

Ab Initio Study of the Dimers of Nodifloridin B

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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 ring-shaped 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 $(\text{CH})_6\text{COOH}$ and contains three conjugated $\text{C}=\text{C}$ 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 $(\text{CH}_2)_5\text{COOH}$. 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_3 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

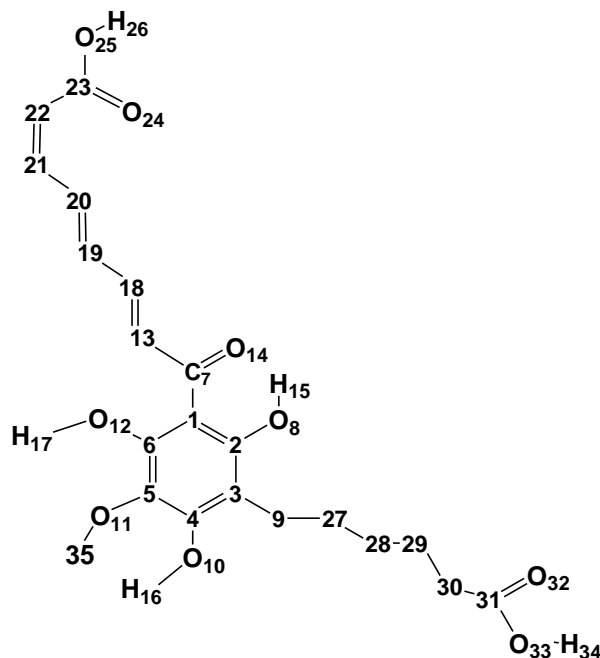


Fig. 1. Structure of the nodifloridin B molecule.

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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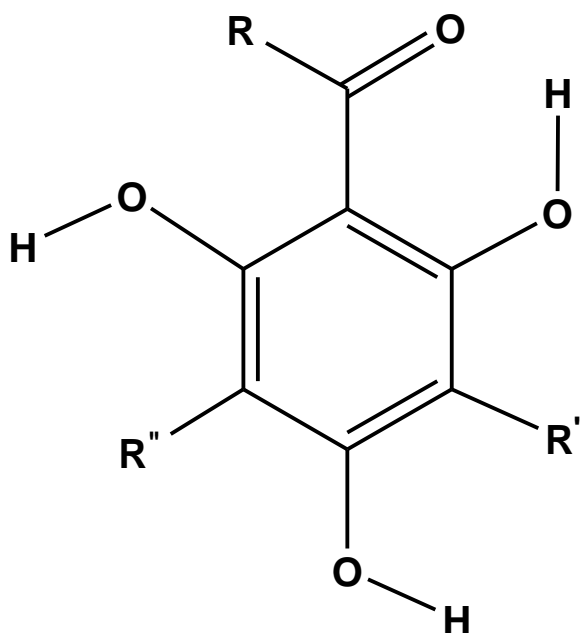


Fig. 2. General structure of acylphloroglucinols. The three OH groups are in meta to each other.

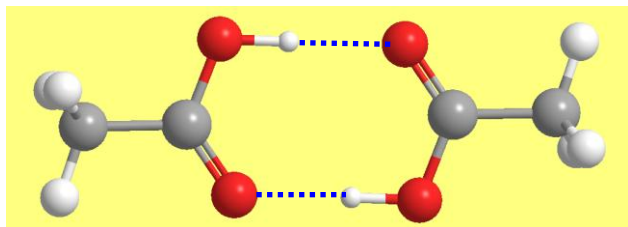


Fig. 3. The dimer of acetic acid. The figure shows the two hydrogen bonds (dotted blue segments) holding together the two acetic acid molecules in the dimer.

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^2 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 were 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

$$E_{\text{interaction}} = E_{\text{dimer}} - E_{\text{monomer-1}} - E_{\text{monomer-2}} \quad (1)$$

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

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

$E_{\text{interaction}}$ 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 IHB.

