

## POLYLACTIC ACID INTER-CHAIN INTERACTIONS

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**ABSTRACT.** Geometry optimization of perpendicular, antiparallel and parallel dimers were employed in order to analyze the relative energy values. The weakest interactions are seen for the perpendicular structures; among those, the strongest are for  $\pi$ ,  $3_{10}$ , while the DeSantis structure affords no local minimum at all. The strongest interactions are seen with parallel structures – of which the largest interaction energies are with the DeSantis and the  $\pi$  monomers (up to 2.8 and 4.2 kcal/mol per unit of lactic acid, respectively).

**Keywords:** *polylactic acid (PLA), supramolecular, computational*

Poly(lactic acid) (PLA) is a biodegradable, biocompatible and compostable aliphatic polyester. It is composed of lactide (LA) repeat units, typically either in the form of poly(L-lactic acid) (PLLA) or poly(D-lactic acid) (PDLA). Both homopolymers are semicrystalline; the naturally occurring form PLLA is about 37% crystalline. When L-isomers and D-isomers are copolymerized in equal proportions, a racemic poly(lactide) is formed. Its molecular chains cannot easily pack together to crystallize, because the side groups are located on both sides of the polymer backbone; consequently, racemic poly(lactide) (PLDLA) is entirely amorphous. Non-racemic copolymers are usually mixed from L-lactide and a racemic (50:50) mixture of L-lactide and D-lactide (PLDLLA).[1,2]

Experimental characterization of PLA often involves measurements of crystallinity, average molecular weight, molecular weight distribution (polydispersity), impurities (such as residual monomers, water, and free radicals), and glass transition temperature. The thermal, mechanical and

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biodegradation properties of PLA are largely dependent on the ratio and distribution of the two stereoisomers of LA within the polymer chains. Water can act as a plasticizer of PLA, which might result in a decrease of  $T_g$  even below body temperature ( $37^\circ\text{C}$ ).[3–5]

The thermal properties of PLA can be changed by copolymerization of PLA with monomers such as glycolide, some lactone derivatives, trimethylene carbonate and also by the addition of cross-linkers and plasticizers. Amorphous PLA and low-crystalline PLA are clear materials with high gloss, while highly crystalline PLA is an opaque white material. It is brittle at room temperature. The amorphous PLA is soluble in most organic solvents such as tetrahydrofuran, chlorinated solvents, benzene, acetonitrile, and dioxane. Crystalline PLA is soluble in chlorinated solvents and benzene at elevated temperatures. Semicrystalline PLA is preferred to amorphous polymer when better mechanical properties are desired. The molar mass of the polymer as well as the degree of crystallinity has a significant influence on the mechanical properties.[6,7,16,8–15]

The molecular-level organization of PLA in materials such as described above is mostly unclear. We have previously considered the possibility that the PLA monomer, in light of its structural reminiscence to the amino acid alanine (technically, the amino group of alanine would be replaced by a hydroxy group in PLA), would form peptide-type elements of secondary structure. Peptide/protein secondary structure elements include repetitive structural motifs based mostly on hydrogen bonds within the chain (for helical structures) or between chains (for pleated sheet structures). We have previously explored in some detail the performance of computational methods in describing peptide secondary structural elements for short peptides (e.g., decamers).[17–20] To this end, we reported geometry optimization results on 4 different types of secondary structures in decaameric units of PLA – helical ( $\alpha$ ,  $\pi$ ,  $3_{10}$ ) and  $\beta$ -sheet. Based on *ab initio* calculations, the  $\alpha$ ,  $\pi$  and  $3_{10}$  structures were found to have very similar energies, with  $\pi$  slightly favored by values within the error limits of the method; in contrast, semiempirical and empirical methods predicted other structures as favorites – and with distinctly larger energy differences. Three types of weak interactions appear to dictate the relative stabilities of secondary structure elements in PLA structures: carbonyl-CH, carbonyl-CH<sub>3</sub>, and carbonyl-ester.[21,22]

Spectroscopic parameters were also predicted for the putative PLA secondary structure elements, in an attempt to aid our on-going efforts in synthesis and characterization of polylactic acid variants.[23] The calculated chemical shifts of both  $^{13}\text{C}$  NMR and  $^1\text{H}$  NMR are slightly larger than the experimental ones. The conclusion was that the secondary structure (if any)

of poly(lactic acid) cannot be conclusively clarified from the calculated IR and NMR spectra, suggesting either a need for using more appropriate computational methods or the occurrence of previously unconsidered elements of secondary structure, or the total lack thereof.[23]

