Conformational behavior of stereo regular substituted polyglycolides is side chain dependent

Fateh S. Nandel[*]**, Roobee Garla**

Department of Biophysics, Panjab University, Chandigarh, India; [*]Corresponding Author: fateh_nandel@yahoo.com

ABSTRACT

Substituted polyglycolides having two asymmetric centers are attractive alternatives to materials derived from petroleum because of their biocompatibility and biodegradability. The conformational behavior of various substituted polyglycolides has been investigated by both quantum mechanical and molecular dynamics approaches. Polymethylglycolide (polylactide) and polyphenylmethylglycolide in RS or SR forms are predicted to adopt 2_7 ribbon type structures with φ, ψ values of ±30, ±50 or ∓30 or ∓50 respectively stabilised by carbonyl-carbonyl interactions. Isopropylglycolide and isobutylglycolide having branching at β & γ positions respectively in their side chains can be realized in all SS form with φ, ψ values lying in right handed helical region. In addition to carbonyl-carbonyl interactions, the hydrophobic interactions between the side chains in isopropylglycolide the C-H-O interactions also contributes to the stability. With cyclic side chains directly attached to C_α of backbone, polyphenylglycolide (polymandelide) and polycyclohexylglycolide are found to adopt left handed helical structure without hydrogen bonds in RR form, stabilised by stacking interactions and hydrophobic interactions respectively. In all the forms of polyphenylglycolide & polycyclohexylglycolide, the cyclic side chains are found to be locked into unfavourable gauche plus conformation. The stability of substituted polyglycolides has been analyzed in terms of various interactions. The carbonyl-carbonyl interactions in all the conformations of all forms of substituted polyglycolides are found to be of highly shielded parallel motif with only one short carbon-oxygen interaction. Simulation studies of substituted polyglycolides in water give a good insight of the approach of water molecules to the backbone.

Keywords: Polyglycolides; Conformation; 2_7 Ribbon Type Structure; Helical Structure without Hydrogen Bonds; Carbonyl-Carbonyl Interactions; Simulation Studies

1. INTRODUCTION

Conventional polymers such as polyethylene, polypropylene and polystyrene persist for many years after disposal due to their resistance to degradation which creates serious environmental problems. This has lead to the search of biodegradable polymers which degrade by the action of microorganisms such as bacteria, fungi and may also be broken down by non-enzymatic processes such as chemical hydrolysis and the degraded products should be non-toxic to living organisms directly or indirectly. Polylactides/polymethylglycolide (PLA), as one of commercially available and biomass-derived polymers, has been attracting much attention from both academic and industrial view points. It has tremendous potential in both traditional and non-traditional applications where thermoplastics are employed. It is because of these reasons, polylactide (PLA) has been explored to a fairly good extent for medical applications [1-16] as rod, plate, screw, fibre, sheet, sponge, beads for bone and tissue engineering [17-20], microsphere for drug delivery system [21] films and foils for wound treatment. PLA have also found applications in agriculture as mulch films and for slow release of pesticides and fertilisers. PLA is widely used in packaging for a broader array of products [22-27] because the level of lactic acid that migrates to food from packaging containers is much lower than the amount of LA used in common food ingredients [28]. Li *et al.* have recently reported the chromatographic separation of polylactides of different stereo chemical compositions on the basis of their solubility in THF [29]. Further, modern and emerging production technologies have lowered its production costs [22-23, 30-31] as it can be now obtained from a renewable

source (corn) with high yield.

Poly-lactic-acid (PLA) has been investigated mainly in the all S form-PLLA [32-35] and there are few reports dealing with poly-D-lactic-acid-PDLA [35-36]. Depending on the preparative conditions, PLLA crystallizes in three forms *i.e.* α, β and γ and PLLA is reported to adopt right handed helical structure. Theoretical calculations on the conformational behaviour of PLLA have been carried out in terms of rotational isomeric state model and Kang *et al*. have analyzed the vibrational spectra of PLLA in the light of the results of this model [37]. Meaurio *et al*. had studied the distribution of conformer population for the semi-crystalline and amorphous PLLA by curve fitting the experimentally attained FTIR spectra. [38] Pan *et al*. [39] have demonstrated that the glass transition temperature of PLLA can be determined from temperature dependent FTIR intensity of 1267 cm^{-1} band arising due to ν_{as}(C-O-C) + δ(CH) vibrational mode. The substituted diglycolides [Ac-{O-C*H(X)-CO}$_2$-OCH$_3$] contain two chiral centres giving rise to identical RR/SS or enantiomeric R, S/S, R forms. Polyglycolides with different alkyl or cyclic (phenyl & cyclohexyl) side chains have been studied with emphasis only on the glass transition temperature using different techniques like DSC, NMR etc. [40-43]. Thus, the conformational behaviour of substituted polyglycolides, in all the forms in the glass transition temperature region remains unexplored.

The backbone of substituted polyglycolides is structurally similar to that of peptide back bone in proteins as the ester bond is isoelectronic to peptide bond. Thus, polylactides/substituted polyglycolides lack amide hydrogen and precluding the formation of hydrogen bond networks that stabilize the peptides secondary structure like helices and beta sheets. A systematic study of the conformational behaviour of various substituted polyglycolides *i.e.* polymethylglycolide, polyphenylmethylglycolide, isopropylglycolide, isobutylglycolide polyphenylglycolide & polycyclohexylglycolide in all RR, all SS and enatiomeric R, S and S, R forms as a function of chain length is worth investigating from the viewpoints: 1) do the polyglycolides adopt secondary structure like peptides or not; 2) do the side chains influence population of a particular form; and 3) what type of interactions stabilizing the adopted structure.

The use of polymers for various applications is characterized by the glass transition temperature [44] which in turn depends upon the nature and type of structure adopted by these polymers and what type of interactions stabilize the adopted conformations. The analysis of the interactions in the most stable states of various forms may provide insight into the nature of glass transition temperature. Knowledge of the interactions may aid in

designing of polymers with desired T_g value by incorporating stretches of polymer's and that too in desired forms *i.e.* all R, all S, alternate R, S forms etc. The simulation studies of substituted polyglycolides in different forms carried out in water, will throw light on the approach of water molecules to the ester moiety and hence, about their degradability.

