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Chiral Optical Properties of a Helical Polymer Synthesized from Nearly Racemic Chiral Monomers Highly Diluted with Achiral Monomers

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Abstract: In polyisocyanates composed only of randomly distributed (*R*) and (*S*) units, the chiral optical properties of the polymer are far out of proportion to the enantiomeric excess of the monomers. This highly disproportionate relationship, which arises from a majority-rule effect among these enantiomeric units on the helical sense of the backbone, is now found to be unaffected, within certain limits, by the overwhelming presence of achiral units randomly distributed along the chain. This experimental result can be explained quantitatively by an analysis based on the one-dimensional random-field Ising model, which shows that dilution of the chiral units with achiral units increases the helical domain size in a manner that compensates for the dilution. In qualitative terms, since the random-field domain size is limited by the "objection" of the minority units to the helical sense dictated by the majority units, dilution of this "objection" acts to increase the domain size. As long as this domain size is not limited by the chain length or by thermal fluctuations, the achiral dilution will not reduce the optical activity of the polymer.

Introduction

The helix is one of the important conformational features of biologically derived polymers, and in forming these structures, nature uses building blocks of one mirror form with the consequence that the helices formed are of a single mirror-image sense.[1] In the case of amino acid derived biomolecules, biological systems can occasionally turn to mirror-related amino acids to accomplish specific structural objectives.[2] In vivo, though, the biological mechanisms at work block the use of "wrong" enantiomer amino acids in the formation of proteins, requiring isomerizing enzymes to introduce these mirror isomers.[2,3] In vitro methods of synthesis of peptides offer, though, no impediment to the placement of mirror-image-related amino acids, and work in this area has discovered the helical changes, following from such enantiomerically mixed monomer units, on the conformational properties of peptides derived from α-helical-forming amino acids.[4] Other biologically interesting polymers have been synthesized from mixed enantiomers.[5]

In using homochiral systems, nature blocks our observation of certain interesting aspects of the cooperativity of helical systems, a cooperativity which can lead to an extreme chiral amplification. This can act to alleviate the burden of synthesizing enantiomerically pure building blocks for these synthetic systems, and this can be seen most clearly in a version of the

Nylons, the polyisocyanates, which are stiff helical polymers with a high degree of cooperativity along the polymer chains.[6] This cooperativity arises from infrequent helical reversals which separate long blocks of opposing helical senses, forcing many units of the chain to take the same helical sense. In this way the chiral bias on each unit of the chain is amplified, with the resulting relative proportions of right- and left-handed segments determined experimentally by measuring the chiral optical properties of the polymers. These polymers are extremely sensitive to very small chiral influences. For example, if the polymers are synthesized with pendant groups that differ from their mirror images only by the substitution of a deuterium for a hydrogen, this slight asymmetry induces a substantial helical excess in the backbone, which leads to an easily measurable optical activity.[7−9] Similarly, in copolymers with a random sequence of chiral and achiral units, very low proportions of

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the chiral units are sufficient to give a substantial optical activity.[10,11] Moreover, copolymers of (R) and (S) chiral units respond sharply to slight differences in the concentrations of the two enantiomers, with an optical activity far out of proportion to the enantiomeric excess of the monomers.[12]

The helical order of both homopolymers and copolymers has been studied theoretically. In homopolymers, because the chiral influence is uniformly applied to each unit of the chain, the system can be described by a statistical thermodynamic theory equivalent to the *uniform* one-dimensional Ising model.[7] The predictions of this theory agree precisely with experimental measurements of the optical activity as a function of temperature and degree of polymerization. Fitting the data yields the two key energetic parameters: the chiral bias energy favoring one helical sense and the energy of a helical reversal.[7–9] In copolymers, because the chiral influence is randomly distributed along the chain, the system must be described by the *random-field* Ising model.[13–15] In this case, the theoretical predictions cannot be calculated exactly, but they can be derived approximately either by an analytical method based on estimating the characteristic size of a helical domain or by numerical transfer-matrix calculations averaged over many realizations of the random sequence of monomers. These approaches have been applied both to random copolymers of enantiomerically pure (or nearly so) chiral units with achiral units (chiral/achiral copolymers) and to (R)/(S) copolymers. The results have been excellent.[11,13–15]

In a recent study, the theoretical approaches discussed above were extended and used to predict the helical order of a new variant of the polyisocyanates composed of (R), (S), *and* achiral units.[16] Specifically, this theoretical work investigated how the disproportionate relationship between optical activity and enantiomeric excess found in (R)/(S) copolymers should be affected by high concentrations of achiral units randomly distributed along the chains. One might expect the introduction of achiral units to substantially reduce the sharpness of this relationship. However, the surprising prediction of this theory was that this dilution of the chiral units with achiral units should have *almost no effect* on measurements of the chiral optical properties. Under limits to be discussed below, the optical activity relationship to enantiomeric excess should be independent of the fraction of achiral units.

The experiments reported here[17] confirm that the chiral optical properties are nearly independent of the fraction of achiral units, up to a remarkably high achiral fraction. In particular, almost the same circular dichroism spectra are observed for a terpolymer of 98.4% achiral units and 1.6% chiral units, with an enantiomeric excess of only 2.8% among these chiral units, as for a copolymer of just the chiral units with the same enantiomeric excess. The CD does not show any substantial

dependence on achiral fraction until the composition reaches 99.2% achiral and 0.8% chiral. As a test of the detailed theoretical predictions, the CD is measured for several different chain lengths of the terpolymers. These experiments show that the CD scales as the square root of the chain length, in agreement with the theory.

As discussed in detail below, the chiral dilution phenomenon is observed where the degree of polymerization and the intervention of thermally activated helical reversals do not limit the domain size dictated by the random field. For this purpose, we designed an achiral isocyanate unit, 2-butylhexyl isocyanate, with an expected high helical reversal energy. Prerequisite study was required of copolymers of this branched achiral isocyanate, as was comparison of this achiral unit to the *n*-hexyl isocyanate group previously studied. CD measurements show that the copolymers with the branched isocyanate units are far more sensitive to low proportions of chiral units than the *n*-hexyl isocyanate derived units, consistent with our expectation of a lowered population of the helical reversal state. This increased energy of the helical reversal in the branched achiral unit was confirmed, as reported in detail below, with quantitative treatment of the data using the statistical theory.

In a twist on usual stereochemical research, precise knowledge of the enantiomeric excess close to the racemic state is more important in this work than information near the enantiomerically pure state. This arises from the fact that the optical activity changes sharply only near the racemic composition, and this change is most important for correlation to the theory and determination of the helical domain size. Since such precise knowledge of enantiomeric excess close to the racemic state is not conveniently accomplished with conventional means for measurements of enantiomeric excess, a new method was devised which used the amplification characteristics of the polymer for this purpose.

