

The geometric isomers of caespitate: a computational study in vacuo and in solution

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Abstract—Caespitate is an acylphloroglucinol isolated from a plant utilized in traditional medicine in South Africa and exhibiting antituberculosis, antibacterial and antifungal activities. The molecule is characterized by a $\text{COCH}(\text{CH}_3)_2$ acyl chain and by a prenyl chain ending with an acetic-acid ester group, in meta to the acyl chain. The double bond of the prenyl chain gives origin to Z and E isomers, with the former being the biologically active one. An extensive computational study of the conformational preferences of the two isomers was carried out in four media (vacuum, chloroform, acetonitrile and water) to try and identify significant differences. The main difference concerns the ability of the prenyl/ester chain to form an intramolecular hydrogen bond with one of the neighbouring OH: the ability is greater for the Z isomer and the corresponding hydrogen bond has greater conformation-stabilizing effect. The difference is also analysed in terms of the competition between intramolecular hydrogen bond engaging the O atoms of the ester function and the $\text{O}-\text{H}\cdots\pi$ interaction between phenol OH and the double bond in the prenyl/ester chain.

Keywords—Acylphloroglucinols, Caespitate, Geometric isomers, Intramolecular hydrogen bonding, Polyphenols.

I. INTRODUCTION

CAESPITATE ($\text{C}_{17}\text{H}_{22}\text{O}_6$, acetic acid 2-methyl-4-(2,4,6-trihydroxy-3-isobutyryl-phenyl)-but-2-enyl ester) is a compound isolated from *Helichrysum caespitium* (Asteraceae), a plant utilized in traditional medicine in the Southern African region for the treatment of bronchopneumonal diseases, tuberculosis, sexually transmitted diseases, and also for wound dressing [1, 2]. The isolated compound exhibits antituberculosis, antibacterial and antifungal activities [1, 2].

Fig. 1 shows the structure of the compound and the atom numbering utilized in this work. The compound is an acylphloroglucinol, i.e., a derivative of phloroglucinol (1,3,5-trihydroxybenzene) characterized by the presence of a COR group (acyl chain). In the caespitate molecule, R is an isopropyl group, $\text{CH}(\text{CH}_3)_2$. The second substituent, in meta to the acyl chain, is $\text{CH}_2\text{CHC}(\text{CH}_3)\text{CH}_2\text{OCOCH}_3$, i.e., a prenyl

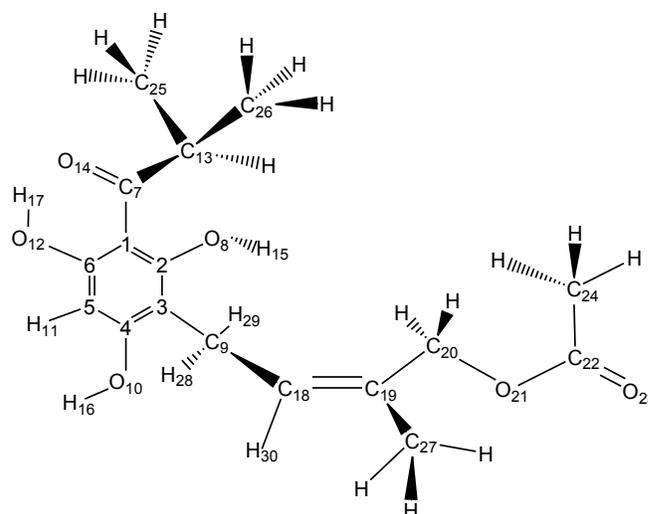


Fig. 1. The Z isomer of caespitate and the atom numbering utilized in this work.

chain ending with an acetic-acid ester group; this substituent will be here denoted as R' . The $\text{C}18=\text{C}19$ double bond in R' gives rise to the Z (fig. 1) and E geometric isomers.

Like in all acylphloroglucinols, the sp^2 oxygen atom of the acyl chain ($\text{O}14$) can form an intramolecular hydrogen bond (IHB) with either of the two ortho OH, i.e., with either $\text{H}15$ or $\text{H}17$; this IHB is here termed “first IHB”, consistently with previous works [3–6]. The presence in R' of two O atoms that can act as acceptors (sp^3 $\text{O}21$ and sp^2 $\text{O}23$) enables the formation of an additional IHB with either $\text{H}15$ or $\text{H}17$, if the geometry of the prenyl/ester chain enables $\text{O}21$ or $\text{O}23$ to come close enough to $\text{H}15$ or $\text{H}17$; this additional IHB is here termed “second IHB” [3, 6].

The current work pertains to an ongoing systematic study of acylphloroglucinols (ACPL), aimed at identifying patterns in relevant features like the role of the first IHB in vacuo [4] and in solution [5] and the other factors expected to influence the conformational preferences of all ACPL molecules [7, 8]. The study has involved the computational investigation of a considerable number (>120) of actual and model structures to provide adequate evidence for pattern-identification and also sufficient starting information for further studies focusing more directly on the investigation of biological activities, in view of the importance of computational methods and

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computable descriptors for drug development [9, 10]. It has also included individual case studies that enabled the investigation of specific features, like the study of nodifloridin [11, 12] which enabled comparison of a phloroglucinol derivative (nodifloridin B) and a phenol derivative (nodifloridin A) with the same acyl chain and close R' substituents. The Z isomer of caespitate [3, 13] was the first compound investigated and was utilised to preliminarily test modelling approaches.

Some ACPL have additional H-bond donors or acceptors that may form a second IHB, largely influencing conformational preferences, above all *in vacuo* and in non-polar media [6]. Among the investigated ACPL, caespitate is the only one with IHB acceptors in R' located after a C=C double bond, so that geometric isomerism may influence the formation of the second IHB. Moreover, the position of the C=C double bond in R' enables O-H... π interaction with the neighbouring phenol OH; these are the same OH that would be involved in the second IHB and, therefore, it is interesting to investigate a possible competition between the two H-bonding interactions and the influence of geometric isomerism on it.

The investigation of the compound extracted from the plant showed that the Z isomer is the biologically active one [2]. The E isomer might not be present in the plant extract utilized for biological activity investigation, but the possibility of it being synthesized and tested is not to be excluded, and this constitutes a reason for its computational study [14]. Even if it proves biologically inactive, a detailed comparison of the two isomers might provide information on the features that might be more directly related to the biological activity of the active one. The influence of geometric isomerism may be among such features, and this information may be of interest for the study of other ACPL molecules and the interpretation of the corresponding results.

Although only conformers with relative energy ≤ 3.5 kcal/mol are usually viewed as potentially interesting in the investigation of biological activities (i.e., as potentially responsible for the activity), the study considers a high number of conformers of the two isomers, including high energy ones, because the comparison of different conformers is functional to evaluate the effect of specific conformational aspects. Particular attention is given to the investigation of the two IHB, because of the importance of IHB for biologically active molecules, where IHB not only largely influence conformational preferences but may also play significant roles in the biological activity mechanism [15].

The computational study of the two isomers considered four media: *in vacuo* and in three solvents differing by their polarity and H-bonding ability (chloroform, acetonitrile and water), selected to mimic the possible media which a biologically active molecule may prefer within a living organism [5, 7]. Since several results for the Z isomer have already been published [3, 13], this paper reports in detail the results for the E isomer and focuses on the comparison between the two isomers.

II. COMPUTATIONAL DETAILS

Given the non-small size of the caespitate molecule and the high number of conformers made possible by the flexibility of R', it was necessary to choose a method enabling reasonable balance between results accuracy and computational affordability. *Ab initio* Hartree Fock (HF) calculations with the 6-31G(d,p) basis set were performed for the two isomers exploring all the predictably interesting geometries *in vacuo*, and then considering the same geometries in the three selected solvents.

The study of ACPL [4, 7] has shown fair performance – for this class of compound – of HF calculations, whose results are often closer to those of the higher-level Møller-Plesset Perturbation Theory (MP2) than those of Density Functional Theory (DFT) calculations with the B3LYP functional. In particular, HF/31++G(d,p) and B3LYP/DFT/6-31G(d,p) calculations performed on selected conformers of the Z isomer showed no significant differences in geometry parameters and conformers' relative energies with respect to the HF/6-31G(d,p) results [3].

Calculations in solution utilized the Polarizable Continuum Model (PCM, [16]). Single point (SP) PCM calculations were performed for most of the conformers calculated *in vacuo*. Re-optimization in solution – important for a better description of the solvation phenomenon [17] and to identify geometry changes prompted by the solvent, but costly for a molecule of this size – was performed for selected low energy conformers of each isomer.

All the calculations were performed with GAUSSIAN 03, Revision D 01 [18].

Throughout this paper, all the energy values reported are in kcal/mol (unless otherwise specified) and all the distances are in angstrom (Å). For conciseness sake, the Z and E isomers are denoted as cspt-Z and cspt-E respectively. The media are denoted with the following acronyms on reporting values: vac (*vacuum*), chlrf (chloroform), actn (acetonitrile) and aq (water).

III. RESULTS IN VACUO

A. Conformational preferences and relative energies

The general study of ACPL required the introduction [4, 7] of a set of symbols to keep track of the geometry features characterizing individual conformers and relevant for the identification of patterns in the influence of each feature. The study of cspt-Z [3] required additional symbols because of the presence of the second IHB and the variety of possibilities for its formation; these symbols are listed in table 1 and are here utilized for both isomers.

Sets of related conformers, i.e., conformers that can be obtained from one another by changing the position of the first IHB or the orientation of H16, or by removing an IHB, are identified by numbers. The numbers are progressive, according to the first time in which a conformer of a given set appears in

Table 1. Symbols (S) utilized to denote the main geometry features of the conformers of caespitate-Z and caespitate-E.

S	geometrical feature
α	both IHB are present and the second IHB engages H15
β	both IHB are present and the second IHB engages H16
γ	only the first IHB is present
$\xi\alpha$	only the second IHB is present and engages H15
$\xi\beta$	only the second IHB is present and engages H16
η	no IHB is present
s	the first IHB engages H17
d	the first IHB engages H15
a	O23 is the acceptor of the second IHB
b	the second IHB is bifurcated on the H
c	O21 is the acceptor of the second IHB
p	the methyls of R are oriented downwards
r	H16 oriented toward R'
w	H16 oriented away from R'
u	H15 or H17, not engaged in the first IHB, is oriented toward R

the relative energy sequence of the given isomer. The numbering is independent for the two isomers.

The acronyms denoting the conformers of the two isomers start with the letter **z** for cspt-Z and **e** for cspt-E. Although in the acronyms utilized to denote conformers in the general study of ACPL [4–8] the information about the presence and position of the first IHB appears first, for caespitate it was opted to firstly indicate about the presence (or absence) and type of the second IHB, as the feature enabling a classification of conformers relevant and convenient for the analysis of results.

Few examples are sufficient to illustrate how the information is compacted in the acronyms. The lowest energy conformer of cspt-Z is z-1- β a-d-r; this is a conformer with both IHB, in which the first IHB engages H15, the second IHB engages H16 and O23, and H16 is oriented toward R'. The conformer z-1- β a-d-r-u derives from z-1- β a-d-r and differs from it only by having H17 oriented toward R; z-1- β a-s-r also derives from z-1- β a-d-r, and differs from it because the first IHB engages H17. The second lowest-energy conformer of cspt-Z is z-2- α a-s-w, with the first IHB engaging H17 and the second IHB engaging H15 and O23; z-2- γ s-w derives from it by removal of the second IHB and z-2- $\xi\alpha$ a-w derives from it by removal of the first IHB. The lowest energy conformer of cspt-E is e-1- γ -d-r, with the first IHB engaging H15 and without second IHB; the second lowest-energy conformer of cspt-E is e-2- α a-s-w, with the first IHB engaging H17 and the second IHB engaging H15 and O23; the fourth lowest-energy conformer of cspt-E is e-4- β a-d-r, with the first IHB engaging H15 and the second IHB engaging H16 and O23;

Some geometry features are mutually exclusive. The presence of a second IHB involving H16 implies «toward R'» orientation of H16. The second IHB can engage H15 only when the first IHB engages H17 (although a bifurcated second IHB engaging both O21 and O23, with bifurcation on H15 or

Table 2. Geometrically viable combinations of the two IHB in caespitate.

first IHB	second IHB	type of conformer (acronym)
H15...O14	H16...O23	β a-d-r
H15...O14	H16...O21	β c-d-r
H15...O14	H16...O23 & H16...O21	β b-d-r
H17...O14	H16...O23	β a-s-r
H17...O14	H16...O21	β c-s-r
H17...O14	H16...O23 & H16...O2	β b-s-r
H17...O14	H15...O23	α a-s-r, α a-s-w
H17...O14	H15...O21	α c-s-r, α c-s-w
H17...O14	H15...O23 & H15...O21	α b-s-r, α b-s-w

H16, appear viable, a bifurcation for which H15 would be simultaneously engaged in the first and second IHB is not viable). Table 2 shows the geometrically viable combinations of the two IHB and the corresponding conformers' acronyms.

Table 3 reports the relative energy of the calculated conformers of cspt-Z and fig. 2 shows the geometries of selected conformers. As already mentioned, the consideration of high energy conformers is functional to the investigation of the influence of specific factors, like the presence or absence of the first or the second IHB, the position of the first IHB (on the same side as R' or on the other side), the atoms forming the second IHB and the geometry of R', the orientation of H16, the orientation of H15 or H17 when not engaged in the first IHB.