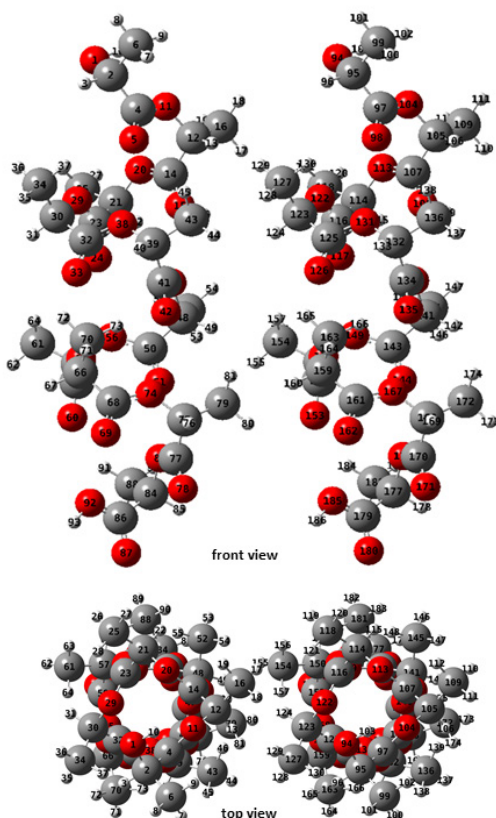
All of the previous computational studies have focused on isolated single chains of PLA. Such studies would be relevant for gas-phase experiments such as in mass spectrometry, but less so for condensed-phase situations. The route towards predicting solid-state PLA structures via quantum mechanical calculations is difficult, if at all possible, with current methodology; lower-level theory models would be even more problematic as we have previously shown.[21] A first step towards such predictions would nevertheless be an attempt to model the interaction of at least two chains of PLA. The nature of the secondary structure elements in PLA implies distinctly difficult capabilities of interchain interactions ranging from two extremes: the  $\alpha$ -helix, where the exterior of the chain features mostly methyl groups which may significantly limit the strength of potential intermolecular interactions, and the  $\beta$ -chains that are optimally designed for intermolecular interactions. To this end, reported here is a molecular-level investigation of the inter-chain weak interactions involving decameric PLA units, as part of an effort ultimately aiming to provide useful data for predicting and controlling macroscopic properties of PLA-based materials.

## RESULTS AND DISCUSSION

The helical and sheet structures of the decameric units of PLA were built only for poly(L-lactic acid) (PLLA). We have previously reported that the energies of the PLLA are generally smaller than in the case of poly(DL-lactic acid) (PDLLA) copolymers.[21]

Overall, two types of weak interactions appear to dictate the relative stabilities of the dimers. One of the non-covalent interactions involves the oxygen atoms of the carbonyl group of one monomeric unit and the hydrogen atoms from the main chain of the other monomeric unit. The other type of non-covalent interaction implies the oxygen atoms of the carbonyl group of one molecule and the hydrogen atom from the methyl group of the second molecule. These C=O $\cdots$ H distances are thus found, in certain instances, to be shorter than the corresponding sum of van der Waals radii (2.72 Å). Figure 1 illustrates a typical dimer structure, with atom numbering further used in the Tables.

The stability of the generated geometries was determined as the difference between the energy obtained during the dimer optimization and 2x the value of the energy received from the monomer optimization.



**Figure 1.** Graphical representation of  $\alpha$  PLA dimers; red represents oxygen, gray the carbon and white the hydrogen atoms.

### ***Perpendicular dimers***

In the case of the perpendicular dimers, the two decameric chains were placed at  $90^\circ$  with respect to each other, intersecting at the middle of the chains. Two types of input geometries were built; one is based on monomers built in the canonical form and the other is based on the HF 3-21G\* pre-optimized monomers (Tables 1 and 2).

**Table 1.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular  $\alpha$ -dimers, cf. unrestricted geometry optimizations.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
2	8.41		O42-H119		2.38	
			H44-O117		2.48	
			H73-O117		2.58	
			O69-H129		2.37	
3	8.47		O42-H119		2.36	
			H44-O117		2.44	
			H73-O117		2.59	
			O69-H129		2.36	
4	17.58	O5-H151			2.23	
		H13-O144			2.36	
			H18-O171		2.44	
			O33-H156		2.59	
		H40-O117			2.24	
			O42-H119		2.48	
				H71-O94(hyd)	2.53	

**Table 2.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular  $\alpha$ -dimers (monomers not pre-optimized separately).

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Distance	Representation
2	7.53	O24-H169		2.48	
			O24-H174	2.62	
			H26-O162	2.33	
		H31-O135		2.33	
3	9.58		O33-H147	2.61	
			O24-H169	2.45	
			O24-H174	2.52	
			H26-O162	2.41	
		H31-O135		2.20	
		O33-H142		2.44	
			O51-H173	2.65	
	H63-O144	2.45			

The  $\alpha$  dimers were constructed by translating the monomer unit by values between 2-6 Å. If the two monomers are situated at an initial 2-3 Å, the perpendicular direction is preserved and four weak interactions between the monomers are established in each of these cases. If the initial structure is based on the optimized monomers, only  $\text{C}=\text{O}\cdots\text{H}(\text{CH}_3)$  interactions are established. However, if the optimization is started from initial 4-5 Å distances between the two optimized monomers, the two units reorient to almost parallel and the number of interactions subsequently increases (Table 1). The weaker the interactions, the more stabilized are the structures, so that the parallel structures are more stable by around 8 kcal/mol as compared to those that remained perpendicular. Overall, each intermolecular interaction adds around 2 kcal/mol to the stabilization energy.

