

Majority Rules in the Copolymerization of Mirror Image Isomers

Mark M. Green,* Bruce A. Garetz, Beth Munoz, and HePing Chang

Department of Chemistry and
Herman F. Mark Polymer Research Institute
Polytechnic University, Six Metrotech Center
Brooklyn, New York 11201

Steven Hoke and R. Graham Cooks

Department of Chemistry and
Aston Laboratory, Purdue University
West Lafayette, Indiana 47907-1393

Received November 22, 1994

We had an interesting surprise when a polyisocyanate prepared from a sample of 2,6-dimethylheptyl isocyanate derived from citronellic acid of low enantiomeric excess exhibited a D-line optical activity indistinguishable from that of a nearly enantiomerically pure sample. This led to the preparation of a series of copolymers prepared from mixtures of the monomer enantiomers of 2,6-dimethylheptyl isocyanate.^{1,2} The results show an extreme nonlinearity between the enantiomeric excess and the optical activity measured at the sodium D-line (Figure 1).³

The polyisocyanates form a stiff helical conformation,⁴ and the enantiomeric pendant groups derived from citronellic acid cause an equal and opposite excess of one of the helical senses, i.e., left-handed for (R).⁵ The circular dichroism (CD) data in Figure 2, which are a measure of the helical conformation,² demonstrate that the copolymer constructed of 56% (R) and 44% (S) is indistinguishable from that of the homopolymer of the (R) enantiomer. Figure 2 shows also the spectrum of a copolymer with only a 2% (S) enantiomeric excess. Even here the CD spectrum is characteristic of the (S) homopolymer, and the extrema are still about one-third as intense. It is surprising that such a helix sense bias can be produced by the tiny excess of the (S) enantiomer.

The prerequisites to understanding the relationship between the enantiomeric excesses of the polymerized monomers and the optical activities (Figures 1 and 2) are the microstructures of the copolymers produced. In this regard, we have demonstrated a random copolymerization for the mirror image monomers reported in Figures 1 and 2 by an unusual tandem desorption chemical ionization mass spectrometric analysis for which purpose the (S) enantiomer was labeled with deuterium.⁶

(1) The enantiomeric excesses were based on the D-line optical activities of the terpene precursors of the isocyanate monomers. Valentine, D.; Chan, K. K.; Scott, C. G.; Johnson, K. K.; Toth, K.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 62.

(2) The synthesis and polymerization conditions are described in the following: Green, M. M.; Andreola, C.; Munoz, B.; Reidy, M. P.; Zero, K. *J. Am. Chem. Soc.* **1988**, *110*, 4063.

(3) The optical activities of the polymers were measured in dilute *n*-hexane solutions at the D-line. The viscosity average degrees of polymerization were estimated from the intrinsic viscosities in chloroform for each sample, presented as enantiomeric excess/degree of polymerization: 95/5800; 80/480; 64/2400; 42/2300; 16/1300; 12/4800; 2/350. The viscosity was related to MW on the basis of the constants in the following: Berger, M. N.; Tidswell, B. N. *J. Polym. Sci. Polym. Symp.* **1973**, *42*, 1063.

(4) For leading references, see: Bur, A. J.; Fetters, L. J. *Chem. Rev.* **1976**, *76*, 727. Cook, R.; Johnson, R. D.; Wade, C. G.; O'Leary, D. J.; Munoz, B.; Green, M. M. *Macromolecules* **1990**, *23*, 3454.

(5) Sato, T.; Sato, Y.; Umemura, Y.; Teramoto, A.; Nagamura, Y.; Wagner, J.; Weng, D.; Okamoto, Y.; Hatada, K.; Green, M. M. *Macromolecules* **1993**, *26*, 4551.

(6) Hoke, S. H.; Cooks, R. G.; Munoz, B.; Chang, H.; Green, M. M. *Macromolecules*, in press. For the basic technique applied to other polyisocyanate copolymers, see: Majumdar, T. K.; Eberlin, M. N.; Cooks, R. G.; Green, M. M.; Munoz, B.; Reidy, M. P. *J. Am. Soc. Mass Spectrom.* **1991**, *2*, 130.

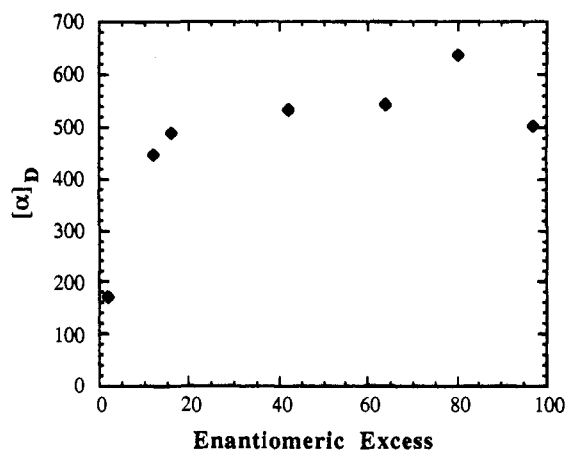


Figure 1. Optical rotation at the sodium D-line $[\alpha]_D$ vs enantiomeric excess of the (S) enantiomer over the (R) enantiomer in the copolymers formed from 2,6-dimethylheptyl isocyanate.