Chemical reasoning and extensive testing on cspt-Z shows that conformers differing only for having the geometry of R or R' reflected with respect to the plane defined by the benzene ring have the same energy. Therefore, conformers belonging to such pairs are denoted with the same acronym as, besides the fact that some torsion angles have the same magnitude but opposite signs, all the relevant geometry characteristics (bond lengths, bond angles, the other torsion angles, parameters of

Table 3. Relative energies of representative conformers of the Z isomer of caespitate. Results in vacuo.

conformer	relative energy (kcal/mol)	conformer	relative energy (kcal/mol)
z-1- β a-d-r	0.000	z-2- α a-s-w-p	5.613
z-2- α a-s-w	0.864	z-1- γ s-w	5.634
z-3- β c-d-r	2.431	z-10- γ s-w	5.703
z-4- β a-d-r	2.890	z-1- γ -d-w	5.906
z-5- β c-d-r	2.981	z-10- γ -d-w	6.028
z-6- α c-s-w	3.358	z-3- γ -d-w	6.030
z-7- α a-s-w	4.135	z-4- γ -d-w	6.049
z-2- α a-s-r	4.143	z-5- γ s-w	6.074
z-1- β a-d-r-u	4.175	z-7- α a-s-r	6.078
z-8- α c-s-w	4.221	z-6- γ -d-r	6.158
z-1- β a-s-r	4.605	z-4- γ s-w	6.221
z-9- γ -d-r	5.197	z-6- γ -d-w	6.266
z-7- γ -d-r	5.286	z-3- β c-d-r-u	6.338
z-1- β a-d-r-p	5.288	z-5- γ -d-r	6.384
z-1- β a-s-r-u	5.426	z-4- β a-s-r	6.387
z-2- γ -d-r	5.503	z-11- β c-d-r	6.506
z-9- γ -d-w	5.523	z-9- γ s-w	6.523

z-5- β c-d-r-u	6.882	z-7- $\xi\alpha$ a-w	14.567
z-3- β c-s-r	6.885	z-21- γ -d-r	14.918
z-11- β c-d-w	6.930	z-21- γ -d-w	15.096
z-3- γ -s-w	6.954	z-4- $\xi\beta$ a-r	15.203
z-6- α c-s-r	6.964	z-6- $\xi\alpha$ c-r	15.205
z-4- β a-d-r-u	6.985	z-22- γ -d-w	15.239
z-5- β c-s-r	7.452	z-19- γ -s-w	15.337
z-3- β c-s-r-u	7.526	z-3- $\xi\beta$ c-r	15.383
z-12- α c-s-w	7.635	z-13- $\beta\beta'$ -s-w	15.407
z-3- β c-d-r-p	7.645	z-13- $\beta\beta$ -d-r-u	16.005
z-8- α c-s-r	7.790	z-20- γ -s-w	15.568
z-10- γ -d-r	7.894	z-10- η -w	15.862
z-5- β c-s-r-u	7.905	z-21- γ -s-w	15.867
z-4- β a-s-r-u	8.132	z-1- η -w	16.062
z-4- β a-d-r-p	8.134	z-5- $\xi\beta$ c-r	16.247
z-6- α c-s-w-p	8.189	z-22- γ -s-w	16.305
z-5- β c-d-r-p	8.239	z-14- $\alpha\beta$ -s-r	16.334
z-5- γ -d-w	8.431	z-4- η -w	16.566
z-10- γ -s-w-u	8.455	z-16- β a-d-w	16.673
z-7- α a-s-w-p	8.700	z-9- η -w	16.721
z-2- α a-s-r-p	8.780	z-18- $\alpha\beta$ -s-r	16.727
z-6- γ -s-w-u	8.917	z-15- γ -d-w	16.958
z-9- γ -d-r-u	9.115	z-3- η -w	17.200
z-11- γ -s-w	9.433	z-17- $\alpha\beta$ -s-r	17.244
z-1- β a-d-r-u-p	9.526	z-14- $\alpha\beta'$ -s-r	17.286
z-1- β a-s-r-p	9.569	z-13- $\beta\beta$ -s-r	17.361
z-5- γ -s-r	9.580	z-13- $\beta\beta$ -s-r-u	17.410
z-9- γ -s-r	9.759	z-16- β a-s-r	17.722
z-11- β c-s-r	9.851	z-21- γ -d-w-u	17.726
z-12- α c-s-r	9.929	z-15- β c-s-r	17.748
z-2- γ -s-r-u	10.193	z-21- γ -s-w-u	17.882
z-7- γ -d-r-u	10.364	z-15- β c-d-r-p	17.916
z-9- γ -d-r-p	10.395	z-16- β a-d-r-p	18.233
z-1- β a-s-r-u-p	10.572	z-9- η -r	18.459
z-10- γ -s-w-p	10.604	z-11- $\xi\alpha$ c-r	18.590
z-9- γ -d-w-p	10.674	z-10- η -w-p	18.666
z-6- γ -s-r-u	11.022	z-21- γ -d-r-u	18.767
z-10- γ -d-w-p	11.120	z-1- η -w-p	18.952
z-2- $\xi\alpha$ a-w	11.386	z-16- β a-s-r-u	18.869
z-9- γ -s-w-p	11.550	z-19- γ -s-r	19.085
z-13- $\beta\beta$ -d-r	11.668	z-21- γ -s-r	19.251
z-11- β c-d-r-p	11.683	z-4- η -w-p	19.443
z-3- β c-s-r-p	11.794	z-21- γ -s-r-u	19.465
z-14- $\alpha\beta$ -s-w	12.312	z-19- γ -d-w-p	19.503
z-5- β c-s-r-p	12.331	z-9- η -w-p	19.560
z-15- β c-d-r	12.585	z-3- η -w-p	20.026
z-13- $\beta\beta'$ -d-w	12.730	z-19- γ -s-r-u	20.190
z-16- β a-d-r	12.868	z-20- γ -s-r-u	20.293
z-10- γ -d-r-p	13.104	z-10- η -r	21.539
z-1- $\xi\beta$ a-r	13.104	z-14- $\xi\alpha\beta$ -w	23.910
z-2- $\xi\alpha$ a-r	13.129	z-13- $\xi\beta\beta'$ -w	24.920
z-10- γ -s-r	13.226	z-19- η -w	25.381
z-6- $\xi\alpha$ c-w	13.282	z-20- η -w	25.638
z-10- γ -s-r-u	13.371	z-14- $\xi\alpha\beta'$ -r	25.674
z-1- $\xi\beta$ a-r	13.407	z-14- $\xi\alpha\beta$ -r	25.703
z-10- γ -s-w-u-p	13.507	z-13- $\xi\beta\beta$ -r	25.730
z-17- $\alpha\beta$ -s-w	13.532	z-18- $\xi\alpha\beta$ -r	25.813
z-18- $\alpha\beta$ -s-w	13.612	z-17- $\xi\alpha\beta$ -r	25.968
z-19- γ -d-r	14.293	z-22- η -w	26.418
z-19- γ -d-w	14.335	z-15- $\xi\beta$ c-r	26.470
z-9- γ -d-r-u-p	14.404	z-5- η -w	27.049
z-20- γ -d-w	14.417	z-19- η -r	27.607
z-7- $\xi\alpha$ a-r	14.468	z-20- η -r	28.116
z-14- $\alpha\beta'$ -w	14.512	z-20- η -r-p	31.067

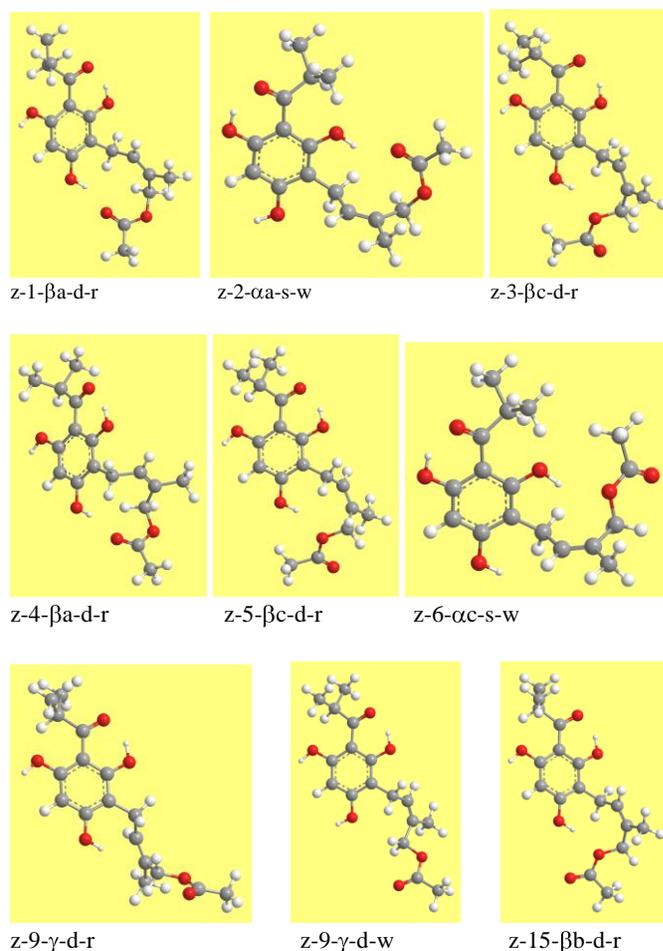


Fig. 2. Conformers of the Z isomer of caespitate, selected to represent different geometry patterns.

the IHB, mutual orientation of the phenol OH) are the same and the energy is the same. Since the acronyms are meant to keep track of the factors that might influence conformational preferences and energies, there is no reason to differentiate between conformers pertaining to pairs of this type.

Table 4 reports the relative energies of the calculated conformers of cspt-E *in vacuo* and fig. 3–5 show the geometries of selected conformers. The absolute energies of the lowest energy conformers of the two isomers are -693906.458 kcal/mol for z-1- β a-d-r and -693902.705 kcal/mol for e-1- γ -d-r.

Comparison of tables 3 and 4 shows the major differences in conformational preferences between the two isomers. For cspt-Z, the role of the second IHB dominates the geometry preferences *in vacuo*, and the variety of low-energy geometries relates to the variety of possible options for the formation of the second IHB. For cspt-E, many low-energy conformers (including the lowest energy one) do not have the second IHB, and the variety of possible geometries relates to the high flexibility of unconstrained R'. This difference may be responsible for the difference in the distribution of low energy conformers for the two isomers: only few low-energy

conformers for cspt-Z and many for cspt-E. For instance, there are only six conformers with energy <3.5 for cspt-Z and 31 for cspt-E. Moreover, while it is realistic to assume that all the low-energy conformers of cspt-Z have been captured in the calculations, this may not be the case for cspt-E.

Calculations have tried to capture the most representative conformers, with particular attention to the low-energy ones. It is however easier to capture all (or nearly all) the possible geometries for the conformers with the second IHB, because

Table 4. Relative energies of representative conformers of the E isomer of caespitate. Results in vacuo.

conformer	relative energy (kcal/mol)	conformer	relative energy (kcal/mol)
e-1- γ -d-r	0.000	e-7- α a-s-w-p	5.842
e-2- α a-s-w	0.343	e-4- γ -s-r-u	6.629
e-3- γ -s-w	0.408	e-13- α a-s-r	6.850
e-4- β a-d-r	0.423	e-2- γ -s-r-u	7.409
e-5- γ -s-w	0.454	e-5- γ -s-r	7.785
e-7- α a-s-w	0.776	e-3- γ -s-r	8.636
e-6- γ -s-w	0.798	e-15- γ -d-r	9.144
e-8- β a-d-r	0.852	e-16- γ -d-r	9.489
e-9- γ -d-r	1.024	e-17- γ -d-r	9.731
e-10- γ -s-w	1.246	e-16- γ -d-w	9.871
e-11- γ -d-r	1.515	e-18- γ -d-r	10.154
e-12- α a-s-w	1.524	e-19- γ -s-w	10.215
e-6- γ -d-r	1.635	e-20- γ -s-w	10.216
e-10- γ -d-r	1.715	e-15- γ -d-w	10.341
e-6- γ -d-w	1.746	e-21- γ -d-r	10.391
e-1- γ -d-w	1.765	e-22- γ -d-w	10.396
e-5- γ -d-w	1.862	e-22- γ -d-r	10.444
e-3- γ -d-w	1.869	e-23- γ -d-w	10.517
e-2- γ -d-w	2.165	e-23- γ -s-w	10.633
e-2- γ -d-r	2.166	e-23- γ -d-r	10.652
e-10- γ -d-w	2.350	e-19- γ -d-w	10.687
e-4- γ -d-w	2.425	e-20- γ -d-r	10.768
e-9- γ -s-w	2.540	e-17- γ -d-w	10.783
e-1- γ -s-w	2.652	e-22- γ -s-w	10.871
e-9- γ -d-w	2.673	e-20- γ -d-w	10.918
e-5- γ -d-r	2.799	e-19- γ -d-r	10.936
e-3- γ -d-r	2.817	e-18- γ -d-w	11.339
e-8- γ -d-w	2.965	e-16- γ -s-w	11.553
e-11- γ -d-w	3.138	e-21- γ -d-w	11.568
e-4- γ -s-w	3.214	e-21- γ -s-w	11.637
e-13- α a-s-w	3.262	e-17- γ -s-w	11.710
e-11- γ -s-w	3.582	e-18- γ -s-w	11.835
e-2- α a-s-r	3.792	e-15- γ -s-w	12.083
e-8- γ -s-w	3.888	e-24- α a-s-w	12.167
e-7- α a-s-r	4.186	e-2- ξ α a-r	12.527
e-6- γ -s-r	4.473	e-6- η -r	13.084
e-1- γ -s-r	4.490	e-4- ξ β a-r	13.166
e-4- β a-d-r-u	4.493	e-8- η -w	13.795
e-10- γ -s-r	4.531	e-20- γ -s-r	13.884
e-9- γ -s-r	4.669	e-17- γ -s-r	14.061
e-14- β a-s	5.038	e-23- γ -s-r	14.469
e-4- β a-s-r	5.043	e-21- γ -s-r	14.493
e-8- β a-s-r	5.149	e-16- γ -s-r	14.589
e-1- γ -d-r-p	5.284	e-22- γ -s-r	14.641
e-2- γ -s-w-u	5.285	e-24- γ -s-r-u	14.785
e-11- γ -s-r	5.499	e-18- γ -s-r	14.817
e-4- β a-d-r-p	5.600	e-24- α a-s-r	15.325
e-4- β a-s-r-u	5.780	e-24- ξ α a-r	23.258

the variety of options for ring formation is limited, although much higher for cspt.Z (as will be analysed later). Capturing all (or nearly all) the possible geometries of the conformers without the second IHB is more difficult. Table 4 shows the dominance of conformers without the second IHB for cspt-E. Therefore, while it is reasonable to assume that all the lower energy conformers of cspt-Z have been captured (and the fact that different inputs started yielding the same optimized geometries supports this assumption), for cspt-E it is only possible to assume that most of them have been captured. This also affects the possibility of considering conformers' populations. For cspt-Z, the lowest energy conformer accounts for 78.6 % population, the second lowest energy conformer for 18.3 % and the third lowest energy conformer for 1.3 %, so that the three low energy conformers account for 98.2 % population. The population of the other conformers is marginal. Overall, the total of conformers with two IHB accounts for 99.9 % population and the total of conformers with only the first IHB for 0.08 %.

For cspt-E, a high number of conformers have significant population; moreover, the fact that many conformers without

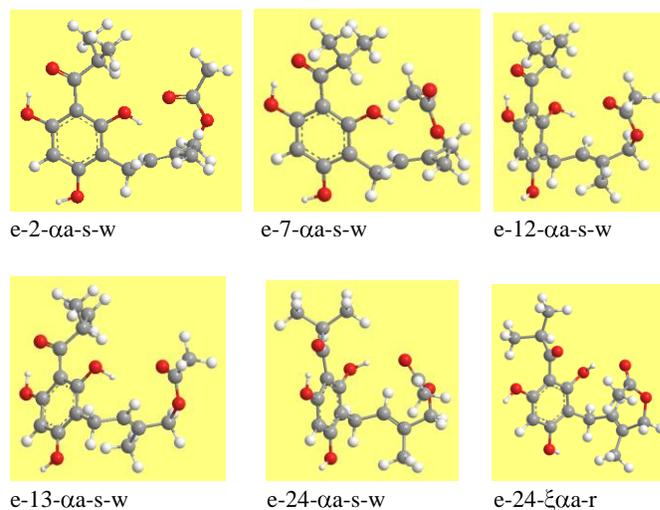


Fig. 3. Conformers of the E isomer of caespitate in which the second IHB engages H15; s-w conformers selected for illustration.

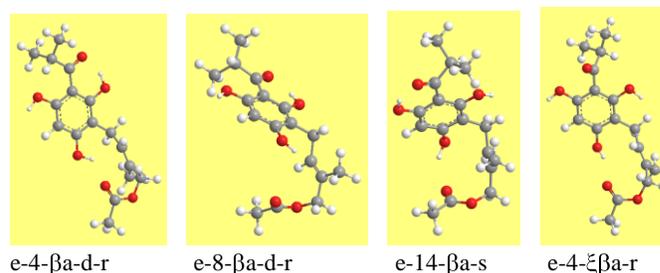


Fig. 5. Conformers of the E isomer of caespitate in which the second IHB engages H16.

