# Ab Initio Study of the Dimers of Nodifloridin B

### Liliana Mammino

Abstract—Nodifloridin B is an acylated phloroglucinol derivative in which both the acyl chain and a substituent in meta to the acyl chain end with a COOH function. Carboxylic acids can form dimers through hydrogen bonds between the COOH functions of two molecules. In the case of nodifloridin B, the presence of two COOH functions in the same molecule enables the formation of different types of dimers: open-shape dimers, in which only one COOH group of a molecule binds to a COOH group of another molecule, and ringshaped dimers, in which each COOH of a molecule binds to a COOH of another molecule. The present computational study analyses the possible shapes of the various types of dimers and compares their relative stabilities and their geometry features.

**Keywords**— Acylphloroglucinols, Dimers of carboxylic acids, Hydrogen bonding, Nodifloridin B.

### I. INTRODUCTION

NODIFLORIDIN-B (concisely denoted as nod-B in this work) is a compound isolated from *Lippia nodiflora* [1], a plant utilized in Chinese traditional medicine to treat swellings and abscesses [2]. Its structure [3] is shown in fig.1, together with the atom numbering utilized in this work. The atom numbering is the same as in previous works [4], [5] to facilitate comparisons and cross references.

Nod-B pertains to the class of compounds termed acylphloroglucinols (ACPL). These are derivatives of phloroglucinol (1,3,5-trihydroxybenzene) characterized by the presence of a COR group (acyl chain). Their general structure is shown in fig. 2. The class is very broad, with a variety of different R and of different substituents in the positions in meta to the acyl chain.

In the nod-B molecule, R is  $(CH)_6COOH$  and contains three conjugated C=C double bonds. The substituent at C3 (which will be concisely denoted as R', consistently with the notation in general studies of ACPL [6], [7]) is  $(CH_2)_5COOH$ . Thus, the nod-B molecule has two carboxylic functions, one at the end of R and one at the end of R'. The molecule also contains an OCH<sub>3</sub> group at C5.

With respect to the general structure of ACPL, nod-B has five additional O atoms (O11, O24, O25, O32 and O33) that

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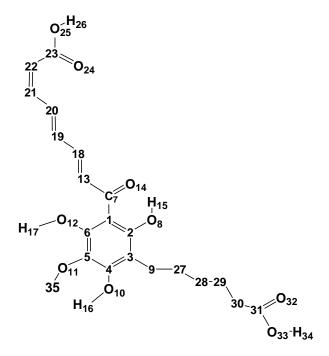


Fig. 1. Structure of the nodifloridin B molecule.

The figure shows the carbon skeleton (with the C atoms replaced by the numbers with which they are denoted in this work), the O atoms, and the H atoms that can be engaged in intramolecular hydrogen bonds. All the other H atoms are hidden, to better highlight the molecular structure.

can act as acceptors of intramolecular hydrogen bonds (IHB). It also contains two additional H atoms that can be involved in IHB (H26 and H34). This gives rise to a huge number of possible IHB combinations and, therefore, to a huge number of different conformers; the conformational preferences of nod-B in vacuo and in solution were investigated in previous works [4], [5].

Carboxylic acids can form dimers by means of two hydrogen bonds (H-bonds) connecting the COOH groups of two molecules. Dimer formation is possible only when both COOH groups are in the more stable Z form, because then all the atoms have the orientation suitable for the formation of the two H-bonds. Fig. 3 shows the two H-bonds for the simple case of the dimer of acetic acid.

In the case of nod-B, the presence of two COOH groups in each molecule gives rise to different possibilities for dimer formation. Some possibilities for open-shape dimers were already investigated in [5]. This work considers both other

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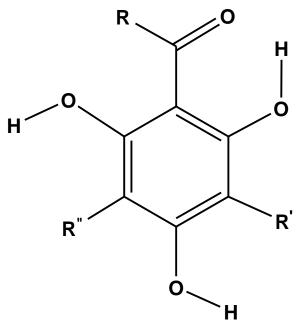


Fig. 2. General structure of acylphloroglucinols. The three OH groups are in meta to each other.

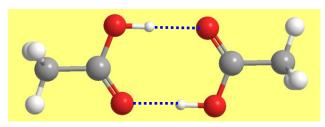


Fig. 3. The dimer of acetic acid.

The figure shows the two hydrogen bonds (dotted blue segments) holding together the two acetic acid molecules in the dimer.

possibilities for open-shape dimers and the closed-shape (or ring-shaped) dimers, investigating their geometric characteristics and comparing their relative stabilities both within each type of dimers and across different types. It also compares the effect of dimer formation on the characteristics of the IHB of each monomer, with particular attention to the IHB between the sp<sup>2</sup> O of COR (O14) and a neighboring OH (the "first IHB" characterizing all ACPL [6], [7]).

The investigation of dimer formation is relevant to the completeness of the study of organic molecules containing carboxylic functions. In the case of nod-B, additional interest stems from the characteristics of the molecule, above all the presence and mutual space arrangement of two COOH functions.

The consideration of nod-B as a significant case-study pertains to an ongoing systematic study of ACPL, aimed at identifying patterns in their conformational preferences and the factors influencing them, [4], [5], [8]. Nod-B constitutes an interesting case for the analysis of the stabilizing effects of additional O–H···O IHB [8]. In general, the investigation of as

many characteristics as possible of the structure and behaviour of biologically active molecules relates to the importance of the information on the finest details of molecular structure and behaviour for a better understanding of the biological activity, and to the importance of computable descriptors for drug development [9], [10].

