Chiral Polymers *Very Important Paper*

Stereocomplexed Poly(Limonene Carbonate): A Unique Example of the Cocrystallization of Amorphous Enantiomeric Polymers**

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Abstract: *We report the cocrystallization of the regio- and stereoregular chiral copolymer poly(limonene carbonate). To the best of our knowledge, this marks the first example of an amorphous, enantiomerically pure polymer that becomes crystalline upon stereocomplexation with its complementary enantiomer. By analyzing X-ray powder diffraction data, we propose a packing model in which sheets of enantiopure chains interdigitate with layers of the opposite enantiomer, forming a "steric zipper".*

Approximately 90% of small molecule racemates crystallize as racemic compounds, where pairs of enantiomers prefer to crystallize in a 1:1 ratio in the unit cell.[1] In contrast, only about 10% of racemic small molecules form mixtures of enantiopure crystals (also called conglomerates), which is perhaps best represented by the manual resolution of enantiopure ammonium sodium tartrate over 160 years ago by Pasteur.[1,2] The tendency of racemates to crystallize as racemic compounds rather than as conglomerates has been explained in terms of the observation that racemic crystals are generally denser than their chiral counterparts (Wallach's rule), perhaps resulting from a wider range of possible space groups, including those that contain mirror and glide planes, as well as center-of-inversion operations.[3] Aside from the intrinsic academic interest in crystallization of racemic small molecules, there are more practical implications, such as the more facile crystallization of racemic proteins.[4]

In the realm of macromolecules, there is a relatively small group of enantiopure polymers that form racemic compounds when enantiomeric chains are combined in a 1:1 ratio; these are most commonly referred to as polymer stereocomplexes.[5] Cocrystallization typically gives rise to higher melting points and higher levels of crystallinity, and can result in an enhancement in polymer performance. One of the most studied examples is poly(lactic acid).[6] Enantiopure semi-crystalline homopolymers poly(L-lactic acid) (PLLA) and poly(D-lactic acid) (PDLA) form a stereocomplex melting at 230°C when mixed in equivalent amounts, which is about 50°C higher than the component polymers. This significant increase in melting temperature allows additional applications of the stereocomplex relative to the enantiopure poly(lactic acid) materials. Such materials also have documented biomedical uses in drug delivery, tissue engineering, and nanostructured surfaces.[7]

An obvious prerequisite for the formation of a polymer stereocomplex is the availability of enantiopure polymers,[8] which can be synthesized by either the enantioselective polymerization of prochiral monomers, or the simple polymerization of enantiopure substrates. One advantage of the latter is that highly enantiopure polymers can be readily synthesized once enantiopure monomers are in hand. Epoxides are an important class of monomers that can be obtained either through enantioselective synthesis[9] or by epoxidation of enantiopure, naturally occurring alkenes, such as limonene and pinene.

We have developed a range of catalysts that are capable of the homo- and copolymerization of epoxide monomers.[10] Despite examining many enantiomeric pairs of polyether and polycarbonate polymers derived from enantiopure epoxides,[11] we have not observed stereocomplexed polymers. In fact in some cases, highly regio- and stereoregular polymers derived from enantiopure epoxides are not even semi-crystalline; an important example is poly(limonene carbonate), (PLC; Figure 1).[12a] Herein, we report that mixing equal amounts of enantiomeric PLC chains unexpectedly results in a semi-crystalline stereocomplex. The PLC stereocomplex was examined by X-ray diffraction analysis, and it was found that the crystal sheets of enantiopure chains interdigitate with layers of the opposite enantiomer. A mechanism that explains the crystallization of the stereocomplex in the general framework of crystallization of chiral compounds is proposed. There is an intrinsic interest for this new class of polymers since they can be synthesized from completely renewable resources.[12a,b] Moreover, the case of PLC represents a unique example in polymer crystallography, where the favorable interaction of opposite enantiomers promotes facile crystallization, while crystallization of enantiopure species does not occur.

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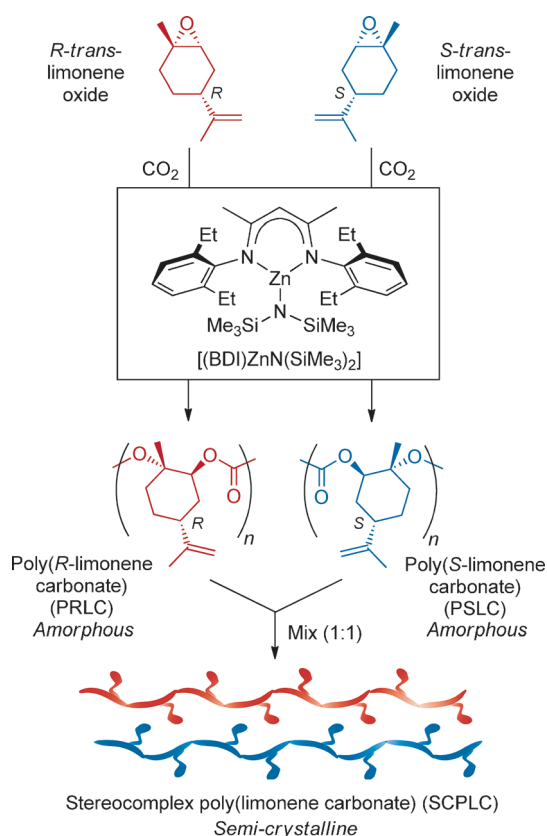E-mail: auriemma@unina.it

