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Resolving the Regioregularity of Poly(*N*-*n*-hexyl-*N*′-phenylcarbodiimide) via Nitrogen-15 Labeling

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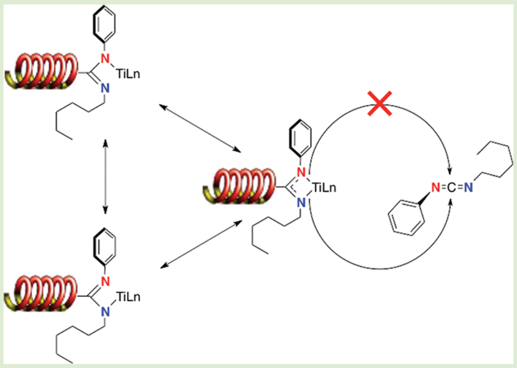
Supporting Information

ABSTRACT: Nitrogen-15 nuclear magnetic resonance (NMR) spectroscopy and infrared spectroscopy (IR) were performed on an isotope-enriched poly(*N*-*n*-hexyl-*N*′-phenylcarbodiimide) to determine directly the connectivity and regioregularity of a polymer. Up to this point, the imine, C═N, IR stretch at 1660−1620 cm^{-1} was thought to be a sufficient handle to elucidate the presence or absence of a regioregular microstructure; however, recent findings cast some uncertainties when expanded to all polycarbodiimides. Therefore, an enriched ^{15}N NMR study was undertaken to unambiguously resolve that a *N*-*n*-hexyl-*N*′-phenylcarbodiimide, when polymerized with a 2,2,2-trifluoroethoxide trichlorotitanium(IV) catalyst in chloroform, will produce a completely regioregular polymer. The only regioisomer present is the one in which the phenyl pendant group is positioned on the imino-nitrogen. The study was expanded to a chiral, (*R*)-BINOL-Ti(IV)-diisopropoxide catalyst which revealed no change in the regioisomer or the degree of regioregularity. In addition to ^{15}N NMR spectra, the IR imine stretch exhibited isotope shifts for poly(*N*-*n*-hexyl-*N*′-phenylcarbodiimide) when labeled on both imino- and amino-nitrogen or solely the imino-nitrogen of ∼11 cm^{-1}; however, no shift was manifested when labeling was restricted to the amino-nitrogen.



The study of structure−property relationships of helical macromolecules is of ongoing interest in the field of polymer science.[1] It has been of particular importance for polycarbodiimides due to their versatile and highly unusual properties and potential complex regioisomers.[2] A synthetic advantage but also a possible complication of polycarbodiimides over other helical polymers is that they possess two pendant groups per repeat unit. This side-chain versatility has led to multiple studies of this family of polymers that display unique solvo- and thermo-controlled optical properties and a range of liquid crystalline properties.[3] Greatly adding to their potential diverse applications, it has been recently reported alkyne functional polycarbodiimides can successfully undergo alkyne−azide cyclization reactions and Sonogashira coupling with aryl halides.[4] These modified materials can show potent antimicrobial activities depending on specific structural features.[5] To even begin to understand these unique properties, the unambiguous determination of the regioregularity of polycarbodiimides is absolutely necessary.

Much of the research from our group in recent years has involved the study of polycarbodiimides synthesized from nonsymmetric, mainly alkyl/aryl substituted carbodiimide monomers.[6] Within this body of work, a common and illusive thread has been determining the connectivity or regioregularity of polycarbodiimide microstructures prepared from nonsymmetric monomers. The synthesis of polycarbodiimides involves the polymerization of carbodiimide monomers using typically a titanium(IV) alkoxide catalyst; however, other early and late transition metals have been explored (Cu, Zr, Ni) and found to be successful. Upon addition of the titanium(IV) catalyst to a carbodiimide monomer solution, the carbodiimide inserts into titanium−oxygen bond, forming a titanium(IV) amindinate complex, and propagation proceeds by subsequent insertions into the titanium−nitrogen bonds. From this titanium(IV) amindinate propagating species and nonsymmetric monomers, various regioisomers can be formed depending on which of the two unique C═N bonds undergoes insertion into the Ti−N bond. These insertions could give rise to two pure regioisomers via selective insertions or regioirregular polymers by nonselective insertions (Figure 1). Presumably a combination of steric and electronic properties controls the regularity of these insertion processes.