## II. COMPUTATIONAL DETAILS

All the calculation where performed in vacuo at the Hartree-Fock (HF) level, using the 6-31G(d,p) basis set. This is the same level of theory utilized in the conformational study of nod-B [4, 5], thus enabling straightforward comparisons. More sophisticated computational methods would be unaffordable because of the high number of atoms (108 in the dimer) and the high number of rotatable bonds (15 in each monomer, while the two (for open-shape dimers) or four (for ring-shaped dimers) H-bonds holding the two monomers together, although not rotatable if they are to bind the COOH groups, add some degrees of freedom in relation to the way in which the two monomers approach each other. Comparison of the performance of HF with that of higher-level-of-theory methods (density functional theory, DFT, and Møller Plesset perturbation theory, MP2) had shown that HF is capable of giving reliable results and reliable patterns-identification for ACPL [6], [7], [11], [12], which justifies the expectation of realistic HF results for the dimers of nod-B.

Calculations were performed with full optimization (fully relaxed geometry), to ensure the best identification of the dimers' geometries. All the calculations were performed with Gaussian03, revision D01 [13].

The interaction energy between the two monomers  $(E_{\text{interaction}})$  is calculated as

$$E_{interaction} = E_{dimer} - E_{monomer-1} - E_{monomer-2} \qquad (1)$$
 where  $E_{dimer}$  is the energy of the dimer and  $E_{monomer-1}$  and  $E_{monomer-2}$  are the energies of the first and the second monomers respectively. When the two monomers are identical, this equation becomes

$$E_{\text{interaction}} = E_{\text{dimer}} - 2 E_{\text{monomer}}$$
 (2)

E<sub>interaction</sub> is corrected for basis set superposition error (BSSE) using the counterpoise method [14].

The work considers dimers of the same conformer (identical monomers) to better single out the characteristics of the given type of dimer, by avoiding the complicating features that would arise from the effects of differences in the geometrical characteristics of two different conformers.

# III. RESULTS

## A. Types of Dimers for Nodifloridin B

In the case of nod-B, dimers can be formed by two types of conformers:

- conformers in which one of the COOH groups is not engaged in IHB, while the other one is;
- conformers in which neither COOH group is engaged in

In the former case, only open-shape dimers are possible. In the latter case, both open-shape dimers and ring-shaped dimers are possible; the open-shape dimers are actually openended, as the presence, at each end of the dimer, of a COOH group available for the formation of other H-bonds may enable the formation of trimeric or longer chains.

For dimers of conformers in which one of the COOH groups is engaged in IHB, only one geometry is possible - the one enabling the two free COOH to bind to each other.

For open-shape dimers of conformers in which none of the COOH groups is engaged in IHB, three combinations of monomers arrangements are possible, differing by the COOH groups that form the intermonomer H-bonds; they are here denoted in the same way as in [5]:

- the COOH at the end of R in one monomer H-bonds to the COOH at the end of R in the other monomer (aa);
- the COOH at the end of R in one monomer H-bonds to the COOH at the end of R' in the other monomer (ab):
- the COOH at the end of R' in one monomer H-bonds to the COOH at the end of R' in the other monomer (bb).

For conformers in which both COOH groups are available (not engaged in IHB), two COOH binding combinations can yield ring-shaped dimers [15]:

- the COOH at the end of R in one monomer binds to the COOH at the end of R' in the other monomer; it will be denoted as I;
- the COOH at the end of the two R chains bind to each other and the COOH at the end of the two R' chains bind to each other; it will be denoted as II.

The two cases imply different mutual positions of the phloroglucinol moieties: away from each other in I and "facing each other" in II.

Moreover, geometrical differences for the ring arise from the orientation of the ether groups at C5, with the following possibilities (respectively denoted, in the dimers' names, with the letter in parenthesis at the end of each description):

- both ether groups are oriented "inward" with respect to the ring, (e);
- the ether group of the first monomer is oriented inward and the ether group of the second monomer is oriented outward,
- the ether group of the first monomer is oriented outward and the ether group of the second monomer is oriented inward, (d);
- both ether groups are oriented outward with respect to the ring, (f).

This gives a total of 8 different geometries for ring-shaped dimers between two given monomers (whether identical or different). The asymmetry of the arrangement of the two monomers with respect to the center of the ring or to any plane through the ring makes cases d and g different even when the two monomers are identical.

## B. Geometries of Open-shape Dimers

The conformational study of nod-B [4], [5] showed that IHB engaging the COOH at the end of R' are preferred to IHB engaging the COOH at the end of R, likely because the latter imply a geometrical strain on R weakening the stabilization from the conjugation of its  $\pi$  bonds. Therefore, the lower

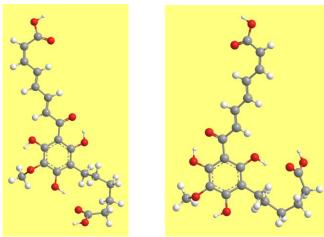
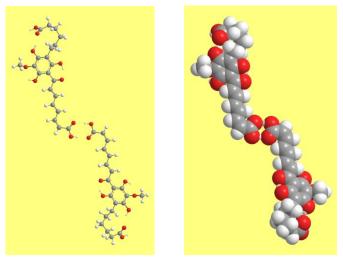


Fig. 4. Conformers of nod-B with the COOH in R not engaged in IHB, utilized for the calculation of dimers in this work: B-3-d-r-c (left) and B-4-s-w-a (right). The COOH in R' is engaged in an IHB.



the dimer of B-3-d-r-c

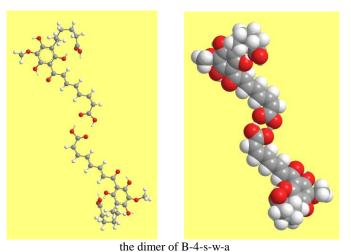


Fig. 5. Dimers of the lower energy conformers of nodifloridin B in which the COOH at the end of the acyl chain is not engaged in IHB.