Figure 1. Copolymerization of limonene oxide and CO₂ to enantiomerically pure, regioregular isotactic copolymers, and formation of semi-crystalline stereocomplex. BDI = β-diiminate.

Figure 2. X-ray powder diffraction profiles of a) the pure enantiomer PSLC or PRLC and b) the SCPLC stereocomplex. Samples in (a) and (b) were obtained by annealing solution cast films at 180°C for 2 h and then at 200°C for 45 min.[13] In order to randomize the orientation of the crystals, the sample in (b) was powdered by milling in liquid nitrogen. c) Calculated X-ray diffraction profile relative to the limit ordered antichiral packing of Figure 4 in the space group symmetry $Pbc2_1$. The Miller indices of the peaks are given in Table S2.

Poly(1S,2S,4R-limonene carbonate) (PRLC) and poly-(1R,2R,4S-limonene carbonate) (PSLC) were synthesized starting from a *cis/trans* mixture of (R)- and (S)-limonene oxide, respectively, at room temperature using the β-diiminate zinc complex of Figure 1. The catalyst readily polymerizes the *trans* diastereomer of the epoxide, leaving the *cis* diastereomer unreacted, and resulting in a highly regio-, diastereo-, and enantiomerically pure polymer.[12a] As synthesized, the enantiopure polymers are not crystalline in spite of the highly regular constitution and configuration, as shown by X-ray powder diffraction profiles (Figure 2a and S2a in the Supporting Information[13]). A 1:1 mixture of PRLC and PSLC was prepared by dissolving equal amounts of each enantiomerically pure polymer ($M_n \approx 50 \text{ kg mol}^{-1}$) in n-hexane. After filtering, the solutions were mixed, resulting in the immediate formation of a precipitate that was decanted and dried in vacuo. ¹H and ¹³C NMR spectra of the PRLC/PSLC mixture were identical to those of PRLC and PSLC. However, contrary to the enantiopure components, the mixed precipitate was crystalline as shown by powder X-ray diffraction (Figure 2b and S2b[13]).

Thermal analysis revealed a glass transition temperature of ca. 120°C for all samples[12a] and a decomposition temperature of ca. 250°C for the enantiopure samples and ca. 265°C in the case of PRLC/PSLC mixture.[13] The 15°C rise in degradation temperature of the racemic mixture supports the hypothesis that the two enantiopure components crystallize as
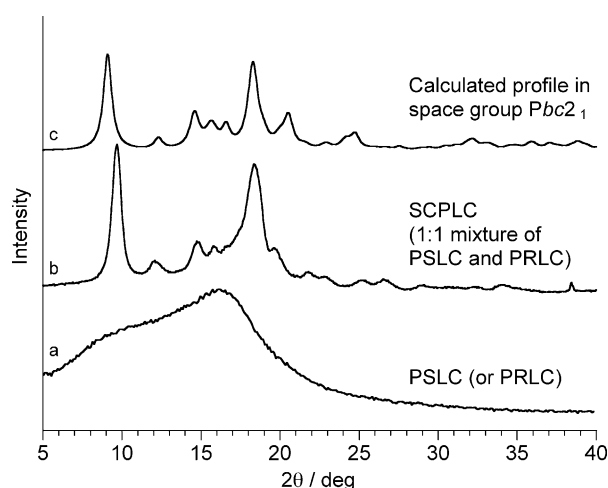
a stereocomplex,[14] and suggests that the interactions established between polymer chains of opposing chirality are stronger than those between polymer chains of the same chirality.[5a] The lack of melting transition for semi-crystalline SCPLC is attributed to a melting temperature (T_m) that is higher than its decomposition temperature.