Insights to a regioregular microstructure of these polymers, and in turn the mode of insertion during polymerization, have previously been probed by observing the position of the imine, C═N, IR stretch in the range of 1660−1620 cm^{-1}.[3a,8] Initially, patterns appeared to emerge indicating the utility of using IR as a tool to determine the presence of a regioregularity, or microstructures, by distinguishing the aryl-imine stretch from the alkyl-imine. The appearance of one predominate imine stretch indicated a regioregular structure, and two or more

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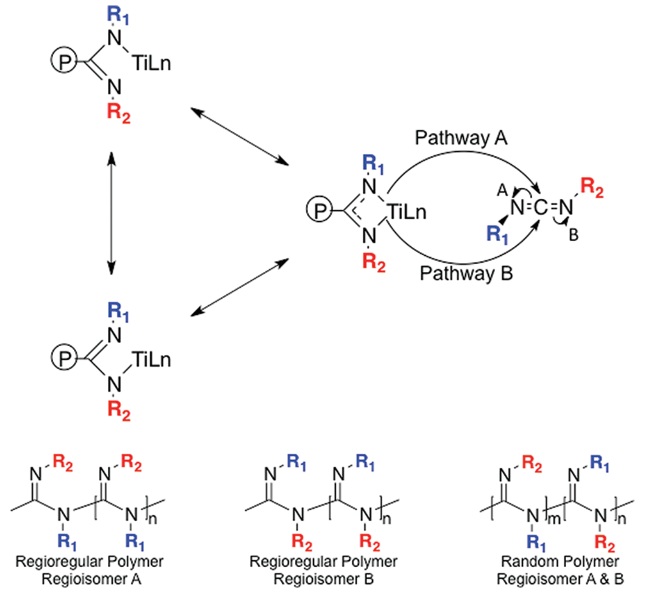


Figure 1. Two pathways for the insertion of carbodiimide monomer into the titanium(IV) amidinate complex. Selective insertions will yield a regioregular polymer containing regioisomer A or B or a regioirregular polymer composed of both regioisomers randomly place along the backbone.

stretches indicated two structural irregularities. However, recent studies have shown the behavior of the imine stretch region of the IR is more complex as it pertains to symmetry, coupled chromphores, and polycarbodiimides possessing certain pendant groups, and this remains a focus of ongoing investigations.[6] Hence, extracting the preferred regioisomer from the imine stretch remains elusive. ^{13}C NMR spectroscopy, a technique widely used in illuminating microstructures of polyisocyanates,[7] polypropylene, and others, has not proven fruitful at the assignment distinguishing a pendant group attached to the imino- or amino-nitrogen (terminology adopted to distinguish between the two nitrogens in the structure: the imine nitrogen versus the backbone (amino) nitrogen). In this work, we report the nitrogen-15 labeling of symmetric and nonsymmetric carbodiimides (Figure 2), their polymerization, and the unambiguous determination of their microstructures using ^{15}N NMR spectroscopy.

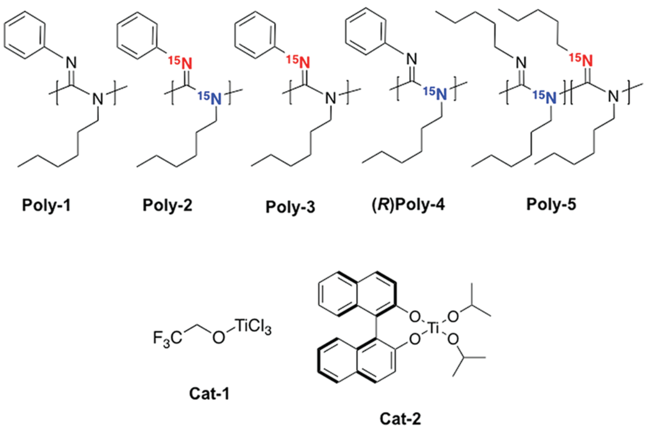
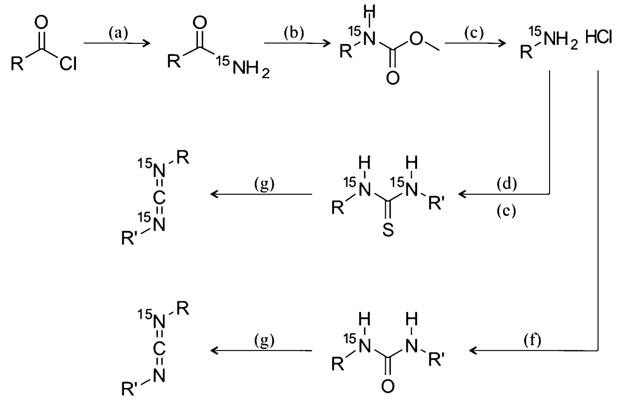