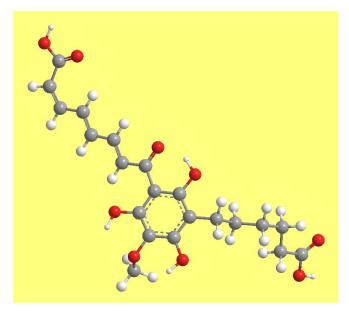


Fig. 6. Optimized geometry of the best conformer of nodifloridin B in which neither of the two COOH groups is engaged in IHB.

energy conformers with one free COOH are those in which the COOH at the end of R is free and only the COOH at the end of R' is engaged in IHB. The two lowest-energy ones among such conformers were here utilized to calculate dimers: they are shown in fig. 4; they were denoted as B-3-d-r-c and B-4-s-w-a in [4], [5] and their relative energies are 2.967 and 3.759 kcal/mol respectively. The corresponding dimers are shown in fig. 5.

Both stick-and-ball models and space filling models are here utilized on representing dimers because the former are more apt to highlight the way in which atoms bond to each other (including the directionality of the intermonomer H-bonds) and the latter are more apt to highlight the overall shape of the dimers. In all figures showing dimers, the dimers are reported in order of decreasing stability (increasing relative energy).

The best conformer of isolated nod-B in which neither COOH group is engaged in IHB (termed B-5-d-w in [4], [5]) has relative energy 4.373 kcal/mol. Its geometry is shown in fig. 6. It is here utilized as monomer for all the other calculated dimers, both open-shape and ring-shaped. Fig. 7 shows the geometries of the open-shape dimers of B-5-d-w.

# C. Geometries of Ring-shaped Dimers

All the possible geometrical combinations of the two monomers were calculated for the ring-shaped dimers of the B-5-d-w conformer. They are shown in fig. 8.

The geometries in which the COOH at the end of R in one monomer binds to the COOH at the end of R' in the other monomer (I) appear to be preferred, likely because they enable the formation of a ring that is broad in similar ways in the vicinity of the two intermonomer binding sites. In cases II, the ring is narrower on the side where the COOH at the end of the two R chains bind to each other and broader on the side where the COOH at the end of the two R' chains bind to each other.

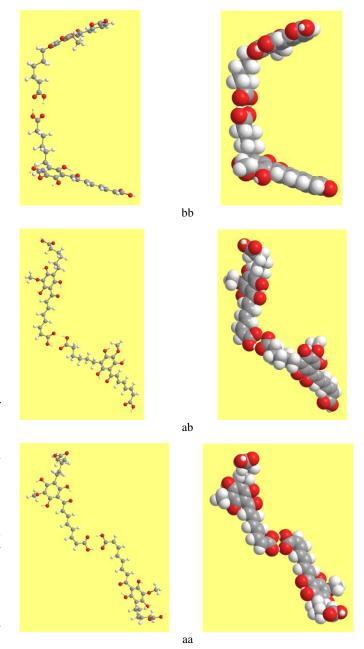
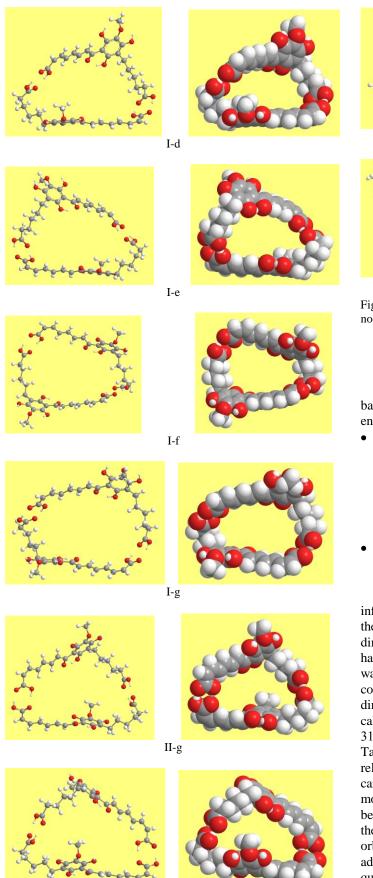


Fig. 7. The three possible combinations for the open-shape dimers of the B-5-d-w conformer of nodifloridin B [5].

likely because of the greater length of R with respect to R', and maybe also because of the poor flexibility of R and the greater flexibility of R'.

The orientation of the ether at C5, although influencing the dimer energy and stability, does not appear to give rise to significant steric hindrances, even when the ether groups of the two monomers are both oriented inwards. The fact that the cases in which both ether groups are oriented outwards are not the lowest energy ones suggests that the inward orientation might involve some slight advantages which, however, are not easy to single out.