Several attempts have been performed to crystallize the enantiopure samples. We found that pure PSLC or PRLC are amorphous and fail to crystallize by casting procedures from tetrahydrofuran (THF) and CH_2Cl_2 solutions (Figure 2a). The X-ray powder diffraction profile of the annealed racemic sample confirms that this sample is crystalline (Figure 2b). It shows Bragg peaks that can be indexed according to an orthorhombic unit cell with parameters $a = 9.71 \pm 0.05$ Å, $b = 10.68 \pm 0.05$ Å and $c = 11.31 \pm 0.05$ Å (chain axis). The main diffraction peaks occur at $d \approx 9.2$, 6.0 and 4.8 Å ($2\theta \approx 9.7$, 14 and 18°, respectively). They correspond to 100, 111 and 021, 200, and 102 reflections, respectively (Table S2).[13] The calculated density, assuming two chains (four monomeric units)/cell, is 1.110 g cm^{-3}, in good agreement with the experimental value of the crystalline density for the stereocomplex equal to 1.128 g cm^{-3}.[13]

Two-dimensional diffraction measurements of oriented specimens confirmed the chain periodicity c of 11.31 Å, along with the occurrence of strong reflections at $2\theta \approx 9.7°$ on the equator, 14° on the first layer line and 18° on the first and second layer lines (data not shown, corresponding Miller indices 100, 111, 021, and 102).

On the basis of the constitution and configuration of PSLC and PRLC chains, the value of chain periodicity $c = 11.31$ Å is compatible with the identical repetition of two monomeric units/period and the presence of a 2/1 helical axis parallel to the chain axis. The line repetition group is **s**(2/1) (Figure 3a)[15] and corresponds to monomers repeating iden-
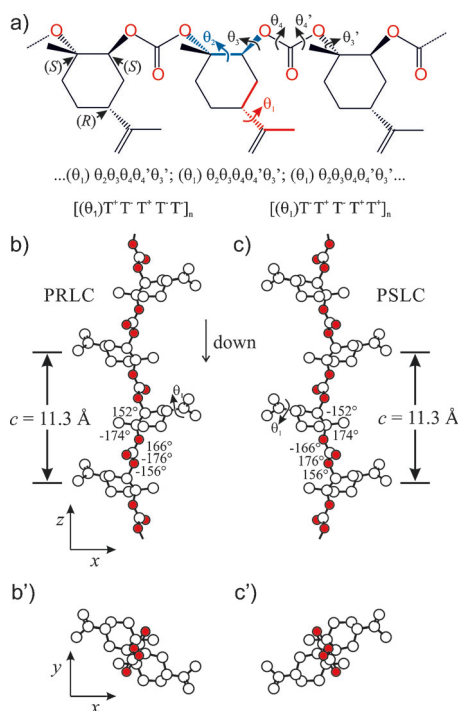
Figure 3. Portions of SCPLC chains. a) The sequence of dihedral angles according to the **s**(2/1) line symmetry group.[15] Low-energy conformations of PRLC (b,b′) and PSLC (c,c′) in 2/1 helical conformation and periodicity $c = 11.3$ Å, in projections parallel (b,c) and perpendicular to the chain axis (b′,c′). Oxygen atoms are red. Symbol T stands for dihedral angles in the *trans* state whereas T⁺ and T⁻ stand for $180° - |\delta|$ and $180° + |\delta|$ with $|\delta|$ a quantity less than 30°. The directional property of PLC chains is evidenced by the arrow between (b) and (c) with the "down" direction associated to chains with the backbone bond connecting the quaternary carbon atoms to the tertiary carbon atom pointing toward the negative direction of z-axis.[15]

Figure 4. Minimum energy packing model for enantiomeric PLC chains in the orthorhombic unit cell ($a = 9.71$ Å, $b = 10.68$ Å and c (chain axis) $= 11.31$ Å) according to the antichiral space group symmetry $Pbc2_1$, in projections perpendicular to the c- (a) and a-axis (b). The chains are isoclined[13] (all up or all down) and alternate with opposite chirality along b according to a fish-bone arrangement. The facing side groups belonging to adjacent ac layers are interdigitated along b forming a "steric zipper"[16] (blue arrows). Oxygen atoms are indicated in red.

tically along the chain axis according to the sequence of dihedral angles $[(\theta_1)\ \theta_2\ \theta_3\ \theta_4\ \theta_4'\ \theta_3']_x$, defined in Figure 3a.

Low-energy conformations with chain periodicity close to the experimental one were built up by fixing the geometry of the rings in the chair conformation, the isopropenyl and methyl substituents in equatorial positions,[12a] θ_1 in the *gauche* state and the backbone dihedral angles in a nearly *trans* state as in the models of Figure 3b,c. A slight twisting of cyclohexane rings and almost complete rotational disorder of the torsion angle θ_1 defining the position of isopropenyl groups is also feasible at low cost of internal energy without impairing the chain periodicity c of 11.31 Å.

Nonchiral packing models of PLC chains in the orthorhombic unit cell were considered while maintaining the 2/1 helical axis of the chains as a crystallographic element of symmetry. The presence of the strong 100 equatorial reflection at low 2θ values ($\approx 9.6°$) and of the strong 111 reflection on the first layer line ($2\theta \approx 14°$) suggests a packing mode of the chains with axes at $(0, 0, z)$ and $(0, ^1/_2, z)$ of the unit cell, according to the space group symmetry $Pbc2_1$ (Figure 4a).