In the discussion below, a brief summary of the theory for chiral/achiral copolymers, (R)/(S) copolymers, and (R)/(S)/achiral terpolymers is presented. Next, the data for the chiral/achiral and (R)/(S) copolymers are presented and analyzed. On the basis of these results, the data for the (R)/(S)/achiral terpolymers are then presented and compared with the theoretical predictions. Finally, the key structural prerequisites for the observations are discussed, which lead to suggestions for other systems that may exhibit these characteristics.

Background

In the theory of cooperative helical order in polyisocyanates,[13,14,16] the polymers are characterized by the chiral order parameter M, which is the fraction of the backbone twisting in one helical sense minus the fraction twisting in the opposing sense. This order parameter is equal to the optical activity normalized by the value for an entirely one-handed helical polymer. The goal of the theory is to predict M in terms of the composition of the polymers and the two key energetic parameters: the helical reversal energy ΔG_r, which gives the energetic cost of a reversal in the sense of helicity along the chain, and the chiral bias $2\Delta G_h$, which expresses the energetic preference of each chiral monomer for a right- or left-handed helix. In the theoretical papers on the quenched random field,[13,14,16] these two energetic parameters were denoted $2J$ and $2h$, respectively, to emphasize the analogy between the theory of polyisocyanates and the random-field Ising model for one-dimensional *magnetic* systems. Here, we return to the notation ΔG_r and $2\Delta G_h$ that was introduced in earlier papers on polyisocyanates[6–9,11,15] in order to emphasize the connection

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of these parameters for the polymer system subject to either a quenched random chiral field or a uniform chiral field.

Approximate values of these energetic parameters are known from earlier work. Experiments on the homopolymers derived from stereospecific placement of deuterium in poly(*n*-hexyl isocyanante) show that the helical reversal energy is $\Delta G_r = 4$ kcal/mol, while the chiral bias energy $2\Delta G_h$ is of the order of only 1 cal/mol.[6−9,15] Empirical force field calculations adjusted for the value of ΔG_r estimated a chiral bias energy of $2\Delta G_h = 0.4$ kcal/mol for a homopolymer constructed of a model of (*R*)-2,6-dimethylheptyl isocyanate, the chiral unit used in the work here.[18] In comprehensive recent work, though, using narrow dispersity fractionated samples of chiral/achiral copolymers with this chiral unit copolymerized with *n*-hexyl isocyanate, the chiral bias energy was found to be far smaller, in the range of 70 cal/mol.[11] It is reasonable that the chiral bias of the (*R*)-2,6-dimethylheptyl isocyanate should vary with the nature of the side chains that surround it along the polymer backbone. These parameters in general can be compared with the thermal energy $RT = 0.58$ kcal/mol at $T = 20$ °C.

For the chiral/achiral copolymers, let *r* be the fraction of chiral units and $1 - r$ be the fraction of achiral units in the polymers. The theory then predicts[14]

$$M = \tanh\left(\frac{\Delta G_h L r}{RT}\right) \tag{1}$$

where *L* is the helical domain size, i.e., the characteristic length of a segment of fixed helicity along the chain. The domain size *L* is determined by two mechanisms: the thermal excitation of helical reversals and the finite length of the polymers. These two effects combine to give

$$\frac{1}{L} = \frac{1}{L_{th}} + \frac{1}{N} \tag{2}$$

where $L_{th} = e^{\Delta G_r/RT}$ is the thermal domain size and *N* is the degree of polymerization.

For the (*R*)/(*S*) copolymers, let *p* be the fraction of (*R*) units and $1 - p$ be the fraction of (*S*) units along the chains. The theoretical prediction is[13]

$$M = \text{erf}[\sqrt{2L}(p - {}^1/_2)] \tag{3}$$

where *L* is again the helical domain size. In this system, the random sequence of (*R*) and (*S*) units with competing chiral biases provides another mechanism to induce helix reversals in addition to the helical reversals induced by thermal fluctuations. The domain size *L* is therefore given by

$$\frac{1}{L} = \frac{1}{L_{rf}} + \frac{1}{L_{th}} + \frac{1}{N} \tag{4}$$

where L_{rf} is the random-field domain size. This length scale is approximately

$$L_{rf} = \left(\frac{\Delta G_r}{2\Delta G_h}\right)^2 \tag{5}$$

For the (*R*)/(*S*) copolymers using the 2,6-dimethylheptyl isocyanate based unit, assuming the energetic parameters $\Delta G_r = 4$ kcal/mol and $2\Delta G_h = 0.4$ kcal/mol mentioned above, L_{rf} is approximately 100, while L_{th} is approximately 1000 and *N* is

(18) Lifson, S.; Felder, C. E.; Green, M. M. *Macromolecules* **1992**, *25*, 4142.

typically in the range 2000−5000. Because L_{rf} is the smallest of these three length scales, it plays the dominant role in determining *L* in the (*R*)/(*S*) copolymers.

Finally, for the (*R*)/(*S*)/achiral terpolymers, which will be investigated experimentally below,[17] let *r* be the fraction of all monomers that are chiral and let *p* be the fraction of chiral monomers that are (*R*). The theory then predicts[16]

$$M = \text{erf}\{\sqrt{2Lr}(p - {}^1/_2)] \tag{6}$$

which is identical to eq 3 except for the factor of *r* indicating the effect of diluting the chiral units with achiral units. The helical domain size is again given by eq 4 in terms of L_{rf}, L_{th}, and *N*. In this system, however, the prediction for the random-field domain size is changed to

$$L_{rf} = \frac{1}{r}\left(\frac{\Delta G_r}{2\Delta G_h}\right)^2 \tag{7}$$

Note that L_{rf} increases when the chiral units are diluted with achiral units (decreasing the chiral fraction *r*), because this dilution reduces the competition between the opposing chiral biases of (*R*) and (*S*) monomers, the key factor determining the random-field domain size. As long as L_{rf} remains the dominant length scale in the system (much smaller than L_{th} and *N*) so that *L* is approximately equal to L_{rf}, the effects of dilution cancel out when eqs 6 and 7 are combined. Hence, the optical activity of these terpolymers should be independent of *r* over a wide range of dilution, until L_{rf} grows comparable to L_{th} or *N*. Beyond that point, further dilution does not significantly increase *L*, and hence further dilution reduces the optical activity.