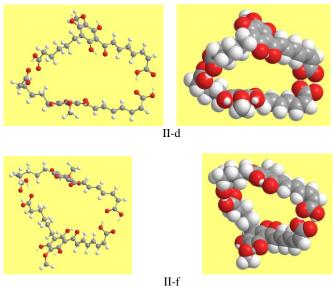


Fig. 8. The possible ring-shaped dimers of the B-5-d-w conformer of nodifloridin B [10].

# D. Comparison of the Various Types of Dimers

Since the conformers' geometry and characteristics are basically maintained in the dimers, the calculated dimers enable two types of comparisons in terms of relative stabilities:

- a comparison of the relative stabilities of dimers of the same type with reference to the relative stabilities of the corresponding monomers. The dimers of B-3-d-r-c and B-4-s-w-a and the aa dimer of B-5-d-w are apt for this comparison, as they have the same type of intermonomer H-bonds (intermonomer H-bonds engaging the COOH at the end of the R chains);
- a comparison of the relative stabilities of the different possible dimers between the same monomers. The dimers of B-5-d-w are apt for this comparison.

A suitable reference for a possible evaluation of the influence of the complex structure of the nod-B molecule on the interactions between the two monomers is offered by the dimer of acetic acid (fig. 3), the simplest carboxylic acid having more than one C atom. Therefore, the dimer of this acid was calculated at the HF/6-31G(d,p) level, so that its results constitute the immediate reference for the comparison with the dimers of nod-B (all calculated at the same level). It was also calculated at the DFT/B3LYP/6-31+G(d,p) and MP2/6-31G(d,p) levels, to assess the "goodness" of the HF results. Table I reports the results of the acetic acid dimer that are relevant for the comparison with the dimers of other carboxylic acids: the interaction energy between the two monomers, the BSSE correction and the length of the H-bonds between the two monomers. The energy difference between the frontier orbitals (HOMO, highest occupied molecular orbital, and LUMO, lowest unoccupied molecular orbital) is added as it is often a relevant descriptor in the analysis of quantitative structure-activity relationships for biologically active molecules. Although HF gives longer distance for the identical intermonomer H-bonds, its results for the other

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Table 1. Relevant quantities for the dimer of acetic acid, in the results of the three calculation methods utilized for this dimer: HF/6-31G(d,p), DFT/B3LYP/6-31+G(d,p) and MP2/6-31G(d,p), respectively denoted as HF, DFT and MP2 in the first column.

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
DFT	-15.519	0.800	1.651	174.096
MP2	-13.351	5.363	1.700	389.740

Table 2. Comparison of relevant quantities for the dimers of the B-3-d-r-c and B-4-s-w-a conformers of nodifloridin B and the aa dimer of the B-5-d-w conformer: relative energy of the conformer (kcal/mol), relative energy of the dimer (ΔΕ, kcal/mol), interaction energy between the two monomers (kcal/mol, corrected for BSSE), and BSSE correction (kcal/mol). The relative energy of the conformers is referred to the lowest energy conformer of nod-B, a conformer in which both COOH are engaged in IHB[4], [5]. The relative energy of the dimers is referred to the lowest-energy dimer among the three considered here.

conformer	relative energy of conformer	relative energy of dimer	interaction energy of dimer	BSSE correction
B-3-d-r-c	2.967	0.000	-12.869	2.142
B-4-s-w-a	3.759	1.555	-12.904	2.149
B-5-d-w	4.373	2.751	-12.921	2.126

quantities are closer to those of MP2 (taken as benchmarks because of being the most sophisticated method among the ones utilized) than the DFT results are. This further supports the assumption that the HF results for the dimers of nod-B can be considered reasonable and that, in particular, they enable reasonable comparisons and identification of trends.

Table 2 reports the relevant quantities for the comparison of the dimers of B-3-d-r-c and B-4-s-w-a and the aa dimer of B-5-d-w. The energy gap between the dimers is close to twice the energy gap between the corresponding isolated conformers, suggesting that, as long as the type of dimer is the same (same type of COOH groups involved), the relative stability of the dimers is determined by the relative stability of the monomers. The interaction energy is close for all the dimers, and only marginally weaker than in the dimer of acetic acid.

Table 3 reports the relative energies ( $\Delta E$ ), the interaction energy between the two monomers, the BSSE correction, the energy difference of the frontier orbitals and the dipole moment of the dimers of the B-5-d-w conformer. While the stability is very similar for the I-type dimers, it depends more extensively on the orientation of the ether at C5 for II-type dimers.  $\Delta E$  of the open-shape dimers is slightly more than twice the  $\Delta E$  of the highest-energy ring-shaped dimers; this suggests that the ring formation does not involve any destabilizing effect (e.g., geometry strains) and that the

Table 3. Comparison of relevant quantities for the dimers of the B-5-d-w conformer of nodifloridin B: relative energy of the dimer ( $\Delta E$ , kcal/mol), interaction energy between the two monomers (kcal/mol, corrected for BSSE), BSSE correction (kcal/mol), HOMO-LUMO energy gap (kcal/mol) and dipole moment (debye). The bb, ab and aa dimers are open-shape dimers [5].