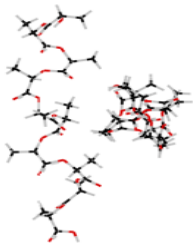
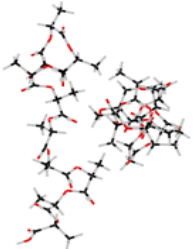
For the 6 Å dimers (not shown), the monomers shifted upon geometry optimization so that they would interact only via the terminal groups, without involving the carboxylic oxygen and hydrogen. The structures resulting from the optimization started at 2 or 3 Å were very similar to each other, with only  $\text{C}=\text{O}\cdots\text{H}(\text{CH})$  and  $\text{C}=\text{O}\cdots\text{H}(\text{CH}_3)$  interactions holding the molecules together, with an average of 1.5 kcal/mol per such interaction.

When the two optimized  $\pi$  monomers were placed at initial distances of 2.5-4.5 Å (Tables 3 and 4), the two units remained perpendicular after geometry optimizations, with six  $\text{O}\cdots\text{H}$  interactions per dimer, at  $\sim 2$  kcal/mol per interaction (Table 3). If the initial distance between the two monomers was set below 2.5 Å, they migrated to a parallel structure (see dedicated section below). Only  $\text{C}=\text{O}\cdots\text{H}(\text{CH})$  and  $\text{C}=\text{O}\cdots\text{H}(\text{CH}_3)$  intermolecular interactions were formed; the carboxylic and hydroxyl oxygen atoms did not participate in dimer stabilizations.

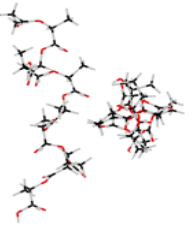
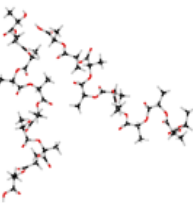
The dimers from the starting structures based on the canonical form placed with starting inter-chain distances of 1.5-2.5 Å led to perpendicular orientations after geometry optimizations (Table 4). It is again the  $\text{C}=\text{O}\cdots\text{H}(\text{CH})$  and  $\text{C}=\text{O}\cdots\text{H}(\text{CH}_3)$  interactions that hold together the final forms in both optimizations. The intermolecular interaction energy is 3 kcal/mol. Increasing the starting distance to 3.5 Å increases the energy to 4.6 kcal/mol, as the hydroxyl and carboxyl groups also participate in the stabilization; however, in this case the dimers are no longer perpendicular to each other. Placing the monomers at a longer distance (5.5 Å) the relative energy value reaches 3.6 kcal/mol, but only one interaction occurs - between the first molecule's hydroxylic hydrogen atom and the second molecule's oxygen atom (structure not shown).

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**Table 3.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular  $\pi$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Distance	Representation
2.5	13.61		O25-H149	2.69	
			H27-O145	2.27	
			O43-H157	2.43	
		H50-O127	2.29		
			O52-H129	2.37	
			H74-O127	2.42	
4.5	14.14		O25-H147	2.45	
			H27-O145	2.38	
		O43-H152	2.38		
			O43-H157	2.52	
			H47-O145	2.60	
			H72-O127	2.42	

**Table 4.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular  $\pi$ -dimers (monomers not pre-optimized separately).

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
2.5	15.12		O43-H149		2.63	
			O43-H157		2.56	
			H45-O145		2.44	
		H50-O127	2.40			
		H82-O127	2.48			
3.5	27.74			O2(hyd)-H94(carb)	1.70	
				O16-H179	2.37	
		H23-O172	2.14			
			O43-H156	2.34		
			H45-O154	2.42		
			H47-O172	2.51		

The optimized  $3_{10}$  monomers placed at 1.5-3.5 Å after the dimer optimizations remain perpendicular (Table 5). In all two cases seen in Table 5, the interactions are established between the same atoms, with similar relative energies.

**Table 5.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular  $3_{10}$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
3.5	6.69	O24-H133			2.29	
			O24-H166		2.71	
			H53-O162		2.55	
4.5	9.33	O24-H133			2.18	
			H26-O126		2.45	
			O51-H137		2.50	
			H53-O135		2.70	

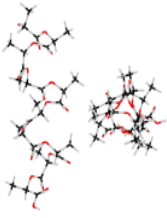
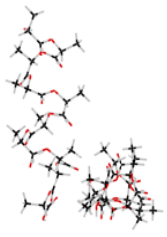
The  $3_{10}$  structure with an initial distance of 4.5 Å differs very little from the real perpendicular structures, showing one more weak interaction between the carbonyl oxygen atom and hydrogen of a methyl group than in the other cases - therefore the relative energy is seen to increase to ~10 kcal/mol.

Starting from structures based on canonical forms, the two units maintain the perpendicular directions at 1.5-2.5 Å distances. The geometries, relative energies, number and type of interactions are the same. If the distance between the initial molecules is longer than 4.5 Å then the monomers are shifted during the geometry optimization. The carboxylic oxygen also participates in the dimer formation. The interactions are created between the same atoms - only the lengths of these are changed by 0.1 Å, and hence the relative energy varies as well (Table 6).



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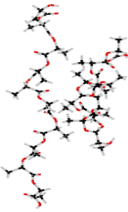
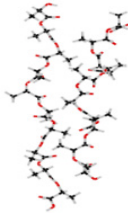
**Table 6.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular  $3_{10}$ -dimers (monomers not pre-optimized separately).

