

## Review Article

# Structural deuterium isotope effects reveal the cooperativity of polymers<sup>†</sup>

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**Abstract:** The signature characteristic of different kinds of polymers, synthetic and natural, is cooperativity arising from the recurring features common to all polymer structures. *Cooperativity* and *amplification* are simply different words expressing the same phenomenon leading one to expect that studies of polymers will allow small effects to be magnified, or, that is, for small effects to have surprisingly large effects on polymer properties. In the work reviewed in this short article we see this amplification at work in two different ways: (1) a synthetic polymer that forms a helical conformation but without preference for helical sense, right or left handed, is caused to take on a large excess of a single helical sense by incorporation of chiral information in surprising ways, including by forming chiral centers by deuterium substitution; (2) two polymers that mix homogeneously with each other by virtue of an unknown attractive interaction are revealed by deuterium labeling to be involved in a weak hydrogen bond between a hydrogen bound to aromatic carbon and an ethereal oxygen. Copyright © 2007 John Wiley & Sons, Ltd.

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## A stiff polymer brings up difficult to answer questions

In the late 1950s, the DuPont Corporation attempted to create a version of nylon, which they hoped would form a fiber with important new kinds of properties. The idea was to polymerize an isocyanate via an addition process leading to a polymer structure, with a backbone consisting only of recurring amide bonds as shown in Figure 1.

A great deal of chemical research was conducted to find the correct conditions to create this polymer, called nylon 1 or polyisocyanate, and high molecular weight polymer was successfully produced (large value of  $n$  in Figure 1), which in fact formed an excellent fiber. The potential commercial value, however, was soon seen to be absent when the polymer was discovered to depolymerize at temperatures near to the boiling point of water and even in cold water in the presence of base.

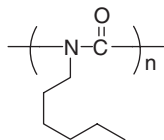
Any cloth made of such a material could never be reasonably laundered.

Although DuPont lost interest in the polyisocyanates their interest in new kinds of polyamides did not diminish as can be seen by the later development of Kevlar and its success as a commercial engineering material. The polyisocyanates passed into the academic world where scientists discovered that the polymer was quite stiff, which meant that it formed highly viscous solutions and at certain concentrations, lyotropic liquid crystals. These characteristics arise when the axial dimension of a polymer, the ratio of length to diameter, becomes large as is found in certain biologically interesting polymers such as alpha-helical sections of proteins or peptides and duplex DNA and certain viruses, which assemble into stiff soluble entities. Examples of the latter are tobacco mosaic virus and filamentous phage. Following on the general interest in such stiff polymers and supramolecular arrays, attention was focused on the polyisocyanates to discover the structural source of its stiff properties.

The first question that arose was the local conformation of the backbone of the polyisocyanates. Although large enough crystals could not be grown to yield atomic resolution X-ray data, fiber diffraction diagrams

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**Figure 1** Structure of poly(hexyl isocyanate).

revealed that the polymer took on a helical conformation. Polymer physicists, recognizing the possibility for the helix to take a right- and left-handed form, put forth the question of helical reversals within a single chain to account for the limit to stiffness of the backbone. This limit had been measured by viscosity and light scattering methods, with the quantitative measure expressed by the concept of persistence length, which showed that although stiff, the polymer exhibited some flexibility. The polymer was aptly described as worm like.

Many tools of polymer physics were used to investigate the question of the source of the flexibility of the polyisocyanates without being able to discriminate between helical reversals and an alternative possibility. The latter involved simply the small torsional motions about the bonds of the backbone, which could accumulate along the chain to give rise to the observed flexibility.

It was known that incorporation of chirality in the side chain of the polyisocyanate gave rise to a large circular dichroism signal in the chromophore of the polymer backbone, demonstrating therefore a large excess helical sense. These optically active polymers in fact did show an increase in persistence length in line with the idea that helical reversals were contributing to the limit on stiffness. This arises from the fact that if one helical sense is predominant, then the number of helical reversals would be reduced. However, this conclusion could not be drawn because NMR experiments showed via line width measurements that incorporation of the chiral group in the side chain led to reduction in torsional motions of the backbone. Whether the incorporation of the chiral moiety was increasing the stiffness because of helical sense excess or because of reduction in local torsional motions could not be distinguished.