2. METHODOLOGY

The backbone of substituted polyglycolides shown in **Figure 1** is similar to peptide backbone. Therefore, the torsion angles have been defined in a similar manner. The bond lengths and bond angles were taken from the literature [45]. The ester group C$_\alpha$COOC$_\alpha$ in its trans configuration was assumed to be planar. The torsion angles were varied systematically, initially in steps of 30°. Energy calculations were carried out using the quantum mechanical method PCILO [46] (perturbative configuration interaction of localized orbital) on a Sun W, Ultra 5-10; Sparc workstation. It may be mentioned that the minima obtained by PCILO calculations were also the minima at the *ab initio* level for the usual amino acids, N-methylated and dehydro amino acids. In addition, the PCILO results [47,48] for peptides containing usual [49] and unusual amino acids [50-51] were in conformity with *ab initio* results [52,53] and knowledge-based crystallographic data. [54,55] The global, local, and low-energy minima & their combinations obtained in the φ, ψ maps and χ curves/maps in substituted diglycolides of the form Ac-{O-C*H(X)-CO}$_2$-OCH$_3$ in identical & enantiomeric forms, have been used to generate the conformational states for substituted polyglycolides. The energies of all the states thus generated have been calculated. The single point energy calculations for 30° interval was further refined by varying φ, ψ and χ values in the neighbourhood of the minima, in steps of 5° and then, in steps of 2°.

The substituted polyglycolides are used for different applications and in different environment therefore, Molecular Dynamic (MD) simulation study in water has been carried out with the help of GROMACS software [56] on the desktop computer, dual Intel Pentium 4, 3.0 GHz. It is worth mentioning that the simulation results obtained by GROMOS force field are found to be in good agreement with the experiment for peptides & peptoids [57]. The starting geometry for simulation studies
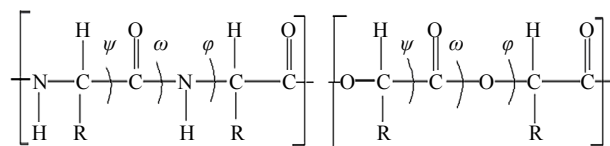

Figure 1. Similarity between peptide and glycolide backbone.

has been taken from QM results for all these molecules. The Dundee-PRODRG2 [58] server was used to obtain the GROMACS topology and coordinate files. Interaction parameters within the design sequence were taken from GROMOS-96 force field ffgmx. Energy of the system was minimized by the Steepest Descent Method, using the convergence criteria of 50 kJ·mol^{-1} followed by Conjugate Gradient method with a force constant of 20 kJ·mol^{-1}. Next, the MD run was carried out in vacuum for 2 ns, with a time step of 2 ps using the Leap Frog Algorithm [59]. The temperature was controlled through weak coupling to a bath of constant temperature [60] using a coupling time; τ_p of 0.1 ps and a reference temperature; T_0 of 300 K. The LINCS algorithm [61] was used to restrict all bonds to their equilibrium lengths and the center of mass motion of the system was removed every step to maintain the effective simulation temperature at 300 K. For the evaluation of coulomb interactions and van der Waals interaction a cut off of 0.9 and 1.0 nm respectively was applied. Long range forces were updated every 10 fs during generation of the neighbor list. The Long Range Electrostatic Interactions were calculated using a Particle Mesh Ewald Summation [62]. Initial velocities of all atoms were obtained from a Maxwellian distribution at the desired initial temperature. On the basis of the final conformation obtained for polyglycolides after 2 ns simulation in vacuum MD, a simple cubic periodic box was set up using the Simple Point Charge (SPC) Water Model [63]. For equilibration of solvent around the model polymers under study, their position was restrained for 20 ps and finally, the MD simulation of 1ns at 300 K, were performed without any restrain. The pressure was controlled using weak coupling with a time constant of 0.5 ps and a reference pressure of 1 Bar.

3. RESULTS AND DISCUSSION

In the beginning, the conformational behaviour of the substituted diglycolides of the type Ac-{O-C*H(X)-CO}$_2$-OCH$_3$ (with X being methyl, alternate phenyl & methyl, isopropyl, isobutyl, phenyl and cyclohexyl) having two chiral centres have been investigated in different forms, *i.e.* all RR, all SS, enantiomeric R, S/S, R etc. and the results are summarised in **Table 1**. The results have further been optimised up to 2° for all the states in different forms and only the results for most stable states of all forms are tabulated in **Table 2**. It is obvious from the results that the predicted states both for Ac-{O-C*H (CH$_3$)-CO}$_2$-OCH$_3$ & Ac-(phenylmethylgly-colide)-OCH$_3$ lay within 2 kcal·mol^{-1}, thus, these molecules can be realized in all the above forms. The enantiomeric R, S/S, R forms in both molecules are found to be degenerate with φ, ψ values of ±30°, ±50° or ∓30°

or ∓50° respectively. The φ, ψ values for low energy states in **Table 2** for all the forms, also lie in the neighborhood of the φ, ψ values for the most stable states. The results obtained for lactide are somewhat at variance with reported results in the SS form [64]. Isopropylglycolide and isobutylglycolide, with branching in the side chain at β and γ position respectively, are predicted to be most stable in all SS form with φ, ψ values in the right handed helical region and isopropylglycolide can also be realized in R, S form. In substituted glycolides with cyclic side chains (aryl or alkyl) directly attach to C$_\alpha$, the φ, ψ values lie in the left helical regions for the most stable forms. Diphenylglycolide may be realized in all the forms, possibly due to the symmetric environment provided by phenyl rings to C$_\alpha$ of backbone where as the φ, ψ values for dicyclohexylglycolide corresponding to the most stable RR form lie in the left helical region with cyclohexyl moiety adopting the chair form. It is interesting to note from the results in **Table 2** that the χ values adopted by side chain in diphenylglycolide depends upon the chain length *i.e.* it is trans in the dimer and gauche$^+$ in tetramer and hexamer where as the χ values in dicyclohexylglycolide are found to be independent of chain length in gauche$^+$ form. In both these substituted glycolides the cyclic (aromatic or aliphatic) side chain not only place restriction on the backbone conformation but are locked into the unfavorable gauche$^+$.