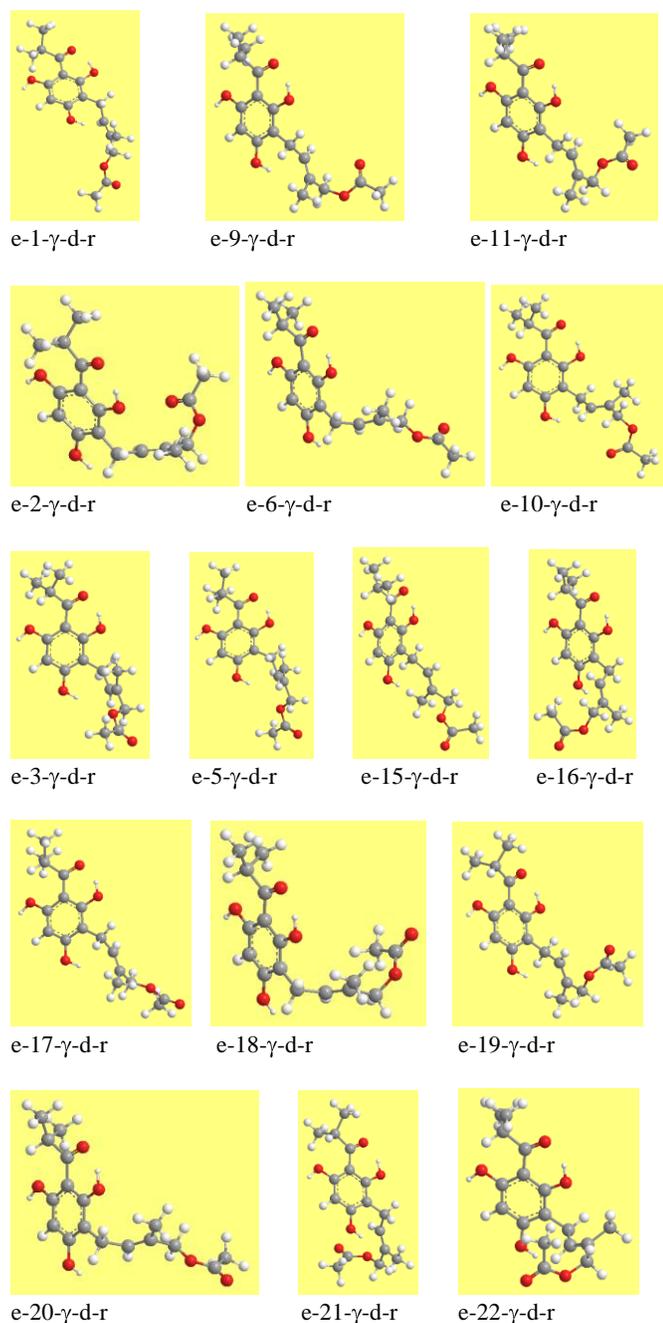


Fig. 5. Conformers of the E isomer of caespitate with only the first IHB. Representative d-r conformers are selected for illustration.

the first IHB appear among the low energy ones suggests caution, because of the probability that not all of them have been captured. Actually, the study considered the geometries of R' that are significantly different from each other. Geometries differing only by small changes in the torsion angles of the last atoms have not been explored systematically, because their exploration is not expected to bring interesting information and would be excessively costly computationally. An example is offered by the geometries of 6- γ s-w and the other conformers shown in fig. 6, differing only by the orientation of O23 and of the H atoms of the terminal methyl

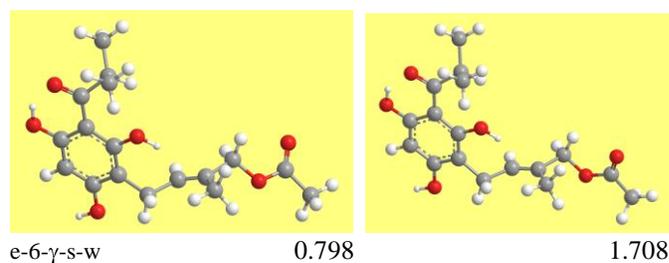


Fig. 6. Example of conformers differing slightly for the orientation of the terminal part of R': e-6- γ -s-w and the conformer on the right. Their relative energies are reported under each image, aligned to the right side of the image.

of R'. It is interesting to note that the corresponding d conformers coincide completely. For cases of this type, only the lower energy conformer has been selected for investigation (e.g., for consideration of the ones that can derive from it). Under these circumstances, a consideration of conformers' population distribution is not viable for cspt-E. The case in fig. 6 also highlights another peculiarity of cspt-E, i.e., the fact that the correspondence between conformers derivable from each other is not always simple, as a given conformer may derive from more than one starting conformer (e.g., e-6- γ -d-w results from inputs shifting the first IHB to the right on either of the conformers in fig. 6).

The comparison of the effects of the geometry features of the phloroglucinol moiety influencing conformational preferences and energies are better analysed through comparative tables. Table 5 compares corresponding conformers differing only by the orientation of H16 for cspt-Z E, and table 6 for cspt-E. The general results for ACPL show preference for toward-R' (r) orientation of H16. Discrepancies with this trend are only few in the case of cspt-Z and considerably more numerous in the case of cspt-E.

The study of ACPL also shows preference for the OH ortho to the acyl chain and not engaged in the first IHB to be oriented away from R (non-u conformers) rather than toward R (u conformers). The preference is due both to greater steric hindrances in u-conformers and to the presence of C-H...O weaker hydrogen bonds in non-u conformers, and is less marked for s-r conformers [7, 19]. It was tested rather extensively on cspt-Z (table 7) and only randomly on cspt-E (table 8). The only discrepancy concerns the e-24- α -s-r / e-24- γ -s-r-u pair, but this is a case where the upward orientation of H15 implies the removal of the second IHB and, therefore, additional factors interfere in influencing the conformers' energy.

Other features common to all ACPL [7] are common to both isomers, like the preference for uniform orientation of the three phenol OH and for "upward" orientation of the methyls of R (whose downward orientation causes ≈ 5 kcal/mol energy increase when the first IHB is present).

Table 5. Comparison of the relative energy (ΔE) of conformers of the Z isomer of caespitate differing only by the orientation of H16. The relative energy difference ($\Delta(\Delta E)$) is evaluated as «energy of the r conformer minus energy of the w conformer».

H16 away from R'		H16 toward R'		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
z-2- α a-s-w	0.864	z-2- α a-s-r	4.143	3.279
z-7- α a-s-w	4.135	z-7- α a-s-r	6.078	1.943
z-6- α c-s-w	3.358	z-6- α c-s-r	6.964	3.606
z-8- α c-s-w	4.221	z-8- α c-s-r	7.790	3.569
z-12- α c-s-w	7.635	z-12- α c-s-r	9.929	2.294
z-14- α b-s-w	12.312	z-14- α b-s-r	16.334	4.022
z-17- α b-s-w	13.532	z-17- α b-s-r	17.244	3.712
z-18- α b-s-w	13.612	z-18- α b-s-r	16.727	3.115
z-14- α b'-s-w	14.512	z-14- α b'-s-r	17.286	2.774
z-7- ξ α a-w	14.567	z-7- ξ α a-r	14.468	-0.099
z-14- ξ α b-w	23.910	z-14- ξ α b-r	25.703	1.793
z-6- ξ α c-w	13.282	z-6- ξ α c-r	15.205	1.923
z-9- γ -d-w	5.523	z-9- γ -d-r	5.197	-0.326
z-6- γ -d-w	6.266	z-6- γ -d-r	6.158	-0.108
z-10- γ -d-w	6.028	z-10- γ -d-r	7.894	1.866
z-5- γ -d-w	8.431	z-5- γ -d-r	6.384	-2.047
z-19- γ -d-w	14.335	z-19- γ -d-r	14.293	-0.042
z-21- γ -d-w	15.096	z-21- γ -d-r	14.918	-0.178
z-21- γ -d-w-u	17.726	z-21- γ -d-r-u	18.767	1.041
z-9- γ -d-w-p	10.674	z-9- γ -d-r-p	10.395	-0.279
z-10- γ -d-w-p	11.120	z-10- γ -d-r-p	13.104	1.984
z-10- γ -s-w	5.703	z-10- γ -s-r	13.226	7.523
z-5- γ -s-w	6.074	z-5- γ -s-r	9.580	3.506
z-9- γ -s-w	6.523	z-9- γ -s-r	9.759	3.236
z-19- γ -s-w	15.337	z-19- γ -s-r	19.085	3.748
z-21- γ -s-w	15.867	z-21- γ -s-r	19.251	3.384
z-6- γ -s-w-u	8.917	z-6- γ -s-r-u	11.022	2.105
z-10- γ -s-w-u	8.455	z-10- γ -s-r-u	13.371	4.916
z-21- γ -s-w-u	17.882	z-21- γ -s-r-u	19.465	1.583
z-9- η -w	16.721	z-9- η -r	18.459	1.738
z-10- η -w	15.862	z-10- η -r	21.539	5.677
z-19- η -w	25.381	z-19- η -r	27.607	2.226
z-20- η -w	25.638	z-20- η -r	28.116	2.478

B. Intramolecular hydrogen bonding and its main patterns

Intramolecular hydrogen bonding shows similar patterns for the first IHB and different patterns for the second IHB and the O-H... π interaction, with the differences ascribable to the effects of geometric isomerism.

The characteristics of the first IHB are similar for the two isomers. The H...O length and the O...O distance of the first IHB have similar ranges and are always shorter when the IHB engages H15 than when it engages H17 (length close to 1.655 for H15...O14 and >1.702 for H17...O14). Table 9 reports the

Table 6. Comparison of the relative energy (ΔE) of conformers of the E isomer of caespitate differing only by the orientation of H16. The relative energy difference ($\Delta(\Delta E)$) is evaluated as «energy of the r conformer minus energy of the w conformer».

H16 away from R'		H16 toward R'		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
e-1- γ -d-w	1.765	e-1- γ -d-r	0.000	-1.765
e-2- α a-s-w	0.343	e-2- α a-s-r	3.792	3.449
e-3- γ -s-w	0.408	e-3- γ -s-r	8.636	8.228
e-4- γ -d-w	2.425	e-4- β a-d-r *	0.423	-2.002
e-5- γ -s-w	0.454	e-5- γ -s-r	7.785	7.331
e-7- α a-s-w	0.776	e-7- α a-s-r	4.186	3.410
e-6- γ -s-w	0.798	e-6- γ -s-r	4.473	3.675
e-8- γ -d-w	2.965	e-8- β a-d-r *	0.852	-2.113
e-9- γ -d-w	2.673	e-9- γ -d-r	1.024	-1.649
e-10- γ -s-w	1.246	e-10- γ -s-r	4.531	3.285
e-11- γ -d-w	3.138	e-11- γ -d-r	1.515	-1.623
e-6- γ -d-w	1.746	e-6- γ -d-r	1.635	-0.111
e-10- γ -d-w	2.350	e-10- γ -d-r	1.715	-0.635
e-5- γ -d-w	1.862	e-5- γ -d-r	2.799	0.937
e-3- γ -d-w	1.869	e-3- γ -d-r	2.817	0.948
e-2- γ -d-w	2.165	e-2- γ -d-r	2.166	0.001
e-9- γ -s-w	2.540	e-9- γ -s-r	4.669	2.129
e-1- γ -s-w	2.652	e-1- γ -s-r	4.490	1.838
e-4- γ -s-w	3.214	e-4- β a-s-r *	5.043	1.829
e-13- α a-s-w	3.262	e-13- α a-s-r	6.850	3.588
e-11- γ -s-w	3.582	e-11- γ -s-r	5.499	1.917
e-8- γ -s-w	3.888	e-8- β a-s-r *	5.149	1.261
e-16- γ -d-w	9.871	e-16- γ -d-r	9.489	-0.382
e-17- γ -d-w	10.783	e-17- γ -d-r	9.731	-1.052
e-18- γ -d-w	11.339	e-18- γ -d-r	10.154	-1.185
e-20- γ -s-w	10.216	e-20- γ -s-r	13.884	3.668
e-15- γ -d-w	10.341	e-15- γ -d-r	9.144	-1.197
e-21- γ -d-w	11.568	e-21- γ -d-r	10.391	-1.177
e-22- γ -d-w	10.396	e-22- γ -d-r	10.444	0.048
e-23- γ -d-w	10.517	e-23- γ -d-r	10.652	0.135
e-22- γ -s-w	10.871	e-22- γ -s-r	14.641	3.770
e-23- γ -s-w	10.633	e-23- γ -s-r	14.469	3.836
e-19- γ -d-w	10.687	e-19- γ -d-r	10.936	0.249
e-20- γ -d-w	10.918	e-20- γ -d-r	10.768	-0.150
e-16- γ -s-w	11.553	e-16- γ -s-r	14.589	3.036
e-21- γ -s-w	11.637	e-21- γ -s-r	14.493	2.856
e-17- γ -s-w	11.710	e-17- γ -s-r	14.061	2.351
e-18- γ -s-w	11.835	e-18- γ -s-r	14.817	2.982
e-24- α a-s-w	12.167	e-24- α a-s-r	15.325	3.158

* In this case, the r \rightarrow w shift removes the second IHB.

parameters of the first IHB for the 20 lowest energy conformers of cspt-Z and table 10 for a considerable selection of conformers of cspt-E.

In ACPL, the first IHB prefers to form on the same side as R'. Tables 11 and 12 show the comparison of corresponding conformers of cspt-Z differing only by the position of the first IHB and tables 13 and 14 show analogous comparisons for the conformers of cspt-E.

For ACPL, the energy increase on first IHB removal provides reliable indications about the IHB strength, because

Table 7. Comparison of the relative energy (ΔE) of conformers of the Z isomer of caespitate differing only by the orientation of the ortho OH not engaged in the first IHB: away from R (non-u) or toward R (u).

The relative energy difference ($\Delta(\Delta E)$) is evaluated as «energy of the u conformer minus energy of the non-u conformer».

free ortho OH away from R		free ortho OH toward R		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
z-1- β a-d-r	0.000	z-1- β a-d-r-u	4.175	4.175
z-3- β c-d-r	2.431	z-3- β c-d-r-u	6.338	3.907
z-4- β a-d-r	2.890	z-4- β a-d-r-u	6.985	4.095
z-5- β c-d-r	2.981	z-5- β c-d-r-u	6.882	3.901
z-1- β a-d-r-p	5.288	z-1- β a-d-r-u-p	9.526	4.238
z-13- β b-d-r	11.668	z-13- β b-d-r-u	16.005	4.337
z-1- β a-s-r	4.605	z-1- β a-s-r-u	5.426	0.821
z-4- β a-s-r	6.387	z-4- β a-s-r-u	8.132	1.745
z-16- β a-s-r	17.722	z-16- β a-s-r-u	18.869	1.147
z-1- β a-s-r-p	9.569	z-1- β a-s-r-u-p	10.572	1.003
z-3- β c-s-r	6.885	z-3- β c-s-r-u	7.526	0.641
z-5- β c-s-r	7.452	z-5- β c-s-r-u	7.905	0.453
z-13- β b-s-r	17.361	z-13- β b-s-r-u	17.410	0.049
z-7- γ -d-r	5.286	z-7- γ -d-r-u	10.364	5.078
z-9- γ -d-r	5.197	z-9- γ -d-r-u	9.115	3.918
z-21- γ -d-r	14.918	z-21- γ -d-r-u	18.767	3.849
z-9- γ -d-r-p	10.395	z-9- γ -d-r-u-p	14.404	4.009
z-21- γ -d-w	15.096	z-21- γ -d-w-u	17.726	2.630
z-10- γ -s-w	5.703	z-10- γ -s-w-u	8.455	2.752
z-21- γ -s-w	15.867	z-21- γ -s-w-u	17.882	2.015
z-10- γ -s-w-p	10.604	z-10- γ -s-w-u-p	13.507	2.903
z-10- γ -s-r	13.226	z-10- γ -s-r-u	13.371	0.145
z-19- γ -s-r	19.085	z-19- γ -s-r-u	20.190	1.105
z-21- γ -s-r	19.251	z-21- γ -s-r-u	19.465	0.214

Table 8. Comparison of the relative energy (ΔE) of conformers of the Z isomer of caespitate differing by the orientation of the ortho OH not engaged in the first IHB: away from R (non-u) or toward R (u).