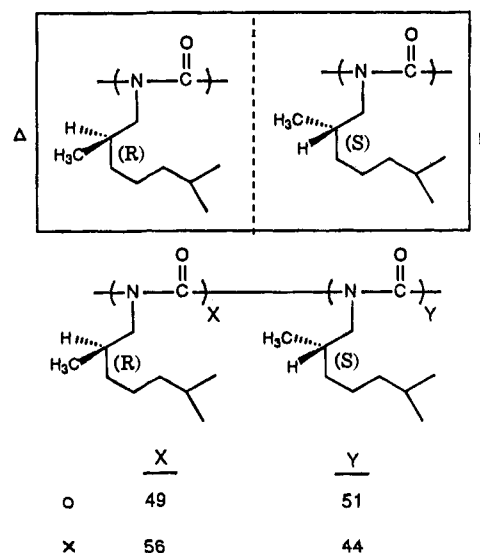
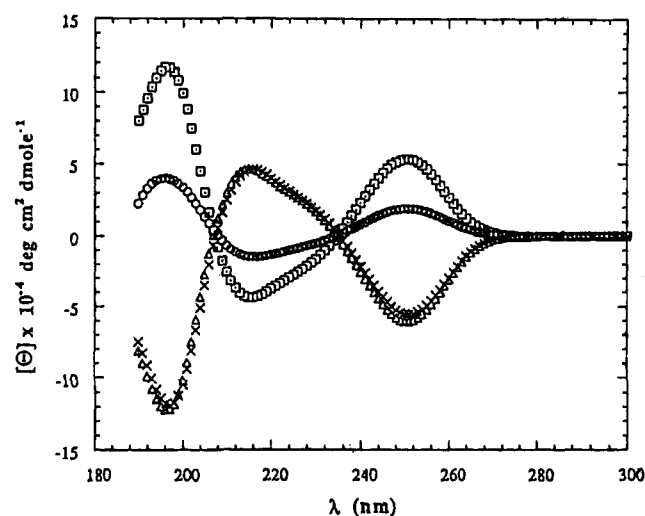


Figure 2. Circular dichroism measurements carried out at room temperature for dilute solutions in normal hexane.

In such a random copolymerization of, for example, the 56/44 (R)/(S) sample, the probability of finding long sequences of the same configuration is extremely small, which requires from the data in Figure 2 that the minority enantiomer pendant groups fit into the helix sense preferred by the majority enantiomer.

An understanding of the relationship of the optical activity

properties in these random copolymers may be found in a statistical thermodynamic theory developed to understand the optical activity properties of the polyisocyanates prepared from stereospecifically deuterated polyisocyanates.⁷ The chain length and temperature dependence of the optical activities of these homopolymers was able to be interpreted in terms of two parameters, the energetic preference for one helical sense per monomer residue and the energetic cost of a helix reversal. The correlation of the experimental data for the stereospecifically deuterated polyisocyanates with the theory showed the helix reversal excess energy to be about 4000 cal/mol in the solvent used in the current work.⁷ This energy has been used to parametrize an empirical force field, allowing, among other conformational insights, an estimation of 400 cal/mol for the excess energy for the (*S*) configuration of the 2,6-dimethylheptyl pendant group residue to fit into the left-handed helix.⁸ The far higher energy of the helix reversal over the chiral bias of the pendant group, i.e., 4000 to 400, should force many units to take the same helical sense irrespective of the pendant group configuration, and in the copolymers under consideration here, it is reasonable, therefore, to average the energies for the (*R*) and (*S*) units favoring the left and right helices, respectively, over these large numbers of cooperating units. The enantiomeric excess and the number of cooperating units will therefore act together to favor the helical sense preferred by the configuration of the majority pendant configuration, i.e., left-handed for (*R*). From the results shown in Figures 1 and 2, this increased cost of the minority helix sense is adequate at ambient temperatures, at least to an enantiomeric excess of 12% with a degree of polymerization 4800, to exclude helix reversals and to enforce, therefore, a single helical sense.

As the enantiomeric excess is reduced and/or the degree of polymerization is reduced below the number of units between helix reversals, so will the average value of the helix sense bias energy be reduced, allowing at some point both helix senses to be populated at ambient energies. This is seen in Figure 2 for the copolymer with an enantiomeric excess of 2%, where the CD spectral form and intensity demonstrate virtually only helical sequences (see below) and where the mean sequence length of helices with the sense preferred by the majority enantiomer is about twice that of helices with the opposite sense.