The φ, ψ values given in **Table 1** and their combinations have been used for the generation various conformational states of polyglycolides of the form Ac-[{O-C*H(X)-CO}$_2$]$_n$-OCH$_3$ with n = 1 - 3 and their energies is computed by optimizing the torsion values up to 2°. Similar results are obtained with n = 2 or 3 and hence only the results for n = 3 are given in **Table 3**. It is obvious from the results that substituted polyglycolide with smallest side chain *i.e.* polymethylglycolide is found to be most stable in the alternate R, S or alternate S, R forms with φ, ψ values in the left & right or right & left helical region. This observation is consistent with computational result by Witzke where the mesomeric form is found to be more stable than PLLA and PDLA [65]. The conformational behavior of polyphenylmethylglycolide because of the alternate lactic residue with small side chain is also found to be similar. The degeneracy of the alternate R, S and alternate S, R form implies their equal population. This very well explains the recent experimental observation that PLA homopolymer exhibit no CD signal in the wavelength range from 190 to 250 nm [66]. A molecular view of polymethylglycolide and polyphenylmethylglycolide in R, S form shown in **Figure 2** is similar in appearance to the 2$_7$ ribbon structure reported in poly ΔLeu peptides with ΔLeu residues being in alternate Z, E or E, Z forms

Table 1. Conformational results (φ, ψ, in degrees) for repeating units of polyglycolides.

Form	1	2	ΔE(kcal/mol)	1	2	ΔE(kcal/mol)
	Ac-dimethylglycolide -OCH$_3$			Ac-phenylmethylglycolide-OCH$_3$		
	60, 30	−60, −30	0.0	60, 30	−60, −30	0.0
	30, 30	−60, −30	1.6	30, 60	−30, 120	1.5
RS	30, 60	−30, −60	1.9	30, −120	−30, −60	1.6
	60, 30	−90, 0	2.4	90, 0	−30, −60	1.7
	30, 60	−30, 120	3.0			
	−60, −30	60, 30	0.1	−60, −30	60, 30	0.9
	−30, −60	30, 60	2.0	−90, 0	60, 30	2.7
SR	−30, −60	30, −120	2.4	−90, 0	90, 0	3.7
	−90, −30	90, 0	3.6	−90, 0	60, 30	4.0
	−60, −30	−60, 0	2.1	−60, −30	−60, −30	1.3
	−60, −30	−60, −30	4.1	−90, 0	−90, 0	3.2
SS	−90, 0	−90, 0	4.4	−30, −60	−30, −60	4.1
	−60, −30	−90, 0	4.5	−60, −30	−90, 0	4.4
	−90, 0	−60, −30	4.7			
	60, 30	60, 30	2.3	60, 30	60, 30	2.1
	−30, 120	30, −120	4.2	90, 0	90, 0	4.0
RR	30, −120	30, −120	4.3	30, 60	30, 60	4.9
	30, 60	30, 60	4.4	90, 0	60, 30	5.2
	−30, −60	0, 90	5.4			
	Ac-diisopropylglycolide-OCH$_3$			Ac-diisobutylylglycolide-OCH$_3$		
	−30, −60	−30, −60	0.0	−30, −60	−60, −30	0.0
SS	−60, −30	−30, −60	1.8	−30, −60	−30, −60	1.1
	−60, 0	−60, 0	2.1	−60, −30	−60, −30	2.0
	60, 0	−30, −60	0.5	60, 0	−30, −60	3.5
RS	90, 0	−30, −60	0.9	60, 30	−30, −60	5.0
	90, 0	−60, −30	2.6	30, 60	−60, −30	5.5
	−60, 0	60, 30	2.1	−60, −30	60, 0	1.2
SR	−90, 0	60, 30	3.8	−30, −60	60, 0	3.9
	−60, 0	60, 0	3.9			
	60, 0	60, 0	2.9	30, −120	150, 60	6.5
	60, 0	30, −120	4.4	30, −120	30, −120	8.9
RR	60, 180	60, 0	5.4			
	60, −150	30, −120	5.6			

	Ac-diphenylglycolide-OCH$_3$			Ac-dicyclohexylglycolide-OCH$_3$		
RR	30, 60	60, 30	0.0	60, 30	60, 30	0.0
	30, 60	30, 60	0.7	90, 0	60, 30	2.5
	30, 60	0, 90	1.9	90, 0	90, 0	4.9
	60, 30	0, 90	2.3			
	60, 0	30, 60	2.5			
	90, 0	30, 60	2.6			
SS	−30, −60	−60, −30	0.1	−60, −30	−60, −30	43.1
	−30, −60	−30, −60	0.7			
	−30, −60	−60, 0	1.2			
	−60, −30	−30, −60	1.6			
	−30, −60	0, −90	1.9			
SR	−60, 0	30, 60	1.6	−60, −30	90, 60	24.0
	−60, 0	60, 30	2.5			
	−90, 0	30, 60	2.8			
	−90, −30	30, 60	3.1			
RS	60, 0	−30, −60	1.6	30, 60	−60, −30	18.0
	60, 0	−60, −30	2.5	30, 60	−30, −60	20.1
	90, 0	−30, −60	3.1			

