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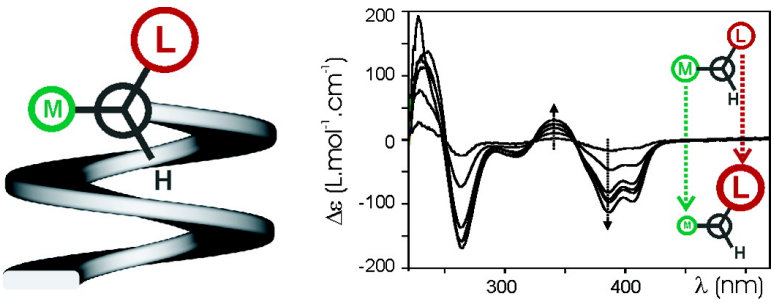

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Chiral Induction in Quinoline-Derived Oligoamide Foldamers: Assignment of Helical Handedness and Role of Steric Effects

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Abstract: Chiral groups attached to the end of quinoline-derived oligoamide foldamers give rise to chiral helical induction in solution. Using various chiral groups, diastereomeric excesses ranging from 9% to 83% could be measured by NMR and circular dichroism. Despite these relatively weak values and the fact that diastereomeric helices coexist and interconvert in solution, the right-handed or left-handed helical sense favored by the terminal chiral group could be determined unambiguously using X-ray crystallography. Assignment of chiral induction was performed in an original way using the strong tendency of racemates to cocrystallize, and taking advantage of slow helix inversion rates, which allowed one to establish that the stereomers observed in the crystals do correspond to the major stereomers in solution. The sense of chiral helical induction was rationalized on the basis of sterics. Upon assigning an R^s or S^s chirality to the stereogenic center using a nomenclature where the four substituents are ranked according to decreasing sizes, it is observed that R^s chirality always favors left-handed helicity and S^s chirality favors right-handed helicity (P). X-ray structures shed some light on the role of sterics in the mechanism of chiral induction. The preferred conformation at the stereocenter is apparently one where the bulkiest group should preferentially point away from the helix, the second largest group should be aligned with the helix backbone, and the smallest should point to the helix.

Introduction

Throughout the history of chemistry, assigning absolute chiral configurations has proven to be a difficult endeavor, lined with adventurous hypotheses and controversies. This is true for chirality at defined stereocenters, and it also applies to helical chirality: determining the absolute right- or left-handed screw sense of a molecular helix is rarely straightforward. The first helix for which this question arose is the peptide α-helix proposed in 1951 by Pauling.[1−3] It was noted that for a given configuration D or L of the amino acids "one sense of the helix would be more stable than the other" because the side chains do not have the same orientation in the right- and left-handed diastereomers. The drawing of the helix proposed by Pauling actually shows the correct relative assignment (D-amino acids in a left-handed helix), but it is simply based on arbitrary choices of both the helical handedness and the amino acids configuration. The structure was long debated,[2] but no definite conclusion about its handedness could be drawn for a decade, until 1961, when the crystal structure of myoglobin at 2 Å resolution was published.[4] In fact, the first helix for which a correct assignment of handedness was proposed was probably the B-DNA double helix in 1953. After the work of Bijvoet on anomalous scattering, it was possible to determine absolute configurations using X-ray.[5] The absolute configuration of β-D-deoxyribofuranose was known[6] and the B helix could be built according to diffraction patterns only with a right-handed sense of helicity. The correctness of the handedness is implicit in Crick's and Watson's paper.[2,7]

Since these seminal works, X-ray crystallography has been extensively used to assign helix handedness. Examples include a number of helicenes,[8] the racemates of which spontaneously resolve into crystals of helices of opposite handedness or, more recently, some constrained β-peptides.[9] However, there are many

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cases where crystals suitable for crystallographic analysis have not been obtained. NMR sometimes allows one to define the helical sense of a helix in solution as, for example, in several families of more flexible β-peptides[10] and related structures.[11] When full assignment of NMR spectra and solution structure resolution is not possible either, helical handedness may be proposed on the basis of circular dichroism (CD) spectra and/or molecular mechanics calculations. This is the case in many helical polymeric structures or in oligomers for which NMR spectra cannot be interpreted as, for example, *m*-phenylene ethynylene oligomers,[12] poly(isocyanates),[13] aliphatic poly(isocyanides),[14] aromatic poly(isocyanides),[15] poly(silylenes),[16] and poly(acetylenes).[17] Hypotheses were also made concerning the helical sense of poly(triphenylmethyl methacrylate) from its properties as a stationary phase in chiral chromatographic separations.[18] Recently, the helical sense of *N*-alkylated poly(*p*-benzamide)s was assigned on the basis of an exciton model analysis of the absorption and CD spectra.[19]