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
2.5	8.13		O42-H115		2.22	
			H44-O108		2.35	
			O69-H119		2.42	
			H71-O117		2.62	
4.5	16.25		O69-H121		2.44	
			O69-H129		2.51	
			H71-O117		2.51	
				O92(carb)-H156	2.49	

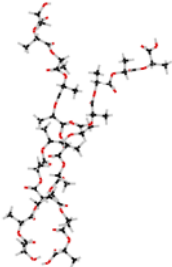
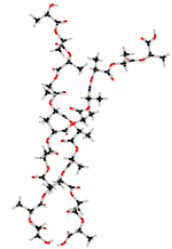
Optimization of the  $\beta$  dimers did not retain the initial perpendicular arrangement, whether starting from structures based on canonical form or previously optimized monomers - with one exception. The optimization of pre-optimized monomers laid at 1-2 Å led to structures in which the intermolecular interaction energy is around 2.8 kcal/mol (Table 7). The closer placement results in a geometry with one more interaction than that placed at 2 Å. The 2-Å and 3-Å structures have the same C=O...H(CH) interactions, and both have two C=O...H(CH<sub>3</sub>) interactions; the 3-Å structure seems to be more stable, although it differs more from the ideal perpendicular form.

As shown in Table 8, the resulting structures based on the canonical forms of the  $\beta$  structures have more stable geometries than those based on the optimized monomers of Table 7.

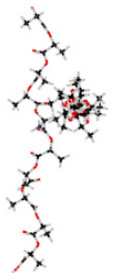
**Table 7.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular  $\beta$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Distance	Representation
2	11.35	O42-H133		2.10	
		H49-O126		2.25	
			O51-H138	2.65	
			H63-O117	2.43	
3	22.63	O42-H133		2.25	
		H49-O126		2.12	
			H64-O117	2.44	
			O69-H112	2.70	

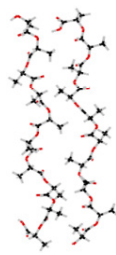
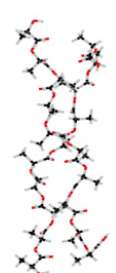
**Table 8.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular  $\beta$ -dimers (monomers not pre-optimized separately).

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
2	29.08		H40(3)-O144		2.35	
		O42-H151(1)			2.25	
			H55(3)-O135		2.32	
			O60-H130(3)		2.45	
			H82(3)-O108		2.69	
				O87(carb)-H95(hyd)	2.09	
3	34.35			O94(hyd)-H93(carb)	1.71	
		O33-H151(1)			2.26	
		H40(1)-O144			2.10	
			H55(3)-O135		2.46	
			O60-H130(3)		2.48	
			H82(3)-O108		2.69	
			O87(carb)-H95(hyd)	2.08		

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Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
4	12.12	O33-H160(1)	O42-H165(3)		2.17	
		H40(1)-O144			2.18	
					2.46	

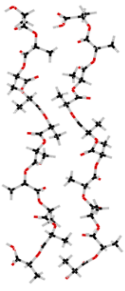
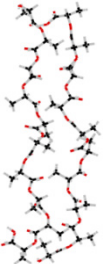
**Table 9.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular DeSantis-dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation	
2	30.88			H4-O181(carb)	2.39		
				O25-H167	2.54		
				H45-O136	2.66		
				H46-O145	2.38		
				H72-O109	2.29		
				O97-H103	2.65		
3	24.72			H23-O181(carb)	2.72		
				H28-O163	2.70		
					H28-O186(carb)		2.64
				O34-H152	2.26		
				H41-O145	2.18		
					H56-O136		2.43
					O61-H120		2.54
					H83-O109		2.69

Similarly to the  $\beta$ -dimers, the optimization of the DeSantis dimers did not result in any perpendicular geometries (Tables 9 and 10). If in the initial structure based on the pre- monomers the two units are at 2 Å, the dimers become parallel, and the intermolecular energy is 5.5 kcal/mol. The initial monomers located at more than 4 Å led to geometries which are neither parallel nor

perpendicular. The minimum value of the intermolecular energy (3.09 kcal/mol) is at the 4-Å laid monomers, with 8 individual interchain short contacts. If the initial monomers are at 7 Å the two molecules are moving away from each other, and only at one end a weak interaction is formed. With the monomers based on the canonical form placed at 2-3 Å, optimization leads to parallel structures. Six common interactions are seen in the two optimized forms, but the carboxyl-hydrogen interactions occur at the different end of the chains. The highest relative energy value appears at the 3-Å dimer in Table 10. Like in the structures based on optimized monomers, the larger distances conduct to dimers in which the molecules are neither parallel nor perpendicular (Table 10).

**Table 10.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the perpendicular DeSantis-dimers (monomers not pre-optimized separately).

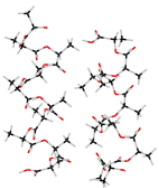
Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
2	32.06			H14-O181(carb)	2.47	
				O25-H167	2.34	
				O34-H152	2.23	
				H41-O145	2.25	
				H56-O136	2.43	
				O61-H131	2.50	
				H72-O109	2.28	
				O79-H103	2.64	
		H83-O99	2.43			
3	34.97			O6(carb)-H94	1.70	
				H14-O172	2.45	
				O34-H152	2.21	
				H41-O145	2.14	
				H56-O136	2.45	
				O61-H131	2.49	
				H72-O109	2.46	
				H83-O99	2.37	

### ***Antiparallel dimers***

For these structures, in most of the cases starting from the canonical form the convergence could not be achieved, and therefore only the results of the dimers of dimers based on optimized monomers are discussed here.