Figure 2. A series of nitrogen-15 enriched polycarbodiimides that were prepared for this study.

After over 20 years of work on the polycarbodiimides we decided to approach the problem of determining the preferred and degree of regioregularity present in these materials by using ^{15}N NMR. Because of the low sensitivity of nitrogen-15 and the lack of N—H bonds for cross-polarization, we elected to employ full enrichment using 98% ^{15}*N*-enriched ammonium chloride as the isotope source. As a starting point, we focused on nitrogen-15 enrichment of both nitrogen functionalities of the *N*-*n*-hexyl-*N*′-phenylcarbodiimide monomer. The nitrogen-15 chemical shifts for small molecule substituted amidines—the repeat unit along the polymer chain—have been previously studied in great detail, and they show large differences in alkyl/aryl imino- and amino-positions, and therefore it was expected minimal differences in regioregularity should be readily detected.[9]

The general synthetic scheme for a series of nitrogen-15 enriched polycarbodiimides (Scheme 1) begins with ^{15}NH$_4$Cl being allowed to react with benzoyl chloride and heptanoyl chloride, yielding a ^{15}*N*-benzamide and ^{15}*N*-heptanamide, respectively.[10] This was followed by a Hofmann rearrangement in methanol to capture the carbamate as methyl ^{15}*N*-phenylcarbamate and methyl ^{15}*N*-hexylcarbamate.[11] Unmasking the carbamate was done by acidolysis in refluxing concentrated HCl producing ^{15}*N*-aniline·HCl and ^{15}*N*-1-hexylamine·HCl, two common starting amines for carbodiimide synthesis that provide relatively high overall yields. For **2** ^{15}*N*-aniline·HCl was allowed to react with thiophosgene, generating a ^{15}*N*-phenyl isothiocyanate,[12] which was immediately allowed to react further with ^{15}*N*-1-hexylamine·HCl providing a di-^{15}N-labeled thiourea. The thiourea was desulfurized using triphenylphosphine dibromide and triethylamine in dichloromethane, a general protocol for forming carbodiimides from thioureas and ureas. The di-^{15}*N*-labeled carbodiimide monomer was then polymerized using trichloro-titanium(IV)-(2,2,2-trifluoroethoxide) catalyst (Cat-1) at a 120:1 monomer to catalyst ratio to form Poly-2. Detailed conditions and characterization are outlined in the Supporting Information.

Scheme 1. General Scheme for the Synthesis of Singly and Doubly ^{15}N Labeled Carbodiimides: (a) ^{15}NH$_4$Cl, KOH, DI H$_2$O, DEE; (b) DBU, NBS, Methanol, Reflux, 45 min; (c) Conc. HCl, Reflux, 12−16 h; (d) Thiophosgene, DCM, NaOH, DIPEA, 0 °C to rt, 12 h; (e) R′-^{15}NH$_2$ HCl, DCM, DIPEA, rt, 6 h; (f) R′-NCO, Et$_3$N, rt, 6 h; (g) PPh$_3$Br$_2$, Et$_3$N, 0 °C to rt, 12 h



Early attempts at collecting ^{15}N NMR spectra for Poly-2 met with some difficulty as a result of the exceedingly long relaxation delay times required to collect adequate spectra. To correct for this slow relaxation, gadolinium(III) acetylacetonate hydrate, Gd(acac)$_3$, a common and effective relaxation reagent, was used at a 0.02 M concentration in CDCl$_3$ substantially reducing the delay time.[13] As seen in Figure 3, Poly-2 is completely regioregular as evidenced by the presence of only two equally intense signals at 136.5 ppm for the imino-nitrogen and 15.5 ppm for the amino-nitrogen relative to ^{15}*N*-benzamide defined as 0.00 ppm. The appearance of two signals precludes a regioirregular microstructure from being a possibility; such a microstructure would lead to an emergence of four ^{15}N NMR signals in the spectra to account for the second regioisomer.

