Mendeleev Commun., 2004, 14(6), 256–257

Taking chiral induction into the nanometre regime: chiral teleinduction in the synthesis of poly(isocyanide)s

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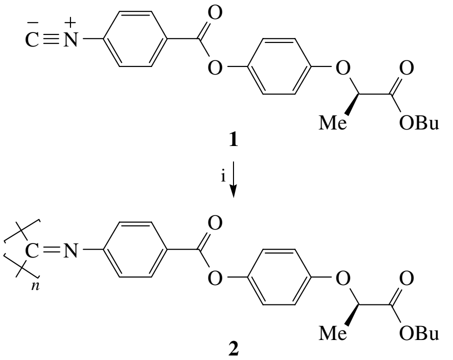
DOI: 10.1070/MC2004v014n06ABEH002043

Diastereoselectivity in the polymerisation of isocyanides has been observed to be operating over approximately 2 nm, which separates the reactive group from the stereogenic centre, as revealed by circular dichroism spectroscopy.

Traditional wisdom in the chemical community implies that if a large chiral induction is desired in a reaction, which operates under kinetic control, then a stereochemical source must be incorporated next to the reactive centres so that steric effects favour one of the two possible faces of attack at the prochiral centre.[1,2] On the other hand, in supramolecular systems, there are several examples of chirality transfer over several length scales in systems which operate under thermodynamic control.[3–10] It is an interesting challenge to try and combine these two contrasting situations so that non-covalent interactions can aid chirality transfer in covalent bond forming processes to achieve the seemingly ‘impossible’ feat of stereoselectivity over nanometre length scales.

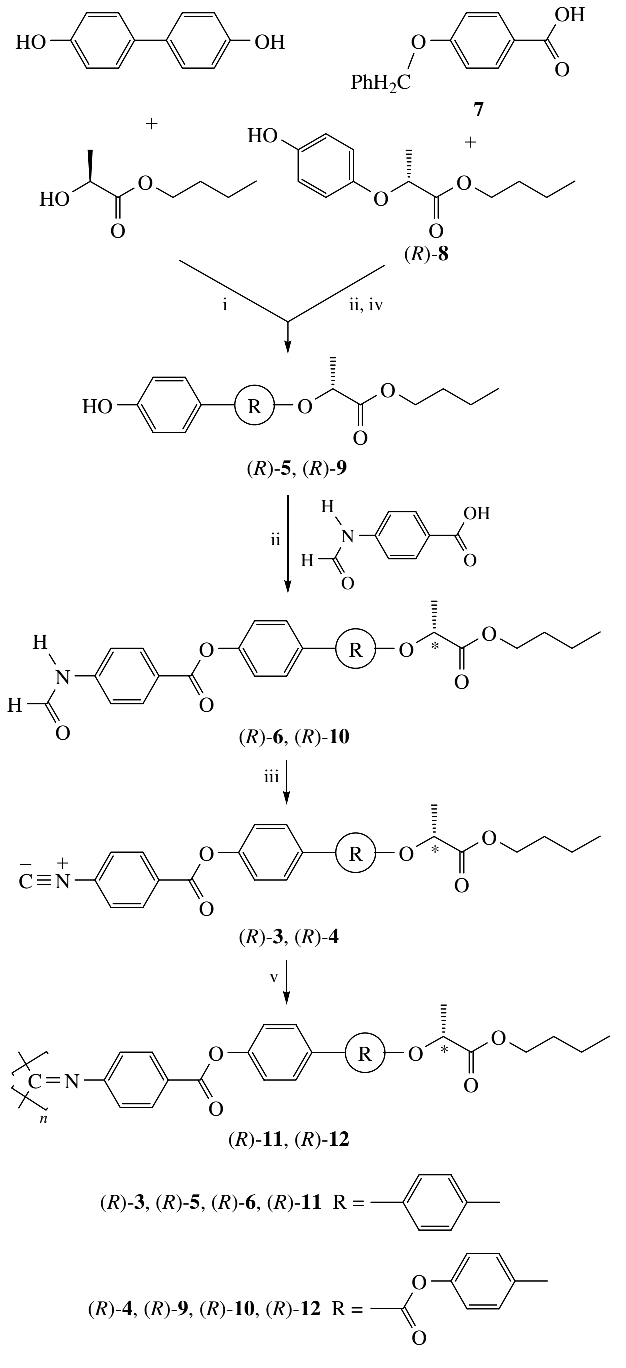
We stumbled across a remarkable example of chiral induction, which takes place during the polymerisation of isocyanides such as **1** (Scheme 1).[11] Here, the stereogenic centre in the monomer is separated by about 16 Å from the isocyanide group, and yet we recorded a significant diastereoselectivity in the chiral backbones of poly(isocyanide)s **2**, the diastereomeric excess was approximated to be 91%.[12] Unlike other chiral polymers, which display equilibria,[13,14] poly(isocyanide)s[15,16] **2** are assumed to have atropoisomeric helical conformations, which are kinetically stable with respect to changes in temperature and solvent.[11]