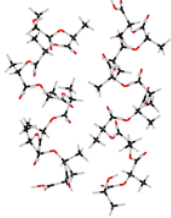
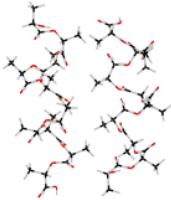
Upon geometry optimization of the  $\alpha$  dimers, regardless of how far the dimers are placed (3-5 Å), the same final geometry was obtained – detailed in Table 11. The two units are stabilized by six weak interactions; five of them are C=O...H(CH<sub>3</sub>) and one C=O...H(CH). Each intermolecular interaction brings around 3 kcal/mol in terms of energy stabilization.

**Table 11.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the antiparallel  $\alpha$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Distance	Representation
3	18.14		O24-H165	2.43	
			H26-O153	2.35	
		O51-H133		2.28	
		H53-O126		2.30	
		O78-H111		2.58	
		H80-O98		2.34	

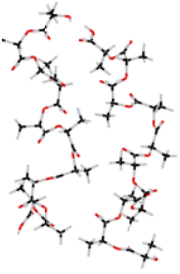
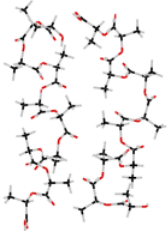
For the 3<sub>10</sub> antiparallel dimers (Table 12), the intermolecular interaction energies are about 0.6-0.7 kcal/mol per O...H contact. If the two units are placed further than 6 Å, an interaction between a carboxyl and a hydroxyl group appears and the intermolecular interaction energy increases to 2.8 kcal/mol.

**Table 12.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the antiparallel 3<sub>10</sub>-dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations	
2.5	4.96	O15-H160			2.28		
					H13-O153		2.26
			H17-O162		2.41		
		O42-H124			2.33		
		H49-O126			2.23		
			O51-H128		2.42		
		O78-H96			2.15		
3.5	3.88				2.69		
					O15-H155		2.39
					H17-O153		2.43
					O42-H156		2.47
		O51-H129	2.72				
O78-H96		2.28					

The optimizations of the  $\pi$  dimers led to two types of results, cf. Table 13. If the initial  $\pi$  monomers are placed at 1 Å, the obtained orientation of the dimers is perpendicular; C=O...H(CH) and C=O...H(CH<sub>3</sub>) weak interactions are key in this structure. Carboxyl and hydroxyl groups additionally participate when the two monomers are at 2-3 Å initial distances. The preferred relative orientation is antiparallel. The intermolecular interaction energy decreases from 3.5 kcal/mol to 2.2 kcal/mol, although the number of interactions is the same.

**Table 13.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the antiparallel  $\pi$ -dimers.

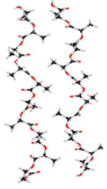
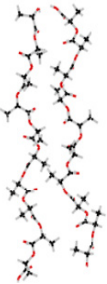
Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations
2	34.74			O2(hyd)-H94(carb)	1.66	
				O25-H185	2.46	
				H29-O181(carb)	2.28	
				H32-O163	2.23	
				O34-H165	2.31	
				O52-H140	2.49	
				H64-O136	2.61	
				O79-H111	2.25	
				H63-O109	2.55	
				H83-O109	2.51	
3	21.57			O2(hyd)-H183	2.31	
				H4-O181(carb)	2.68	
				O6-H185	2.60	
				O34-H165	2.45	
				H36-O163	2.32	
				O52-H116	2.41	
				O52-H140	2.49	
				H59-O109	2.24	
				O79-H111	2.33	
				H83-O109	2.41	

After the optimization the  $\beta$  dimers remain antiparallel (Table 14). Weak interactions are noted between carboxyl and hydroxyl groups of the two molecules, varying between 4 and 9, and the interaction energy decreases from 4.5 kcal/mol (2 Å) to 3.5 kcal/mol (3 Å) and 3 kcal/mol (4 Å), respectively.

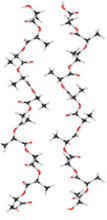
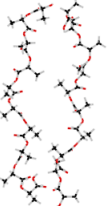
Two types of geometries are obtained upon optimizing the structure described by DeSantis. When the two units are positioned at 2-4 Å, they remain antiparallel with interaction energy of  $\sim 3.4$  kcal/mol per interaction. If the two units are placed further than 5 Å, they will be perpendicular, and the interactions are formed at the termini of the chains (Table 15).