Results and Analysis

1. Chiral/Achiral Copolymers. The first step in this experimental study is to investigate the optical activity of the chiral/achiral copolymers with the 2-butylhexyl achiral unit so as to estimate the helical reversal energy of these branched achiral units. Because these units are much bulkier than the *n*-hexyl units studied earlier, this energy is expected to be substantially larger than the helical reversal energy for the *n*-hexyl units. For this reason, these copolymers should be even more sensitive to low chiral fractions than the copolymers with the *n*-hexyl units. This is graphically demonstrated in Figure 1, which shows a large difference in the circular dichroism intensity for copolymers of identical composition but of varying side chains from an *n*-hexyl to a 2-butylhexyl group. Knowledge of the helical reversal energy is a critical parameter for the (*R*)/(*S*)/achiral terpolymers since this energy controls the thermal domain size which, together with the degree of polymerization, sets a limit on the random-field domain size.[16] The purpose of the experiment on the copolymers with the 2-butylhexyl achiral unit is to measure the optical activity as a function of the chiral fraction *r* and analyze it in terms of the theory discussed above in order to extract the helical reversal energy. For this experiment, 11 copolymer samples were synthesized with different values of the chiral fraction *r* ranging from 10^{-6} to 10^{-1}. Table 1 shows the data for three measurements of chiral optical properties: the CD intensity $[\theta]$ at 254 nm and the specific rotation $[\alpha]$ at 589 and 365 nm. As should be found, these three measurements are approximately proportional to each other for all the samples. Note that the chiral optical properties are substantial over the entire range of *r*. In particular, $[\theta]_{254}$ is easily measurable even for $r = 10^{-}.^6$ Thus, as shown in the single example in Figure 1, these copolymers have a much sharper response to low chiral
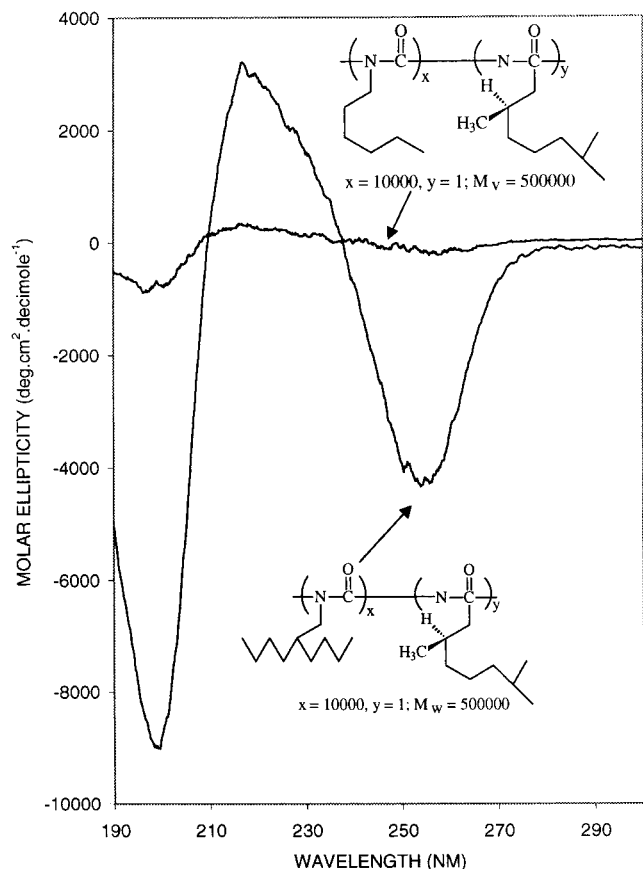
Figure 1. Structure and circular dichroism spectra for the copolymers of (*R*)-2,6-dimethylheptyl isocyanante with 2-butylhexyl isocyanate and with *n*-hexyl isocyanate.

Table 1. Optical Activities and Chain Lengths of Chiral/Achiral Copolymers with 2-Butylhexyl Achiral Units

sample	r	$[\theta]_{254}$, deg cm^2 dmol^{-1}	$[\alpha]_{589}$	$[\alpha]_{365}$	$10^{-2}[\eta]$, cm^3 g^{-1}	M_v	N
A	1×10^{-3}	40 736	438.4	1664.1	11.9	2.5×10^5	1400
B	1×10^{-2}	54 736	592.5	2260.0	14.1	3×10^5	1600
C	2×10^{-2}	57 262	613.3	2362.7	27.5	6×10^5	3300
D	5×10^{-2}	50 592	540.7	2086.4	33.0	8×10^5	4400
E	1×10^{-1}	49 282	524.4	2029.2	28.3	6×10^5	3300
F	1×10^{-4}	2 625	18.0	73.0	8.2	2×10^5	1100
G	1×10^{-5}	375	0.0	0.0	2.0	6×10^4	330
H	1×10^{-6}	327	0.0	8.0	22.4	5×10^5	2700
I	1×10^{-5}	1 056	8.8	36.0	21.0	5×10^5	2700
J	1×10^{-4}	4 312	36.5	149.8	26.2	6×10^5	3300
K	2.4×10^{-2}	41 500	405.0	N/A	1.1	3×10^4	160

fractions than the chiral/achiral copolymers investigated in earlier experiments.[10,11]

Although the copolymer samples studied here are polydisperse, it is important to estimate the average chain length of each sample. For that reason, the intrinsic viscosity [η] of each sample was measured. From the viscosity data, the molecular weight M_v was extracted, using the known hydrodynamic properties of poly(hexyl isocyanate).[19] The degree of polymerization N was then estimated by normalizing by the molecular weight of the 2-butylhexyl units, $N = M_w/183$. Table 1 shows the results for [η], M_v, and N. Most of the samples have an average degree of polymerization in the range 2700–4400 monomers, although some are much shorter. Especially in the

(19) Murakami, H.; Norisuye, T.; Fujita, H. *Macromolecules* **1980**, *13*, 345; see Figure 8.
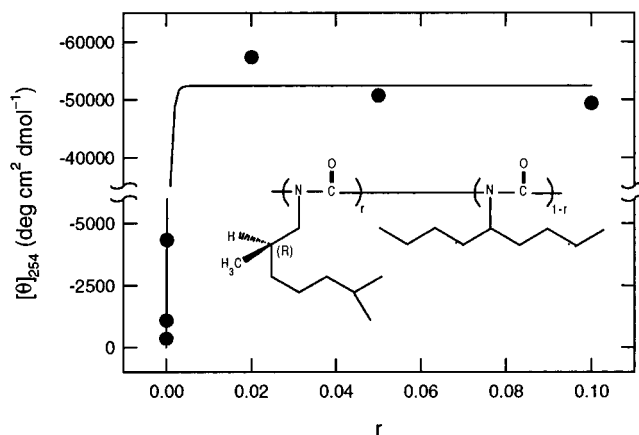

Figure 2. Circular dichroism (CD) of chiral/achiral copolymers at 254 nm as a function of *r*, the fraction of chiral units. These copolymers have the structure shown in the inset, with two butyl chains in the achiral units. There is a substantial CD even for *r* as low as 10^{-6}.

higher molecular weight samples, the degree of polymerization is underestimated since the viscosity data were not shear-corrected, causing the measured value to be smaller than the true value. Still, as we shall see, much use can be made of these data since the critical information is the lower limit to the helical reversal energy.