**How might it be possible to cause a substantial favoring of one helical sense of the polymer without having any perceptible effect on the local torsional motions? Isotopic substitution could be the answer**

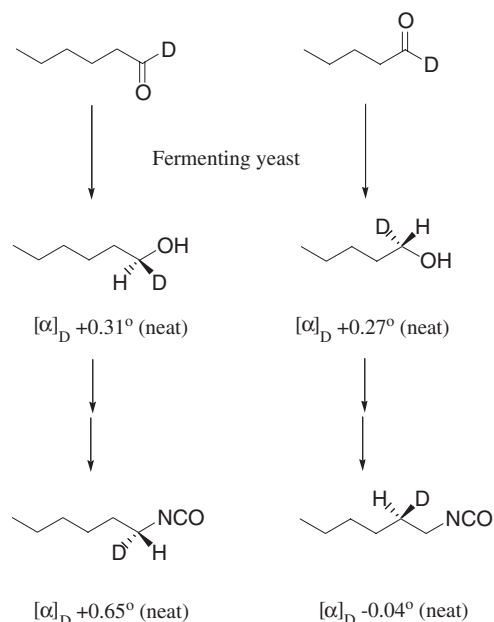
Normally isotopic substitution has only small effects on the torsional motions of the bonds involved. This fact suggests that deuterium replacement of one of the

hydrogens on a methylene group near to the backbone of the polyisocyanate might cause no perceptible change in the persistence length of the polymer from torsional motions.

If the deuterium substitution was stereospecific, then the affected methylene group would become a chiral center causing the left- and right-handed helical conformations of the backbone to be related diastereomerically, and therefore of unequal probability. But the energetic difference between the helical senses as a function of a per-unit substitution of deuterium must be a very small energy, perhaps a tiny fraction of ambient energy. Could such a small per-unit effect have any consequence on the helical sense excess? The answer could be yes considering the cooperative nature of polymers. If we imagine that many units along the chain are forced to take on a single helical sense before the chain either ends or finds the energy to make a helical reversal, then the helical sense of these units would be affected by this per unit isotopic substitution multiplied by all the units forced to act together.

We have described what could be termed a *cooperative structural chiral isotope effect* and this idea stimulated a significant synthetic effort outlined in Figure 2.

Using fermenting yeast on a deuterated aldehyde as shown in Figure 2 followed by several synthetic steps, yields the deuterated monomeric isocyanates, which are optically active by virtue of the deuterium substitution. The optical activity is minute as expected from its isotopic source, becoming nearly zero when the

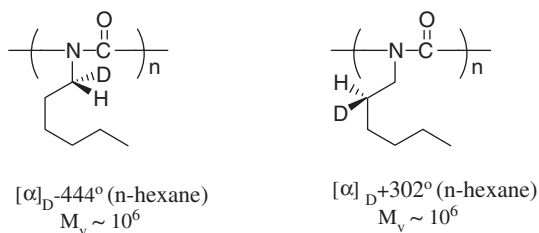


**Figure 2** Key intermediates and optical activities at the sodium D line for the synthesis of (left) (*R*)-1-deuterio-*n*-hexyl isocyanate and (right) (*R*)-2-deuterio-1-hexyl isocyanate.