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 open-ended, 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, (g);
- 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 π bonds. Therefore, the lower

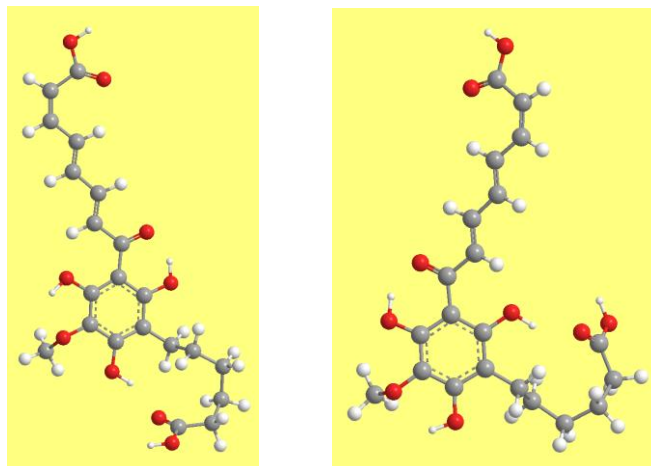
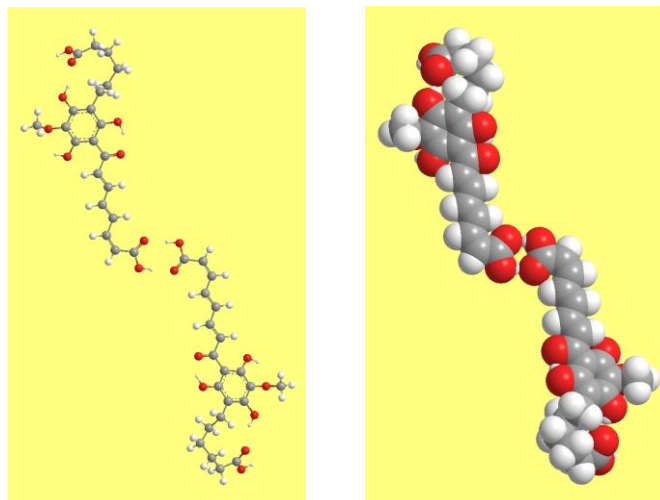
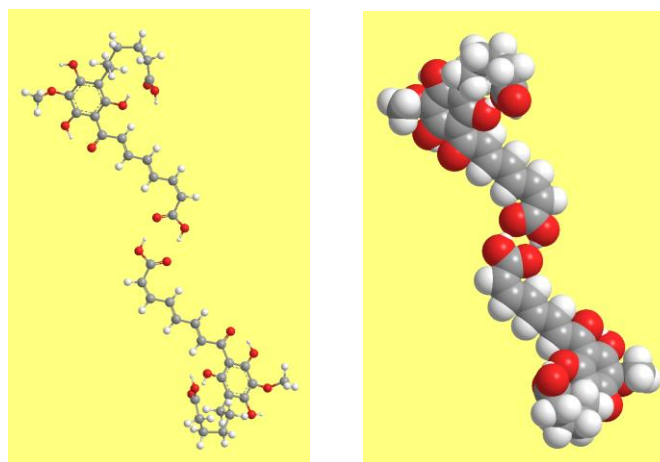


Fig. 4. Conformers of nod-B with the COOH in R not engaged in IHB, utilized for the calculation of dimers in this work: B-3-d-r-c (left) and B-4-s-w-a (right). The COOH in R' is engaged in an IHB.



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



the dimer of B-4-s-w-a

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.