and hence these structures are named as 2_7 ribbon type structures[67]. These structures are stabilized by the network of carbonyl-carbonyl interactions between the ith residue and i^{th} + 1 residue ($d_{O_i-C_{i+1}} = 2.2 + 0.05$ Å and $d_{O_i-O_{i+1}} = 2.7 \pm 0.05$ Å). It may be mentioned that the splitting of carbonyl stretching in IR spectroscopy has also been attributed to the carbonyl-carbonyl interactions in polylactides [38]. In addition to the carbonyl- carbonyl interactions in polyphenylmethylglycolide, C-H$\cdots\pi$ interactions between methyl moiety of ith residue and phenyl ring of both i^{th} − 1 and i^{th} + 1 residue are also observed. The importance of C-H$\cdots\pi$ interactions is well established in literature [68]. Graphical view in **Figure 2** of polylactide in alternate R, S form clearly depicts that it adopts a structure with slight curvature where alternate methyl groups are placed on the either side of the backbone. Likewise, in polyphenylmethyl-glycolide, the phenyl moiety lies on one side and methyl group lies on the other side of the backbone. Such a disposition of side chains around the backbone may give rise to sheets like structure by association of two or more strands by hydrophobic interactions. A model building study involving two polylactide chain in the alternate S, R form to give rise to a zipper like structure (**Figure 3**)
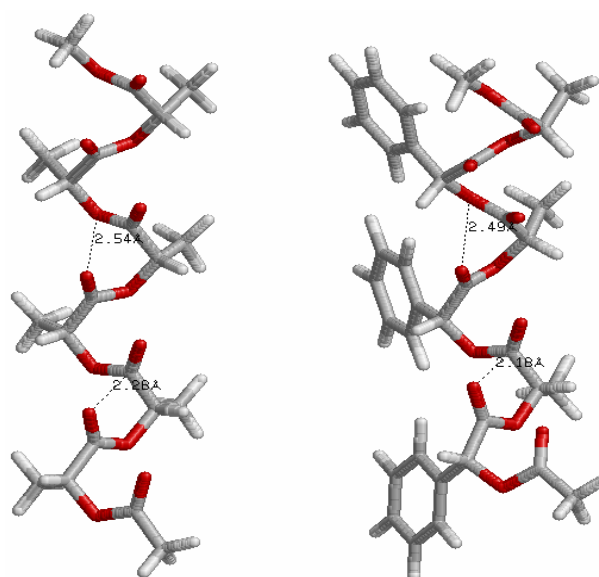

Figure 2. A molecular view of polylactide and polyphenyl-methylglycolide in alternate R, S form adopting 2_7 ribbon type structure stabilised by various interactions.

similar to leucine zipper in proteins in which carbonyl oxygen point on one side of the plane of molecule are

Table 2. Most stable state ($\varphi, \psi, \omega, \chi$ in degrees) for substituted glycolides.

Form	1	2	ΔE(kcal/mol)	1	2	ΔE(kcal/mol)
	Ac-dimethylglycolide-OCH₃			**Ac-phenylmethylglycolide-OCH₃**		
RS	**27, 56** 174 180	**−29, −58** −174 60	0.0	**26, 56** 180 175	**−35, −50** −176 60	0.0
SR	**−29, −56** −174 60	**26, 56** 174 60	0.1	**−52, −28** −174 −178	**25, 58** 174 180	1.1
SS	**−60, −30** −174 60	**−65, −10** 170 180	2.3	**−50, −30** 176 176	**−24, −56** 178 60	1.6
RR	**52, 34** 172 178	**22, 56** −174 −178	2.6	**60, 30** 180 −179	**62, 11** 164 64	2.4
	Ac-diisopropylglycolide-OCH₃			**Ac-diisobutylylglycolide-OCH₃**		
SS	**−25, −60** 180 180(−60)	**−40, −70** −172 180(−60)	0.0	**−25, −60** −172 −40	**−20, −70** −172 −40	0.0
RS	**60, 0** −176 −65(55)	**−25, −60** 180 180(−60)	0.7	**45, 25** −178 70	**−25, −60** −178 −75	3.8
SR	**−60, 0** 172 −55(65)	**60, 30** 176 55(175)	2.5	**−25, −60** −172 −75	**50, 20** −172 75	1.5
RR	**60, 10** 180 −70(170)	**55, 15** 180 −70(170)	3.1	**50, −140** 178 40	**160, 30** −178 175	6.8
	Ac-diphenylglycolide-OCH₃			**Ac-dicyclohexylglycolide-OCH₃**		
RR	**35, 50** 178 173	**60, 30** −178 170	0.0	**52, 36** 178 55	**52, 36** 176 55	0.0
SS	**−32, −54** 180 178	**−60, −30** 180 −173	0.3	**−44, −32** 180 94	**−61, −25** 180 85	43.1
SR	**−38, −40** 178 170	**30, 56** 170 172	0.3	**−51, −25** 176 85	**84, 63** 170 62	24.6
RS	**44, 26** −176 180	**−27, −58** −176 180	0.7	**29, 56** 176 59	**−50, −27** −172 85	18.2

φ, ψ values are given in bold, ω in italics and χ_1, χ_2 in normal text.

accessible to water molecules for interaction. Possibly, polylactides in this type of sheet like structure are being used in encapsulation of drugs and mulch films.

The helical structures both left and right handed are found to be less stable in both polylactides and polyphenylmethylglycolides but the left handed helical structure is predicted to be more stable than right helical structure by at least 2 kcal due to comparatively stronger hydrophobic interactions between the sides chains in the all RR form as compared to the all SS form. The $d_{Oi-Oi+2}$

are found to be less than the sum of their van der Waal's radii in helices corresponding to RR/SS forms, suggesting the repulsion nature of this interaction and as apparent from $d_{O_i-O_{i+2}}$ (= 2.20 ± 0.02 Å) values the repulsive interactions are negligible in the RS or SR forms. It is the magnitude of the attractive nature of carbonyl-carbonyl interactions and the repulsive forces between carbonyl oxygen of the ith residue and ester oxygen of ith + 2 and i^{th} + 3 residues which dictate the structure adopted by polyglycolides. This also explains very well that the

Table 3. Most stable conformers for substituted polyglycolides with φ, ψ, ω and χ being in degrees.

