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Trapped Kinetic States, Chiral Amplification and Molecular Chaperoning in Synthetic Polymers: Chiral Induction in Polyguanidines through Ion Pair Interactions

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Structure−property relationships operate across a range of length scales. Demonstrations over short lengths (10^{-1} to 10^{1} nm) are replete within small molecule organic chemistry,[1] whereas longer-length scale (10^{1} to 10^{2} nm) relationships are best illustrated by biological macromolecules.[2] Interestingly, organization of peptide structures (e.g., chain folding, aggregation, assembly, and translocation) are not left to chance but are carefully mediated by molecular chaperones[3] (i.e., one molecule dictating the conformation of another molecule). In contrast and to our detriment, few analogous examples of mediated conformational control exist in synthetic polymers. Why emphasize structure and order in polymeric systems? Simply put, many of the interesting, higher-order properties of macromolecules (high strength and modulus, piezoelectric, optoelectronic, ferroelectric, nonlinear optical, etc.) are only expressed in materials displaying order and exactitude in their structures. We herein report an example of induced conformational order imposed on a synthetic polymer: the conversion of an effectively achiral polymer into an optically active, helical rod by use of a chiral chaperone.

Of the synthetic polymers that exhibit some degree of conformational order, the helical subclass[4] (e.g., polyisocyanates)[5] has been of particular interest. These polymers are best modeled as single macromolecular chains that possess regions of right- and left-handed screw senses separated by helix reversals[6] (i.e., conformations that change the signs of the backbone dihedral angles). Their hierarchical structural levels include macromolecular chirality,[5,7] chiral switching,[8] liquid crystallinity,[9] and unusual amplification properties (e.g., induced homochirality).[1,7c,10] Intrigued by the possibility of induced conformational order, we performed chiro-optic experiments on polyguanidine derivatives, a related helical polymer that, unperturbed, exists as a racemate.

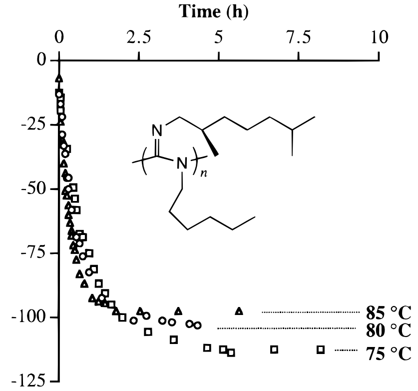
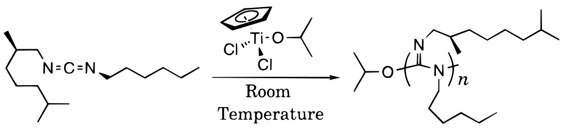


Figure 1. The specific rotation of poly-**1** as a function of time and annealing temperature.

Initial control experiments on the homopolymer formed from *N*-(*R*)-2,6-(dimethylhexyl)-*N*′-hexylcarbodiimide, **1** ([α] = +7.6°),[11] uncovered some interesting and unexpected results. Poly-**1** was prepared by a previously reported living polymerization technique using titanium(IV) isopropoxide catalyst (eq 1).[12]



(1)

1, $[\alpha]^{20}_{365}$ **= + 7.6°**

Poly-1, $[\alpha]^{20}_{365}$ **= + 7.5°**

Because homochiral helical polymers often display large optical rotations,[7] we were surprised to find that the poly-**1** displayed a specific rotation essentially identical to its monomer ([α] = +7.5° (*c* = 0.24, hexane)) when all polymerization and isolation procedures were carried out at room temperature. We discovered, however, that if dilute solutions of poly-**1** are annealed at higher temperatures (30−85 °C), their optical rotations change sign, dramatically increase in magnitude (i.e., [α] = +7.5° to [α] = −157.5° (*c* = 0.24, hexane)) and ultimately reach plateau values (Figure 1).[13] These rotational changes are likewise accompanied by a strong enhancement of their CD bands. This observation is consistent with an irreversible evolution of the chains from kinetically controlled conformations to thermodynamically controlled conformations: a very unusual observation for either synthetic or biologically derived polymers. Arrhenius analysis from the decay data of poly-**1** yields an activation energy of ca. 6.4 ± 0.3 kcal/mol for this process.

The plateau value varies with annealing temperature showing decreased magnitudes at elevated temperatures (Figure 1). Once annealed, the optical rotations vary regularly and reversibly with temperature. The specific rotation of the virgin poly-**1** (+7.6°) is never observed again and linearly extrapolates to a hypothetical value that would be obtained only at temperatures exceeding the decomposition of the polymer (ca. 180 °C). All of these observations are consistent with a system in dynamic equilibrium

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(11) All optical rotation data was measured at 365 nm. Unless otherwise noted, the specific rotations of polymer samples were taken at 20 °C and 2 mg/mL in chloroform.

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(13) Positive optical rotations are observed for samples of poly-**1** that have been isolated with only minimal time dissolved in solution as slow annealing occurs at room temperature. The samples used in Figure 1 had initial rotations between −10° and −15°.