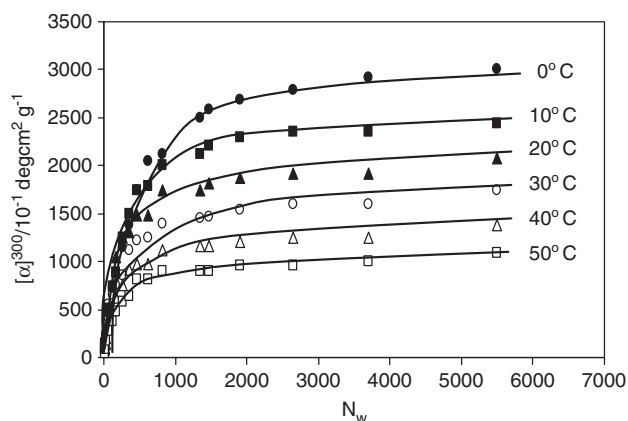
deuterated carbon is isolated from the isocyanate function by a methylene group. However, the optical activity picture changes greatly on polymerization to the polyisocyanate as seen in Figure 3 from both the magnitude and sign of the optical activity compared to the monomers in Figure 2.

Circular dichroism studies of the two deuterated polymers in Figure 3 demonstrate that the source of the chiral optical characteristics arise from the chromophore of the helix, and therefore arise from a large excess of one helical sense in each polymer. This excess helical sense as measured by the chiral optical properties was found to depend strongly on both temperature and the molecular weight of the polymer. This quantitative information, shown in Figure 4, was gathered in collaboration with Professors A. Teramoto and T. Sato of Osaka University undertaking the considerable effort necessary to fractionate the deuterated polymers into a wide range of narrow molecular weight fractions.

The abscissa in Figure 4 is simply the molecular weight of the fraction divided by the weight of a single monomer unit and therefore is the degree of polymerization,  $N_w$ , the W designating that it is a weight



**Figure 3** Optical activities at the sodium D line for (left) poly (*R*)-1-deuterio-*n*-hexyl isocyanate and (right) poly (*R*)-2-deuterio-1-hexyl isocyanate;  $M_v$ , viscosity average molecular weight.



**Figure 4** Dependence of  $[\alpha]_{300}$  on degree of polymerization for fractionated  $\beta$ -PdHIC in 1-chlorobutane at indicated temperatures. Open symbols, experimental data; solid curves, theoretical calculated values.

average molecular weight. It is impossible in synthetic polymers produced in this manner to attain samples of a single molecular weight. For this reason, each point on the graph represents a range of molecular weights, although a narrow range. The ordinate presents the optical activity for each degree of polymerization studied while the data in the table show how these parameters vary with temperature.

The qualitative explanation for how the cooperative properties of the helical polymer will amplify the per unit chiral influence favoring one helical sense is beautifully supported by the quantitative data in Figure 4, and justifies the effort made to synthesize the stereospecifically deuterated polymers (Figure 3). At each temperature, the optical activity rises steeply with increasing  $N_w$  to plateau values that increase with decreasing temperature. The inverse relationship between plateau optical activity and temperature fits the expected effect of the helical reversals. At high values of  $N_w$  the limit to the cooperativity will be the number of units in a single helical sense, which can only be interrupted by a helical reversal. The population of helical reversals will decrease with increasing temperature, therefore, causing longer blocks of units to take the same helical sense, and therefore increasing the factor multiplying the per unit chiral influence. The consequence will be increasing optical activity with decreasing temperature. Moreover, this optical activity will not depend on  $N_w$  because the cooperativity limit is determined by the intervention of a helical reversal rather than end of the polymer chain. At low values of  $N_w$  the chains are too short to allow the intervention of helical reversals, and therefore the limit to cooperativity becomes  $N_w$  and this parameter determines the optical activity, as seen at the low values of  $N_w$  in Figure 4.