To compare the experimental data with the theoretical predictions, it is best to consider the samples with longer average chain lengths, in the range 2700–4400 monomers. For shorter chain lengths, the chiral optical properties are quite sensitive to chain length rather than to the helical reversal energy, and hence these samples are less interesting for our present purpose. For that reason, the analysis is restricted to samples C, D, E, H, I, and J in Table 1. Figure 2 shows the CD intensity $[\theta]_{254}$ of these six samples, plotted as a function of r. According to eq 1, the data are fit to the function a tanh br, where a is the saturated value and $b = \Delta G_h L/RT$. The results are $a = -52\,000$ and $b = 840$. Analogous fits for the specific rotations $[\alpha]_{589}$ and $[\alpha]_{365}$ give $b = 660$ and 700, respectively. Averaging the results of the three fits yields the estimate $\Delta G_h L/RT = 730$. Combining this estimate with eq 2 for the domain size L gives the combination of parameters

$$\frac{\Delta G_h}{RT}\left(e^{-\Delta G_r/RT} + \frac{1}{N}\right)^{-1} = 730 \qquad (8)$$

Taking $N = 3500$ as a rough value for the average chain length and $RT = 0.58$ kcal/mol at $T = 20$ °C, this equation defines a locus of possible values for the energetic parameters $2\Delta G_h$ and ΔG_r, which is plotted in Figure 3. Any point along that curve is consistent with the data.

As discussed in the previous section, estimates of the chiral bias range from 0.4 kcal/mol in empirical force field studies of the chiral homopolymer[18] to 0.07 kcal/mol in the extensive experimental study of the copolymers of (*R*)-2,6-dimethylheptyl isocyanate and hexyl isocyanate.[11] Assuming that the chiral bias energy of the copolymer with the 2-butylhexyl achiral unit falls in this range, eq 8 places a lower limit of about 5 kcal/mol on the helical reversal energy. If the chiral bias is even slightly less than 0.4 kcal/mol, the helical reversal energy must be well above 5 kcal/mol, as shown by the locus of acceptable values in Figure 3. Indeed, if $2\Delta G_h$ is as low as 0.25 kcal/mol, then ΔG_r can be arbitrarily high, in the sense that it cannot be determined by this experiment. A more precise determination of the energetic parameters for these copolymers would require
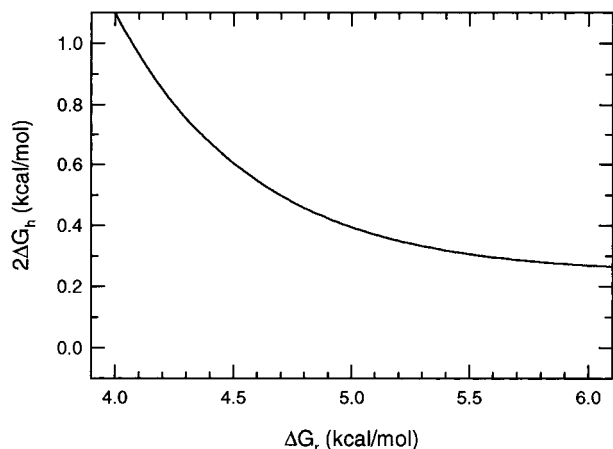
Figure 3. Locus of values of the energetic parameters $2\Delta G_h$ and ΔG_r that are consistent with the data for chiral/achiral copolymers shown in Figure 2.

experiments using fractionated samples with precisely defined chain lengths, as has been done for the *n*-hexyl-based copolymers.[11] In particular, fractionated samples with very long chain lengths, perhaps synthetically inaccessible, will be needed for sensitivity to high values of the helical reversal energy. As we shall see, though, our uncertainty on the value of ΔG_r is not critical to a quantitative fit of the theory to the experiment on the (*R*)/(*S*)/achiral terpolymer, since it is only necessary that the thermal domain size be far larger than the random-field domain size, and this is easily the case, even with the minimum values of ΔG_r, for the branched achiral unit discussed here.

2. (*R*)/(*S*) Copolymers. The next step in this study is to investigate the optical activity of the (*R*)/(*S*) copolymers very close to the racemic point. This experiment has two purposes. First, the experiment provides a precise calibration of the enantiomeric excess around the racemic point. This calibration is essential for the experiments on (*R*)/(*S*)/achiral terpolymers that will be presented below. Second, the experiment shows how sharply the copolymers respond to slight differences in the concentrations of the two enantiomers. Through this measurement, the helical domain size can be determined.

From earlier experiments on (*R*)/(*S*) copolymers,[12] it is known that the optical activity changes rapidly over a range of composition within a few percent of the racemic point. To quantify how rapidly the optical activity changes, one must calibrate very small values of the enantiomeric excess. This calibration problem is unusual in stereochemistry, because most stereochemical experiments are carried out with highly enantiomerically enriched materials. The situation is made more difficult because the (*R*) and (*S*) reagents are not enantiomerically pure[20] and moreover, on the basis of their optical activities, have different levels of enantiomeric purity.[21]

To solve this problem, a new approach was developed, which takes advantage of the chiral amplification in this copolymer system. In this approach, several (*R*)/(*S*) copolymers were synthesized with different compositions near the racemic point. For each of these copolymers, let *w* be the weight fraction of the (*R*) reagent and let $1 - w$ be the weight fraction of the (*S*) reagent. By comparison, *p* is the fraction of monomers that are actually (*R*) and $1 - p$ is the fraction of monomers that are actually (*S*). The values of *w* are known accurately from the

(20) For chromatographic analysis allowing correlation of enantiomeric excess of 2,6-dimethylheptyl isocyanate to optical activity see: Valentine, D.; Chan, K. K.; Scott, C. G.; Johnson, K. K.; Toth, K.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 62.
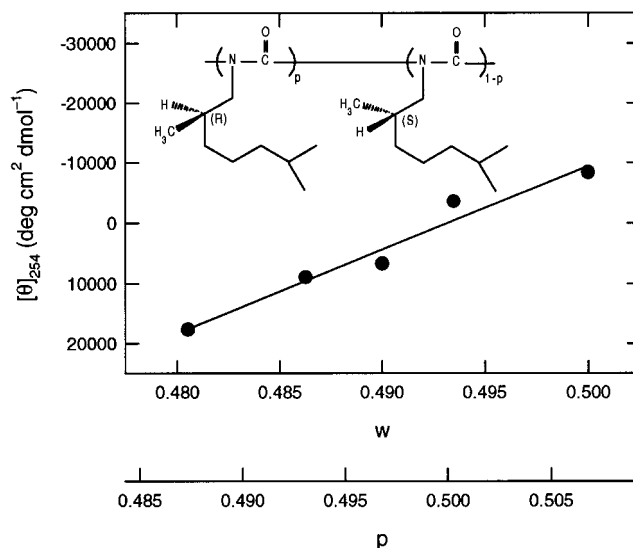
(21) See Experimental Section.