Scheme 1 *Reagents and conditions*: i, CH_2Cl_2, $NiCl_2{\cdot}6H_2O$, MeOH, air, room temperature.

Since we observed diastereoselectvity over a long monomer such as **1**, we were keen to see how far the transfer of chirality over a large distance (or teleinduction) could be pushed. Therefore, we have prepared monomers (*R*)-**3** and (*R*)-**4** (Scheme 2), in which an additional phenyl ring or a phenyl benzoate group, respectively, is incorporated compared with compound **1** with the same butyl lactate-derived side chain.

The Mitsunobu reaction[17] of 4,4′-biphenol (1.6 equiv. to favour mono-adduct formation) with (*S*)-butyl lactate (1 equiv.) gave chiral phenol (*R*)-**5** after column chromatography. This phenol was coupled to 4-formamidobenzoic acid with DCC to give formamide derivative (*R*)-**6**, which was dehydrated with diphosgene to give isocyanide (*R*)-**3**. A similar sequence was used to prepare isocyanide (*R*)-**4**, starting with the coupling of acid **7** with phenol (*R*)-**8**[11] using DCC followed by deprotection



Scheme 2 *Reagents and conditions*: i, THF, DIAD, 0 °C, Ar; ii, DCC, DMAP, CH_2Cl_2, room temperature; iii, diphosgene, CH_2Cl_2, NEt_3, Ar, 0 °C; iv, Degussa Pd/C, EtOH/cyclohexene (4:1); v, CH_2Cl_2, $NiCl_2{\cdot}6H_2O$, MeOH, air, room temperature.

of the phenol group to give (*R*)-**9**, and so on. All these compounds were characterised by NMR, IR and mass spectrometry. The optical activity of monomers (*R*)-**3** and (*R*)-**4** is dominated by the characteristics of the butyl lactate residue coupled to the phenyl unit. For (*R*)-**3**, the $[\alpha]_{546}^{25}$(CHCl$_3$) is +30 deg cm^2 g^{-1}, and for (*R*)-**4** it is +28 deg cm^2 g^{-1}. In the circular dichroism spectra of these compounds, there is a positive Cotton effect centred on 282 nm arising from the n–π^* transition of the carbonyl group of the butyl lactate moiety.

The polymers were prepared by the nickel(II) catalytic system developed by Nolte and coworkers.[18,19] Polymerisation of (*R*)-**3** yielded polymer (*R*)-**11** as a yellow powder in 91% yield after precipitation in methanol, while (*R*)-**12** was produced in the same form in 93% yield using the same procedure. The polymers are solids presumably because of their rigid nature, a result of the steric hindrance around the backbone, which gives rise to the helical secondary structure. The butyl lactate groups make the polymers very soluble in organic solvents, although they are insoluble in hexane, acetonitrile, short-chain alcohols and water. The ^{1}H NMR spectra of the polymers show a broad set of resonances between approximately 5.5 and 8 ppm (indicative of close contact between the aromatic rings in the side chains), while the alkyl chain substituents are more narrow but still poorly resolved compared with the isocyanide precursors.