The lines through the experimental points in Figure 4 are not drawn to fit the data points, but rather derive from numerical analytical methods used to fit the data to the two critical energy parameters controlling the cooperative behavior of the polymer, the energy of a helical reversal,  $G_r$ , and the energy by which a per unit stereospecifically placed deuterium atom favors one over the other helical sense  $G_h$ . The equations for the extreme situations of short and long chains, derived from the partition function written to describe this conformational-energy picture, developed in collaboration with S. Lifson of the Weizmann Institute, are presented below:

$$\ln \left( \frac{[\alpha]_m + [\alpha]}{[\alpha]_m - [\alpha]} \right) = \frac{2G_h N}{RT} \quad (1)$$

$$[\alpha] = [\alpha]_m \frac{lG_h 2/RT}{[(lG_h/RT)^2 + 1]^{1/2}} \quad (2)$$

In short chains (Equation (1)) where  $N_w$  is much smaller than the cooperative length determined by  $G_r$  ( $l = \exp(G_r/RT)$ , where  $R$  is the gas constant, the number of cooperating units depends directly on  $N_w$ . The effect of the temperature,  $T$ , on the helical sense ratio, as measured by the optical activity, is similar to that of other equilibria. This effect appears as an unusually steep dependence of the optical activity on degree of polymerization.

In long chains (Equation (2)), where  $l$  is small compared to  $N_w$  and the population of reversals rises sharply with  $T$ , the number of cooperating units depends strongly on  $T$  and not on chain length. This effect appears as an unusually steep dependence of the optical activity on temperature.

By this combination of statistical physical theory with the experimental effect of temperature and molecular weight on the optical activity of the deuterated polymer it was possible to determine the values of  $G_r$  and  $G_h$  as approximately 4 kcal/mol and 1 cal/mol, respectively. As predicted by the qualitative picture first drawn for this system, the helical sense excess is determined by a combination of a large energy, the cost of a helical reversal, and a small energy, the chiral structural isotope effect favoring one over the other helical sense.

The energy of the structural deuterium isotope effect although related to the zero point energy difference of the diastereotopic hydrogens on the substituted methylene group is far too small to be detected by a vibrational experiment to discern these carbon hydrogen modes. It is certain, however, that the C–H bond with the lower zero point energy, when substituted by deuterium, will be the favored state. Since the zero point energies of the diastereotopic hydrogens interconvert as the helix changes sense, the helical sense favored will be that which places the deuterium in the position with the lower zero point energy.

The details and references to the work and results outlined in the discussion above can be found in two reviews,<sup>1,2</sup> which also discuss extensions of this work derived from two other expectations of high levels of cooperativity. In the above work amplification was seen as a consequence of the cooperative nature of the helical polymer studied. One only has to observe human society to see two other faces of a cooperative system. One is the manner in which armies function and the other in the way in which democratic governments work. In the former, it is essential that many obey the commands of few, as, for example, sergeants control soldiers. In the latter, it is essential that the minority agrees to be governed by the majority view. Experiments have been conducted on the polyisocyanates with parallels to the behavior of sergeants and

soldiers and to the nature of majority rule. Because these experiments do not involve isotopes they will only be discussed in outline here.

In the sergeants and soldiers experiments, small proportions of chiral units are randomly copolymerized with achiral units. The chiral units are not chiral by virtue of isotopic substitution as discussed above but rather from conventional chiral moieties as derived, for one example, from terpenes. Many experiments of this kind have been carried out with the polyisocyanates<sup>1,2</sup> and with other helical polymers and supramolecular helical assemblies as well<sup>3</sup> demonstrating large non-linearities, that is, small proportions of the chiral sergeants control large numbers of the randomly copolymerized soldiers.

In the majority rule experiments, random copolymers have been synthesized from enantiomers with proportions differing only slightly from the racemic state, again demonstrating large non-linearities, that is, a small excess of one enantiomer leads to a large excess of one helical sense over the other in the resulting polymer. These kinds of experiments have been demonstrated in varying helical polymers subject to the same structural characteristics as the polyisocyanates, that is, helical senses in dynamic equilibrium with high levels of cooperativity.<sup>4</sup> Polyisocyanates have proven to be a model system with the first insight derived from an experiment using isotopic labeling.