POLYLACTIC ACID INTER-CHAIN INTERACTIONS

**Table 14.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the antiparallel  $\beta$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations
2	17.98			O4(hyd)-O185	2.39	
			H18-O108		2.24	
			O60-H129		2.22	
			H81-O108		2.35	
3	32.31			O1(hyd)-H186(carb)	1.66	
		H13-O171			2.27	
			O24-H155		2.51	
		O33-H151			2.30	
		H40-O144			2.23	
			H44-O135		2.42	
			O51-H128		2.71	
		O60-H124			2.37	
			H81-O108		2.33	
			H18-O171		2.31	
			O33-H156		2.31	
			H44-O135		2.49	
			O60-H129		2.45	
			H81-O108		2.31	

**Table 15.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the antiparallel DeSantis-dimers.

Distance	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations
2	19.01			O2(hyd)-H174	2.31	
			O43-H148		2.39	
		H59-O127			2.36	
		O79-H107			2.25	
				O88(carb)-H97	2.30	
		H92-O99		2.55		
4	14.84			O2(hyd)-H174	2.31	
		O79-H107			2.40	
				O88(carb)-H97	2.47	
			H92-O99		2.40	

### Parallel dimers

The parallel structures were obtained by translating a decameric unit with 1-6 Å. Starting from the previously optimized  $\alpha$  monomers the two helices hold their directions at any distance apart (Table 16). If they are positioned at 1 - 2 Å, the interaction energy is 3.2 kcal/mol per interaction- and slightly larger if the initial distance is 3-5 Å.

**Table 16.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel  $\alpha$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations	
2	25.93		O5-H121			2.52	
				H7-O94(hyd)		2.38	
			O33-H129			2.40	
			H40-O117			2.61	
			O60-H183			2.47	
			H72-O144			2.46	
				O87(carb)-H178		2.12	
				H97(carb)-O171		1.67	
3	26.78		O5-H129			2.41	
				H7-O94(hyd)		2.38	
			O33-H156			2.54	
			H45-O117			2.49	
			O60-H183			2.50	
			H72-O144			2.32	
				O87(carb)-H178		2.11	
				H93(carb)-O171		1.69	

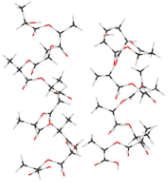
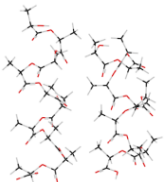
The  $\alpha$  structures based on the canonical form laid at 1-3 Å maintain the parallel orientation upon geometry optimization (Table 17). Increasing the distance, the dimers lose their parallel orientations and at 6 Å the two units become perpendicular (not shown). Only two interactions keep the molecules together, and the interaction energy per interaction is 3.1 kcal/mol.

For the dimers based on optimized  $\pi$  monomers, longer initial inter-chain distances led to smaller numbers of interactions, but the intermolecular binding energy per individual non-covalent contact increases from 3.8 kcal/mol to 5.6 kcal/mol. In no case do the optimized dimers actually feature parallel structures (Table 18). Four interactions occur in the optimized monomers placed at 3 Å; the relative energy is the same as at 2 Å dimers, but the number of interactions is only half compared to the 2-Å structure.

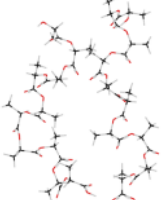
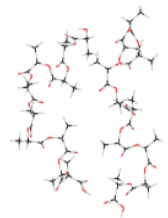


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**Table 17.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel  $\alpha$ -dimers (monomers not pre-optimized separately).

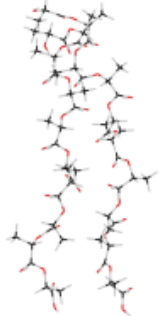
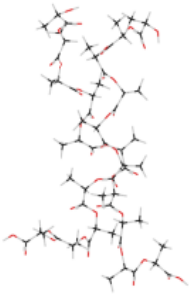
Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations
2 Å	4.12		O15-H129		2.41	
			O42-H128		2.33	
				H80-O180(carb)	2.40	
			H81-O153	2.68		
3 Å	4.12		O15-H129		2.42	
			O42-H128		2.33	
				H80-O180(carb)	2.40	
			H81-O153	2.68		

**Table 18.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of parallel  $\pi$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations
2	27.25			H1(carb)-O181(carb)	1.68	
			O16-H139	2.44		
			H19-O109	2.58		
			H28-O127	2.44		
			O70-H156	2.51		
	O88(carb)-183	2.32				
3	27.9			H1(hyd)-O181	1.67	
		H4-O99		2.47		
			H28-O127	2.34		
			O88-H183	2.38		

The parallel-placed  $\pi$  monomers based on the canonical form do not maintain their orientation upon geometry optimization, as they become intertwined with each other. Most interactions are of the  $\text{C}=\text{O}\cdots\text{H}(\text{CH})$  and  $\text{C}=\text{O}\cdots\text{H}(\text{CH}_3)$  types, with no involvement of the carboxyl and hydroxyl groups. A 1.8 kcal/mol stabilization energy per interaction is seen in the 2-Å dimer (Table 19).

**Table 19.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel  $\pi$ -dimers (monomers not pre-optimized separately).