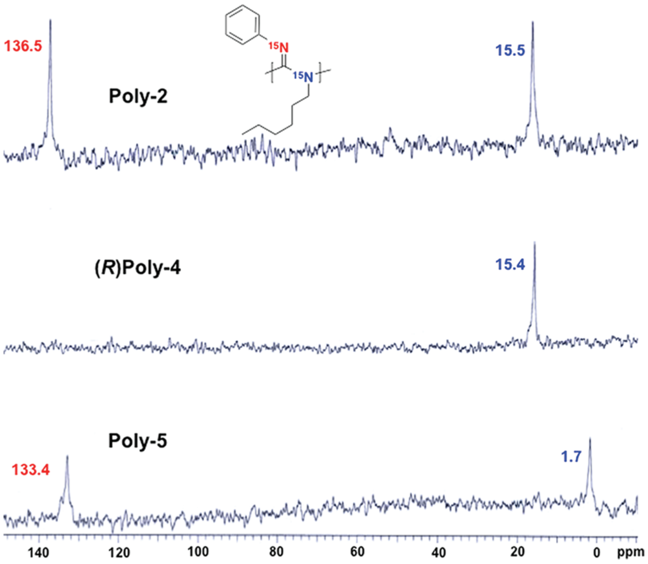


Figure 3. The ^{15}N NMR spectra of Poly-2, (*R*)Poly-4, and Poly-5 in CDCl$_3$ with 0.02 M Gd(acac)$_3$.

With the complete regioregularity of Poly-2 confirmed, we proceeded to assigning the specific regioisomer present; that is, was the phenyl group on the imino- or amino-position? From the chemical shifts alone it is not possible to unambiguously assign the connectivity of the regioisomer that was actually formed. Therefore, a singly ^{15}N enriched polycarbodiimide, Poly-3, enriched at the aryl pendant group was synthesized. Starting with ^{15}*N*-aniline the reaction with 1-hexylisocyanate afforded a mono-^{15}N-labeled urea, which was dehydrated and polymerized at a 150:1 monomer to Cat-1 ratio following general protocol. The ^{15}N NMR spectrum of Poly-3 shows only one peak at 136.4 ppm relative to ^{15}*N*-benzamide matching the chemical shift for imino-nitrogen from Poly-2. The nitrogen-15 signals of both Poly-2 and Poly-3 verify that a nonsymmetric carbodiimide monomer will polymerize to a completely regioregular microstructure when using Cat-1 as the catalyst, and the regioisomer for this polymer is aryl-imino and alkyl-amino. Hence, the polymerization of the phenyl-hexyl monomer is polymerized with complete selectivity wherein monomer insertion proceeds exclusively through the C=N-hexyl bond.

From these findings some new insight can be extracted about the mechanism of polymerization. It has be long understood that a covalent titanium(IV) amidinate complex is the active propagation species.[14] If we view the propagation from a hypothetical ionic extreme, the question reduces to which of the two amidinate resonances forms and which is the more nucleophilic nitrogen. From this ionic perspective the *n*-hexyl nitrogen is the more nucleophilic when bearing the negative charge, whereas the charge located on the phenyl nitrogen can be delocalized into the aromatic ring and, hence, is stabilized. As a control experiment, a singly labeled symmetric monomer was also prepared, ^{15}*N*,*N*′-di-*n*-hexylcarbodiimide, **5**, from ^{15}*N*-1-hexylamine·HCl and subsequently polymerized at a 120:1 monomer to Cat-1 ratio. From Figure 3, Poly-5 proved to be fully statistical with two signals of equal intensity at 133.4 ppm and 1.9 ppm. This experiment shows: (1) the absence of any kinetic isotope effect; and (2) when statistical distributions are expected, statistical distributions are seen.

