

Switching of Chiral Induction in Helical Aromatic Oligoamides Using Solid State–Solution State Equilibrium

Hua Jiang,[†] Christel Dolain,[†] Jean-Michel Léger,[‡] Heinz Gornitzka,[§] and Ivan Huc*[†]

Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, 33607 Pessac Cedex, France, Laboratoire de Pharmacochimie, 146 rue Léo Saignat, 33076 Bordeaux, France, and Laboratoire d'Hétérochimie Fondamentale et Appliquée, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex 4, France

Received November 10, 2003; E-mail: i.huc@iecb.u-bordeaux.fr

Inducing the handedness of helical polymers or oligomers has attracted widespread interest because of its possible applications in optical devices or data storage and also because of its relevance to chiral amplification as it may have occurred at the early stages of life. Helical/nonhelical transitions and even inversion of helical chirality have been achieved upon changing solvent polarity or temperature,¹ binding of chiral counterions,² binding of chiral or nonchiral neutral guests molecules,³ protonation,⁴ irradiation using unpolarized⁵ or circularly polarized⁶ light, or electrochemical inputs.⁷ We now report that solution state–solid state equilibrium provides an original means to control helical handedness in synthetic oligomers.

We have recently presented oligoamides of 8-amino-2-quinolinecarboxylic acid and their unusually stable helical structures held by hydrogen bonds between amide protons and adjacent quinoline nitrogens and by extensive intramolecular aromatic stacking.⁸ For example, an octameric strand folds into a helix extending to over three turns.⁸ Unlike the previously described oligomers, octamer **1** (Figure 1) bears a chiral *R*-phenethylamino end group at the C terminus, introduced so as to shift the equilibrium between right-handed (*P*) and left-handed (*M*) helical conformers. Chiral induction in **1** was demonstrated by circular dichroism spectroscopy (CD). In contrast with the silent CD spectra of helical oligomers bearing no chiral groups, the spectrum of **1** features intense bands in the absorption region of the quinoline rings between 250 and 450 nm (Figure 2). The *R*-phenethylamino group interacts differently with neighboring quinoline rings in the *R*-*P* and the *R*-*M* diastereoisomers, leading to different stabilities of the *P* and *M* helices in solution.

The extent of chiral induction was evaluated by ¹H NMR. The *P* and *M* helices of **1** invert slowly on the NMR time scale, and the *R*-*P* and *R*-*M* diastereoisomers give rise to distinct signals which can be directly integrated (Figure 1a). The proportions indicate a ratio of 10:1, which correspond to a diastereomeric excess of 82%. The same proportions were observed in other solvents such as DMSO-*d*₆ and toluene-*d*₈, showing that neither helix stability nor chiral induction itself is affected by the polarity of the environment. The diastereomeric excess was found to vary almost negligibly with temperature between –30 and 80 °C.

Crystals of **1** were grown over a few days upon diffusion of *n*-hexane into a toluene solution. We presumed that the two diastereoisomers should have similar solubilities and since one is 10 times more abundant than the other, we expected the major diastereoisomer to reach its solubility limit and crystallize first, thereby shifting the equilibrium in its favor. However, X-ray diffraction analysis of the crystals shows that, unexpectedly, the

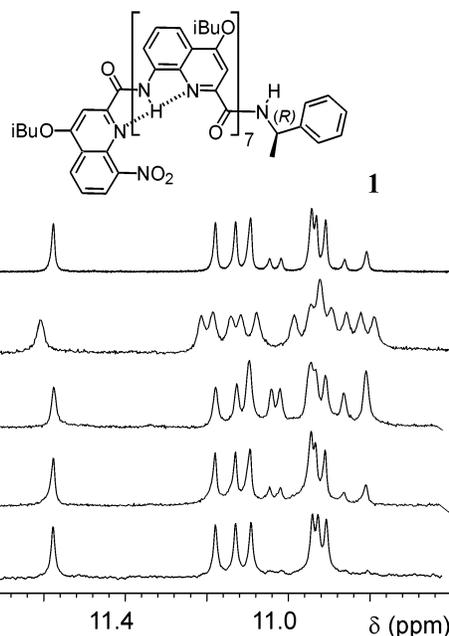


Figure 1. Structure of compound **1** depicting the expected intramolecular hydrogen bonds and part of its 400 MHz ¹H NMR spectra in CDCl₃ showing the signals of the seven intramolecularly hydrogen bonded amide protons (a) at equilibrium at 25 °C, (b) at –30 °C just after dissolving crystals grown from toluene, (c) sample (b) after 30 min at 25 °C, (d) sample (c) after 1 day at 25 °C, and (e) at 25 °C just after dissolving crystals grown from benzene.