The molecular weights and polydispersities of the polymers, as determined by size exclusion chromatography, are as follows: (*R*)-**11** $\overline{M}_\mathrm{w}$ 79.1, $\overline{M}_\mathrm{n}$ 24.1, and $\overline{M}_\mathrm{z}$ 185.5 kDa, with $\overline{M}_\mathrm{w}/\overline{M}_\mathrm{n}$ of 3.3; (*R*)-**12** $\overline{M}_\mathrm{w}$ 84.2, $\overline{M}_\mathrm{n}$ 60.3, and $\overline{M}_\mathrm{z}$ 99.8 kDa, with $\overline{M}_\mathrm{w}/\overline{M}_\mathrm{n}$ of 1.4. The polydispersities are high in common with other polymers generated using the NiCl$_2$·6H$_2$O catalyst and in accord with the non-living nature of polymerisation using this method.

The most remarkable feature of these polymers is their optical activity. Polarimetry of the polymers gives specific optical rotations as follows: for (*R*)-**11** or (*R*)-**12**, $[\alpha]_{546}^{25}$(CHCl$_3$) is +174 or –61 deg cm^2 g^{-1}, respectively. Recall that, for the monomers, the optical rotation was of the order of +30 deg cm^2 g^{-1}. Therefore, there has been an amplification of optical activity upon polymerisation and, in the case of (*R*)-**12**, an inversion in its sign.

The circular dichroism spectra of aromatic poly(isocyanide)s show a Cotton effect centred on 363 nm arising from the polymer backbone, an effect which is non-existent in the monomers. The spectra of polymers (*R*)-**11** and (*R*)-**12** (Figure 1) clearly evidenced that the polymer backbone has an optically active conformation. There are Cotton effects centred on 363 nm of similar magnitudes, which are positive for (*R*)-**11** and negative for (*R*)-**12**. The diastereoselectivity of the reaction does not rival that witnessed in the formation of (*R*)-**2**,[11] in which the Cotton effect at 363 nm had a $\Delta\varepsilon$ of +5.9 dm^3 mol^{-1} cm^{-1}, compared with a little over 1 dm^3 mol^{-1} cm^{-1} for polymers (*R*)-**11** and (*R*)-**12**, but in perspective it is remarkable that the effect is seen at all. This result shows that a chiral message has been passed over approximately 2 nm from the stereogenic centre to the growing poly(isocyanide) backbone.

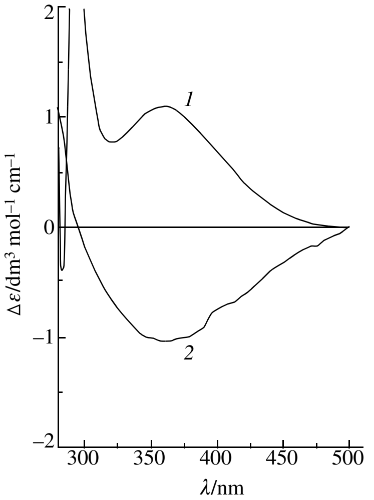


Figure 1 The circular dichroism spectra (in THF at room temperature) of polymers (*1*) (*R*)-**11** (positive Cotton effect at 363 nm) and (*2*) (*R*)-**12** (negative Cotton effect at 363 nm).

We propose that the reason for the relatively high diastereoselectivities observed in these polymerisations results from the twisted conformation in the phenyl benzoate units between the RC$_6$H$_4$COO unit (which is generally planar[20]) and the other phenyl ring, the angle formed being in the range 30 to 90° in the solid state with a maximum population at around 80°.[20,21] Why the compound with two phenyl benzoate moieties [(*R*)-**12**] should have opposite backbone chirality to that with one phenyl benzoate moiety and one biphenyl unit [(*R*)-**11**] is not clear. The biphenyl unit can adopt twisted conformations,[22–27] although the tendencies are not as marked as for the phenyl benzoate unit. It seems, therefore, that the nature of the surroundings to the stereogenic centre are capable of influencing the conformation that the spacer adopts. Our ongoing studies will seek to clarify this point.

The above results demonstrate that chirality transfer active during diastereoselective reactions is possible over extremely large distances (as far as 21 Å) provided that a chiral semi-rigid conformation can be adopted by the spacer in between the stereogenic centre and the reactive terminus.

This work was supported by the DGI, Spain (project no. BQU 2003-00760) and the DGR in Catalonia (project no. 2001SGR00362).

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Received: 20th September 2004; Com. 04/2368