			Residue number				
Form	**1**	**2**	**3**	**4**	**5**	**6**	**ΔE(kcal/mol)**
			Ac-(lactide)$_6$-OCH$_3$				
RSRSRS	**30, 50** 178 60	**–35, –50** –178 60	**30, 50** 178 55	**–35, –50** –178 65	**30, 50** 178 60	**–35, –45** 180 60	0.0
SRSRSR	**–35, –50** 180 60	**30, 50** 180 60	**–35, –50** –178 60	**30, 50** 178 60	**–35, –50** 180 55	**30, 50** 178 55	0.4
RSSRRS	**25, 60** 170 60	**–60, –30** –178 55	**–35, –40** 172 55	**30, 55** 176 65	**25, 60** 172 60	**–35, –50** –176 60	2.0
RRRRRR	**30, 50** 178 60	**30, 50** 178 60	**30, 50** 178 60	**30, 50** 178 60	**30, 50** 178 60	**25, 50** 178 60	5.1
SSSSSS	**–35, –50** 178 60	**–60, –30** 180 60	**–60, –30** 180 60	**–35, –50** 180 60	**–35, –50** 180 60	**–35, –50** 180 50	7.9
			Ac-(phenylmethylglycolide)$_6$-OCH$_3$				
RSRSRS	**27, 56** 174 30	**–29, –58** –170 55	**22, 64** 174 30	**–31, –60** –168 66	**41, 43** 172 38	**–36, –49** –172 58	0.0
SRSRSR	**–31, –51** 180 22	**28, 56** 172 60	**–35, –45** 180 30	**30, 55** 172 60	**–31, –51** 180 20	**29, 61** 174 66	0.6
RSSRRS	**30, 55** 172 55	**–60, –30** –172 60	**–55, –25** 170 60	**30, 60** –172 70	**30, 45** 176 40	**–35, –50** –172 50	3.9
RRRRRR	**60, 30** 162 55	**52, 20** –172 50	**50, 30** 178 68	**58, 26** –178 54	**60, 30** 172 62	**58, 20** –172 60	7.7
SSSSSS	**–60, –30** 180 30	**–60, –20** 180 60	**–40, –35** –174 60	**–75, –15** –174 60	**–60, –30** –174 60	**–65, –10** –172 50	9.8
			Ac-(isopropylglycolide)$_6$-OCH$_3$				
SSSSSS	**–30, –55** –172 180(–60)	**–30, –55** –172 180(–60)	**–30, –60** –172 180(–60)	**–25, –60** –172 180(–60)	**–25, –60** –176 180(–60)	**–20, –65** –172 175(–65)	0.0
SRSRSR	**–30, –55** –172 –80(40)	**65, 10** 172 50(–70)	**–25, –65** –174 –80(40)	**65, 15** 170 170(–70)	**–25, –60** –172 180(–60)	**60, 10** 178 170(–70)	3.7
RSSRRS	**50, 30** 170 –50(70)	**–25, –65** –176 180(–60)	**–30, –60** –172 –85(35)	**65, 0** –178 175(–65)	**55, 15** 180 175(–65)	**–20, –65** –176 180(–60)	4.2
RSRSRS	**55, 10** –174 –70(50)	**–30, –60** –172 –85(35)	**60, 10** 174 170(–70)	**–25, –65** –172 –85(35)	**60, 20** 174 170(–70)	**–25, –60** –172 180(–60)	5.1
RRRRRR	**60, 0** –172 –60(60)	**60, 0** 178 –60(60)	**60, 0** 178 –60(60)	**65, –5** 178 –60(60)	**60, 10** 180 –60(60)	**60, 10** 180 –60(60)	6.1

Ac-(isobutylglycolide)₆-OCH₃							
SSSSSS	**−30, −60** −176 −80	**−30, −60** −174 −75	**−25, −60** −174 −85	**−25, −60** −172 −85	**−25, −60** −174 −90	**−30, −60** −172 −90	0.0
SRSRSR	**−30, −60** −172 −30	**35, 50** 172 80	**−30, −55** −172 −150	**30, 50** 172 90	**−30, −60** −172 −30	**30, 50** 174 80	3.0
RRRRRR	**25, −115** 180 60	**150, 30** 180 150	**25, −115** 180 50	**150, 30** −178 170	**25, −115** −178 45	**155, 30** −176 170	9.0
RSRSRS	**80, −30** 180 80	**−15, −75** −172 −80	**55, 25** 170 60	**−15, −75** 180 −115	**50, 25** 174 80	**−20, −60** 170 −95	9.4
RSSRRS	**30, 55** 180 70	**−25, −55** 170 −100	**−30, −55** −172 −80	**35, 50** 170 125	**30, 55** 170 70	**−30, −45** 170 −100	14.4
Ac-(phenylglycolide)₆-OCH₃							
RRRRRR	**45, 35** 176 38	**48, 36** −178 47	**52, 32** −178 47	**30, 58** −172 55	**32, 56** 176 39	**28, 56** 174 41	0.0
RSSRRS	**30, 50** 172 45	**−45, −35** −172 30	**−55, −20** −172 55	**25, 50** −172 60	**30, 60** −174 55	**−40, −45** −172 30	2.5
RSRSRS	**24, 60** 172 50	**−52, −30** −172 50	**24, 60** 172 56	**−52, −28** −172 50	**32, 50** 174 54	**−54, −34** −172 56	8.8
SRSRSR	**−52, −28** 180 50	**24, 60** 172 50	**−52, −28** −172 50	**30, 60** 172 58	**−54, −28** −172 50	**34, 50** 174 50	11.6
SSSSSS	**−52, −28** −172 60	**−52, −24** −172 60	**−68, −28** −176 60	**−54, −30** −174 60	**−66, −22** −176 60	**−60, −30** −172 60	12.7
Ac-(cyclohexylglycolide)₆-OCH₃							
RRRRRR	**35, 50** 174 61	**41, 42** 174 50	**48, 43** 172 65	**47, 41** 172 61	**50, 35** 172 60	**60, 30** −174 51	0.0
RSRSRS	**50, 38** 178 65	**−60, −30** −166 85	**30, 60** 160 65	**−60, −30** −166 85	**30, 60** 162 65	**−60, −30** 174 85	153.0
SSSSSS	**−60, −30** −165 85	**−60, −30** 180 85	**−60, −30** 180 85	**−60, −30** 180 85	**−60, −30** 180 85	**−60, −30** 180 85	190.1

φ, ψ values are given in bold, ω in italics and χ₁, χ₂ in normal text.

enantiomeric form RSSRRS is more stable than the helical structures corresponding to all RR and all SS form but less stable than the alternate enantiomeric forms.