The relative energy difference ($\Delta(\Delta E)$) is evaluated as «energy of the u conformer minus energy of the non-u conformer».

H16 away from R'		H16 toward R		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
e-2- α a-s-w	0.343	e-2- γ -s-w-u	5.285	4.942
e-4- β a-d-r	0.423	e-4- β a-d-r-u	4.493	4.070
e-2- α a-s-r	3.792	e-2- γ -s-r-u	7.409	3.617
e-4- β a-s-r	5.043	e-4- β a-s-r-u	5.780	0.737
e-24- α a-s-r	15.325	e-24- γ -s-r-u	14.785	-0.540

the O \leftrightarrow O repulsion is significantly smoothed by the off-plane shift of O14, taking it away from O8 or O12 [3–5]. The energy increase on removing H17...O14 has the same range (8–9 kcal/mol) for both isomers, whereas for H15...O14 the increase is 12–14 kcal/mol for cspt-Z and \approx 10 kcal/mol for cspt-E. Table 15 shows the energy increase on first IHB removal for selected conformers of cspt-Z and table 16 for selected conformers of cspt-E. Only few conformers without the first

Table 9. Parameters of the first IHB in the 20 lowest energy conformers of the Z isomer of caespitate. The relative energy *in vacuo* is reported for reference purposes.

conformer	relative energy <i>in vacuo</i>	parameters of the first IHB		
		H...O	O...O	O- \dot{H} -O
z-1- β a-d-r	0.000	1.655	2.509	146.9
z-2- α a-s-w	0.864	1.706	2.540	145.1
z-3- β c-d-r	2.431	1.656	2.509	146.3
z-4- β a-d-r	2.890	1.661	2.511	146.5
z-5- β c-d-r	2.981	1.656	2.508	147.4
z-6- α c-s-w	3.358	1.731	2.558	152.0
z-7- α a-s-w	4.135	1.706	2.538	144.1
z-2- α a-s-r	4.143	1.720	2.550	144.4
z-1- β a-d-r-u	4.175	1.719	2.555	145.7
z-8- α c-s-w	4.221	1.710	2.541	141.8
z-1- β a-s-r	4.605	1.719	2.550	146.9
z-9- γ -d-r	5.197	1.654	2.507	147.7
z-7- γ -d-r	5.286	1.653	2.506	142.3
z-1- β a-d-r-p	5.288	1.713	2.547	145.8
z-1- β a-s-r-u	5.426	1.768	2.587	144.3
z-2- γ -d-r	5.503	1.662	2.513	144.0
z-9- γ -d-w	5.523	1.673	2.519	147.3
z-2- α a-s-w-p	5.613	1.775	2.589	150.4
z-1- γ -s-w	5.634	1.707	2.540	152.8
z-10- γ -s-w	5.703	1.703	2.536	150.6

Table 10. Parameters of the first IHB in the conformers of the E isomer of caespitate. The relative energy *in vacuo* is reported for reference purposes.

conformer	relative energy <i>in vacuo</i>	parameters of the first IHB		
		H...O	O...O	O- \dot{H} -O
e-1- γ -d-r	0.000	1.653	2.507	148.6
e-2- α a-s-w	0.343	1.726	2.555	144.0
e-3- γ -s-w	0.408	1.705	2.538	143.5
e-4- β a-d-r	0.423	1.656	2.510	149.7
e-5- γ -s-w	0.454	1.707	2.540	143.4
e-7- α a-s-w	0.776	1.694	2.531	143.9
e-6- γ -s-w	0.798	1.706	2.539	143.4
e-8- β a-d-r	0.852	1.656	2.509	146.0
e-9- γ -d-r	1.024	1.655	2.507	145.8
e-10- γ -s-w	1.246	1.705	2.538	143.3
e-11- γ -d-r	1.515	1.658	2.510	145.8
e-12- α a-s-w	1.524	1.722	2.550	144.1
e-6- γ -d-r	1.635	1.656	2.508	148.7
e-10- γ -d-r	1.715	1.657	2.508	148.6
e-6- γ -d-w	1.746	1.672	2.519	14
e-1- γ -d-w	1.765	1.671	2.518	145.1
e-5- γ -d-w	1.862	1.673	2.520	145.1
e-3- γ -d-w	1.869	1.673	2.520	145.2
e-2- γ -d-w	2.165	1.670	2.518	145.4
e-2- γ -d-r	2.166	1.656	2.508	145.8
e-10- γ -d-w	2.350	1.671	2.519	145.3
e-4- γ -d-w	2.425	1.679	2.524	145.0
e-9- γ -s-w	2.540	1.702	2.536	143.5
e-1- γ -s-w	2.652	1.703	2.536	143.2
e-9- γ -d-w	2.673	1.677	2.521	144.8
e-5- γ -d-r	2.799	1.653	2.507	146.1
e-3- γ -d-r	2.817	1.649	2.504	146.1

Table 10. Continuation

e-8- γ -d-w	2.965	1.674	2.521	145.2
e-11- γ -d-w	3.138	1.672	2.519	145.2
e-4- γ -s-w	3.214	1.695	2.530	144.7
e-13- α -s-w	3.262	1.725	2.554	142.4
e-11- γ -s-w	3.582	1.702	2.535	143.5
e-2- α -s-r	3.792	1.744	2.569	143.8
e-8- γ -s-w	3.888	1.715	2.568	145.0
e-7- α -s-r	4.186	1.707	2.540	143.8
e-6- γ -s-r	4.473	1.720	2.572	144.2
e-1- γ -s-r	4.490	1.729	2.556	142.9
e-4- β -d-r-u	4.493	1.720	2.557	144.2
e-10- γ -s-r	4.531	1.718	2.549	143.3
e-9- γ -s-r	4.669	1.728	2.556	142.9
e-14- β -s	5.038	1.741	2.565	142.5
e-4- β -s-r	5.043	1.706	2.556	144.2
e-8- β -s-r	5.149	1.729	2.556	142.9
e-1- γ -d-r-p	5.284	1.726	2.558	143.5
e-2- γ -s-w-u	5.285	1.763	2.582	142.0
e-11- γ -s-r	5.499	1.725	2.553	142.9
e-4- β -d-r-p	5.600	1.726	2.558	143.6
e-4- β -s-r-u	5.780	1.771	2.588	141.8
e-7- α -s-w-p	5.842	1.762	2.579	141.6
e-4- γ -s-r-u	6.629	1.768	2.586	141.9
e-13- α -s-r	6.850	1.742	2.567	142.6
e-2- γ -s-r-u	7.409	1.773	2.590	141.9
e-5- γ -s-r	7.785	1.730	2.557	142.7
e-3- γ -s-r	8.636	1.728	2.555	142.8
e-15- γ -d-r	9.144	1.654	2.507	146.0
e-16- γ -d-r	9.489	1.651	2.505	145.9
e-17- γ -d-r	9.731	1.657	2.509	145.7
e-16- γ -d-w	9.871	1.664	2.512	145.3
e-18- γ -d-r	10.154	1.660	2.512	145.8
e-19- γ -s-w	10.215	1.722	2.566	142.9
e-20- γ -s-w	10.216	1.702	2.535	143.5
e-15- γ -d-w	10.341	1.669	2.517	145.3
e-21- γ -d-r	10.391	1.650	2.503	145.9
e-22- γ -d-w	10.396	1.662	2.512	145.6
e-22- γ -d-r	10.444	1.649	2.503	146.0
e-23- γ -d-w	10.517	1.667	2.516	145.5
e-23- γ -s-w	10.633	1.713	2.544	143.3
e-23- γ -d-r	10.652	1.650	2.504	146.0
e-19- γ -d-w	10.687	1.669	2.515	145.1
e-20- γ -d-r	10.768	1.660	2.510	145.5
e-17- γ -d-w	10.783	1.673	2.519	145.1
e-22- γ -s-w	10.871	1.710	2.542	143.3
e-20- γ -d-w	10.918	1.675	2.521	145.1
e-19- γ -d-r	10.936	1.655	2.506	145.5
e-18- γ -d-w	11.339	1.682	2.525	144.7
e-16- γ -s-w	11.553	1.713	2.543	143.1
e-21- γ -d-w	11.568	1.666	2.513	145.0
e-21- γ -s-w	11.637	1.709	2.541	143.3
e-17- γ -s-w	11.710	1.700	2.533	143.5
e-18- γ -s-w	11.835	1.696	2.531	143.6
e-15- γ -s-w	12.083	1.703	2.536	143.4
e-24- α -s-w	12.167	1.735	2.561	142.7
e-20- γ -s-r	13.884	1.724	2.552	143.0
e-17- γ -s-r	14.061	1.725	2.552	142.9
e-23- γ -s-r	14.469	1.734	2.561	142.8
e-21- γ -s-r	14.493	1.732	2.558	142.7
e-16- γ -s-r	14.589	1.725	2.553	142.9
e-22- γ -s-r	14.641	1.722	2.551	143.1
e-24- γ -s-r-u	14.785	1.769	2.587	141.9
e-18- γ -s-r	14.817	1.713	2.543	143.2
e-24- α -s-r	15.325	1.759	2.607	143.7

IHB were calculated for cspt-E because the study of ACPL [7] had shown that they are totally unpopulated. For lower energy (non-u, non-p) conformers, the lowering of the computed harmonic vibrational frequencies of the donor OH caused by the first IHB is 7-8%/cspt-Z and 7%/cspt-E for O12-H17 and 9-10%/cspt-Z and 8%/cspt-E for O8-H15. These data show that discrepancies between the two isomers, although not remarkable, concern more the first IHB forming on the same side as R'.

The main difference between the two isomers is related to the different ability of R' towards ring formation, which is determined by the difference around the C18=C19 double bond and in turn determines the possibility of formation of the second IHB. In cspt-Z, the two longer branches attached to C18 and C19 are on the same side of the double bond and this facilitates the closing of a ring, with the second IHB linking the two branches. Moreover, the ring thus resulting does not contain H atoms oriented internally to it. This enables cspt-Z to form second IHBs in which either O23 or O21 or both O23 and O21 (bifurcation on the H atom) have the role of acceptors, with corresponding 11-member or 9-member rings

Table 11. Comparison of the relative energies (ΔE) of conformers of the Z isomer of caespitate differing only by the position of the first IHB – engaging H15 (d) or H17 (s). Conformers with H16 oriented toward R' (r).

The relative energy difference ($\Delta(\Delta E)$) is evaluated as «energy of the s-r conformer minus energy of the d-r conformer».

first IHB engaging H15		first IHB engaging H17		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
z-1- β -d-r	0.000	z-1- β -s-r	4.605	4.605
z-4- β -d-r	2.890	z-4- β -s-r	6.387	3.497
z-16- β -d-r	12.868	z-16- β -s-r	17.722	4.854
z-3- β -c-d-r	2.431	z-3- β -c-s-r	6.885	4.454
z-5- β -c-d-r	2.981	z-5- β -c-s-r	7.452	4.471
z-11- β -c-d-r	6.506	z-11- β -c-s-r	9.851	3.345
z-15- β -c-d-r	12.585	z-15- β -c-s-r	17.748	5.163
z-13- β -b-d-r	11.668	z-13- β -b-s-r	17.361	5.693
z-1- β -d-r-u	4.175	z-1- β -s-r-u	5.426	1.251
z-4- β -d-r-u	6.985	z-4- β -s-r-u	8.132	1.147
z-3- β -c-d-r-u	6.338	z-3- β -c-s-r-u	7.526	1.188
z-5- β -c-d-r-u	6.882	z-5- β -c-s-r-u	7.905	1.023
z-13- β -b-d-r-u	16.005	z-13- β -b-s-r-u	17.410	1.405
z-1- β -d-r-p	5.288	z-1- β -s-r-p	9.569	4.281
z-3- β -c-d-r-p	7.645	z-3- β -c-s-r-p	11.794	4.149
z-5- β -c-d-r-p	8.239	z-5- β -c-s-r-p	12.331	4.092
z-1- β -d-r-u-p	9.526	z-1- β -s-r-u-p	10.572	1.046
z-9- γ -d-r	5.197	z-9- γ -s-r	9.759	4.562
z-5- γ -d-r	6.384	z-5- γ -s-r	9.580	3.196
z-10- γ -d-r	7.894	z-10- γ -s-r	13.226	5.332
z-19- γ -d-r	14.293	z-19- γ -s-r	19.085	4.792
z-21- γ -d-r	14.918	z-21- γ -s-r	19.251	4.333
z-21- γ -d-r-u	18.767	z-21- γ -s-r-u	19.465	0.698

Table 12. Comparison of the relative energies (ΔE) of conformers of the Z isomer of caespitate differing only by the position of the first IHB – engaging H15 (d) or H17 (s). Conformers with H16 oriented away from R' (w).

The relative energy difference ($\Delta(\Delta E)$) is evaluated as «energy of the s-s conformer minus energy of the d-w conformer».

first IHB engaging H15		first IHB engaging H17		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
z-9- γ -d-w	5.523	z-9- γ -s-w	6.523	1.000
z-1- γ -d-w	5.906	z-1- γ -s-w	5.634	-0.272
z-10- γ -d-w	6.028	z-10- γ -s-w	5.703	-0.325
z-3- γ -d-w	6.030	z-3- γ -s-w	6.954	0.924
z-4- γ -d-w	6.049	z-4- γ -s-w	6.221	0.172
z-5- γ -d-w	8.431	z-5- γ -s-w	6.074	-2.357
z-19- γ -d-w	14.335	z-19- γ -s-w	15.337	1.002
z-20- γ -d-w	14.417	z-20- γ -s-w	15.568	1.151
z-21- γ -d-w	15.096	z-21- γ -s-w	15.867	0.771
z-22- γ -d-w	15.239	z-22- γ -s-w	16.305	1.066
z-21- γ -d-w-u	17.726	z-21- γ -s-w-u	17.882	0.156
z-10- γ -d-w-p	11.120	z-10- γ -s-w-p	10.604	-0.516
z-9- γ -d-w-p	10.674	z-9- γ -s-w-p	11.550	0.876
z-13- β b'-d-w	12.730	z-13- β b'-s-w	15.407	2.677

Table 13. Comparison of the relative energies (ΔE) of conformers of the E isomer of caespitate differing only by the position of the first IHB – engaging H15 (d) or H17 (s). Conformers with H16 oriented toward R' (r).