Figure 4. CD intensity of (*R*)/(*S*) copolymers at 254 nm as a function of *w*, the weight fraction of the (*R*) starting material. As discussed in the text, these measurements are used to calibrate *p*, the fraction of (*R*) monomers.

weighing process, and the corresponding values of *p* must be determined. In general, *p* is a linear function of *w*, i.e.

$$p = wf_R + (1 - w)(1 - f_S) \tag{9a}$$

where f_R and f_S are the optical purities of the (*R*) and (*S*) reagents, respectively. This equation can be rewritten as

$$p - {}^1/_2 = (f_R + f_S - 1)(w - w^*) \tag{9b}$$

where $w^* = (f_S - {}^1/_2)/(f_R + f_S - 1)$ is the weight fraction at the racemic point. Because the optical purities of the reagents are close to 1, the linear relationship simplifies to

$$p - {}^1/_2 = w - w^* \tag{9c}$$

In principle, w^* could be determined by simply measuring the optical activity of the mixed enantiomers and extrapolating through the zero point. The magnitude of the optical activity near the racemic point, though, is too small to yield the precision necessary for our purpose. Formation of the copolymers with their chiral optical amplification solves this problem. Thus, to determine w^*, the circular dichroism intensity $[\theta]_{254}$ was measured for each of the copolymers. Figure 4 shows the data as a function of *w*. Because these copolymers are all very close to the racemic point, the data can be fit to the linear function

$$[\theta]_{254} = a(w - w^*) \tag{10}$$

A linear regression gives $a = -1.4 \times 10^6$ and $w^* = 0.493$. Using these results, the value of *p* can be determined for any (*R*)/(*S*) copolymer sample. This will be essential for the analysis of the (*R*)/(*S*)/achiral terpolymer data below, where very small differences in the enantiomeric excess make a large difference in the fit to the theory.

Apart from the calibration of the enantiomeric excess, the data presented in Figure 1 can also be used to determine the helical domain size. From earlier experiments,[12] it is known that the circular dichroism of these copolymers increases rapidly as a function of enantiomeric excess and then saturates at approximately $[\theta]_{254} = -52000$. The results presented here provide more data close to the racemic point than the earlier
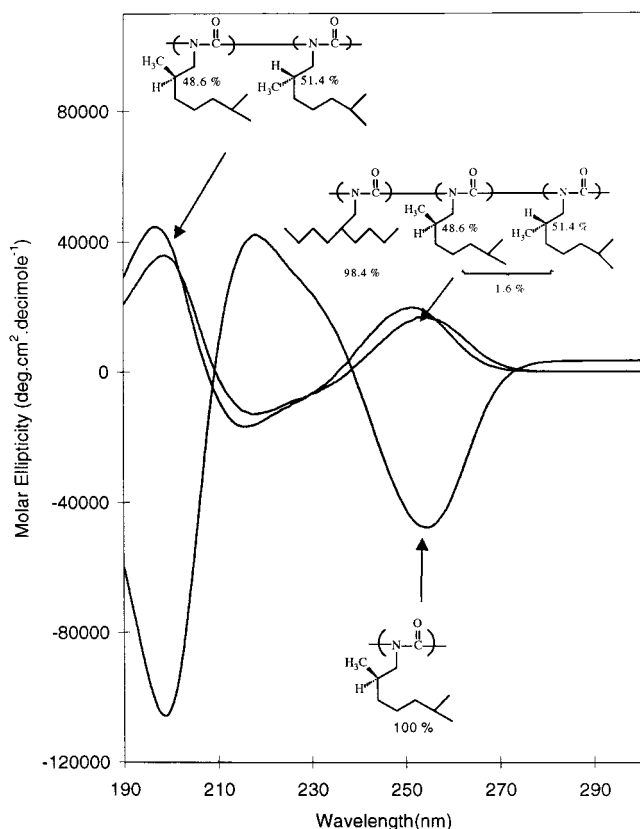
Figure 5. CD spectra of poly((R)-2,6-dimethylheptyl isocyanate), an (R)/(S) copolymer of this chiral group with an enantiomeric excess of 2.8%, and an (R)/(S)/achiral terpolymer with 98.4% 2-butylhexyl achiral units and 1.6% chiral units, also with an enantiomeric excess of 2.8%.

experiments, and hence they show more clearly how the copolymers respond to low values of the enantiomeric excess.

To analyze the data very close to the racemic point, note that eq 3 predicts $dM/dp = (8L/\pi)^{1/2}$ at $p = 1/2$. By comparison, the linear regression discussed above, normalized by the saturated value $[\theta]_{254} = -52\,000$, gives $dM/dp = dM/dw = 27$. Equating these expressions gives the helical domain size of $L = 280$ monomers. This is somewhat larger than the length scale of $L = 100$ that is expected from eqs 4 and 5, assuming the helix reversal energy $\Delta G_r = 4$ kcal/mol and chiral bias $2\Delta G_h = 0.4$ kcal/mol. It is also larger than the more precise value of $L = 164$ calculated through numerical simulations with the same parameters.[13] The discrepancy suggests that there is some error in the energetic parameters. Most likely, the chiral bias for the (R)-2,6-dimethylheptyl pendant group should be lower than 0.4 kcal/mol, in agreement with the recent analysis of the chiral/achiral copolymers.[11]

3. (R)/(S)/Achiral Terpolymers. Based on these results for the (R)/(S) and for the chiral/achiral copolymers, it is now possible to investigate polyisocyanates composed of (R), (S), and achiral units. As noted earlier, the theory predicts that the dilution of chiral units with achiral units increases the random-field domain size L_{rf}. The chiral order parameter M is independent of dilution as long as L_{rf} is the smallest length scale in the polymers. Once L_{rf} grows comparable to L_{th} or N, the helical domain size is limited by thermal fluctuations or chain length, and it ceases to grow with dilution. Beyond that point, M decreases as the dilution proceeds further. The purpose of the experiments is now to test those predictions.