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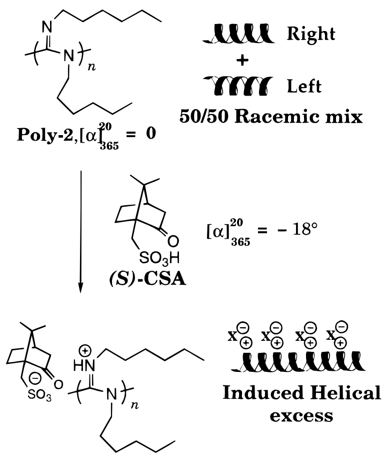
Scheme 1



between two states (helical senses in this case) displaying different optical properties (i.e., optical rotations and molar ellipticities).

We found that protonating the backbone[14] effectively catalyzes the otherwise slow annealing process. In the presence of 5 equiv of benzoic acid, the magnitude of the optical rotation immediately increases from the initial value [α] = +7.5° (hexane) to [α] = −144° (chloroform) upon dissolution of the polymer.

On the basis of these findings, we explored the prospect of removing the side-chain chirality and inducing conformational order by exploiting the acid−base chemistry of the guanidines.[14] Using a chiral perturbator, our hope was to synergistically couple the acid catalysis with cooperativity resulting from ion pairing in order to bias a racemic mixture of helices to one of predominantly a single helix sense.[15] To this end, when poly(di-*n*-hexylcarbodiimide), poly-**2**, was protonated with varying amounts of (*S*)-camphorsulfonic acid ((*S*)-CSA), ([α] = −19.0° (*c* = 0.20)), a large increase in the net specific rotation[16] was observed (Scheme 1).

The specific rotations are opposite in sign and an order of magnitude greater than the rotations due to (*S*)-CSA. At low acid concentrations (e.g., 70 guanidinyl repeats per proton) in chloroform, protonated poly-**2** shows very small specific rotations, but as the concentration is increased, the rotation becomes nonlinear and a net specific rotation greater than 250° was observed. As expected, the enantiomeric acid, (*R*)-CSA, in combination with poly-**2** shows mirror image behavior (Figure 2). These effects are interpreted as a biasing of the helical distribution of poly-**2** by tight ion pairing between the protonated guanidine backbone and the chiral counterions.

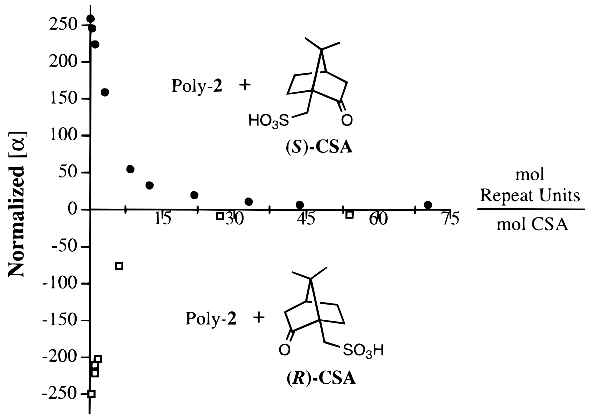


Figure 2. The normalized specific rotation of poly-**2** as a function of acid concentration (mol of polymeric repeats:mol of camphorsulfonic acid) ((*S*) = solid dots, (*R*) = stars).

Annealing solutions of poly-**2**·(*S*)-CSA under mild conditions leads to an even further increase in the specific rotation. After the polymer (45 °C, 76 h) was annealed in the (*S*)-CSA/chloroform mixture, the specific rotation was greater than 350°, but the rotation still had not reached a plateau after this time period. The time scale for this increase in rotation is on the order of hours at 45 °C and is not reversible upon cooling the sample to 20 °C, indicating that this increase is not due to simple changes in the state of ion pairing.

Changing the polarity of the solvent, changes the effectiveness of the chaperoning. A solution of poly-**2** in an (*S*)-CSA/THF solution (acid concentration = 4.25 acid equivalents:polymeric repeats) showed [α] = 55° as compared to 250° using chloroform at the same concentration. The much lower specific rotation is believed to be due to the more distanced ion pairing in polar solvents. The annealing behavior supports this view: heating samples in THF (45 °C, 43 h) shows no increase in specific rotation.

In conclusion, our initial probes into the topological characteristics of polyguanidines has shown that (1) they can adopt kinetically controlled conformations protected by barriers sufficiently high to allow their isolation; (2) the transformation from kinetically controlled to thermodynamically controlled conformations can be catalyzed by acids; and (3) these characteristics can be used in concert to bias an initially racemic mixture of helices of poly-**2** to a state which contains helices of predominantly one handedness. Currently, we are investigating the structural parameters that control these properties. Results from our current studies that range from the fundamental (the aforementioned structural studies) to the applied (the use of polyguanidines as media for chiral separations, optical switching elements, and fire retardant materials) will be reported shortly.

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(16) Net rotations are calculated by subtracting the rotational contribution of the acid from the observed rotation.