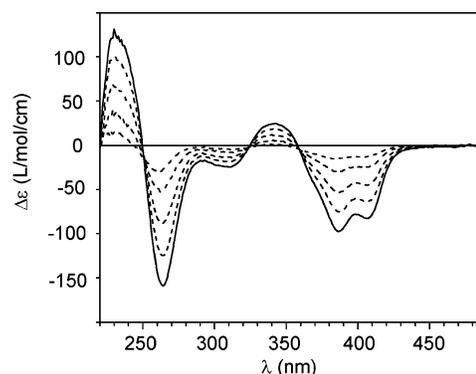


Figure 2. CD spectra of **1** in CHCl₃ at 25 °C: at equilibrium (solid line) and 40, 100, 200, and 420 min after dissolving crystals grown from toluene (dotted lines from weak to intense spectra, respectively).

two diastereoisomers cocrystallize (Figure 3).⁹ The asymmetric unit contains one right-handed and one left-handed helical diastereoisomer. In both cases, the terminal phenyl group lies stacked face-to-face with the second quinoline ring of the sequence. The helices

[†] Institut Européen de Chimie et Biologie.

[‡] Laboratoire de Pharmacochimie.

[§] Laboratoire d'Hétérochimie Fondamentale et Appliquée.

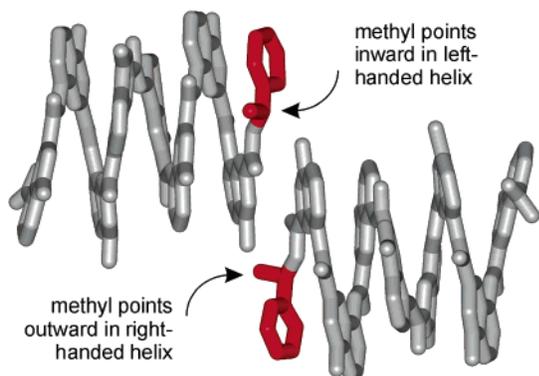


Figure 3. Crystal structure of **1** (asymmetric unit) showing the diastereomeric right-handed and left-handed helices. Included toluene solvent molecules, isobutyl side chains, and hydrogens have been omitted for clarity.

are almost mirror images but for the position of the methyl group on the asymmetric carbon, which points inward in the left-handed helix and outward in the right-handed helix. No obvious difference between the helices indicates which should be the most stable in solution. Because of the presence of two *R* asymmetric centers, the structure belongs to a non-centrosymmetric space group (*P1*). However, the symmetry between the two helices is such that the structure can accurately be solved in centrosymmetric space group *P*-1, except for the position of the methyl group, which is then found statistically distributed between two possible positions.

The equilibrium shift that takes place upon crystallization is slowly reverted after redissolving the crystalline powder. For instance, the NMR spectrum of freshly dissolved crystals at -30 °C shows a 1/1 mixture of diastereoisomers reflecting the composition of the solid state (Figure 1b). After raising the temperature to 25 °C, the proportions are almost unchanged (Figure 1c), and equilibrium is reached only after approximately 1 day (Figure 1d). On the basis of NMR measurements, the half-life of helix inversion was calculated at 154 ± 13 min. The CD spectrum follows the same trend: a very weak signal can be measured after dissolving the crystalline powder (Figure 2), reflecting a quasiracemic mixture, and the spectrum builds up to reach its equilibrium value after 1 day.

We grew crystals from other solvents than toluene and found that the *P* and *M* helices of **1** also cocrystallize as a 1:1 mixture from chlorobenzene. On the other hand, crystals grown from benzene are different and NMR shows that they contain exclusively the major diastereomer (Figure 1e). These different crystallizations are all reproducible; however, we found that crystals containing both diastereomers can be grown from benzene as well upon seeding with crystals from toluene. Thus, the chiral induction observed in solutions of **1** is reversibly switched off upon crystallization from toluene and is enhanced up to 100% upon crystallization from benzene. These different crystal compositions presumably arise from different packing modes imposed by different included solvent molecules. Unfortunately, the crystals from benzene are unsuitable for X-ray diffraction analysis and did not allow us to absolutely assign the major diastereoisomer in solutions of **1** to the *M* or *P* helix.

The tendency of enantiomers to cocrystallize in a majority of cases and to separate as conglomerates in a minority of cases is well-known. As we^{8,10} and others¹¹ have observed, this trend is followed by the *P* and *M* enantiomeric conformers of helical aromatic oligoamides which do not bear asymmetric centers. All

X-ray structures reported up to now belong to centrosymmetric space groups, and no conglomerate has been observed. The same phenomenon is observed with **1** in toluene and chlorobenzene despite the fact that the *R*-*P* and the *R*-*M* conformers of **1** are diastereoisomers and, more importantly, despite the fact that the solution from which the crystals grow is significantly enriched in one of the two species. Few examples of cocrystals of diastereoisomers have been reported, but never in association with chiral induction.¹² In the case of **1**, helical chirality apparently “weighs” more than the asymmetric center in the crystallization process and the diastereoisomers behave as if they were enantiomers.

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Supporting Information Available: Crystallographic data in CIF format. Synthetic procedure for the preparation of **1**, monitoring of the chirality induction after dissolving crystals, and calculation of the half-life of helix inversion in pdf format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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