The relative energy difference ($\Delta(\Delta E)$) is evaluated as «energy of the s-r conformer minus energy of the d-r conformer».

first IHB engaging H15		first IHB engaging H17		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
e-1- γ -d-r	0.000	e-1- γ -s-r	4.490	4.490
e-4- β a-d-r	0.423	e-4- β a-s-r	5.043	4.620
e-8- β a-d-r	0.852	e-8- β a-s-r	5.149	4.297
e-9- γ -d-r	1.024	e-9- γ -s-r	4.669	3.645
e-11- γ -d-r	1.515	e-11- γ -s-r	5.499	3.984
e-6- γ -d-r	1.635	e-6- γ -s-r	4.473	2.838
e-10- γ -d-r	1.715	e-10- γ -s-r	4.531	2.816
e-5- γ -d-r	2.799	e-5- γ -s-r	7.785	4.986
e-3- γ -d-r	2.817	e-3- γ -s-r	8.636	5.819
e-4- β a-d-r-u	4.493	e-4- β a-s-r-u	5.780	1.287
e-16- γ -d-r	9.489	e-16- γ -s-r	14.589	5.100
e-17- γ -d-r	9.731	e-17- γ -s-r	14.061	4.330
e-18- γ -d-r	10.154	e-18- γ -s-r	14.817	4.663
e-21- γ -d-r	10.391	e-21- γ -s-r	14.493	4.102
e-22- γ -d-r	10.444	e-22- γ -s-r	14.641	4.197
e-23- γ -d-r	10.652	e-23- γ -s-r	14.469	3.817
e-20- γ -d-r	10.768	e-20- γ -s-r	13.884	3.116

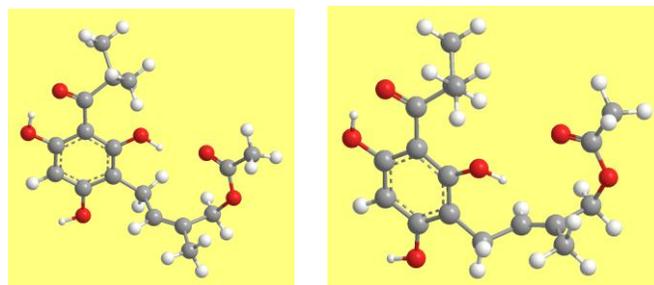
and a high variety of different geometries. In cspt-E, the two branches attached to C18 and C19 are on different sides of the C18=C19 double bond, which makes it more difficult for them

Table 14. Comparison of the relative energies (ΔE) of conformers of the E isomer of caespitate differing only by the position of the first IHB – engaging H15 (d) or H17 (s). Conformers with H16 oriented away from R' (w).

The relative energy difference ($\Delta(\Delta E)$) is evaluated as «energy of the s-s conformer minus energy of the d-w conformer».

first IHB engaging H15		first IHB engaging H17		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
e-3- γ -d-w	1.869	e-3- γ -s-w	0.408	-1.461
e-5- γ -d-w	1.862	e-5- γ -s-w	0.454	-1.408
e-6- γ -d-w	1.746	e-6- γ -s-w	0.798	-0.948
e-10- γ -d-w	2.350	e-10- γ -s-w	1.246	-1.104
e-1- γ -d-w	1.765	e-1- γ -s-w	2.652	0.887
e-4- γ -d-w	2.425	e-4- γ -s-w	3.214	0.789
e-9- γ -d-w	2.673	e-9- γ -s-w	2.540	-0.133
e-8- γ -d-w	2.965	e-8- γ -s-w	3.888	0.923
e-11- γ -d-w	3.138	e-11- γ -s-w	3.582	0.444
e-16- γ -d-w	9.871	e-16- γ -s-w	11.553	1.682
e-19- γ -d-w	10.687	e-19- γ -s-w	10.215	-0.472
e-20- γ -d-w	10.918	e-20- γ -s-w	10.216	-0.702
e-15- γ -d-w	10.341	e-15- γ -s-w	12.083	1.742
e-22- γ -d-w	10.396	e-22- γ -s-w	10.871	0.475
e-23- γ -d-w	10.517	e-23- γ -s-w	10.633	0.116
e-17- γ -d-w	10.783	e-17- γ -s-w	11.710	0.927
e-18- γ -d-w	11.339	e-18- γ -s-w	11.835	0.496
e-21- γ -d-w	11.568	e-21- γ -s-w	11.637	0.069

to form a ring. A ring is unavoidably more geometrically strained and the donor and acceptor remain at a greater distance (figure 6). As a result, the only type of second IHB formed in cspt-E engages O23, as O23 protrudes from the skeleton of R' and is therefore able to sufficiently approach the donor; this IHB closes an 11-member ring (the difficulty in closing a smaller ring makes the 9-member ring, which would result from an IHB with O21, impossible). In addition, H30 is often oriented toward the inner part of the ring, with a destabilizing steric effect.



z-2- α a-s-w

e-2- α a-s-w

Fig. 6. Comparison of the effect of the mutual position of the longer substituent around the C18=C19 double bond on the easiness with which the donor and acceptor of the second IHB may approach each other. The two atoms can approach more closely in the Z isomer than in the E isomer.

Table 15. Energy increase on first IHB removal for selected conformers of the Z isomer of caespitate. The energy increase ($\Delta(\Delta E)$) is evaluated as «energy of the conformer without the first IHB minus energy of the conformer with the first IHB».

first IHB present		first IHB removed		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
z-1- β a-d-r	0.000	z-1- ξ β a-r	13.104	13.104
z-4- β a-d-r	2.890	z-4- ξ β a-r	15.203	12.313
z-3- β c-d-r	2.431	z-3- ξ β c-r	15.383	12.952
z-5- β c-d-r	2.981	z-5- ξ β c-r	16.247	13.266
z-15- β c-d-r	12.585	z-15- ξ β c-r	26.470	13.885
z-13- β b-d-r	11.668	z-13- ξ β b-r	25.730	14.062
z-13- β b'-s-w	15.407	z-13- ξ β b'-w	24.920	9.513
z-2- α a-s-w	0.864	z-2- ξ α a-w	11.386	11.385
z-6- α c-s-w	3.358	z-6- ξ α c-w	13.282	9.924
z-7- α a-s-w	4.135	z-7- ξ α a-w	14.567	10.432
z-14- α b-s-w	12.312	z-14- ξ α b-w	23.910	11.598
z-2- α a-s-r	4.143	z-2- ξ α a-r	13.129	8.986
z-7- α a-s-r	6.078	z-7- ξ α a-r	14.468	8.390
z-6- α c-s-r	6.964	z-6- ξ α c-r	15.205	8.241
z-18- α b-s-r	16.727	z-18- ξ α b-r	25.813	9.086
z-17- α b-s-r	17.244	z-17- ξ α b-r	25.968	8.724
z-14- α b'-s-r	17.286	z-14- ξ α b'-r	25.674	8.388
z-9- γ -d-r	5.197	z-9- η -r	18.459	13.262
z-10- γ -d-r	7.894	z-10- η -r	21.539	13.645
z-9- γ -d-w	5.523	z-9- η -w	16.721	11.198
z-3- γ -d-w	6.030	z-3- η -w	17.200	11.170
z-4- γ -d-w	6.049	z-4- η -w	16.566	10.517
z-19- γ -d-w	14.335	z-19- η -w	25.381	11.046
z-20- γ -d-w	14.417	z-20- η -w	25.638	11.221
z-22- γ -d-w	15.239	z-22- η -w	26.418	11.179
z-9- γ -d-w-p	10.674	z-9- η -w-p	19.560	8.886
z-10- γ -d-w-p	11.120	z-10- η -w-p	18.666	7.546
z-1- γ -s-w	5.634	z-1- η -w	16.062	10.428
z-10- γ -s-w	5.703	z-10- η -w	15.862	10.159
z-19- γ -s-r	19.085	z-19- η -r	27.607	8.522

Table 16. Energy increase on first IHB removal for selected conformers of the E isomer of caespitate. The energy increase ($\Delta(\Delta E)$) is evaluated as «energy of the conformer without the first IHB minus energy of the conformer with the first IHB».

first IHB present		first IHB removed		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
e-4- β a-d-r	0.423	e-4- ξ β a-r	13.166	12.743
e-6- γ -d-r	1.635	e-6- η -r	13.084	11.449
e-8- γ -d-w	2.965	e-8- η -w	13.795	10.830
e-2- α a-s-r	3.792	e-2- ξ α a-r	12.527	8.735
e-24- α a-s-r	15.325	e-24- ξ α a-r	23.258	7.933

The parameters of the second IHB are different for the two isomers. In cspt-Z, the length of the second IHB is always well below the sum of the van der Waals radii of O and H (2.7 Å), whether it engages O21 or O23, and only in bifurcated IHB one of the two lengths may exceed this sum. In cspt-E, the length is frequently greater than the sum of the two van der Waals radii. Cases of this type require the selection of a cut-off value for the H...O distance below which the interaction is considered an H-bond, and this, in turn, requires the identification of a viable criterion. For bifurcated IHB in cspt-Z, the selected criterion referred to the behavior on attempted IHB removal: since it is not removed by a 180° rotation of the donor unless one of the two bond lengths exceeds 3.00 Å, this value was selected as cut-off length for the second IHB. In cspt-E, the criterion is offered by the H...O distance patterns: this distance is either below 3.20 Å (and the geometry of R' has a ring shape) or considerably longer (and the geometry of R' is open); therefore, 3.20 Å was selected as the cut-off value. This value coincides with the one often utilized as a criterion for weak H-bonds. Although the selection of a cut-off value for threshold H-bond length contains some inherent arbitrariness [20], the selections made here for the two isomers of caespitate proved apt to enable consistent analysis and interpretation of the computational results. The range of the OĤO bond angle is mostly 140–150° for cspt-Z and 120–135° for cspt-E. Table 17 reports the parameters of the second IHB for conformers of cspt-Z and table 18 for those of cspt-E.

Table 17. Parameters of the second IHB in relevant conformers of the Z isomer of caespitate. The relative energy *in vacuo* is reported for reference purposes.

conformer	relative energy <i>in vacuo</i>	parameters of the second IHB		
		H...O	O...O	O-Ĥ...O
z-1- β a-d-r	0.000	1.967	2.860	142.9
z-2- α a-s-w	0.864	1.992	2.856	140.4
z-3- β c-d-r	2.431	2.074	2.962	152.3
z-4- β a-d-r	2.890	2.033	2.933	150.3
z-5- β c-d-r	2.981	2.079	2.972	149.5
z-6- α c-s-w	3.358	2.128	2.999	144.9
z-7- α a-s-w	4.135	2.021	2.914	149.1
z-2- α a-s-r	4.143	1.984	2.870	144.8
z-1- β a-d-r-u	4.175	1.974	2.866	143.3
z-8- α c-s-w	4.221	2.163	3.039	148.3
z-1- β a-s-r	4.605	1.994	2.895	147.6
z-1- β a-d-r-p	5.288	1.972	2.864	142.8
z-1- β a-s-r-u	5.426	1.977	2.867	141.3
z-2- α a-s-w-p	5.613	1.954	2.830	135.3
2- α a-s-w-p	5.613	1.954	2.830	135.3
7- α a-s-r	6.086	1.931	2.858	147.9
3- β c-d-r-u	6.338	2.077	2.962	148.1
4- β a-s-r	6.387	1.970	2.891	159.5
13- β b-d-r	11.668	2.105	3.037	158.0
		2.062	2.978	161.8

Table 18. Parameters of the second IHB in relevant conformers of the E isomer of caespitate. The relative energy *in vacuo* is reported for reference purposes.

conformer	relative energy <i>in vacuo</i>	parameters of the second IHB		
		H...O	O...O	O...H...O
e-2- α -s-w	0.343	2.641	3.345	120.5
e-4- β a-d-r	0.423	2.833	3.508	119.1
e-7- α -s-w	0.776	2.961	3.592	123.9
e-8- β a-d-r	0.852	3.100	3.712	108.1
e-12- α -s-w	1.524	2.178	3.062	134.1
e-13- α -s-w	3.262	2.569	3.355	134.8
e-2- α -s-r	3.792	2.424	3.242	141.5
e-7- α -s-r	4.186	2.842	3.568	134.2
e-4- β a-d-r-u	4.493	2.963	3.628	122.8
e-14- β a-s	5.038	2.149	2.980	130.6
e-4- β a-s-r	5.043	2.623	3.450	141.6
e-8- β a-s-r	5.149	3.102	3.835	135.6
e-4- β a-d-r-p	5.600	2.839	3.526	120.0
e-4- β a-s-r-u	5.780	3.004	3.667	135.2
e-7- α -s-w-p	5.842	2.879	3.521	123.1
e-13- α -s-r	6.850	2.441	3.290	146.6
e-24- α -s-w	12.167	2.143	3.056	163.4
e-2- ξ α -r	12.527	2.306	3.186	150.8
e-4- ξ β a-r	13.166	2.312	3.214	158.1
e-24- α -s-r	15.325	3.064	3.471	154.7
e-24- ξ α -r	23.258	2.169	3.033	154.2

The evaluation of the energy of the second IHB is not easy, because the 180° rotation of the donor OH causes extensive, often dramatic changes in the geometry of R' (fig. 7) and, therefore, the energy difference between the two conformers (with and without the second IHB) cannot be ascribed only or mainly to the second IHB. Moreover, the removal is not always possible. For cspt-Z, the second IHB can be removed when it involves only O23 or only O21, with the exception of z-1- β a-d-r where, on attempted removal, O10H16 rotates back to the orientation that enables the second IHB [3]. Bifurcated IHB in cspt-Z cannot be removed as, on 180° rotation of the donor OH, the geometry of R' rearranges yielding a new conformer having a bifurcated IHB with different parameters [3], (fig. 8). For cspt-E, the second IHB can be removed in most cases, but in some cases the donor OH rotates back to the orientation that enables the second IHB. Moreover, the outcome may be remarkably different for different ways of removing the second IHB.

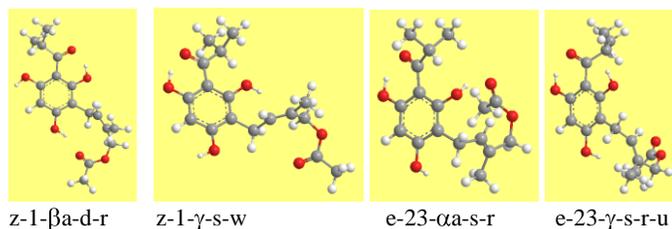


Fig.7. Illustration of cases of dramatic geometry changes on second IHB removal by 180° rotation of the donor OH: z-1- γ s-w results from z-1- β a-d-r and e-23- γ s-r-u from e-23- α a-s-r.

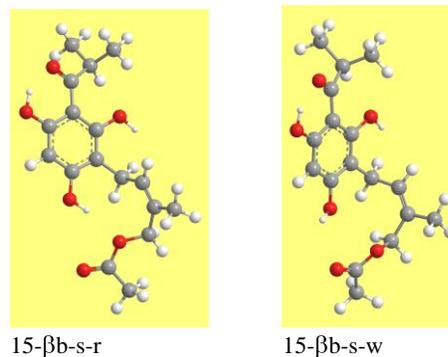


Fig. 8. Example of failure to remove a bifurcated second IHB from conformers of the Z isomer of caespitate. On 180° rotation of the donor O10H16, the geometry of R' rearranges to form a new bifurcated second IHB.

Removing the second IHB from an α conformer implies an upward rotation of H15, yielding a u conformer, which implies an energy increase with respect to the non-u one and, therefore, an overestimation of the second IHB energy. It is difficult to decide whether the best reference for the second IHB energy is the u conformer thus obtained or the lowest energy conformer with a similar geometry of R', which would be a conformer in which H15 gets engaged in the first IHB. The latter would imply an underestimation of the second IHB energy, because a d conformer usually has lower energy than a corresponding s conformer. In energy terms, the outcomes may be considerably different. For instance, removing the second IHB from e-2- α a-s-w ($\Delta E = 0.343$) by engaging H15 in the first IHB yields e-2- γ -d-r ($\Delta E = 2.166$), while removing it by 180° rotation of the donor yields e-2- γ -s-r-u ($\Delta E = 7.409$); the case is illustrated in fig. 9.

In many cases, the removal of the second IHB from an α conformer by upward rotation of H15 is not viable because, on optimization, H15 rotates downward forming the second IHB again. It is the case, e.g., with e-7- α a-s-w, e-10- α a-s-w, e-12- α a-s-w and e-7- α a-s-r.