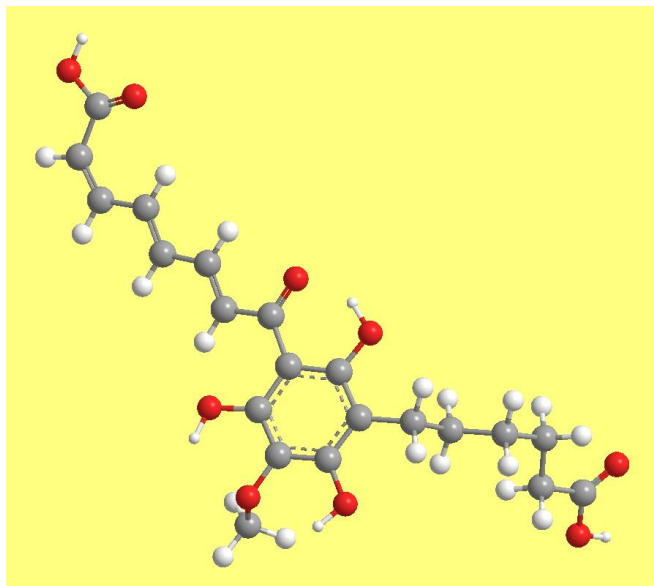


Fig. 6. Optimized geometry of the best conformer of nodifloridin B in which neither of the two COOH groups is engaged in IHB.

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,

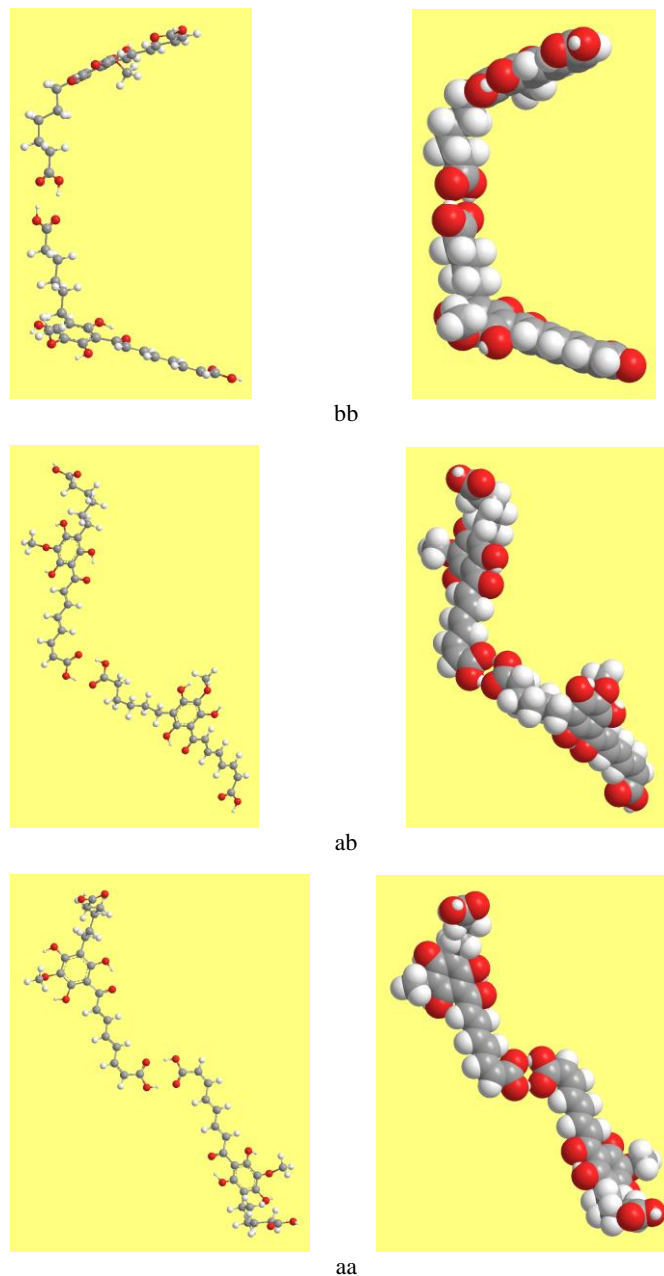


Fig. 7. The three possible combinations for the open-shape dimers of the B-5-d-w conformer of nodifloridin B [5].

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.