The model of Figure 4a is characterized by ac layers of isoclined[15] and isochiral chains alternating along b with ac layers of chains having the same directionality but opposite chirality. Therefore the structural model includes two chains
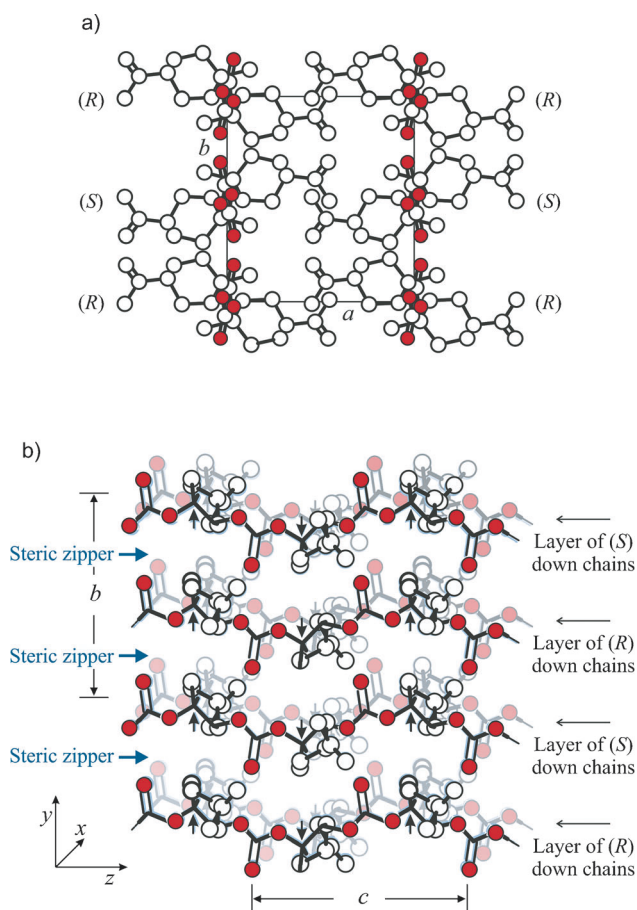
per unit cell and corresponds to racemic crystals where chains of opposite chirality alternate along b according to a fish-bone arrangement, whose spine runs parallel to the a axis (Figure 4a). Crystallization is driven by the tight interdigitation of the side chains of opposite chirality belonging to adjacent ac layers, that are faced along b forming a "steric zipper".[16]

The X-ray powder diffraction profile calculated for the structural model of Figure 4 (Figure 2c) is in in good agreement with the experimental profile (Figure 2b). A good agreement was obtained whatever the position of isopropenyl groups around the C−C bond (θ_1) and also for models including slight conformational distortions of the cyclic groups as well as substitution type disorder of up and down chains in the lattice positions.

Although the agreement of the experimental and calculated profiles can be further improved, the overall good agreement already achieved for the model of Figure 4a indicates that nonchiral structural models containing enantiomorphic chains packed according to the space group

symmetry *Pbc*2₁ may be considered a good description for the crystal structure of PRLC/PSLC samples. In this model, the tight interdigitation of the side groups belonging to enantiomeric stems of PLC in the crystals according to the steric zipper (Figure 4b) favors the crystallization of the stereocomplex, forming racemic crystals, probably also due to kinetic factors. We propose that pure enantiomers of PLC, in spite of the regular constitution and configuration, fail to crystallize probably because the interactions between isochiral chains are too weak to overcome the nucleation barrier, thus limiting crystallization from a kinetic point of view. The kinetic argument is also supported by preliminary dynamic light scattering measurements that evidence a slow (non-diffusive) relaxation mode in semi-dilute solutions, which, in the case of the PRLC/PSLC mixtures, is lower than that of the pure components.[13] This may indicate that the stereocomplex is partly formed already in solution, and that these stereocomplex aggregates, upon evaporation of solvent act as nuclei for the crystallization.

In conclusion, we report the first example of an amorphous, enantiomerically pure polymer that becomes crystalline upon stereocomplexation with its complementary enantiomer. Using powder X-ray diffraction, a structural model for the polymer was determined, in which sheets of enantiopure chains intercalate with those of the opposite enantiomer, forming type of molecular Velcro. As with other biodegradable stereocomplex polymers, we anticipate biomedical uses, such as drug delivery, tissue engineering, and nanostructured surfaces. Future work will focus on the discovery of new stereocomplex polymers derived from enantiopure epoxides,[17] as well as further exploring structural characterization and potential applications of these materials.

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