When the removal of the second IHB is possible, the energy increase ($\Delta E_{\text{sec-IHB-removal}}$) is ≤ 6.02 for cspt-Z and ≤ 4.94 for cspt-E; however, these values comprise contributions from the extensive geometry changes of R' on becoming unconstrained and also from the changes in the orientation of

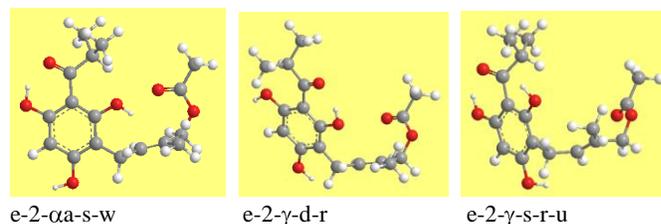


Fig. 9. Illustration of different outcomes from different ways of removing the second IHB. Removing the second IHB from e-2- α a-s-w by engaging H15 in the first IHB yields e-2- γ -d-r, removing it by 180° rotation of the donor yields e-2- γ -s-r-u.

the phenol OH concerned. Table 19 shows the energy increase on second IHB removal for conformers of cspt-Z and table 20 for conformers of cspt-E. For cases like that of e-2- α -s-w, table 20 includes both the comparison with e-2- γ -s-w-u and the comparison with e-2- γ -d-w (in terms of inputs “genetics”, e-2- γ -s-w-u is derived from 2- α -s-w and e-2- γ -d-w from e-2- γ -s-w-u).

Table 19. Energy increase on second IHB removal for relevant conformers of the Z isomer of caespitate. The energy increase ($\Delta(\Delta E)$) is evaluated as «energy of the conformer without the second IHB minus energy of the conformer with the second IHB».

second IHB present		second IHB removed		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
z-1- β a-d-r	0	z-1- γ -d-w	5.906	5.906
z-1- β a-s-r	4.605	z-1- γ -s-w	5.634	1.029
z-1- ξ β a-r	13.104	z-1- η -w	16.062	2.958
z-2- α a-s-r	4.143	z-2- γ -s-r-u	10.193	6.05
z-3- β c-d-r	2.431	z-3- γ -d-w	6.030	3.599
z-3- β c-s-r	6.885	z-3- γ -s-w	6.954	0.069
z-3- ξ β c-r	15.383	z-3- η -w	17.200	1.817
z-4- β a-d-r	2.890	z-4- γ -d-w	6.049	3.159
z-4- β a-s-r	6.387	z-4- γ -s-w	6.221	-0.166
z-4- ξ β a-r	15.203	z-4- η -w	16.566	1.363
z-5- β c-d-r	2.981	z-5- γ -d-w	8.431	5.45
z-5- β c-d-r	2.981	z-5- γ -d-r	6.384	3.403
z-5- β c-s-r	7.452	z-5- γ -s-w	6.074	-1.378
z-5- β c-s-r	7.452	z-5- γ -s-r	9.580	2.128
z-5- ξ β c-r	16.247	z-5- η -w	27.049	10.802
z-6- α c-s-w	3.358	z-6- γ -s-w-u	8.917	5.559
z-6- α c-s-r	6.964	z-6- γ -s-r-u	11.022	4.058
z-11- β c-s-r	9.851	z-11- γ -s-w	9.433	-0.418
z-15- β c-d-r	12.585	z-15- γ -d-w	16.958	4.373

Table 20. Energy increase on second IHB removal for relevant conformers of the E isomer of caespitate. The energy increase ($\Delta(\Delta E)$) is evaluated as «energy of the conformer without the second IHB minus energy of the conformer with the second IHB».

second IHB present		second IHB removed		$\Delta(\Delta E)$
conformer	ΔE	conformer	ΔE	
e-2- α a-s-w	0.343	e-2- γ -s-w-u	5.285	4.942
e-2- α a-s-w	0.343	e-2- γ -d-w	2.165	1.822
e-2- α a-s-r	3.792	e-2- γ -s-r-u	7.409	3.617
e-2- α a-s-r	3.792	e-2- γ -d-r	2.166	-1.626
e-24- α a-s-r	15.325	e-24- γ -s-r-u	14.785	-0.54
e-4- β a-d-r	0.423	e-4- γ -d-w	2.425	2.002
e-8- β a-d-r	0.852	e-8- γ -d-w	2.965	2.113
e-4- β a-s-r	5.043	e-4- γ -s-w	3.214	-1.829
e-4- β a-s-r-u	5.780	e-4- γ -s-r-u	6.629	0.849

Considerations on the conformers' distribution enable some inferences for cspt-Z, while they are not viable for cspt-E. For cspt-Z, the relative energy of the best conformer without the second IHB is 5.2, which suggests that the stabilization due to the second IHB might have this magnitude [3]. For cspt-E, the fact that the lowest energy conformer does not have the second IHB, and other γ conformers are among the lowest energy ones, prevents inferences of this type. In any case, both the comparison of the second IHB length and the fact that many low energy conformers of cspt-E do not contain the second IHB constitute evidence that the second IHB is considerably stronger in cspt-Z than in cspt-E.

Both the parameters and the energy increases on IHB removal show that the second IHB is considerably weaker than the first IHB. In the conformers of cspt-Z, the lowering of the computed harmonic vibrational frequencies of the donor OH caused by the second IHB is $\leq 2.7\%$ for IHB with O23 and $\leq 1.9\%$ for IHB with O21; the value is nearly double (4.9%) for the best bifurcated second IHB. In the conformers of cspt-E, the frequency lowering is $< 2.0\%$ for O8-H15 and $< 1.5\%$ for O10-H16.

A peculiarity of the caespitate molecule is the simultaneous presence in R' of O atoms that can be H-bond acceptors to phenol OH in ortho to R' and of a double bond in a position enabling O-H $\cdots\pi$ interaction with the same phenol OH. It becomes interesting to investigate whether the two interactions (the second IHB and the O-H $\cdots\pi$ interaction) are mutually exclusive, collaborative or competitive. In cspt-Z, where the second IHB is stronger, it appears to be dominant with respect to the O-H $\cdots\pi$ interaction: the H of the phenol OH is oriented toward the acceptor O, not toward the double bond. In cspt-E, the second IHB and the O-H $\cdots\pi$ interaction co-exist, and the latter appears to be dominant: the H of the donor phenol OH is oriented more toward the double bond than toward the acceptor O (fig. 10). Better directionality of the O-H $\cdots\pi$ interaction corresponds to better energy; for instance, e-2- α -s-w has better energy than e-8- α -s-w and more favourable directionality of the O-H $\cdots\pi$ interaction. The rare conformers of cspt-E that have a second IHB but no O-H $\cdots\pi$ interaction have high energy; an example is e-22- α -s-w.

In conformers without the second IHB, the O-H $\cdots\pi$ interaction becomes dominant, and the lower-energy γ conformers have it, as clearly shown by the directionality of a neighbouring phenol OH with respect to the C18=C19 double bond (fig. 11). The O-H15 $\cdots\pi$ interaction may be present in s conformers, but not in d conformers; the O-H16 $\cdots\pi$ interaction may be present in r conformers, but not in w conformers. The role of the O-H15 $\cdots\pi$ interaction is likely responsible for the decreased preference for the first IHB to form on the same side as R observed for cspt-E (while for cspt-Z – like for most ACPL – d-r conformers have better energy than corresponding s-w ones).

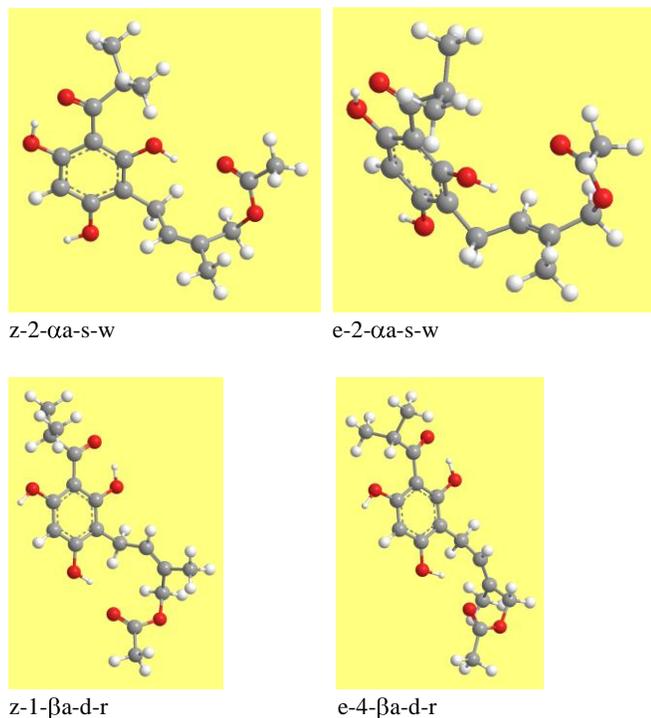


Fig. 10. Orientation of the donor phenol OH in conformers having the second IHB: directly toward the acceptor O in conformers of the Z isomer, dominantly toward the double bond in conformers of the E isomer.

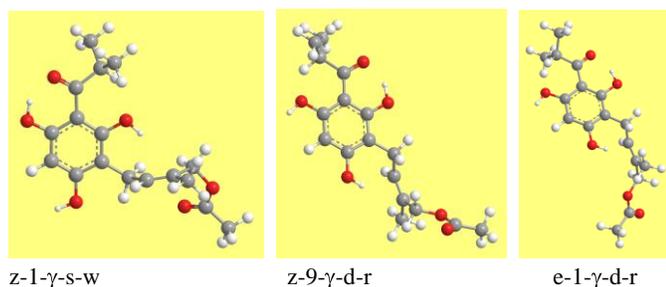


Fig. 11. Orientation of phenol OH toward the C18=C19 double bond in conformers where the geometry of R' makes the double bond accessible for O–H... π interaction.

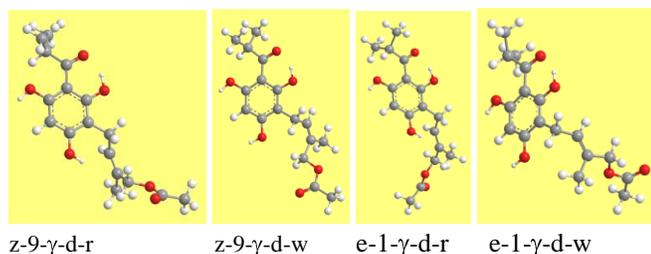


Fig. 12. Examples of remarkable geometry changes resulting from the removal of the O–H... π interaction by 180° rotation of H16, yielding the w conformer from an r conformer.

Removing the O–H... π interaction may cause remarkable geometry changes, like in the removal from z-9- γ -d-r or e-1- γ -d-r by 180° rotation of H16 yielding the corresponding w conformers (fig. 12).

IV. RESULTS IN SOLUTION

A. Results from PCM calculations

PCM calculations consider the bulk solvent effect on the molecule. The performed calculations with full re-optimization in solution show that the geometry of the conformers does not change significantly with respect to *in vacuo*. Table 21 compares the relative energy for cspt-Z and table 22 for cspt-E, considering the conformers for which PCM calculations were performed with full-reoptimization in solution. Tables 23 and 24 compare the relative energy for cspt-Z and cspt-E considering the results from single point PCM calculations in solution.

For cspt-Z, like for most ACPL, the energy gaps between conformers narrow in solution and the number of conformers with relative energy below a certain value tends to increase as the solvent polarity increases. For cspt-E, the number of conformers with low relative energy decreases with increasing medium polarity.

For most ACPL, relative energies from full-reoptimization and from single-point calculations in solution do not differ significantly; this is true also for cspt-Z, while significant discrepancies are observed for some conformers of cspt-E in water solution.

It had been reasonably established that the first IHB does not break in solution, including water solution [5]; its parameters for selected conformers of cspt-E in different solvents are reported in table 21. For ACPL with a second IHB, it becomes interesting to investigate whether it remains in solution. The most informative data about the effect of the solvent on the permanence of the second IHB is the energetics (tables 22–25). For cspt-Z, the number of lower energy conformers having both the first and the second IHB decreases as the medium polarity increases: 9/vac, 5/chlrf, 4/actn, while, in water, the first 5 lowest energy conformers have only the first IHB. For cspt-E, while some conformers with the second IHB appear among the low energy ones in less polar media, no populated conformer has it in water. Thus, the results of both isomers show that the second IHB is not present in water.

The two isomers differ also for the trends of the parameters of the second IHB, when present in solution [6]. This can be observed only from full-reoptimization PCM results (as single-point calculations do not involve changes to the initial geometry). For cspt-Z, the second IHB is shorter in chloroform and in acetonitrile than *in vacuo* (by 0.002–0.025/chlrf and 0.006–0.038/actn) and longer in water (by 0.014–0.039/aq). For cspt-E, the length always increases in solution with respect to *in vacuo* (by 0.007–0.129/chlrf, 0.005–0.248/actn and 0.238–0.522/aq).

Table 21. Parameters of the first IHB for selected conformers of the E isomer of caespitate in different solvents. The results in solution are from full-reoptimization PCM calculations.

conformer	medium	parameters of the first IHB		
		H...O	O...O	OHO
e-1- γ -d-r	vac	1.653	2.507	148.6
	chlrf	1.653	2.509	146.4
	actn	1.653	2.510	146.6
e-2- α -s-w	vac	1.726	2.555	144.0
	chlrf	1.722	2.555	143.6
	actn	1.721	2.555	143.8
	aq	1.739	2.567	142.9
e-4- β -d-r	vac	1.656	2.510	149.7
	chlrf	1.655	2.511	146.5
	actn	1.655	2.512	146.7
	aq	1.696	2.540	144.9
e-6- γ -s-w	vac	1.702	2.536	143.5
	chlrf	1.698	2.536	144.2
	actn	1.696	2.536	144.4
	aq	1.738	2.564	142.6
e-7- α -s-w	vac	1.695	2.531	144.2
	chlrf	1.688	2.529	144.5
	actn	1.690	2.531	144.6
e-10- γ -s-w	vac	1.705	2.538	143.3
	chlrf	1.697	2.536	144.2
	actn	1.696	2.536	144.4
e-12- α -s-w	vac	1.722	2.550	144.1
	chlrf	1.727	2.558	143.3
	actn	1.728	2.559	143.5
	aq	1.751	2.575	142.5
e-6- γ -d-r	vac	1.656	2.508	148.7
	chlrf	1.658	2.511	146.0
	actn	1.660	2.513	146.1
	aq	1.676	2.526	145.6
e-10- γ -d-r	vac	1.657	2.508	148.6
	chlrf	1.656	2.510	146.1
	actn	1.656	2.510	146.3
	aq	1.669	2.520	145.9
e-6- γ -d-w	vac	1.672	2.519	145.2
	actn	1.665	2.518	146.2
	aq	1.679	2.528	145.7
e-2- γ -d-r	vac	1.656	2.508	148.5
	chlrf	1.656	2.510	146.2
	actn	1.656	2.511	146.3
e-1- γ -s-w	vac	1.703	2.536	143.2
	chlrf	1.700	2.538	144.0
	actn	1.699	2.537	144.3
e-8- γ -d-w	vac	1.674	2.521	148.1
	chlrf	1.666	2.518	145.9
	actn	1.664	2.517	146.2
e-4- γ -s-w	vac	1.695	2.530	144.7
	chlrf	1.705	2.541	143.9
	actn	1.710	2.546	144.0
e-13- α -s-w	vac	1.725	2.554	142.4
	chlrf	1.723	2.556	143.5
	actn	1.723	2.556	143.7
e-7- α -s-r	vac	1.707	2.540	143.8
	chlrf	1.695	2.534	144.3
	actn	1.695	2.536	144.5
e-6- γ -s-r	vac	1.744	2.569	143.8
	chlrf	1.709	2.545	143.9
	actn	1.706	2.543	144.2

Table 22. Comparison of the relative energy of the lower energy conformers of the Z isomers of caespitate in different media, considering full re-optimization in solution.

conformer	relative energy			
	vac	chlrf	actn	aq
z-1- β -d-r	0.000	0.000	0.000	2.237
z-2- α -w	0.864	0.742	0.622	2.936
z-3- β -d-r	2.431	2.214	2.150	3.770
z-4- β -d-r	2.890	3.311	*	5.765
z-5- β -d-r	2.991	3.034	3.000	4.887
z-6- α -w	3.358	2.896	2.635	4.142
z-7- α -w	4.135	4.247	4.292	6.627
z-1- β -d-r-u	4.180	4.880	5.111	7.123
z-8- α -w	4.221	3.950	3.731	5.494
z-9- γ -d-r	5.197	4.551	4.295	5.252
z-7- γ -d-r	5.286	4.458	3.980	3.587
z-1- β -d-r-p	5.288	5.097	5.014	6.807
z-9- γ -d-w	5.523	3.257	2.158	0.000
z-2- α -w-p	5.613	5.310	5.130	7.035
z-1- γ -d-w	5.906	3.721	2.566	0.718
z-10- γ -d-w	6.028	*	2	0.038
z-3- γ -d-w	6.030	3.720	2.546	0.391
z-4- γ -d-w	6.049	3.805	2.567	0.724
z-11- β -d-r	6.506	*	2.151	8.013

* For this conformer, the full-reoptimization in the given solvent did not converge.