Polyisoproylglycolide and polyisobutylglycolide are found to be most stable in all SS form adopting the right handed helical structure without hydrogen bonds with φ, ψ values of approximately −30°, −60° stabilized by various interactions shown in **Figure 4**. It is due to weaker hydrophobic interactions and the carbonyl-carbonyl in-

teractions, the left handed helices in the all RR form is found to be less stable. Polyvaline and polyleucine peptides in the helical structure are used as surfactant by incorporating amino acid residue like lysine/aspartic or glutamic at termini positions. Similarly, polyisopropylglycolide and polyisobutylglycolide can also be exploited (by controlling chain length) as surfactant by incorporating charged amino acid residues at either terminus.

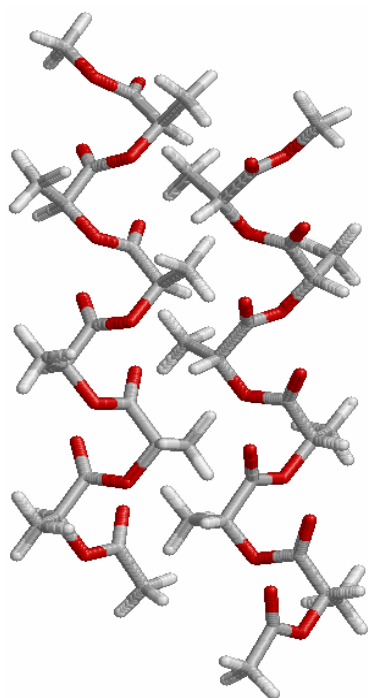Polyphenylglycolide & polycycloglycolide have been

Figure 3. A model showing the formation of zipper like structure between two polylactides molecules in alternate S, R form.
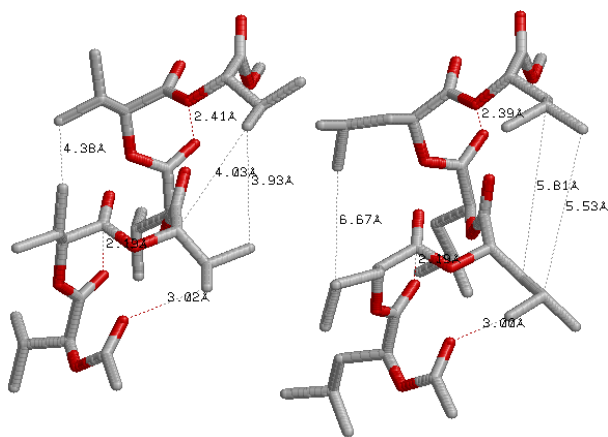

Figure 4. Polyisopropylglycolide and polyisobutylglycolide, without hydrogen bonds adopting right handed helical structure corresponding to most stable enatiomer in the SS form.

studied with emphasis on thermal & hydrolytic degradation, rheological and visco elastic properties [43,69]. These polyglycolides are found to be most stable in the all RR form, adopting the left handed helical structures. In, Polyphenylglycolide the conformational state corresponding to the enantiomeric form RSSRRS lies within 2.5 kcal/mol of the most stable where as the conformations for pure enantiomeric forms lies higher in energy. The bulky side chains not only increase rotational barrier but also decrease the magnitude of carbonyl interactions.

On the basis of ^{1}H NMR results in methine region a high degree of stereo regularity for R, R-dicyclohexylglycolide has been reported and the isotactic nature of the polymer has been confirmed by ^{13}C NMR results [70]. The computational results together with graphical view shown in **Figure 5** clearly depict the identical and equivalent environment for methine moieties in the helical structure. Thus, the conformational results are not only in agreement with the reported experimental finding but provide more information about the adopted structure & the interactions which stabilise the structure. The computational results also reveal that these molecules cannot be realized in the all SS form because of stearic clash between the side chains of ith and i[th] + 3 residues.

3.1. Modelling of Carbonyl-Carbonyl Interactions

Based on a systematic study between ketonic groups in the Cambridge structure database carbonyl-carbonyl interactions [71,72] have been modeled by three main types of interaction motifs. Importance of carbonyl-carbonyl interactions as a stabilizing factor in α-helices, β-sheets and right-handed twist is well-documented [73,74] and are substantiated by interacting two acetone molecules in different geometries. In one of the geometries, the carbonyl groups of two acetone molecules are vertically above each other with their carbonyl groups aligned in an antiparallel direction, whereas in the other, one acetone molecule's carbonyl group approaches the carbonyl group of the second molecule in a perpendicular direction. As expected, the interaction energy corresponding to the first geometry was found to be approximately ~45 kcal·mol^{−1} and may not reflect the quantitative nature of the carbonyl-carbonyl interactions, as this model envisages a pair of such interactions without any repulsion. The interaction energy, ΔE found to be between 4 and 10 kcal mol^{−1} depending upon the approach of one acetone molecule over the length of the carbonyl group of the second acetone molecule in the perpendicular direction. The carbonyl-carbonyl interactions also stabilize the partially allowed Ramachandran conformations of aspartic acid and asparagines [75] and helical structures without hydrogen bonds in peptides constructed from achiral and unusual amino acids [67,76, 77].

