable, the best way to assess HF performance is versus the MP2 results.

When MP2 calculations would be too demanding to be performed on each individual molecule of a given class, an approach that could ensure a reduction in the risk of missing some relevant aspect would be that of making both HF and DF+ calculations and, whenever significant discrepancies appear, utilize MP2 or other higher-level approaches to clarify the discrepancy (in the studies considered in this work, this was done, e.g., to verify the off-plane shift of the sp^2 O of COR in ACPL when the first IHB is removed: the shift is much smaller in DFT than in HF results; MP2 calculations showed that the HF results were the more reliable). The increasing ensemble of information about poor identification of relevant aspects by DFT calculations recommends to avoid performing only DFT calculation for a given study (e.g., utilizing only DFT calculations for the study considered in [35] would have prevented the identification of some conformers of the molecules concerned].

When experimental results are available, or when MP2 calculations are affordable, the comparison of the results of different methods may also help identify regularities in the discrepancies; in such a case, it would be possible to identify scaling factors enabling the correction of values that are overestimated or underestimated in a rather systematic way. For instance, in the case of ACPL, the discrepancy between the IHB parameters in the HF results and in the DFT results

appears to be fairly constant for the same type of conformers across structures. This would suggest the possibility of identifying scaling factors for each category of conformers (d-r, s-w, etc.) to be utilized to obtain a more realistic estimation of IHB characteristics from DFT results. Although the identification of such scaling factors would go beyond the scope of the current work, it can be viewed as an interesting possibility.

It would also be interesting to investigate whether there could be criteria to identify such scaling factors in a way that they can be applied to all molecules, or whether the scaling factors differ with the type of molecular structure (i.e., with the class of compounds). In the latter hypothesis, scaling factors could be identified for classes of compounds or ensembles of classes of compounds, and categories of conformers within them..

Finally, it can be recalled that, for investigation objectives other than trends-identification, it becomes important to evaluate a method's ability with regard to the proposed objectives.

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