dimer	relative energy ΔE	inter- action energy	BSSE correct- ion	HOMO LUMO gap	dipole moment
I-d	0.000	-15.477	4.425	215.123	9.496
I-e	0.197	-19.541	4.422	215.210	10.093
I-f	0.277	-19.463	4.417	216.334	8.304
I-g	0.486	-19.246	4.425	216.422	9.767
II-g	2.988	-16.784	4.426	217.513	6.446
II-e	3.825	-15.941	4.429	218.361	4.689
II-d	4.187	-11.131	4.389	218.486	3.470
II-f	4.271	-15.515	4.396	218.398	4.967
bb	8.808	-13.109	2.250	217.946	3.813
ab	8.929	-13.047	2.189	217.225	7.448
aa	9.115	-12.921	2.126	217.764	3.239

Table 4. Parameters of the intermonomer hydrogen bonds in the dimers of the B-3-d-r-c and B-4-s-w-a conformers of nodifloridin B and in the aa dimer of B-5-d-w.

conformer	H-bond considered	parameters of the H-bond		I-bond
		O…H (Å)	OO (Å)	OĤO
B-3-d-r-c	H26···O24′	1.817	2.778	176.9
	H26'···O24	1.817	2.778	176.9
B-4-s-w-a	H26···O24′	1.818	2.779	176.9
	H26'O24	1.818	2.778	176.9
B-5-d-w	H26···O24′	1.818	2.779	176.8
	H26'O24	1.818	2.779	176.8

greater stabilization of the ring-shaped dimer is mostly due to the presence of two additional intermonomer H-bonds. The interaction energy between the two monomers in the ringshaped dimers is nearly twice that of the open-shaped dimers, as predictable from the presence of a double number of intermonomer H-bonds.

The comparison of the parameters of the H-bonds is relevant because the H-bond length is a good indicator of the H-bond strength and the other parameters help assess the quality of the H-bond (e.g., its directionality). The comparison requires the identification of the relevant atoms in each monomer. Thus, for each dimer, the atoms of one monomer will be numbered as in fig. 1 and the corresponding atoms of the other monomer with the same numbers, but primed (e.g., the sp<sup>2</sup>O of COR is O14 for one monomer and O14′ for the other monomer).

Table 4 reports the parameters of the H-bonds between the two monomers in the three open-shape dimers where the monomers are bonded to each other through the COOH at the end of R. The H-bond lengths do not differ from those in the acetic acid dimer.

Table 5 reports the parameters of the H-bonds between the two monomers for all the dimers of B-5-d-w. Both table 4 and table 5 show that, for open-shape dimers, the two H-bonds have the same parameters if the two COOH are attached to corresponding chains, i.e., both at the end of R or both at the end of R', whereas the parameters may be different if one of the COOH is attached to R and the other to R'. For ringshaped dimers, the lengths differ considerably, as one of the

Table 5. Parameters of the intermonomer hydrogen bonds in the dimers of the B-5-d-w conformer of nodifloridin B.

dimer	H-bond	par	ameters of th	e H-bond
	considered	OH		OĤO
		O…H (Å)	O…O (Å)	ОНО
		(A)	(A)	
I-d	H26···O32′	1.798	2.760	176.4
	H34'O24	1.822	2.782	175.3
	H34···O24′	1.869	2.817	168.3
	H26'···O32	1.789	2.743	170.7
I-e	H26···O32′	1.798	2.760	176.4
	H34'O24	1.822	2.782	175.3
	H34···O24′	1.869	2.817	168.3
	H26'···O32	1.789	2.743	170.7
I-f	H26···O32′	1.802	2.765	176.0
	H34'O24	1.822	2.780	174.1
	H34···O24′	1.865	2.816	169.5
	H26'···O32	1.786	2.741	171.0
I-g	H26···O32′	1.787	2.751	177.2
	H34'···O24	1.824	2.784	175.6
	H34···O24′	1.873	2.817	167.1
	H26'···O32	1.792	2.744	169.1
II-g	H26···O24′	1.762	2.722	174.9
	H26'···O24	1.908	2.852	166.9
	H34···O32′	1.788	2.749	175.9
	H34'O32	1.853	2.814	176.2
II-e	H26···O24′	1.761	2.720	144.4
	H26'···O24	1.916	2.857	165.9
	H34···O32′	1.790	2.751	175.4
	H34'···O32	1.849	2.810	176.1
II-d	H26···O24′	1.761	2.720	174.4
	H26'···O24	1.916	2.857	165.9
	H34···O32′	1.790	2.751	175.4
	H34'O32	1.849	2.810	176.1
II-f	H26···O24′	1.764	2.723	174.5
	H26'O24	1.912	2.854	166.0
	H34···O32′	1. 792	2. 752	175.5
	H34'O32	1.842	2.803	176.2
bb	H34···O32′	1.823	2.783	176.6
	H34'O32	1.823	2.783	176.6
ab	H26···O32′	1.811	2.772	176.7
	H34'O24	1.830	2.890	176.2
aa	H26···O24′	1.818	2.779	176.8
	H26'···O24	1.818	2.779	176.8

Table 6. Parameters of the intramolecular hydrogen bonds in the isolated conformers and in the dimers of B-3-d-r-c and B-4-s-w-a and the aa dimer of B-5-d-w.