The CD and UV spectra of the polyisocyanates are sensitive measures of small changes in the helical conformation.^{2,9,10} The identity in form and wavelength for the various spectra in Figure 2 therefore demonstrate that the presence of the "wrong" pendants causes no change in the helical conformation from that found in the homochiral polyisocyanate. This may be expected to depend on the steric nature of the side chain, and in fact, copolymerization of racemic but considerably bulkier chiral side chains in the polyisocyanates appears, from polymer

dimensional arguments, to form blocks of mirror image units and incorporate helix reversals.⁹

In polypeptides where the stereogenic center is in the backbone with fewer conformational choices within the helical arrangement, there is clear evidence that copolymers of near to equal proportions of enantiomeric units cause large changes in, or even loss, of the helical conformation.¹¹ Although the data are difficult to interpret quantitatively because, in contrast to the polyisocyanates,⁶ the microstructure has not been determined, smaller proportions of the wrong enantiomer, with therefore less total strain, do appear to be incorporated into helical sequences.^{11,12} Recently, the incorporation of mirror image units into other biologically interesting systems has been of increasing interest.¹³

The results in the polypeptides and in the polyisocyanates are consistent with the cooperativity necessary for majority rule, which may be expressed in one way as the difficulty of introducing a defect in an otherwise uniform arrangement. This principle suggests parallel experiments to the above in both macromolecular and supramolecular cooperative systems, where the helical motif is of increasing interest.^{13,14} The nonlinear relationship of the polyisocyanates to chiral pendant enantiomeric excess shown here may also be of importance in chiral optical technology.^{15,16}

Acknowledgment. We thank the Chemistry and Materials Divisions of the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the financial support for this research. We are indebted to Professor Herbert Morawetz for his help on the interpretation of these results and wish him well on the occasion of his eightieth birthday.

JA943856A

(11) Masuda, Y.; Miyazawa, T.; Goodman, M. *Biopolymers* **1969**, *8*, 515. Bovey, F. A.; Ryan, J. J.; Spach, G.; Heitz, F. *Macromolecules* **1971**, *4*, 433. Paolillo, L.; Temussi, P.; Trivellone, E.; Bradbury, E. M.; Crane-Robinson, C. *Macromolecules* **1973**, *6*, 831.

(12) Downie, A. R.; Elliott, A.; Hanby, W. E.; Malcolm, B. R. *Proc. R. Soc. London* **1957**, *A242*, 325.

(13) The most prominent example is gramicidin A: Lorenzi, G. P.; Jackle, H.; Tomasic, L.; Rizzo, V.; Pedone, C. *J. Am. Chem. Soc.* **1982**, *104*, 1728. References therein. For recent examples, see: Schnur, J. M.; Ratna, B. R.; Selinger, J. V.; Singh, A.; Jyothi, G.; Easwaran, K. R. K. *Science* **1994**, *264*, 945. Khazanovich, N.; Granja, J. R.; McRee, D. E.; Milligan, R. A.; Ghadri, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 6011. Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4105. Madura, J. D.; Wierzbicki, A.; Harrington, J. P.; Maughon, R. H.; Raymond, J. A.; Sikes, C. S. *J. Am. Chem. Soc.* **1994**, *116*, 417. Gulik-Krzvwicki, T.; Fouquey, C.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 163. Urata, H.; Ueda, Y.; Suhara, H.; Nishioka, E.; Akagi, M. *J. Am. Chem. Soc.* **1993**, *115*, 9852. Hashimoto, Y.; Iwanami, N.; Fujimori, S.; Shudo, K. *J. Am. Chem. Soc.* **1993**, *115*, 9883.

(14) Fujiki, M. *J. Am. Chem. Soc.* **1994**, *116*, 6017. Goodwin, A.; Novak, B. M. *Macromolecules* **1994**, *27*, 5520. Hanessian, S.; Gomtsyan, A.; Simard, M.; Roelens, S. *J. Am. Chem. Soc.* **1994**, *116*, 4495. Schnur, J. M.; Ratna, B. R.; Selinger, J. V.; Singh, A.; Jyothi, G.; Easwaran, K. R. K. *Science* **1994**, *264*, 945. Mascal, M.; Moody, C. J.; Morrell, A. I.; Slawin, A. M. Z.; Williams, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 813. Lehn, J. M. *Makromol. Chem. Macromol. Symp.* **1993**, *69*, 1. Ito, Y.; Ihara, E.; Murakami, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1509. Magnus, P.; Danikiewicz, W.; Katoh, T.; Huffman, J. C.; Folting, K. *J. Am. Chem. Soc.* **1990**, *112*, 2465.

(15) Feringa, B. L.; Jager, W. F.; De Lange, B. *Tetrahedron* **1993**, *49*, 8267.

(16) Zhang, M.; Schuster, G. B. *J. Am. Chem. Soc.* **1994**, *116*, 4852.

(7) Lifson, S.; Andreola, C.; Peterson, N. C.; Green, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 8850. Gu, H.; Nakamura, Y.; Sato, T.; Teramoto, A.; Green, M. M.; Andreola, C.; Peterson, N. C.; Lifson, S. *Macromolecules* **1995**, *28*, 1016.

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

(9) Green, M. M.; Gross, R. A.; Cook, R.; Schilling, F. C. *Macromolecules* **1987**, *20*, 2636.

(10) Green, M. M.; Khatri, C. A.; Reidy, M. P.; Levon, K. *Macromolecules* **1993**, *26*, 4723.