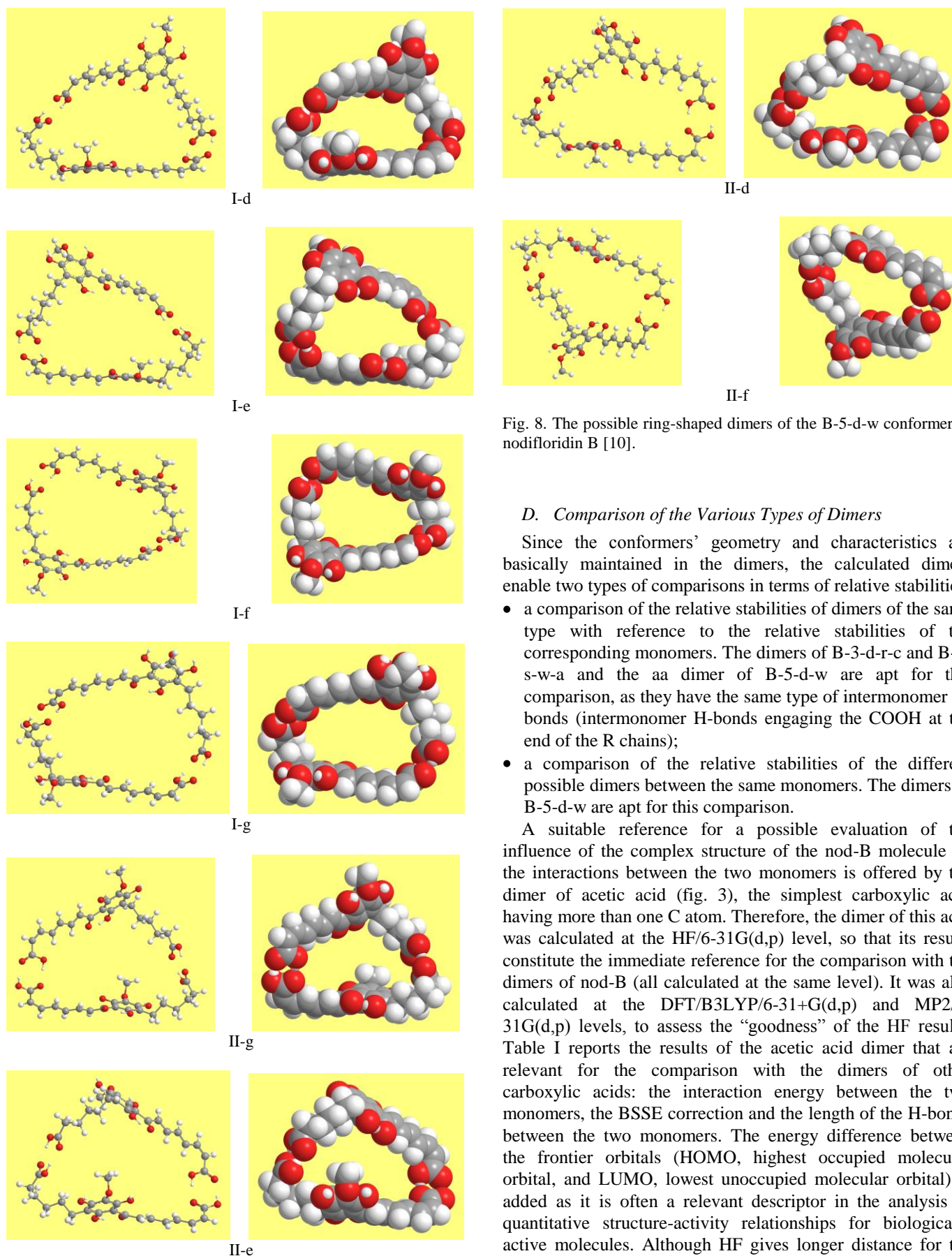


Fig. 8. The possible ring-shaped dimers of the B-5-d-w conformer of nodifloridin B [10].