As a first test of the theory, Figure 5 compares the circular dichroism spectra of three polyisocyanates. The most intense

spectrum is associated with a pure chiral homopolymer, which has a single helical sense and hence the maximum saturated circular dichroism. The second curve shows the circular dichroism of an (R)/(S) copolymer with an enantiomeric excess of 2.8%. This copolymer has circular dichroism peaks that are roughly one-third the intensity of the corresponding peaks for the homopolymer. The third spectrum is the circular dichroism of an (R)/(S)/achiral terpolymer with 98.4% achiral 2-butylhexyl units and only 1.6% chiral units, again with an enantiomeric excess of 2.8%. The terpolymer has almost the same circular dichroism spectrum as the (R)/(S) copolymer.

The enantiomeric excesses of the copolymer and terpolymer studied here were determined using the calibration established in the previous section. As shown in Figure 5, the copolymer has the molar ellipticity $[\theta]_{254} = +20\,000$. The calibration of eqs 9 and 10 therefore implies that $p - 1/2 = -0.014$; i.e., the enantiomeric excess is approximately 2.8%. Because the terpolymer was synthesized with the identical ratio of (R) and (S) reagents, its enantiomeric excess is also 2.8%. Without the calibration, there would have been an unacceptable uncertainty in the enantiomeric excess this close to the racemic point.

The near coincidence of the circular dichroism spectra of the co- and terpolymers is seen in the general light of the theory discussed above[16] to arise from the increase in the random-field domain size L_{rf} not overtaking either the degree of polymerization N or the thermal domain size L_{th}. For the latter, the 2-butylhexyl achiral unit plays a critical role. The high helical reversal energy for these units makes L_{th} so large that L_{rf} is still the smallest length scale in the terpolymer, even for a dilution as large as 98.4%.

Clearly, the circular dichroism intensity cannot be independent of dilution for *arbitrary* dilutions. To find the limits of this dilution independence, an (R)/(S)/achiral terpolymer was synthesized with 99.2% achiral units and only 0.8% chiral units, with an enantiomeric excess of 0.64%. Figure 6 shows the circular dichroism spectrum of that terpolymer, compared with the spectrum of an (R)/(S) copolymer with the same enantiomeric excess (again determined by the calibration from the previous section). In this case, the circular dichroism intensity of the terpolymer is reduced by about a factor of 3 compared with the copolymer. This reduction indicates that, at this extreme dilution, the random-field domain size L_{rf} is no longer the smallest length scale in the terpolymer. Instead, the helical domain size is limited by either the thermal domain size or the chain length.

To determine whether the thermal domain size or the chain length is the limiting length scale in this terpolymer, the optical activity was measured as a function of chain length. The theory predicts that the helical domain size L should be limited by the chain length N for short chains (for $N \ll L_{rf}$ and $N \ll L_{th}$) and that L should be independent of N for longer chains. Hence, the optical activity should increase with N for short chains and then become independent of N for longer chains. In the limit of short chains ($N \ll L_{rf}$ and $N \ll L_{th}$) near the racemic point ($M \ll 1$), the prediction of eq 6 for the chiral order parameter M simplifies to

$$M^2 = (8/\pi)(p - 1/2)^2 rN \qquad (11)$$

Thus, in this limit, the square of the circular dichroism should be proportional to N with a known coefficient. This prediction is remarkable both because it depends sensitively on the enantiomeric excess near the racemic point and because it does *not* depend on any energetic parameters.
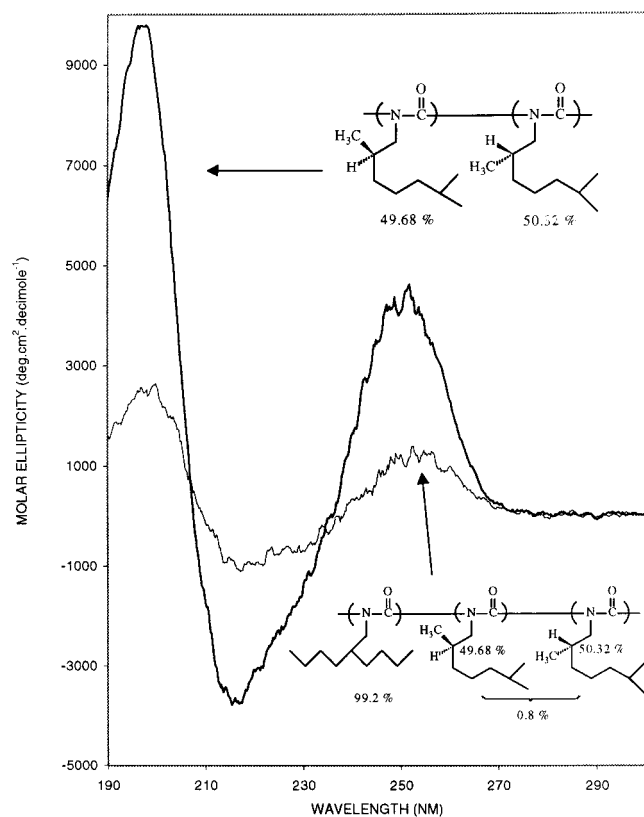
Figure 6. CD spectra of an $(R)/(S)$ copolymer with an enantiomeric excess of 0.64% and an $(R)/(S)$/achiral terpolymer with 99.2% achiral units and 0.8% chiral units, also with an enantiomeric excess of 0.64%.

Figure 7. Top: Dependence of the CD intensity at 254 nm on degree of polymerization N for the copolymer and terpolymer shown in Figure 6. Bottom: The same data for the terpolymer, presented in terms of the normalized chiral order parameter M. The regression line shows that M^2 scales linearly with N, as predicted by the theory discussed in the text.

To test this prediction, the polydisperse copolymer and terpolymer samples presented in Figure 6 were fractionated, as described in the Experimental Section, into samples of different chain lengths. Figure 7 shows the circular dichroism peak intensities at 254 nm as a function of chain length N. The results for the copolymer and the terpolymer are quite different. For the copolymer, the circular dichroism is almost independent of N; it has only a weak dependence for the shortest chains with $N < 400$. This result shows directly that the copolymer has a random-field domain size L_{rf} of only a few hundred monomers, consistent with the results of the previous section. By contrast, for the terpolymer, the CD depends strongly on N over the full range of N up to 4000, which shows that both L_{rf} and L_{th} are substantially greater than 4000 monomers in the terpolymer. The measured circular dichroism was converted to the chiral order parameter M by normalizing it by the circular dichroism of a chain of a single helical sense, $[\theta]_{254} = -52\,000$. The resulting values of M^2 are plotted as a function of N in the bottom of Figure 7. This plot shows that M^2 scales linearly with N, as predicted by eq 11. The linear fit also gives a coefficient of 4.3×10^{-7}, which can be compared with the predicted value of $(8/\pi)(p - {}^1/_2)^2 r = 2.1 \times 10^{-7}$ for $p - {}^1/_2 = 0.0032$ and $r = 0.008$. The discrepancy in the coefficient arises because the predicted value is quite sensitive to the enantiomeric excess. Aside from the numerical uncertainty about the precise enantiomeric excess, the agreement between theory and experiment is excellent.