In the third column, "isol" denotes the isolated monomer and "dim" denotes the monomer in the dimer. The values for the monomer are reported only once for each bond, because the two monomers are identical in each of the dimers considered.

conf-	IHB	where	parar	neters of the	IHB
ormer	considered		OH	00	OĤO
			(Å(	(Å)	
B-3-	H15O14	isol	1.684	2.531	145.3
d-r-c		dim	1.684	2.531	145.3
	H15'O14'	dim	1.684	2.531	145.3
	H16-O32	isol	1.991	2.888	157.3
		dim	1.991	2.888	157.2
	H16'···O32'	dim	1.991	2.888	157.2
	H17···O11	isol	2.057	2.620	116.5
		dim	2.057	2.621	116.4
	H17'O11'	dim	2.057	2.621	116.4
B-4-	H17O14	isol	1.728	2.559	143.4
s-w-a		dim	1.727	2.559	143.4
	H17'···O14'	dim	1.727	2.559	143.4
	H15-O32	isol	2.002	2.888	155.0
		dim	2.002	2.888	155.0
	H15'O32'	dim	2.002	2.888	155.0
	H16O11	isol	2.116	2.656	114.7
		dim	2.116	2.656	114.7
	H16'O11'	dim	2.116	2.656	114.7
B-5-	H15O14	isol	1.699	2.540	144.6
d-w		dim	1.699	2.540	144.6
	H15'O14'	dim	1.699	2.540	144.6
	H16O11	isol	2.221	2.720	112.0
		dim	2.21	2.720	112.0
	H16'O11'	dim	2.221	2.729	112.0
	H17O11	isol	2.163	2.783	113.4
		dim	2.163	2.783	113.4
	H17'O11'	dim	2.163	2.783	113.4

H-bonds is toward the inner side of the ring, and the other toward its outer side. The length of the shorter H-bond toward the inner side of the ring is 1.786–1.798 for I-type dimers and 1.761–1.792 for II-type dimers; the length of the longer H-bond toward the outer side of the ring is 1.802–1.873 for I-type dimers and 1.849–1.916 for II-type dimers.

Table 6 compares the parameters of the IHB in the three open-shape dimers bonded to each other through the COOH at the end of R. The values are reported individually to better highlight the extent of the correspondence: fluctuations are rare, affect only the last digit and to an extent so small as to remain below error range. It can be concluded that, for this type of dimers, the dimer formation does not affect the IHB.

Table 7 reports the parameters of the first IHB for the dimers of B-5-d-w. In the isolated monomer, the length of the first IHB is 1.699, the O···O distance is 2.540 and the OĤO angle is 144.6° (table 6). In each ring-shaped dimer, the parameters of the first IHB of one monomer remain close to those of the isolated monomer, while they increase slightly for the other monomer. In the open-shape dimers, the parameters

Table 7. Parameters of the first IHB in the two monomers of the dimers of B-5-d-w.

dimer	first IHB	paran	neters of the H	-bond
	considered	O…H	OO	OĤO
		(Å)	(Å)	
		1 = 10		1110
I-d	H15O14	1.719	2.555	144.0
	H15'O14'	1.699	2.540	144.6
I-e	H15O14	1.719	2.555	144.0
	H15'O14'	1.699	2.540	144.6
I-f	H15O14	1.715	2.551	144.0
	H15'O14'	1.697	2.539	144.7
I-g	H15O14	1.713	2.550	144.1
	H15'O14'	1.703	2.543	144.5
II-g	H15O14	1.694	2.538	144.9
	H15'O14'	1.750	2.583	143.9
II-e	H15O14	1.702	2.544	144.8
	H15'···O14'	1.750	2.583	143.9
II-d	H15O14	1.702	2.544	144.8
	H15'O14'	1.750	2.583	144.4
II-f	H15O14	1.701	2.543	144.7
	H15'···O14'	1.746	2.580	144.0
bb	H15O14	1.700	2.540	144.6
	H15'O14'	1.700	2.540	144.6
ab	H15O14	1.698	2.539	144.6
	H15'O14'	1.700	2.540	144.6
aa	H15O14	1.699	2.540	144.6
	H15'O14'	1.699	2.540	144.6

of both first IHB remain close to those of the isolated monomer.

The formation of open-shape dimers does not imply any strain on the geometry of the monomers. Previous considerations on relative energies and interaction energies suggest that also the formation of ring-shaped dimers does not imply significant geometry strains; however, it is interesting to confirm by checking the geometry of individual monomers, above all in order to identify possible deviations from planarity of the  $\pi$  system of R (a system of three conjugated C=C double bonds). Table 8 reports the torsion angles of the carbon atoms of the acyl chain in the ring-shaped dimers of B-5-d-w. The values for the open-shape dimer in which the two monomers bind through the COOH at the end of R (aa) are also reported, as well as the values for the isolated monomer. While, in the open-shape dimer, the values are practically the same as in the isolated monomers, some differences are observed in the ring-shaped dimers, likely to account for the closing of the ring. However, the differences are not so large as to suggest significant strain. It can therefore be inferred that the formation of ring-shaped dimers is geometrically favored by the mutual positions of R and R' with respect to the benzene ring in the nod-B molecule, and also by their length factors that prevent strain on ring-closing.