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

	C19'-C20'-C21'-C22'	-163.7
	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
	C18-C19-C20-C21	-177.2
	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
	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
	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 monomer	C2-C1-C7-C13	163.5
	C1-C7-C13-C18	174.9
	C7-C13-C18-C19	178.9
	C13-C18-C19-C20	179.7
	C18-C19-C20-C21	179.9
	C19-C20-C21-C22	179.9
	C20-C21-C22-C23	0.0

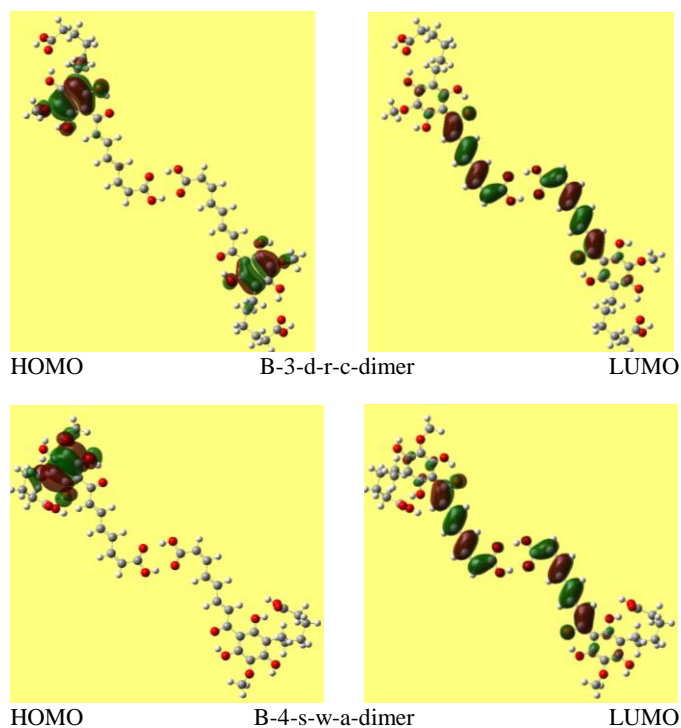


Fig. 9. The frontier orbitals of the dimers of B-3-d-r-c and B-4-s-w-a.

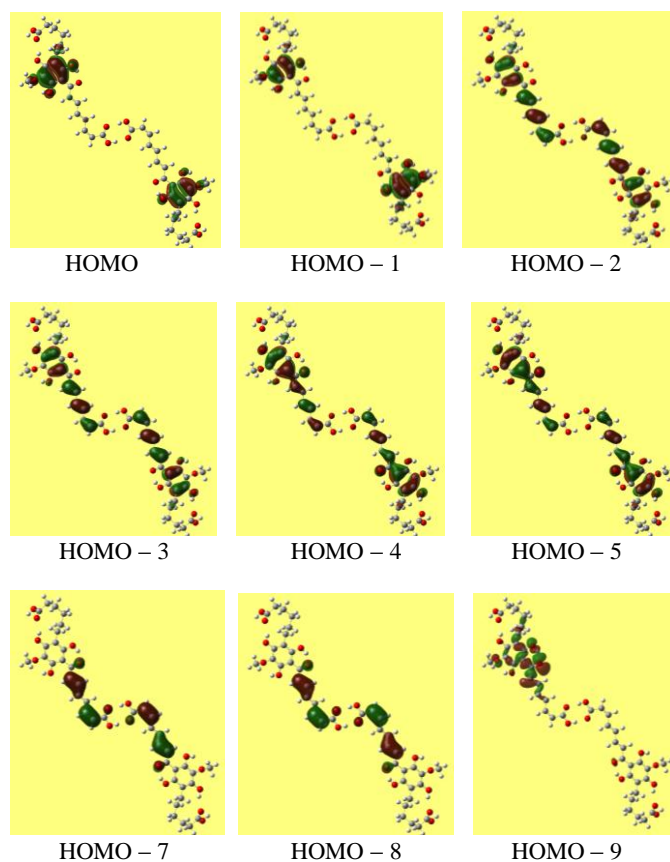


Fig. 10. The nine highest occupied molecular orbitals in the dimer of B-3-d-r-c.