Discussion

The results presented show that the highly disproportionate relationship between optical activity and enantiomeric excess, which has earlier be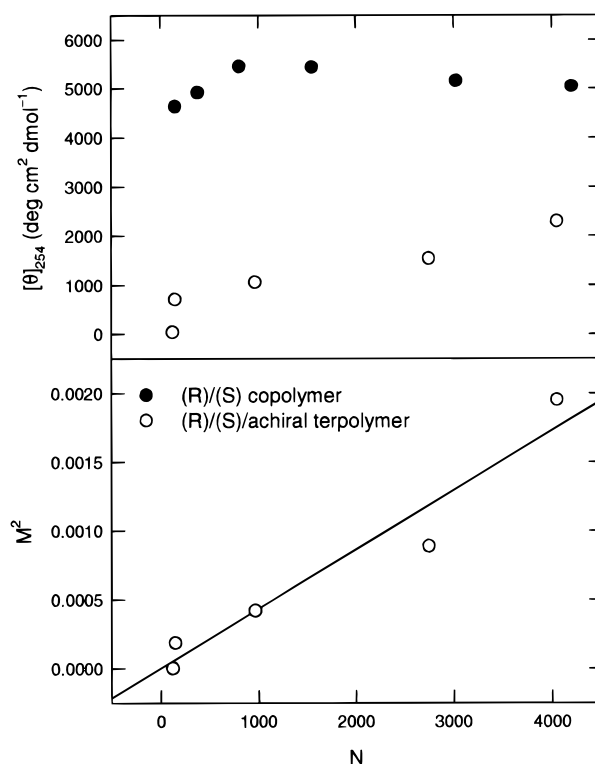en observed in $(R)/(S)$ copolymers, also occurs in $(R)/(S)$/achiral terpolymers. Dilution of the chiral units with achiral units has hardly any effect on the sharpness of this relationship, up to a very high achiral fraction. At this point, it is natural to ask whether this disproportionate relationship is likely to occur in other systems—in synthetic polymers, biological polymers, or other chemical systems with mixtures of units with opposite handedness. The theoretical approach developed for polyisocyanates can be used to address this question.

One requirement for a system to show the disproportionate relationship between optical activity and enantiomeric excess is that the (R) and (S) units must remain well mixed, without phase-separating into regions of opposite handedness. If phase separation occurs, then the system will have regions that make opposite contributions to the optical activity, and the measured optical activity will just be proportional to the size or population of these regions, which will be proportional to the enantiomeric excess. For example, this occurs in mixtures of the (R) and (S) forms of a diacetylenic lipid in alcohol/water solution, which apparently phase-separates into right- and left-handed tubules.[22,23] This is also the case for the phase properties of thermotropic liquid crystals prepared from achiral bent mesogenic molecules which separate into chiral regions of opposite handedness.[24] By contrast, in polyisocyanates, the polymerization process ensures that the (R) and (S) forms remain mixed in a quenched random sequence.[25] This mixing is likely to occur

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in other polymer systems in which the polymerization process is independent of the handedness of the monomers.[26] It may also occur in nonpolymeric systems if the intermolecular attraction and repulsion are independent of the molecular handedness—especially where other cooperative analogies to the polyisocyanates have already been observed.[27]

A second requirement is that the energetic parameters of a system must be in the right range. For polymers, this range can be expressed quantitatively using the theoretical predictions of eqs 3−5. To see a sharp response to a small enantiomeric excess in eq 3, the helical domain size L must be at least of order 100. This implies that the three length scales N, L_{th}, and L_{rf} must all be at least of order 100. The requirement that $N > 100$ is just a constraint on the length of the chains. The requirement that $L_{th} > 100$ implies that the helical reversal energy must be sufficiently large, i.e.

$$\Delta G_r > RT \ln(100) \tag{12}$$

which is approximately 2.7 kcal/mol at room temperature. The requirement that $L_{rf} > 100$ is the most interesting constraint, because it implies that the chiral bias must be sufficiently *small*, i.e.

$$\Delta G_h < \Delta G_r/20 \tag{13}$$

If the chiral bias of the monomers is larger than that, then the polymer is not sufficiently cooperative to have a sharp relationship between optical activity and enantiomeric excess. This is the mathematical expression of the fact that too large a bias favoring one helical sense, following from the symmetry of the system, means an equivalent bias against that helical sense by the minority units. This minority bias, or objection, limits the cooperativity and therefore the excess of the majority helical sense. How much the chiral bias may limit the cooperativity depends on the cost of the helical reversal, ΔG_r. The larger the energetic cost of the helical reversal, the larger the chiral bias can be without limiting the cooperativity since the limit to the cooperativity necessarily imposes an increased population of helical reversals in the chain. However, the chiral bias cannot be arbitrarily small. The theoretical argument that goes into deriving eq 3 requires that $\Delta G_h\sqrt{L}$ is at least an order of magnitude greater than RT. This implies a constraint on L_{rf}, L_{th}, and N. The constraint on L_{rf} is roughly equivalent to eq 12; the other two constraints are

$$\Delta G_h > \frac{10RT}{\sqrt{e^{\Delta G_r/RT}}} \tag{14a}$$

$$\Delta G_h > \frac{10RT}{\sqrt{N}} \tag{14b}$$

Thus, the chiral bias must be within the limited range given by eqs 13 and 14. The chiral bias can be minute if N and ΔG_r are large enough. This would mean a very large value of L, which could lead to a large excess of one helical sense as demonstrated

by eq 3 even for a very small enantiomeric excess of these chiral units with a very small chiral bias.

In polyisocyanates, the constraints specified here are all satisfied. This may not be the case in other polymers of (R) and (S) units, although it would certainly be interesting to attempt to fit other systems into these constraints if possible.[26,27] In biopolymers, the problem is often that the chiral bias $2\Delta G_h$ is too large for eq 13. For example, DNA has a transition between the right-handed B conformation and the left-handed Z conformation. This transition is controlled by a sequence of units which, although not mirror images of each other, have some energetic preference for the B or Z forms. A typical value of that energetic preference is 1 kcal/mol, while the helix reversal energy is 5 kcal/mol, and hence the random-field domain size is roughly 25 nucleotides.[28] This cooperative length scale is too short to see a sharp response of optical activity to composition. Although the necessary energetic information is not available, polypeptides seem to be subject to the majority-rule effect within certain limits of the proportions of the enantiomers.[4]

There may be a technological benefit from this effort since photoswitchable groups have been appended to the polyisocyanates,[29] including even a photoresolvable group.[30] Because the present work demonstrates that terpolymerization with achiral groups can occur without consequence on the chiral optical properties of the polymer, it allows independent manipulation of the helical reversal energy and the chiral bias as well as the material characteristics of the polymer, such as glassy properties or solubility or polymer miscibility. These latter parameters can be controlled with the achiral group.