### The cooperative nature of a polymer blend is revealed by isotopic labeling

Polymers are very different from small molecules with regard to questions of miscibility. The tendency in small molecules is toward miscibility, while the opposite is the situation for polymers. The source of the difference resides in the entropy of mixing, which is high for mixing small molecules and far less for mixing polymers, where the high molecular weights mean that far fewer molecules make up the ensemble. The consequence of this entropic difference is that polymers will not mix unless there is some attractive soft interaction, that is, some favorable enthalpic term for the miscible state.

What becomes quite interesting is that the cooperative properties of polymers allow such a necessary favorable interaction to be small on a per unit basis compared to ambient energies. This means that the interaction may not rise above the detection level of spectroscopic methods, which by their nature probe individual interactions rather than their cooperative consequence. And similarly such small interactions may not be detectable via theoretical probes such as molecular mechanics or quantum

mechanical calculations, which normally are not sensitive to effects in the energy range below about several hundred calories.

The situation described above finds archetypical form in a blend between polystyrene (PS) and poly(vinyl methyl ether) (PVME). These two polymers have long been known to mix over a very wide range of proportions, with no evidence for phase separation, forming therefore what is termed a miscible blend. From the first observation of this blend it was realized that an attractive interaction had to be responsible but it was not understood what this interaction could be. Certain critical clues that could not be interpreted at first arose from the fact that a solvent such as chloroform, and other chlorinated solvents with hydrogen bonding characteristics such as methylene chloride and trichloroethylene used to dissolve the polymers lead to phase separated states, while toluene, benzene and tetrachlorethylene allowed the miscible blend to form.

Other insights arose from NMR studies, which showed a close spatial relationship between the methyl group of the PVME and the hydrogens on the aromatic ring of the PS.

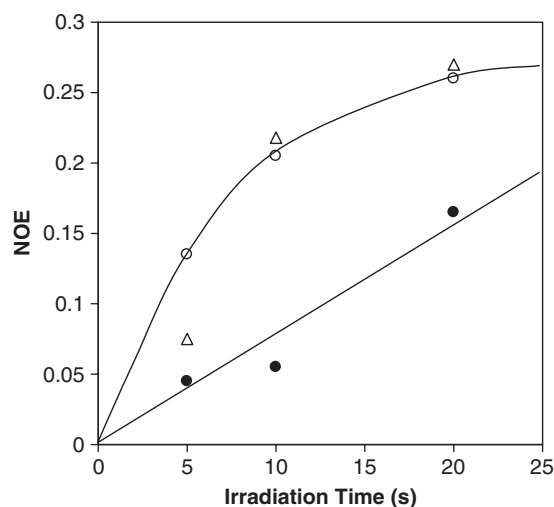
The situation remained with this uncertainty on interpretation until experiments with deuterium labeling focused considerable attention on this blend.

The typical thermal characteristic of blends of polymers is a lower critical solution temperature above which the blend components separate. This arises from the soft interaction holding the polymer components in a miscible state, an exothermic effect, and the absence of a favorable entropic mixing term. The general immiscibility of blends with increased temperature effectively demonstrates the unimportance of entropy of mixing. When every hydrogen atom in the PS component of the blend with PVME is replaced with deuterium, in an experiment designed to enhance neutron scattering experiments, the blend was found, to the great surprise of the researchers, to maintain its miscibility to a temperature 40°C higher than for the fully hydrogenated components.

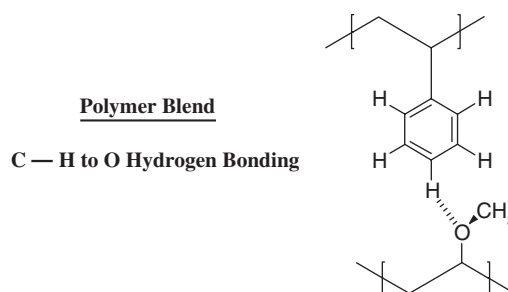
The result of the fully deuterated PS on the blend was not long in the literature before another experiment showed that if the aliphatic hydrogens on the backbone of the PS were replaced with deuterium there was no effect on the lower critical solution temperature. However, if the aromatic hydrogens in the PS were replaced with deuterium, the entire 40°C effect was again observed. Although this effort certainly pointed to the aromatic ring of the PS as key to the soft interaction responsible for the miscibility of the PS and PVME, the precise nature of this interaction was not clear. There was one speculation of perhaps a pi interaction

between the aromatic electron cloud and the ether methyl group of the PVME.