Initial	$\Delta E$	$\text{C}=\text{O}\cdots\text{H}(\text{CH})$	$\text{C}=\text{O}\cdots\text{H}(\text{CH}_3)$	Distance	Representation
2	25.89	O16-H107		2.32	
			O16-H130	2.28	
			H20-O99	2.56	
		O34-H125		2.33	
		O34-H143		2.51	
			O34-H148	2.53	
			H41-O136	2.36	
			H46-O118	2.49	
		O52-H161		2.37	
			H56-O145	2.27	
		H59-O154		2.06	
			H64-O136	2.35	
	O70-H176	2.42			
	H92-O172	2.35			
4	28.25	O16-H107		2.32	
			H20-O99	2.56	
		O34-H125		2.33	
			O34-H148	2.40	
		H41-O136		2.43	
			H46-O118	2.48	
			O52-H166	2.55	
			H56-O145	2.61	
		H59-O154		2.19	
			H64-O136	2.31	
			O70-H176	2.33	
			H82-O163	2.56	

The dimer based on optimized  $3_{10}$  monomers remains parallel if the two units are placed at 1-3 Å, but the monomers are slightly shifted relative to each another (Table 20). The dimer is held together by  $\text{C}=\text{O}\cdots\text{H}(\text{CH})$  and  $\text{C}=\text{O}\cdots\text{H}(\text{CH}_3)$  weak interactions, at  $\sim 2$  kcal/mol each. On the other hand, upon increasing the initial distance to 4 Å there are more inter-chain interactions.

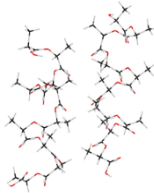
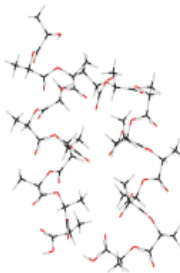
## POLYLACTIC ACID INTER-CHAIN INTERACTIONS

**Table 20.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel  $3_{10}$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Distance	Representation
2	12.47	O42-H151		2.55	
			H44-O144	2.40	
			H45-O117	2.62	
			O69-H175	2.43	
			O69-H183	2.55	
			H71-O153	2.57	
3	11.95		H44-O117	2.37	
		O69-H151		2.16	
		H76-O144		2.33	
			O78-H183	2.45	
			H80-O171	2.62	
4	14.9		H17-O117	2.41	
		O42-H151		2.47	
			H46-O117	2.70	
		H49-O144		2.65	
			H54-O144	2.55	
		O69-H151		2.70	
		H76-O153		2.29	

The  $3_{10}$  monomers based on the canonical form placed at 2-4 Å maintain the parallel orientation upon geometry optimization (Table 21), but the two monomers are shifted with respect to each other. The relative orientation of the monomers obtained starting with the monomers at 5 Å is not parallel anymore; the connection is formed only at one end of the monomers (not shown).

**Table 21.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel  $3_{10}$ -dimers (monomers not pre-optimized separately).

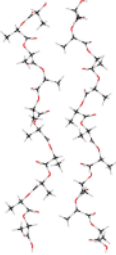
Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations
2	5.86		O15-H119		2.51	
			H45-O117		2.45	
			H71-O144		2.51	
3	24.11		O24-H138		2.45	
		O51-H133			2.49	
			O51-H165		2.49	
		H58-O126			2.24	
			H63-O98		2.40	
				O78-H186(carb)	1.71	
				H80-O185(carb)	2.56	
			H90-O153		2.33	
			O51-H133		2.49	
			O51-H165		2.49	
			H58-O126		2.24	
				H63-O98	2.40	
		O78-H186(carb)	1.71			
		H80-O185(carb)	2.56			
	H90-O153		2.33			

Only the optimizations of the  $\beta$  monomers placed at 1 Å did converge. If the two monomers are moved away from each other no connections are made. In the 1-Å case the structure remains parallel, and seven interactions, of 2.9 kcal/mol each, keep the molecules together (Table 22).


If the initial geometry is based on the canonical form, the two  $\beta$  sheets are coiling around each other (Table 23). This entails fifteen intermolecular contacts/interactions, at  $\sim 1$  kcal/mol each. If the two monomers are further than 1 Å, no connections are formed (as in the case of  $\beta$  dimers based on optimized monomers).

POLYLACTIC ACID INTER-CHAIN INTERACTIONS

**Table 22.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel  $\beta$ -dimers.

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
1	20.59			O1(hyd)-H97	2.34	
			O15-H111		2.19	
			H36-O117		2.40	
		O42-H133		2.45		
			O51-H137		2.44	
		H58-O153		2.19		
			O78-H174		2.31	

**Table 23.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel  $\beta$ -dimers (monomers not pre-optimized separately).

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representation
1 Å	11.42	O6-H97			2.58	
			O6-H112		2.57	
		H13-O108			2.43	
			O24-H115		2.25	
		H31-O126			2.55	
		O42-H133			2.20	
			H46-O126		2.58	
		H49-O144			2.72	
		O60-H151			2.30	
		H67-O162			2.43	
			H82-O162		2.41	
			H71-O171		2.70	
			O78-H184		2.71	
				O87(carb) – H173	2.63	
		H93(carb) – O180	1.82			

The parallel structure is maintained in the DeSantis dimers based on optimized monomers at 2 Å. Increasing the distance to 3 Å, this orientation is lost (Table 24) and the intermolecular interaction energy decreases from

5.2 kcal/mol to 3.3 kcal/mol. However, the number of interactions increases, and the carboxyl groups evolve more interactions than in the case of dimers laid at 2 Å. If the initial monomers are further than 3 Å, no weak interactions are noted between them (not shown).