Expanding these studies, we investigated whether another common catalyst, (*R*)-BINOL-titanium(IV)-diisopropoxide, Cat-2, used in these polymerizations gave a different selectivity than Cat-1. Cat-2 with its chiral (*R*)-BINOL (or *S*-BINOL) ligand has been used to kinetically bias and lock the polycarbodiimide helical backbone into a preferred helical enantiomer during polymerization to yield optical activity polymers. In this experiment, ^{15}*N*-*n*-hexyl-*N*′-phenylcarbodiimide was polymerized using Cat-2 at a 120:1 ratio to yield (*R*)Poly-4 enriched at the alkyl pendant group nitrogen. This catalyst with its helical biasing had no effect on the preferred regioisomer as seen in ^{15}N NMR spectra of (*R*)Poly-4 (Figure 3). The ^{15}*N*-amino signal was 15.5 ppm matching the amino-signal for Poly-2 and serves as additional confirmation of the assigned regioisomer.

As discussed earlier, the regioregularity of polycarbodiimides has historically been estimated using absorptions in the imine, infrared stretching region. With these isotopic labeled polycarbodiimides now available, the IR imine stretch can be further explored and compared to the ^{15}N NMR findings as seen in Figure 4. The increased mass of label nitrogen will give rise to an isotope IR shift for imine stretch to longer wavelengths. Unlabeled Poly-1 was previously reported to have a single imine stretch of 1626 cm^{-1} while for Poly-2 the imine stretch is shifted to 1612 cm^{-1} as a consequence of the

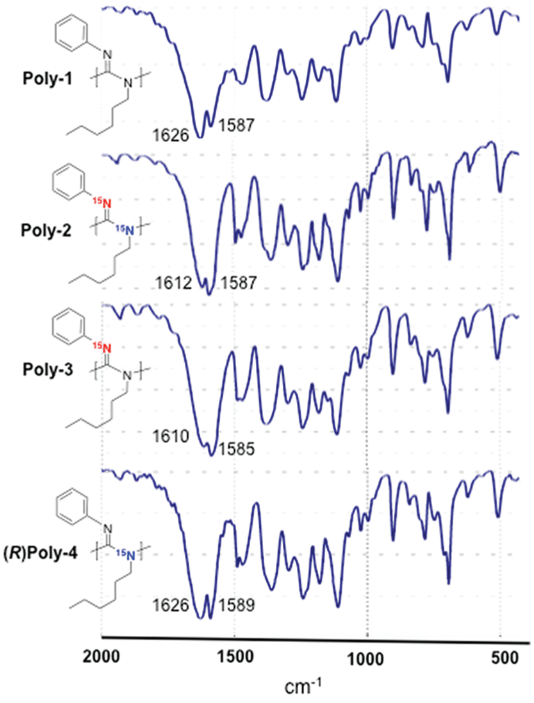


Figure 4. IR spectra of Poly-1, Poly-2, Poly-3, and (*R*)Poly-4.

isotope enrichment. The peaks of 1585−1589 cm^{-1} are the result of aryl C═C stretching and are not affected by the enrichment. The imine stretch remains shifted for Poly-3 with the imino-nitrogen exclusively labeled. Meanwhile the chiral (*R*)Poly-4, containing enrichment exclusively in the amino-position, was free of isotopic effects and therefore an imine stretch returning to 1626 cm^{-1}.

In summary, the regioregularity of polycarbodiimides, of the nonsymmetric *N*-(*n*-hexyl)-*N*′-phenyl carbodiimide monomer, has been identified as completely regioregular via ^{15}N NMR spectroscopy. While, as expected, a symmetric polycarbodiimide without any electronic or steric biasing has a completely random distribution of enrichment across the nitrogen rich backbone. In addition to the regioregularity, the preferred regioisomer was assigned with alkyl on the amino-position and aryl on the imino-position entirely. The assigned regioisomers were confirmed via an isotopic IR shift of the imine stretch of labeled imine nitrogen. Studies are currently underway in resolving the regioregularity of others in the polycarbodiimide family.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization of nitrogen-15 labeled reagents. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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