3.2. Interactions

The right handed helical structure corresponding to the all SS form in polyisopropylglycolide and polyisobutylglycolide shown in **Figure 4** are stablised by carbonyl carbonyl interactions and C-H—O interactions
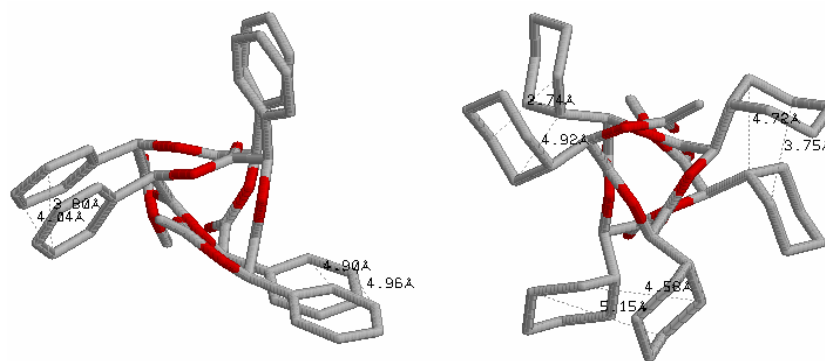
Figure 5. Formation of left handed helical structure in the most stable enatiomeric form (RR) in polymandelide and polydicyclohexylglycolide stabilized by various interactions.

between C_γ/C_δ of methyl group of ith + 3 residue side chain with carbonyl oxygen of ith residue. In polyisobutylglycolide, C-H—O interactions are also noticed between C_β-H of ith + 3 residue and carbonyl oxygen of ith residue (**Figure 4**). The C-H—O interactions are well documented and discussed in detail for inclusion complexes, as determinant of stability and specificity in trans membrane helix and in biological structure. [79,80] Hydrophobic interactions are found to be operative in polyisopropylglycolide but absent in polyisobutylglycolide. The magnitude of carbonyl-carbonyl interactions appears to be similar in polylactides and polyisopropylglycolides on the basis of distance ($d_{O_i - C_{i+1}}$ = 2.4 - 2.6 Å). The distance between carbonyl oxygen's of ith and ester oxygen of ith + 3 residue lies in the range 2.3 to 2.5 Å. The van der Waal radius of oxygen is 1.45 Å and thus the repulsive interactions between carbonyl oxygen's of ith and ester oxygen of ith + 3 residues may be operative. The stability of any state arises due to the net result of attractive and repulsive interactions and thus, may influence the magnitude of glass transition temperature.

A molecular view of polyphenylglycolide and polycyclohexylglycolide in the left helical structure shown in **Figure 5** reveals that both these molecules are stabilized by the network of carbonyl-carbonyl interactions ($d_{O_{i-1} \cdots C_i}$ = 2.2 to 2.7 Å, but weaker as compare to corresponding form in polylactides) and by C-H—O interactions between the carbonyl oxygen of ith − 1 residue and C_α of ith + 2 residue (in polyphenylglycolide) and C_γ-H and C_β-H of ith + 2 residue with carbonyl oxygen of ith − 1 (d_{O-H} = 2.4 − 2.6 Å) (in cyclohexylglycolide). In addition to these interactions, the $C_{\beta-\gamma-\delta}$ face of aromatic ring of the ith residue is involved in stacking interactions with the $C_{\gamma-\delta-\xi}$ face of aromatic ring of the ith + 3 residues in polyphenylglycolide and the stacking interactions are usually stronger than the hydrophobic interactions. The hydrophobic interactions between the side chain of ith and i^{th} + 3 residues also contribute towards the stability of this

state in polycyclohexylglycolide. The carbonyl-carbonyl interactions are operative in all the conformations of all forms of substituted polyglycolides with highly shielded parallel motif with only one short carbon-oxygen interacttion. The quiet high T_g of polyphenylglycolide and polyc-yclohexylglycolide can be explained in terms of the network of the these interactions. Polylactides lack this type of network of interactions and that may be the reason for their is comparatively low T_g. Thus, the nature of non-covalent interactions by proper choice of side chains and chirality can be exploited for the construction and designing of polymers in required handed structures.

3.3. Simulations

The conformational results for various polyglycolides after 1 ns simulation in water are summarized in **Table 4**. The molecular view of polylactide (**Figure 6(a)**) with water molecules within 3 Å of its surface clearly show that almost all of the carbonyl oxygen are involved in interactions with water molecules {d_{O-H} = 1.5 - 2.1 and d_{O-O} = 2.4 - 3.0 Å and the angle $\angle O \cdots H$-O being in the range 149.9° - 174.7°}. This observation is consistent with the fact that in water, ester bond undergo hydrolysis and thus provides explains for the use of polylactides as sutures, mulch films etc. The degradation products of polylactides are non-toxic as lactate is produced in body by the process of anaerobic glycolysis. Similar results were obtained for polyphenylmethylglycolide.

Polyisopropylglycolide and polyisobutylglycolide having branching at β and γ positions respectively exhibit almost similar behaviour on simulation in water. The results in **Table 4** reveal that due to the interaction of water molecules with backbone, consecutive turns (analogous to that in proteins) of the type VIa, Type I and γ are introduced at the C terminal in polyisopropulglycolide. As a function of simulation time the molecule start

Table 4. Simulations results for substituted polyglycolides after 1 ns simulation in water.