In order to complete the comparison of the different types of dimers, it is interesting to compare the frontier molecular

Table 8. Torsion angles of the C atoms of the acyl chain in the dimers of B-5-d-w.

dimer	torsion angle considered	value of the
anner	torsion ungre considered	torsion angle
I-d	C2-C1-C7-C13	155.5
I-e	C1-C7-C13-C18	-170.7
	C7-C13-C18-C19	176.4
	C13-C18-C19-C20	-175.5
	C18-C19-C20-C21	178.5
	C19-C20-C21-C22	-176.0
	C20-C21-C22-C23	-0.1
	C2'-C1'-C7'-C13'	-163.3
	C1'-C7'-C13'-C18'	-169.6
	C7'-C13'-C18'-C19'	-179.0
	C13'-C18'-C19'-C20'	-175.6
	C18'-C19'-C20'-C21'	178.3
	C19'-C20'-C21'-C22'	-173.3
I-f	C20'-C21'-C22'-C23'	1.1
1-1	C2-C1-C7-C13 C1-C7-C13-C18	154.6 -169.3
	C7-C13-C18-C19	176.5
	C13-C18-C19-C20	-174.6
	C18-C19-C20-C21	178.6
	C19-C20-C21-C22	-176.2
	C20-C21-C22-C23	0.3
	C2'-C1'-C7'-C13'	-165.1
	C1'-C7'-C13'-C18'	-168.4
	C7'-C13'-C18'-C19'	179.8
	C13'-C18'-C19'-C20'	-174.6
	C18'-C19'-C20'-C21'	178.0
	C19'-C20'-C21'-C22'	-172.1
	C20'-C21'-C22'-C23'	1.3
I-g	C2-C1-C7-C13	156.3
	C1-C7-C13-C18	-170.1
	C7-C13-C18-C19	176.6
	C13-C18-C19-C20	-175.1
	C18-C19-C20-C21	178.7
	C19-C20-C21-C22 C20-C21-C22-C23	<del>-176.6</del>
	C2'-C1'-C7'-C13'	0.3
	C1'-C7'-C13'-C18'	-163.1 -170.4
	C7'-C13'-C18'-C19'	-170.4 -179.6
	C13'-C18'-C19'-C20'	-175.4
	C18'-C19'-C20'-C21'	178.4
	C19'-C20'-C21'-C22'	-172.5
	C20'-C21'-C22'-C23'	1.6
II-g	C2-C1-C7-C13	-166.9
11 5	C1-C7-C13-C18	-162.1
	C7-C13-C18-C19	-178.0
	C13-C18-C19-C20	-175.5
	C18-C19-C20-C21	-177.2
	C19-C20-C21-C22	-178.5
	C20-C21-C22-C23	2.7
	C2'-C1'-C7'-C13'	-154.5
	C1'-C7'-C13'-C18'	-162.2
	C7'-C13'-C18'-C19'	-178.8
	C13'-C18'-C19'-C20'	-166.0
	C18'-C19'-C20'-C21'	179.3

	G10/ G20/ G21/ G22/	162.7
-	C19'-C20'-C21'-C22'	-163.7
11	C20'-C21'-C22'-C23'	5.1
II-e	C2-C1-C7-C13	-164.4
II-d	C1-C7-C13-C18	-161.2
-	C7-C13-C18-C19	-177.0
	C13-C18-C19-C20	-174.6
<u> </u>	C18-C19-C20-C21	-177.2
<u> </u>	C19-C20-C21-C22	-177.5
_	C20-C21-C22-C23	2.9
_	C2'-C1'-C7'-C13'	-154.1
	C1'-C7'-C13'-C18'	-163.1
_	C7'-C13'-C18'-C19'	-178.8
_	C13'-C18'-C19'-C20'	-167.2
<u> </u>	C18'-C19'-C20'-C21'	179.0
	C19'-C20'-C21'-C22'	-163.3
	C20'-C21'-C22'-C23'	5.0
II-f	C2-C1-C7-C13	-166.0
	C1-C7-C13-C18	-162.0
	C7-C13-C18-C19	-177.9
	C13-C18-C19-C20	-175.4
	C18-C19-C20-C21	-177.1
	C19-C20-C21-C22	-78.5
	C20-C21-C22-C23	2.7
	C2'-C1'-C7'-C13'	-155.4
	C1'-C7'-C13'-C18'	-164.3
	C7'-C13'-C18'-C19'	-178.5
	C13'-C18'-C19'-C20'	-167.6
	C18'-C19'-C20'-C21'	179.2
	C19'-C20'-C21'-C22'	-163.2
	C20'-C21'-C22'-C23'	5.1
aa	C2-C1-C7-C13	163.5
	C1-C7-C13-C18	175.0
	C7-C13-C18-C19	179.9
	C13-C18-C19-C20	179.7
	C18-C19-C20-C21	180.0
<u>_</u>	C19-C20-C21-C22	180.0
_	C20-C21-C22-C23	0.0
	C2'-C1'-C7'-C13'	163.5
_	C1'-C7'-C13'-C18'	175.0
	C7'-C13'-C18'-C19'	179.8
	C13'-C18'-C19'-C20'	179.7
	C18'-C19'-C20'-C21'	180.0
	C19'-C20'-C21'-C22'	180.0
	C20'-C21'-C22'-C23'	0.0
isolated	C2-C1-C7-C13	163.5
monomer	C1-C7-C13-C18	174.9
1		
<u> </u>	C7-C13-C18-C19	178.9
	C13-C18-C19-C20	179.7
-	C13-C18-C19-C20 C18-C19-C20-C21	179.7 179.9
  -  -	C13-C18-C19-C20	179.7

orbitals. Fig. 9 shows the frontier orbitals for the dimers of B-3-d-r-c and B-4-s-w-a (i.e., the dimers of conformers in which the COOH at the end of R' are engaged in IHB). Fig. 10 shows the nine highest occupied molecular orbitals for the

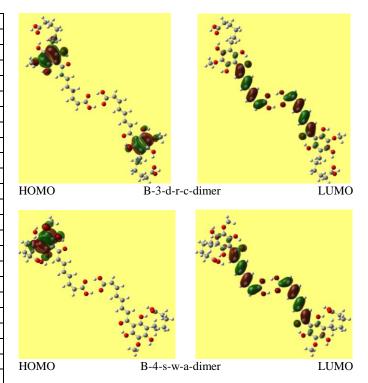


Fig. 9. The frontier orbitals of the dimers of B-3-d-r-c and B-4-s-w-a.