As a final point, the chiral amplification properties investigated here may help to supply mechanisms that have been sought to connect the detection of circularly polarized light in outer space to the observation of homochirality in living organisms on earth.[31]

Experimental Section

All air-free manipulations were carried out in an oxygen- and moisture-free, argon-filled TS-4000 series (MO-10-M) glovebox (Vacuum Atmospheres, Hawthorne, CA) or by using custom designed vacuum-line techniques. Routine infrared spectra were recorded on a Shimadzu IR-435 spectrometer or on a Perkin-Elmer 1600 series FTIR. [1]H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a General Electric GN300 FTNMR (300 MHz) spectrometer.[32] Intrinsic viscosities were measured using a size 50 single-bulb Cannon−Ubbeholde dilution viscometer uncorrected for shear with flow times greater than 100 s. Polarimetric measurements were carried out on a Perkin-Elmer 141 spectropolarimeter at 589 and 365 nm using a 1-dm jacketed cell. Circular dichroism spectroscopy was carried out using a JASCO 710 spectrophotometer with cylindrical quartz cells of 0.1 cm path length. Gel permeation chromatography was performed on a Waters chromatograph using a Waters 510 pump and a Waters 440 UV detector at 254 nm. Chloroform was used as a mobile phase on the following set of TSK−gel analytical columns: G4000H$_{XL}$ (10^4 Å pore size), G5000H$_{XL}$ (10^5 Å pore size), and GMH$_{XL}$-HT (1500−10^7 Å pore size), all 30 cm long and with inside diameters of 7.8 mm connected in series, with a flow rate of 1.0 cm^3/min. The GPC instrument was calibrated at 30 °C with PHIC standards samples kindly

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(32) We are grateful to the National Institutes of Health supported NMR facility at the City University of New York, College of Staten Island, for the use of this equipment.

supplied from the laboratory of Professor Akio Teramoto, Osaka University, Osaka, Japan.

2-Butylhexyl Isocyanate. 2-Butylhexanoic acid was prepared according to the literature.[33] The crude product, which gave satisfactory spectroscopic characteristics,[34] was purified by distillation: bp 102–104 °C/0.5 Torr; yield 66.8%. The conversion of the carboxylic acid to 2-butylhexyl isocyanate was synthesized by following established methods.[35] The isocyanate was purified just prior to polymerization by distillation from calcium hydride; bp 52–54 °C/0.2 Torr.

(R)-(+)-2,6-Dimethylheptyl Isocyanate. (R)-(+)-Citronellic acid was synthesized by the known methods.[36] The crude product was distilled at bp 105–107 °C/0.5 Torr (lit.[36] 111–112 °C /0.6 Torr): yield 71.9%; $[\alpha]^{25}_D$ = +9.96 (c 5.00, CHCl$_3$) (lit.[36] $[\alpha]^{25}_D$ = +10.30 (c 5.00, CHCl$_3$)). (R)-(+)-Citronellic acid was hydrogenated using 5% Pd/C as a catalyst at 25 psi for 6 h to give (R)-(+)-3,7-dimethyloctanoic acid, which was purified by distillation: bp 80–82 °C/0.45 Torr; yield 94.6%; $[\alpha]^{25}_D$ = +7.34 (c 5.00, CHCl$_3$) (lit. $[\alpha]^{25}_D$ = +7.00 (c 5.00, CHCl$_3$)). (R)-(+)-2,6-Dimethylheptyl isocyanate was prepared from the corresponding acid according to the literature.[35] The crude product was purified by distillation: bp 48 °C/0.40 Torr; yield 54.0%; $[\alpha]^{25}_D$ = +2.26 (c 5.00, CHCl$_3$). It was similarly distilled again over calcium hydride before polymerization.

(S)-(−)-2,6-Dimethyl Isocyanate. (S)-(−)-3,7-Dimethyloctanol was synthesized by hydrogenation of (S)-(−)-citronellol purchased from Aldrich Chemical Co., under conditions identical with those noted above. The crude product was purified by distillation: bp 52 °C/0.10 Torr; $[\alpha]^{25}_D$ = −4.77 (neat). (S)-(−)-3,7-Dimethyloctanoic acid was prepared by the Jones oxidation. The crude product was purified by distillation: bp 78–80 °C/0.025 Torr; $[\alpha]^{25}_D$ = −6.13 (c 5.00, CHCl$_3$). (S)-(−)-2,6-Dimethylheptyl isocyanate was prepared from the corre-

sponding acid as above.[35] Distillation as for the enantiomer above yielded the polymerizable material with $[\alpha]^{25}_D$ = −1.82 (c 5.00, CHCl$_3$).

General Procedure for Polymerization. In a drybox, an oven-dried 6 in. test tube with a sidearm equipped with magnetic stirring bar and rubber septum is charged with the isocyanates weighed accurately with a balance in the drybox to 0.1 mg followed by the required amount of DMF or toluene. The tube is capped with a rubber septum, taken out of the drybox, and connected to the vacuum line under a positive argon flow. The tube is cooled to −58 °C, for DMF. The initiator, NaCN/DMF (prepared by heating 120 mg of NaCN in a 5 mL volumetric flask equipped with magnetic stirring bar in a vacuum oven at 120 °C overnight), is added. This flask is transferred to the drybox, 5 mL of DMF or toluene[36] is added, and the mixture is allowed to stir for 2 h, upon which the formation of gel or precipitate is observed. Polymerization is quenched with chilled methanol after 1–5 h. The polymer is collected on the sintered-glass crucible and washed with methanol. The polymer is then dried under vacuum in an oven at 40 °C overnight. The white solid is obtained typically in more than 80% yield.

GPC Copolymer and Terpolymer Fractionation. The polydisperse copolymer and terpolymer samples were fractionated by gel permeation chromatography, under the conditions described above in this section; and 200 μL samples of the polymer (3 mg dissolved in 3 mL of CHCl$_3$) were injected. The fractionated samples were collected every 30 s. starting from 11 min after each injection. Molecular weights and polydispersities of the fractionated samples were determined again by reinjection of analytical concentrations in the GPC. The solvent was evaporated by purging with argon gas, and the dried samples were further dried in a vacuum oven overnight. The fractionated samples were dissolved in hexane for circular dichroism measurements where the concentrations of the samples were determined by the molar ellipticity values at 250 nm.

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