**Table 24.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel DeSantis-dimers.

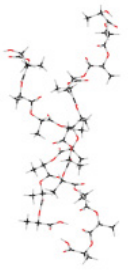
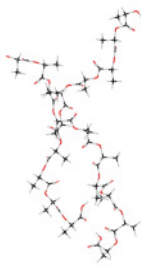
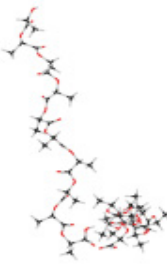
Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations
2	41.82			H1(carb)-O181(carb)	1.70	
				O2(hyd)-H104(hyd)	1.82	
				H4-O99	2.35	
				O25-H131	2.45	
				H46-O136	2.42	
				O52-H157	2.45	
				H73-O163	2.55	
				O79-H94(carb)	1.66	
3	35.98			H1(carb)-O181(carb)	1.71	
				O25-H130	2.37	
				H28-O95(hyd)	2.50	
				H29-O109	2.36	
				O34-H116	2.28	
				H46-O136	2.24	
				O52-H157	2.41	
				H73-O163	2.72	
				O79-H94(carb)	1.64	
				H56-O181(carb)	2.63	
O61-H94(carb)	1.68					

## METHODS

Five types of decameric units of polylactic acid were built and optimized using the Hyperchem package as previously described.[21,23] These are analogous to those seen in protein structure - helical structures ( $\alpha$ ,  $\pi$ ,  $3_{10}$ ), a  $\beta$ -sheet, and the structure proposed by DeSantis.[21] The dimers were constructed by translating a decameric unit by various values (generally in the range of 2-10 Å), as illustrated in the Tables and text.

Parallel, antiparallel as well as perpendicular structures were considered. Geometry optimizations were performed with the HF method and 3-21G\* basis set as implemented in Gaussian, without any constraints on the geometry – including the inter-dimer distance or orientation.[24] Larger basis sets and either a post-HF or a specialized density functional theory variant would afford more accurate results, but they were deemed computationally prohibitive for the set of models examined here.

**Table 25.** Initial distances (“Initial”, Å) between monomers, relative energies ( $\Delta E$ , kcal/mol), weak interactions (Å) and graphical representations of the parallel DeSantis-dimers (monomers not pre-optimized separately).

Initial	$\Delta E$	C=O...H(CH)	C=O...H(CH <sub>3</sub> )	Other	Distance	Representations
2	34.80			H1(carb)-O181	1.71	
				O25-H140	2.33	
				H32-O145	2.27	
				H46-O136	2.57	
				O52-H152	2.28	
				H63-O172	2.54	
				H73-O163	2.49	
				O79-H94(carb)	1.70	
3	35.63			H1(carb)-O181	1.71	
				O25-H129	2.42	
				O25-H140	2.36	
				H32-O145	2.21	
				O43-H157	2.45	
				H46-O136	2.37	
				O52-H158	2.72	
				H63-O172	2.47	
4	26.27			H73-O162	2.56	
				O79-H94(carb)	1.71	

## CONCLUSIONS

Optimizations of  $\alpha$ ,  $\pi$ ,  $3_{10}$  deca-lactic acid helices placed perpendicularly to each other does in several cases retain this geometry. The geometries obtained from the optimizations of nearly all  $3_{10}$  helices are perpendicular. Optimization of perpendicular  $\beta$  dimers led only once to perpendicular direction. In turn, the structure described by DeSantis does not yield perpendicular dimers after the optimizations. In the case of  $\alpha$  and DeSantis dimers, parallel instead of perpendicular structures are obtained upon geometry optimization. This is not valid for  $\pi$ ,  $3_{10}$  and  $\beta$  dimers: their most stable geometries are neither parallel nor perpendicular.

Minima for antiparallel and parallel dimer structures were obtained for all the five types of secondary structure – though in several cases severe distortions were noted (e.g., coiling or disordered structures of the monomers).

Table 26 shows a summary of the data collected in the present study – i.e., inter-chain interaction energies calculated per unit of lactic acid. These values are expected to be useful in predicting interaction energies between chains of lengths different from the decameric structures examined in the present study. The weakest interactions are seen for the perpendicular structures; among those, the strongest are for  $\pi$ ,  $3_{10}$ , while the DeSantis structure affords no local minimum at all. The strongest interactions are seen with parallel structures – of which the largest interaction energies are with the DeSantis and the  $\pi$  monomers (up to 2.8 and 4.2 kcal/mol per unit of lactic acid, respectively), and the weakest interactions are seen for the  $\alpha$  and  $3_{10}$  helices. These results are in line with expectations, insofar as these two canonical helical forms are more compact and predominantly offer methyl groups towards the outside of the helix[21], whereas the DeSantis structure mimics partial structural data obtained from crystalline PLA.[23]

**Table 26.** Relative energies (kcal/mol) of inter-chain interactions per unit of lactic acid.

$\Delta E$	$\alpha$	$\pi$	$3_{10}$	$\beta$	DeSantis
Perpendicular	1.0	1.5	0.9-1.6	1.2	-
Antiparallel	1.8	2.2-3.5	0.4-0.5	1.8-3.2	1.5-1.9
Parallel	0.4-2.7	2.6-2.8	0.6-2.4	1.1-2.1	2.6-4.2



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