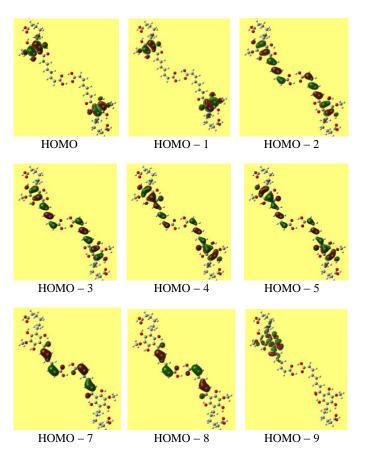
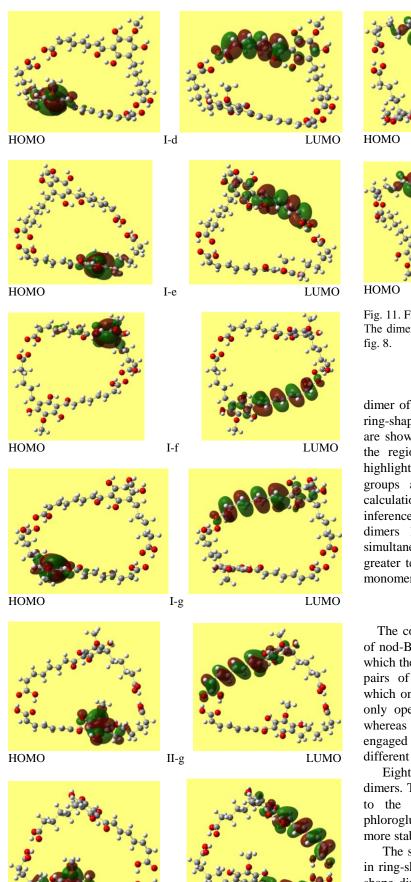


Fig. 10. The nine highest occupied molecular orbitals in the dimer of B-3-d-r-c.



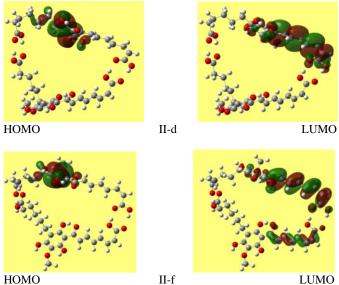


Fig. 11. Frontier orbitals for the ring-shaped dimers of B-5-d-w. The dimers' geometries are shown from the same perspectives as in fig. 8.

dimer of B-3-d-r-c. Fig. 11 shows the frontier orbitals for the ring-shaped dimers of B-5-d-w. In all the figures, the dimers are shown from a perspective that gives specific emphasis to the regions of the H-bonds between monomers and also highlights characteristics like the orientation of the ether groups at C5 and C5'. Although it would require the calculation of many more dimers to make statistically-based inferences, it appears that the frontier orbitals in open-shape dimers have a tendency to extend to both monomers simultaneously, whereas those of ring-shaped dimers have greater tendency to be located in one or the other of the two monomers.

#### IV. CONCLUSIONS

The computational study reported here confirms the ability of nod-B to form both open-shape and ring-shaped dimers, in which the monomers are respectively linked by one pair or two pairs of H-bonds between COOH groups. Conformers in which one of the COOH groups is engaged in IHB can form only open-shape dimers, with only one geometry possible, whereas conformers in which neither of the COOH groups is engaged in IHB can form both open-shape dimers, with three different geometry possibilities, and ring-shaped dimers.

Eight different geometries are possible for ring-shaped dimers. Those in which the COOH in R of one monomer bind to the COOH in R' of the other monomer and the phloroglucinol moieties are not "facing each other" are the more stable.

The strength of the interaction between the two monomers in ring-shaped dimers is nearly double the strength in open – shape dimers. This can be ascribed to the similar strength of the H-bonds between COOH groups. The slight decrease with respect to an exactly double value can be ascribed both to the

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fact that the intermonomer H-bonds on the outer side of the ring are more strained (as indicated by the longer H···O distance) and to the slight deviations from planarity of the conjugated  $\pi$  system in R on forming the ring. The mutual positioning and lengths of the acyl chain and the R' chain in the nod-B molecule appear to enable the formation of ring-shaped dimers without excessive strain on the geometry of either chain.

The results obtained in this study can be considered representative of possible trends for dimers of other conformers of nod-B with analogous characteristics, i.e., conformers with only one COOH not engaged in IHB and conformers in which both COOH are available (not engaged in IHB), because all monomers' combinations yielding different geometries have been taken into account, thus including all the factors that may influence the dimers' stability, such as the orientation of the ether group at C5 with respect to the dimer ring in ring-shaped dimers. Therefore, the results have also predictive significance for other dimers of nod-B.

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