poly glycolide	Residue no									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
methyl	**64, –85**	**–65, 123**	**57, 34**	**–57, 108**	**100, –35**	**–64, 114**	**87, –39**	**–74, –27**	**67, –124**	**–59, –26**
	–164	–177	–173	–178	178	–151	174	–169	178	–166
phenyl/methyl	**63, –123**	**–73, –5**	**136, 36**	**–79, –10**	**73, –154**	**–63, –15**	**53, –162**	**–72, –22**	**176, 44**	**–103, 25**
	180	–179	–164	–177	167	154	–174	–179	–178	168
isopropyl	**–75, –4**	**–84, 14**	**–134, –28**	**–90, 35**	**–65, 114**	**–48, –9**	**–88, –21**	**–80, –37**	**–96, 80**	**–84, 156**
	–179	171	–171	173	–168	175	170	144	–171	–179
	–83 (48)	–76 (49)	–31(–153)	–86(30)	–87(31)	–56(67)	–72(54)	–176(64)	–51(–178)	–72(50)
isobutyl	**–68, –36**	**–77, –5**	**–92, –32**	**–69, –4**	**–97, –24**	**–67, –16**	**–80, –28**	**–77, –14**	**–77, –21**	**–73, –17**
	175	172	176	166	174	164	–178	169	164	179
	–63	–58	–65	–70	–147	–56	–168	–90	–76	–86
phenyl	**88, 6**	**68, 18**	**68, 26**	**75, 12**	**102, 1**	**128, –10**	**74, 32**	**57, 38**	**86, 32**	**149, 68**
	171	150	–177	–178	–172	–179	170	–176	–171	175
	99	137	126	118	99	97	108	147	113	138
cyclohexyl	**53, 35**	**70, 18**	**87, 18**	**104, 22**	**77, 36**	**60, 23**	**92, –21**	**89, 41**	**65, 40**	**90, –104**
	–168	179	–158	–175	–176	–165	180	–153	174	169
	54	73	59	64	32	49	49	74	43	44

φ, ψ values are given in bold, ω in italics and χ_1, χ_2 in normal text.
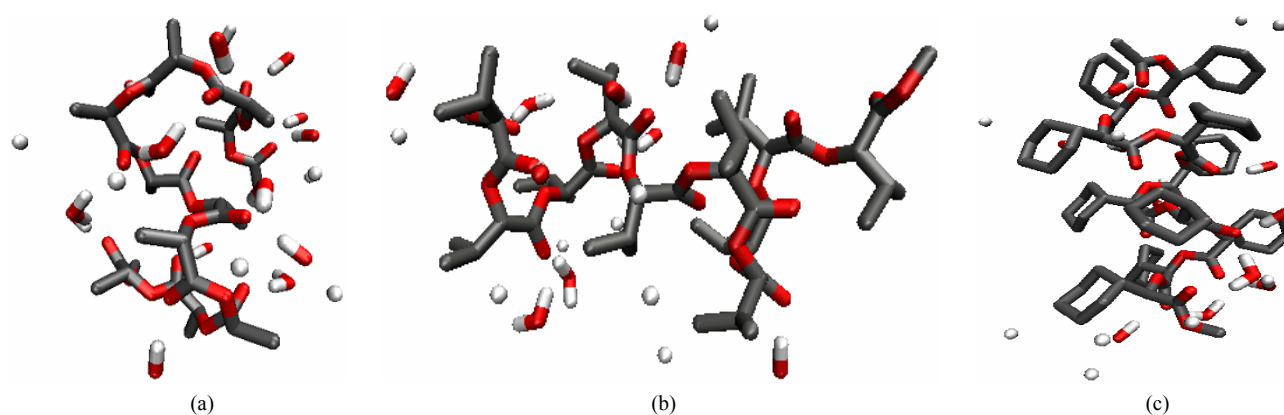

Figure 6. Molecular view of substituted glycolides after 1 ns simulation in water with the interacting water molecules within 3 Å of the substituted glycolides. (a) Polylactide; (b) polyisopropylglycolide; (c) polycyclohexylglycolide.

adopting compact structure with decrease in the number of water molecules interacting with backbone with the increase in hydrophobic interactions between the side chains. The molecular view of polyisopropylglycolide after 1ns simulation in water is shown in **Figure 6(b)** reveals that the branching at β position protects the backbone from approach of water molecules.

The backbone φ, ψ angles, both for polyphenylglycolide and polycyclohexylglycolide on simulation also remain in the left handed helical region. The left helical structure in polycyclohexylglycolide shown in **Figure 6(c)** is characterized by average φ, ψ values of 49.5, 27.5° analogous to the 3_{10} helix in peptides, rotation per residue $\theta = 100°$, rise per residue $h = -1.68$ Å. It is worth

mentioning here that by circular dichroism measurements it has been shown, poly (D-dicyclohexyl glycine) forms more stable and ordered structure due to stronger non covalent interactions in water, ethanol or triluoroethanol in comparison with poly (D-phenylglycine) [81]. In polyphenylglycolide, due to interaction of water molecules with backbone, a kink is introduced in the middle. The analysis of simulation results for polyisobutylglycolide, polyphenylglycolide and polycyclohexylglycolide reveals that numbers of water molecules interacting with backbone carbonyl group are found to remain constant as a function of simulation time having preference for the C terminal. This may implies that the hydrolysis of these polyglycolides may start from C ter-

minal. Both, in case of polyphenylglycolide and polycyclohexylglycolide, the number of water molecules protruding to interact with backbone is less in comparison to other substituted polyglycolides. This may be regarded as that these glycolides are more resistant to water hydrolysis.

4. CONCLUSIONS

The conformational behavior of substituted polyglycolides has been found to depend on the nature of side chains. Polylactide and polyphenylmethylglycolide can be realized in both the enantiomeric forms R, S/S, R forms with φ, ψ values giving rise to the 2_7 ribbon like structure which are stabilised by carbonyl-carbonyl interactions. Polyisopropylglycolide and isobutylglycolide having branching at β & γ respectively in their side chains it is the all S form which is observed to be the most stable with φ, ψ values lying in right handed helical region of Ramachandran plot stablised by hydrophobic interactions. Both polyphenylglycolide and polycyclohexylglycolide, having cyclic side chain directly attach to C_α group of backbone are found to be most stable in the all R form and adopt left handed helical structure stabilised by stacking interactions and hydrophobic interactions respectively. It is nature and magnitude of various interactions dictate the most stable form of polyglycolides and their structure together with handedness. Simulation studies in water reveal that the approach of water molecules to the backbone depends on the bulkiness of side chain and the adopted structure.

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