Table 23. Comparison of the relative energy of the lower energy conformers of the E isomers of caespitate in different media, considering full re-optimization in solution.

conformer	relative energy			
	vac	chlrf	actn	aq
e-1- γ -d-r	0.000	0.000	1.169	*
e-2- α -s-w	0.343	0.661	1.725	4.263
e-4- β -d-r	0.423	0.557	1.683	4.020
e-6- γ -s-w	0.762	0.507	1.432	3.665
e-7- α -s-w	0.776	1.038	2.151	*
e-10- γ -s-w	1.246	1.184	2.147	*
e-12- α -s-w	1.524	1.991	3.159	5.981
e-6- γ -d-r	1.635	0.789	1.676	1.831
e-10- γ -d-r	1.715	1.558	2.421	2.702
e-6- γ -d-w	1.746	*	0.000	0.000
e-2- γ -d-r	2.166	1.861	2.731	*
e-4- γ -d-w	2.425	0.869	*	*
e-1- γ -s-w	2.652	1.607	2.184	*
e-8- γ -d-w	2.966	1.409	1.620	*
e-4- γ -s-w	3.214	2.504	2.985	*
e-13- α -s-w	3.262	3.542	4.622	*
e-8- γ -s-w	3.790	*	3.520	*
e-5- α -s-r	4.186	4.024	4.960	*
e-6- γ -s-r	4.473	3.474	4.022	5.930
e-6- γ -r	13.318	10.032	9.274	*

* For this conformer, the full-reoptimization in the given solvent did not converge.

Table 24. Comparison of the relative energy of the lower energy conformers of the Z isomers of caespitate in different media, considering single-point PCM results in solution.

conformer	relative energy			
	vac	chlrf	actn	aq
z-1- β a-d-r	0.000	0.000	0.000	2.168
z-2- α a-s-w	0.864	0.713	0.598	2.640
z-3- β c-d-r	2.431	1.747	2.115	3.534
z-4- β a-d-r	2.890	2.259	3.490	5.499
z-5- β c-d-r	2.981	2.762	3.610	4.676
z-6- α c-s-w	3.358	3.392	2.578	3.951
z-7- α a-s-w	4.135	4.322	4.248	6.358
z-2- α a-s-r	4.143	4.372	3.410	6.847
z-1- β a-d-r-u	4.180	6.771	5.214	9.258
z-8- α c-s-r	4.221	3.462	3.748	5.325
z-1- β a-s-r	4.605	3.531	3.410	6.981
z-9- γ -d-r	5.197	3.667	4.272	5.143
z-7- γ -d-r	5.286	3.122	4.075	3.620
z-1- β a-d-r-p	5.288	4.851	5.003	6.788
z-1- β a-s-r-u	5.426	8.410	5.779	9.685
z-2- γ -d-r	5.503	4.429	4.698	5.801
z-9- γ -d-w	5.523	0.510	2.191	0.000
z-2- α a-s-w-p	5.613	5.931	6.866	9.332
z-1- γ -s-w	5.634	4.321	4.754	6.436
z-10- γ -s-w	5.703	4.071	4.030	5.347
z-1- γ -d-w	5.906	1.266	2.675	0.740
z-10- γ -d-w	6.028	2.28	2.310	0.014
z-3- γ -d-w	6.030	1.241	2.589	0.412
z-4- γ -d-w	6.049	1.418	2.747	0.824
z-5- γ -s-w	6.074	4.993	5.372	6.593
z-7- α a-s-r	6.078	7.979	6.694	10.988
z-5- γ -s-w	6.126	5.129	5.414	6.540
z-6- γ -d-r	6.158	3.769	4.505	3.544
z-4- γ -s-w	6.221	4.372	4.954	4.450
z-6- γ -d-w	6.266	1.572	2.906	2.433
z-3- β c-d-r-u	6.338	7.848	7.316	10.698
z-5- γ -d-r	6.384	4.239	5.142	4.799
z-4- β a-s-r	6.387	7.933	6.524	10.683
z-11- β c-d-r	6.506	6.010	6.308	7.112
z-9- γ -s-w	6.523	3.244	4.327	3.765
z-5- β c-d-r-u	6.882	8.883	8.160	11.819
z-3- β c-s-r	6.885	5.931	5.843	8.791
z-11- β c-d-w	6.930	2.336	3.746	1.808
z-3- γ -s-w	6.954	3.792	4.707	4.209
z-6- α c-s-r	6.964	6.280	5.683	7.793
z-4- β a-d-r-u	6.985	9.533	8.629	12.546
z-5- β c-s-r	7.452	7.294	6.610	9.453
z-3- β c-s-r-u	7.526	8.598	7.961	11.193
z-12- α c-s-w	7.635	7.378	7.019	8.557
z-3- β c-d-r-p	7.645	7.453	7.111	8.106
z-8- α c-s-r	7.790	7.515	6.815	9.230
z-10- γ -d-r	7.894	7.459	7.386	7.793
z-5- β c-s-r-u	7.905	8.489	8.685	12.146
z-4- β a-s-r-u	8.132	8.731	9.180	13.077

The energetics of the solution process is described by the solvation free energy or solvent effect (ΔG_{solv}) and its electrostatic (G_{el}) and non electrostatic ($G_{\text{non-el}}$) components [21, 22]. Tables 26–28 report these quantities for the conformers of cpst-E in the three solvents considered, from the results of PCM single-point calculations.

Table 25. Comparison of the relative energy of the lower energy conformers of the E isomers of caespitate in different media, considering single-point PCM results in solution.

conformer	relative energy			
	vac	chlrf	actn	aq
e-1- γ -d-r	0.000	0.135	1.134	3.314
e-2- α a-s-w	0.343	0.765	1.732	4.272
e-3- γ -s-w	0.408	0.408	1.228	3.433
e-4- β a-d-r	0.423	0.717	1.657	4.040
e-5- γ -s-w	0.454	0.436	1.281	3.404
e-7- α a-s-w	0.776	1.152	2.115	4.611
e-6- γ -s-w	0.798	0.662	1.419	3.364
e-8- β a-d-r	0.852	1.088	2.058	4.358
e-9- γ -d-r	1.024	1.149	2.010	4.125
e-10- γ -s-w	1.246	1.308	2.104	4.179
e-11- γ -d-r	1.515	1.617	2.496	4.493
e-12- α a-s-w	1.524	2.137	3.248	6.050
e-6- γ -d-r	1.635	0.932	1.698	2.077
e-10- γ -d-r	1.715	1.724	2.594	3.006
e-6- γ -d-w	1.746	0.000	0.000	0.055
e-1- γ -d-w	1.765	0.050	0.126	0.000
e-5- γ -d-w	1.862	0.185	0.174	0.122
e-3- γ -d-w	1.869	0.197	0.180	0.128
e-2- γ -d-w	2.165	0.896	1.089	1.243
e-2- γ -d-r	2.166	2.004	2.662	3.258
e-10- γ -d-w	2.350	0.779	0.811	1.004
e-4- γ -d-w	2.425	1.025	1.121	*
e-9- γ -s-w	2.540	2.409	3.095	3.842
e-1- γ -s-w	2.652	1.904	2.285	2.775
e-9- γ -d-w	2.673	0.878	0.867	0.954
e-5- γ -d-r	2.799	2.839	3.744	5.554
e-3- γ -d-r	2.817	2.858	3.716	*
e-8- γ -d-w	2.965	1.556	1.667	1.829
e-11- γ -d-w	3.138	1.396	1.453	1.606
e-4- γ -s-w	3.214	2.773	3.170	4.031
e-13- α a-s-w	3.262	3.660	4.693	6.957
e-11- γ -s-w	3.582	3.107	3.590	4.167
e-2- α a-s-r	3.792	3.784	4.534	6.960
e-7- α a-s-r	4.186	4.219	5.094	7.301
e-1- γ -s-r	4.490	3.975	4.634	6.323
e-4- β a-d-r-u	4.493	5.579	6.871	9.991
e-10- γ -s-r	4.531	4.497	5.227	6.870
e-9- γ -s-r	4.669	4.691	5.619	7.133
e-14- β a-s	5.038	5.734	6.870	9.551
e-8- β a-s-r	5.149	4.897	5.561	7.683
e-1- γ -d-r-p	5.284	5.137	6.086	8.011
e-2- γ -s-w-u	5.285	5.338	6.036	7.183
e-11- γ -s-r	5.499	5.194	5.876	7.277
e-4- β a-d-r-p	5.600	5.721	6.585	8.733
e-4- β a-s-r-u	5.780	6.455	7.556	10.575
e-7- α a-s-w-p	5.842	6.175	7.086	9.425
e-4- γ -s-r-u	6.629	6.567	7.184	8.332
e-13- α a-s-r	6.850	6.759	7.500	9.768
e-2- γ -s-r-u	7.409	7.559	8.397	9.919
e-5- γ -s-r	7.785	7.079	7.634	9.089
e-3- γ -s-r	8.636	8.182	8.810	10.409
e-15- γ -d-r	9.144	7.772	8.057	9.025
e-16- γ -d-r	9.489	8.234	8.597	9.873
e-17- γ -d-r	9.731	8.089	8.227	9.074
e-16- γ -d-w	9.871	6.883	6.529	6.175
e-18- γ -d-r	10.154	8.514	8.732	9.918
e-20- γ -s-w	10.216	8.398	8.360	9.219
e-15- γ -d-w	10.341	7.224	6.641	5.624
e-21- γ -d-r	10.391	8.795	8.955	10.289

* The calculation does not converge in water solution.

Table 26. Thermodynamic quantities of the solution process in chloroform, for the conformers of the E isomer of caespitate.

conformer	relative energy <i>in vacuo</i>	thermodynamic quantities of the solution process		
		ΔG_{solv}	G_e	$G_{\text{non-el}}$
e-1- γ -d-r	0.000	-1.14	-5.07	3.93
e-2- α a-s-w	0.343	0.91	-4.78	5.69
e-3- γ -s-w	0.408	-0.45	-5.21	4.76
e-4- β a-d-r	0.423	-0.64	-4.91	4.27
e-5- γ -s-w	0.454	4.77	-5.22	4.15
e-7- α a-s-w	0.776	0.69	-4.83	5.52
e-6- γ -s-w	0.798	-1.18	-5.34	4.16
e-8- β a-d-r	0.852	-0.30	-4.97	4.67
e-9- γ -d-r	1.024	-0.99	-5.08	4.09
e-10- γ -s-w	1.246	-0.56	-5.14	4.58
e-11- γ -d-r	1.515	-0.80	-5.10	4.31
e-12- α a-s-w	1.524	5.79	-4.59	3.96
e-6- γ -d-r	1.635	-1.96	-5.91	3.95
e-10- γ -d-r	1.715	-0.83	-5.20	4.37
e-6- γ -d-w	1.746	-3.04	-6.95	3.91
e-1- γ -d-w	1.765	-2.97	-6.92	3.96
e-5- γ -d-w	1.862	-2.74	-6.88	4.14
e-3- γ -d-w	1.869	-2.37	-6.88	4.51
e-2- γ -d-w	2.165	-1.21	-6.47	5.26
e-2- γ -d-r	2.166	-0.06	-5.37	5.31
e-10- γ -d-w	2.350	-2.49	-6.78	4.29
e-4- γ -d-w	2.425	-1.74	-6.61	4.86
e-9- γ -s-w	2.540	-0.83	-5.34	4.51
e-1- γ -s-w	2.652	-1.78	-5.95	4.18
e-9- γ -d-w	2.673	-2.83	-7.00	4.17
e-5- γ -d-r	2.799	-0.73	-5.17	4.44
e-40-d-r	2.817	-0.65	-5.17	4.52
e-8- γ -d-w	2.965	-1.40	-6.62	5.22
e-11- γ -d-w	3.138	-2.49	-6.95	4.46
e-4- γ -s-w	3.214	-0.48	-5.65	5.17
e-13- α a-s-w	3.262	0.81	-4.81	5.62
e-11- γ -s-w	3.582	-0.78	-5.68	4.90
e-2- α a-s-r	3.792	0.39	-5.21	5.60
e-7- α a-s-r	4.186	0.50	-5.17	5.67
e-1- γ -s-r	4.490	-1.51	-5.72	4.21
e-4- β a-d-r-u	4.493	0.70	-4.12	4.82
e-10- γ -s-r	4.531	-0.53	-5.24	4.71
e-9- γ -s-r	4.669	-0.67	-5.18	4.51
e-14- β a-s	5.038	0.74	-4.51	5.25
e-8- β a-s-r	5.149	-0.42	-5.46	5.04
e-1- γ -d-r-p	5.284	-1.14	-5.28	4.14
e-2- γ -s-w-u	5.285	1.08	-5.15	6.24
e-11- γ -s-r	5.499	-0.77	-5.51	4.74
e-4- β a-d-r-p	5.600	-0.56	-5.08	4.52
e-4- β a-s-r-u	5.780	0.38	-4.53	4.91
e-7- α a-s-w-p	5.842	0.98	-4.87	5.85
e-4- γ -s-r-u	6.629	-0.69	-5.27	4.58
e-13- α a-s-r	6.850	0.40	-5.30	5.70
e-2- γ -s-r-u	7.409	1.29	-5.05	6.35
e-5- γ -s-r	7.785	-1.08	-5.91	4.83
e-3- γ -s-r	8.636	-0.27	-5.66	5.39
e-15- γ -d-r	9.144	-2.74	-6.58	3.84
e-16- γ -d-r	9.489	-1.81	-6.46	4.65
e-17- γ -d-r	9.731	-3.15	-6.85	3.70
e-16- γ -d-w	9.871	-3.16	-8.19	5.03
e-18- γ -d-r	10.154	-2.48	-6.85	4.37
e-20- γ -s-w	10.216	-2.90	-7.02	4.12
e-15- γ -d-w	10.341	-4.42	-8.32	3.90
e-21- γ -d-r	10.391	-2.05	-6.80	4.75

Table 27. Thermodynamic quantities of the solution process in acetonitrile, for the conformers of the E isomer of caespitate.