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

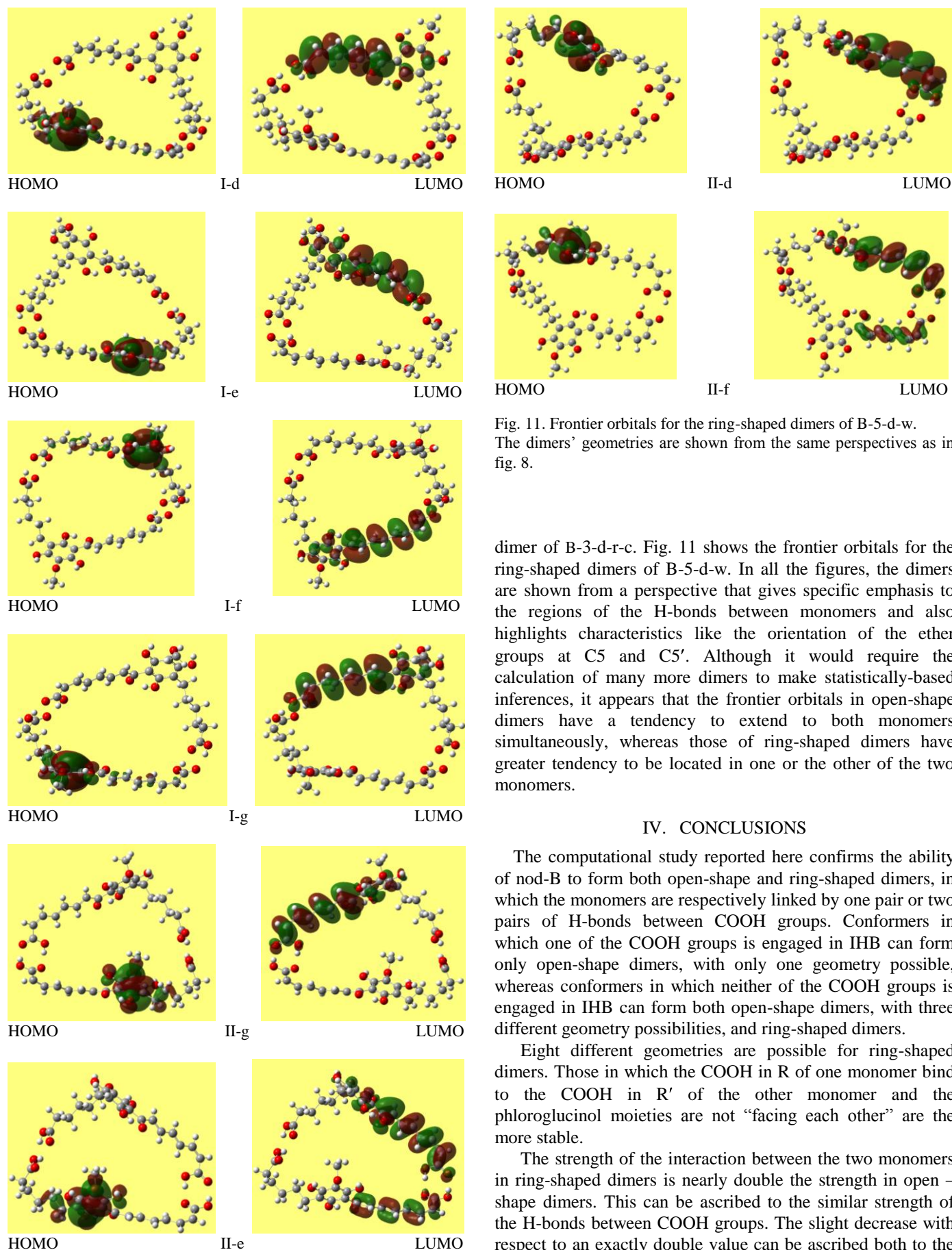


Fig. 11. Frontier orbitals for the ring-shaped dimers of B-5-d-w. The dimers' geometries are shown from the same perspectives as in fig. 8.

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

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 π 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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