A revealing isotopic experiment in which synthetic work allowed replacement of the para hydrogen, and then one of the meta hydrogens, and then one of the ortho hydrogens, was greatly useful in demonstrating that a steric factor was at work in the soft interaction responsible for the blend. This could be shown by how the lower critical solution temperature changed with the site of deuterium incorporation, which was even more effectively demonstrated by NMR experiments. Nuclear Overhauser enhancement of the signals for the deuterated para, ortho and meta signals are shown in Figure 5, which confirm the picture of the attractive interaction in the blend in Figure 6. Whereas the para and meta deuterium substituted carbons show a large interaction demonstrating the proximity of these atoms with the methyl group of the PVME, the effect of the ortho deuterated carbon is far less. The lessened ability of the ortho hydrogen to participate, points to a steric



**Figure 5** Intensity of the deuterated aromatic carbon signal as a function of NOE irradiation time for PVME blends with (●) ortho, (○) meta and (△) para deuterated polystyrene. See Reference<sup>5</sup> for details.



**Figure 6** Attractive interaction between polystyrene (PS) and poly(vinyl methyl ether) (PVME) in the blend.

effect retarding the soft interaction responsible for the blend miscibility. However, it is not the methyl group of the PVME that is participating in the soft interaction with the aromatic hydrogen atoms but rather the adjacent oxygen atom. The methyl group of the PVME is simply acting as a reporter of the approach of the aromatic hydrogen atoms of the PS to the ether oxygen of the PVME.

The experiments discussed here and others summarized<sup>5</sup> form a convincing case that the responsible factor for the miscibility of this blend is a C–H to O hydrogen bond, a weak example of hydrogen bonding that is of wide interest but had not been recognized as playing an important role in polymer science and in polymer blending. In general, observation of such a weak interaction, with an energy just a fraction of that of a normal hydrogen bond, is very difficult because its effect on the properties of the system is quite small. However, in the polymer blend this small interaction is magnified by the cooperative nature of the blend, to cause a very large effect on both the miscibility of the two polymers, and as well a very large structural deuterium isotope effect on this miscibility. Moreover, the result requires that the hydrogen bonding interaction, in this situation, is stronger for C–D to O compared to C–H to O, which is not easily predictable and may be of theoretical interest.

## Summary

There is a significant literature on the use of isotopic labeling in studies of polymers, but here we focus on only two of these studies, which arise out of work at the Herman F. Mark Polymer Research Institute of the Polytechnic University. One involves the use of deuterium substitution to create a chiral stereogenic center, which then influences the relative stabilities of left- and right-handed helical conformations of a dynamically racemic helical polymer. The per-unit effect per mole is minute, but is magnified by the cooperative character of the polymer to cause a large effect on the conformational properties of the polymer. The consequence is that a large excess of a single helical sense is observed.

The insight from this experiment caused many experiments to follow in which the cooperative nature of chiral polymers was explored in a wide variety of structural systems.

The second experiment discussed here showed how deuterium labeling could be used to reveal the secret of how two polymers interact in an attractive manner to form a miscible blend. Following from thermodynamic and NMR experiments, deuterium labeling of PS demonstrates that the aromatic hydrogens are involved in a weak hydrogen bonding interaction with the ether oxygen of PVME. This C–H to O hydrogen bond, which is of considerable interest as contributing to the properties of biological systems, had not been well recognized in the polymer literature and this work may point to new directions to influence the mixing of polymers leading to new kinds of materials.

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