conformer	relative energy <i>in vacuo</i>	thermodynamic quantities of the solution process		
		ΔG_{solv}	G_e	$G_{\text{non-el}}$
e-1- γ -d-r	0.000	3.73	-7.03	10.76
e-2- α a-s-w	0.343	12.49	-6.78	4.85
e-3- γ -s-w	0.408	4.11	-7.34	11.45
e-4- β a-d-r	0.423	4.22	-6.93	11.15
e-5- γ -s-w	0.454	4.06	-7.34	11.40
e-7- α a-s-w	0.776	5.44	-6.83	12.26
e-6- γ -s-w	0.798	3.39	-7.54	10.93
e-8- β a-d-r	0.852	4.50	-6.96	11.46
e-9- γ -d-r	1.024	3.76	-7.18	10.94
e-10- γ -s-w	1.246	4.03	-7.31	11.34
e-11- γ -d-r	1.515	3.88	-7.18	11.06
e-12- α a-s-w	1.524	6.13	-6.44	12.57
e-6- γ -d-r	1.635	2.73	-8.10	10.84
e-10- γ -d-r	1.715	3.96	-7.29	11.25
e-6- γ -d-w	1.746	0.90	-9.91	10.81
e-1- γ -d-w	1.765	1.01	-9.80	10.81
e-5- γ -d-w	1.862	1.12	-9.85	10.97
e-3- γ -d-w	1.869	1.53	-9.85	11.38
e-2- γ -d-w	2.165	2.72	-9.24	11.97
e-2- γ -d-r	2.166	4.35	-7.67	12.01
e-10- γ -d-w	2.350	1.48	-9.70	11.18
e-4- γ -d-w	2.425	2.18	-9.47	11.64
e-9- γ -s-w	2.540	3.74	-7.61	11.35
e-1- γ -s-w	2.652	2.48	-8.53	11.01
e-9- γ -d-w	2.673	1.10	-9.97	11.07
e-5- γ -d-r	2.799	3.98	-7.22	11.20
e-40-d-r	2.817	4.04	-7.27	11.30
e-8- γ -d-w	2.965	2.49	-9.46	11.96
e-11- γ -d-w	3.138	1.44	-9.85	11.29
e-4- γ -s-w	3.214	3.70	-8.21	11.91
e-13- α a-s-w	3.262	5.63	-6.73	12.36
e-11- γ -s-w	3.582	3.48	-8.16	11.64
e-2- α a-s-r	3.792	4.94	-7.42	12.36
e-7- α a-s-r	4.186	5.15	-7.26	12.40
e-1- γ -s-r	4.490	3.01	-8.02	11.03
e-4- β a-d-r-u	4.493	5.91	-5.79	11.70
e-10- γ -s-r	4.531	4.01	-7.47	11.48
e-9- γ -s-r	4.669	4.13	-7.21	11.34
e-14- β a-s	5.038	5.66	-6.33	12.00
e-8- β a-s-r	5.150	4.04	-7.75	11.79
e-1- γ -d-r-p	5.284	3.67	-7.29	10.96
e-2- γ -s-w-u	5.285	5.55	-7.41	12.96
e-11- γ -s-r	5.499	3.65	-7.79	11.43
e-4- β a-d-r-p	5.600	4.20	-7.18	11.38
e-4- β a-s-r-u	5.780	5.40	-6.39	11.79
e-7- α a-s-w-p	5.842	5.60	-6.92	12.52
e-4- γ -s-r-u	6.629	3.83	-7.61	11.44
e-13- α a-s-r	6.850	4.92	-7.51	12.43
e-2- γ -s-r-u	7.409	5.90	-7.18	13.08
e-5- γ -s-r	7.785	3.26	-8.32	11.58
e-3- γ -s-r	8.636	4.28	-7.99	12.27
e-15- γ -d-r	9.144	1.41	-9.25	10.66
e-16- γ -d-r	9.489	2.42	-9.06	11.47
e-17- γ -d-r	9.731	0.88	-9.67	10.54
e-16- γ -d-w	9.871	0.29	-11.51	11.80
e-18- γ -d-r	10.154	1.51	-9.59	11.10
e-20- γ -s-w	10.216	0.84	-10.02	10.86
e-15- γ -d-w	10.341	-1.12	-11.87	10.74
e-21- γ -d-r	10.391	1.90	-9.60	11.50

Table 28. Thermodynamic quantities of the solution process in water, for the conformers of the E isomer of caespitate.

conformer	relative energy in vacuo	thermodynamic quantities of the solution process		
		ΔG_{solv}	G_e	$G_{\text{non-el}}$
e-1- γ -d-r	0.000	-9.01	-16.03	7.02
e-2- α a-s-w	0.343	-6.04	-15.41	9.37
e-3- γ -s-w	0.408	-8.45	-16.32	7.86
e-4- β a-d-r	0.423	-8.11	41.50	7.62
e-5- γ -s-w	0.454	-8.67	-16.39	7.72
e-7- α a-s-w	0.776	-6.40	-15.51	9.10
e-6- γ -s-w	0.798	-9.57	-16.77	7.20
e-8- β a-d-r	0.852	-7.84	-15.83	7.99
e-9- γ -d-r	1.024	-8.98	-16.24	7.26
e-10- γ -s-w	1.246	-8.67	-16.41	7.74
e-11- γ -d-r	1.515	-8.98	-16.36	7.38
e-12- α a-s-w	1.524	-5.14	-14.82	9.68
e-6- γ -d-r	1.635	-11.79	-18.90	7.11
e-10- γ -d-r	1.715	-10.41	-18.05	7.64
e-6- γ -d-w	1.746	-13.94	-21.03	7.09
e-1- γ -d-w	1.765	-14.02	-21.11	7.08
e-5- γ -d-w	1.862	-13.81	-21.08	7.27
e-3- γ -d-w	1.869	-13.35	-21.08	7.73
e-2- γ -d-w	2.165	-11.74	-20.26	8.52
e-2- γ -d-r	2.166	-9.68	-18.25	8.57
e-10- γ -d-w	2.350	-13.11	-20.69	7.57
e-9- γ -s-w	2.540	-10.27	-18.04	7.77
e-1- γ -s-w	2.652	-11.92	-19.22	7.29
e-9- γ -d-w	2.673	-13.61	-21.06	7.45
e-5- γ -d-r	2.799	-8.93	-16.59	7.66
e-8- γ -d-w	2.965	-11.89	-20.48	8.59
e-11- γ -d-w	3.138	-13.15	-20.87	7.73
e-4- γ -s-w	3.214	-10.06	-18.52	8.46
e-13- α a-s-w	3.262	-6.36	-15.65	9.29
e-11- γ -s-w	3.582	-10.65	-18.76	8.11
e-2- α a-s-r	3.792	-6.94	-16.17	9.23
e-7- α a-s-r	4.186	-6.95	-16.23	9.27
e-1- γ -s-r	4.490	-10.19	-17.51	7.32
e-4- β a-d-r-u	4.493	-5.61	-13.84	8.23
e-10- γ -s-r	4.531	-9.11	-17.00	7.89
e-9- γ -s-r	4.669	-9.15	-16.88	7.72
e-14- β a-s	5.038	-5.96	-14.83	8.87
e-8- β a-s-r	5.150	-8.43	-16.81	8.38
e-1- γ -d-r-p	5.284	-9.23	-16.54	7.31
e-2- γ -s-w-u	5.285	-7.66	-17.44	9.78
e-11- γ -s-r	5.499	-9.76	-17.56	7.80
e-4- β a-d-r-p	5.600	-8.26	-16.21	7.95
e-4- β a-s-r-u	5.780	-6.19	-14.55	8.36
e-7- α a-s-w-p	5.842	-6.31	-15.76	9.44
e-4- γ -s-r-u	6.629	-9.84	-17.64	7.80
e-13- α a-s-r	6.850	-7.02	-16.42	9.40
e-2- γ -s-r-u	7.409	-6.91	-16.83	9.92
e-5- γ -s-r	7.785	-9.91	-18.04	8.13
e-3- γ -s-r	8.636	-8.60	-17.57	8.97
e-15- γ -d-r	9.144	-12.58	-19.46	6.88
e-16- γ -d-r	9.489	-10.95	-18.96	8.01
e-17- γ -d-r	9.731	-13.26	-20.00	6.74
e-16- γ -d-w	9.871	-14.61	-23.04	8.43
e-18- γ -d-r	10.154	-12.13	-19.58	7.44
e-20- γ -s-w	10.216	-13.24	-20.34	7.10
e-15- γ -d-w	10.341	-17.07	-24.06	6.99
e-21- γ -d-r	10.391	-11.42	-19.44	8.03

B. Adducts with explicit water molecules

Considering adducts with explicit water molecules is important when the solute molecule can form H-bonds with water molecules, because these bonds are not taken into account explicitly by the PCM model [14]. The energy ($E_{\text{molec-aq}}$) of the interaction between the solute molecule and the n water molecules in an adduct is calculated as

$$E_{\text{molec-aq}} = E_{\text{adduct}} - (E_{\text{molec}} + n E_{\text{aq}})_{\text{isolated}} - E_{\text{aq-aq}}$$

The energy of the water-water interactions ($E_{\text{aq-aq}}$) is evaluated through a single-point calculation on the water molecules arranged in the same way as in the adduct, but without the solute molecule. Both the energy of the adduct (E_{adduct}) and $E_{\text{aq-aq}}$ are corrected for BSSE (basis set superposition error).

Adducts were calculated for a suitable number of each conformer-type (with both IHB, with only the first IHB, etc.). Two types of adducts were considered: adducts with only one water molecule H-bonded in turn to one of the donor or acceptor sites of the solute (meant to estimate the H-bonding strength of individual sites) and adducts with water molecules H-bonded to all the donor/acceptor sites and others bridging them, to approximate the first solvation layer. The results for the adducts of cspt-Z have been included in [6] and are here recalled only for comparison with the adducts of cspt-E. Fig. 13 shows representative adducts of cspt-Z and fig. 5 shows adducts of cspt-E, considering adducts with water molecules approximating the first solvation layer.

The adducts of both isomers show patterns consistent with those identified as generally common for acylphloroglucinols [15] for the hydrophobic character of the region in the vicinity of the first IHB, for the preference for squares of O atom in association with free OH, and for the arrangement of water molecules in the region between O10H16 and O12H17. The region around R' shows features determined by the presence of the ester function. Water molecules tend to insert themselves between the O in R' and a neighboring phenol OH, breaking the second IHB if present. The optimization process shows this; the example of e-2- α -s-w-11aq is reported in fig. 16 as illustration.

There are no relevant differences in the patterns of the adducts of the two isomers.

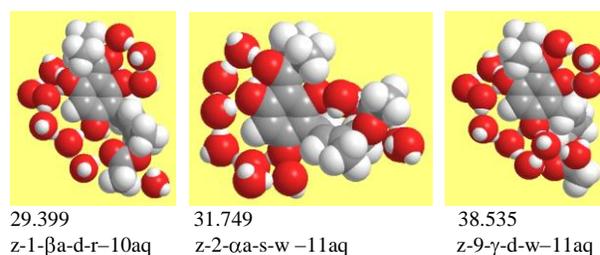


Fig. 14. Representative adducts of the Z isomer of caespitate with explicit water molecules approximating the first solvation layer. The molecule water interaction energy (kcal/mol) is reported under each image, followed by the name of the conformer and the number of surrounding water molecules.

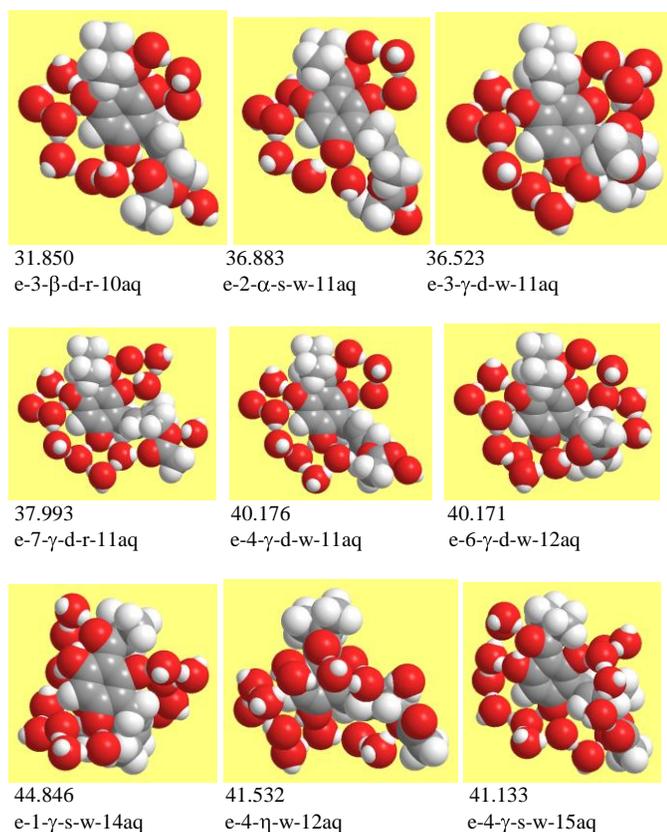


Fig. 15. Representative adducts of the E isomer of caespitate with explicit water molecules approximating the first solvation layer. The molecule water interaction energy (kcal/mol) is reported under each image, followed by the name of the conformer and the number of surrounding water molecules.

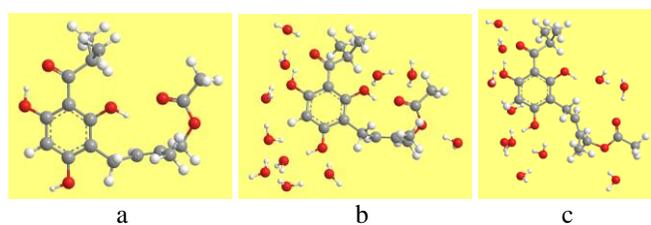


Fig. 16. Illustration of the disruption of the second IHB on competition with intermolecular solute-solvent hydrogen bonds in the case of e-2-α-s-w-11aq.

a) Optimized geometry of e-2-α-s-w *in vacuo*, with the second IHB engaging H15 and O23; b) Input geometry of the adduct of e-2-α-s-w with 11 explicit water molecules approximating the first solvation layer; c) Result of the optimization: the second IHB breaks in favor of intermolecular H-bonds with water molecules; this causes major changes in the geometry of R', as two water molecules insert themselves between H15 and O23.

V. CONCLUSIONS

The major differences between the two geometric isomers of caespitate concern:

- the ability of R' to form the second IHB and the stabilizing effect of this IHB both much greater for cspt-Z;
- the O atoms of R' that can be engaged in the second IHB both O21 and O23 for cspt-Z, only O23 from cspt-E;
- the variety of possible geometries with the second IHB – greater for cspt-Z because of the possibility of forming second IHB engaging O21, O23, or O21 and O23 simultaneously, which results in greater variety of possible rings;
- the dominance of the second IHB for cspt-Z and of the O–H...π interaction for cspt-E, as conformer-stabilizing interactions;
- the number of low-energy conformers, much greater for cspt-E.

All these differences could have a role in determining biological activity differences between the two isomers. IHB are known to play roles in bioactivities and, therefore, the formation of the second IHB and its permanence in non-hydroxyl media may account for some aspects of the bioactivity of cspt-Z. A high number of low energy conformers (as in the case of cspt-E) facilitates rapid mutual interconversion, which might prevent the conformer that could be responsible for bioactivity to “live” long enough to exert it. The differences between the two isomers are more marked *in vacuo* and decrease with increasing solvent polarity, remaining significant in non-polar media; they might therefore account for the differences in biological activities as, within living organisms, these molecules are more likely to have higher presence in non-polar phases.

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