Despite many improvements, circular dichroism and molecular mechanics calculations rarely provide unambiguous data. The results obtained should be handled with great care,[20] and most assignments based on these methods are tentative. An interesting example of a revised assignment is that of peptide nucleic acid (PNA) double helices. When these compounds are functionalized with chiral residues, for example, a single terminal chiral amino acid, they exist preferentially as a single diastereomeric form. The assignment of helical handedness initially proposed[21] for these double helices from CD studies and theoretical calculations was later proven to be wrong by further CD studies.[22]

A common feature of the molecular helices for which handedness has been assigned unambiguously, mostly by X-ray crystallography, is that they exist predominantly as a single diastereomer: α-helices of L-amino acids are, in principle, at equilibrium between their right- and left-handed forms, but this latter species is experimentally unseen and virtually absent. It is actually remarkable that just a few chiral centers in a helical chain[23,24] or that chiral centers quite remote from the helical backbone[25] often allow one screw sense to prevail. One may anticipate that, in a given molecular helix, a weak chiral induction and the interconversion and coexistence of both diastereomeric forms in solution should make handedness assignment even more challenging. Here, we report our success at unambiguously assigning the handedness of helical quinoline-derived oligoamide foldamers bearing a single chiral terminal group, which brings about a weak chiral induction (diastereomeric excess, de < 85%) and allows both helical forms to coexist and interconvert. To the best of our knowledge, handedness assignment under such conditions had not yet been reported. The method that we have used relies on an original crystallographic study of the racemate rather than the single enantiomers. We think that this approach bears some generality and might be useful in a number of cases.

Previously, we have shown the ability of oligoamides of 8-amino-2-quinolinecarboxlic acid to fold into helices stabilized by extensive intramolecular aromatic stacking and by intramolecular hydrogen bonds between amide protons and adjacent quinoline nitrogens.[26,27] These helical structures have been characterized in the solid state and in solution and have been shown to be remarkably stable in nonpolar and polar solvents over a wide range of temperature, for example, at 120 °C in DMSO. We have demonstrated the possibility to design *meso*-helices from these scaffolds, that is to say, helices bearing both a right-handed and a left-handed segment.[28] We have also shown that a terminal chiral phenethylamino group slightly biases the equilibrium between the right-handed and the left-handed helix and gives rise to chiral induction in solution.[29] Both intramolecular and intermolecular chiral inductions have been reported in related oligomers.[30] However, in none of these cases was the helical sense unambiguously assigned. As shown in the following, a study of octameric strands **1**−**8** and of tetrameric strand **9** (Chart 1) combining NMR spectroscopy, circular dichroism, and X-ray crystallography has allowed us to assign the handedness of chiral induction in these oligomers and to shed some light on its mechanism, in particular, on the role of steric effects.

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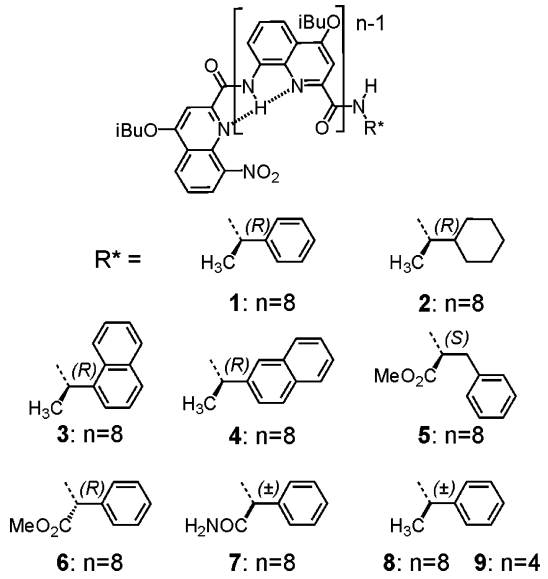
Chart 1. Structures of Compounds **1**−**9**[a]



[a] Note that **8** is the racemate of **1**.

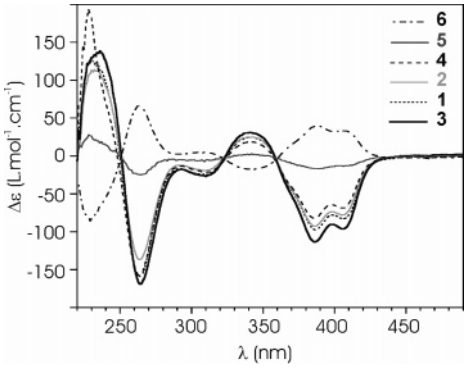


Figure 1. CD spectra of 1 mM solutions of chiral octamers **1**−**6** in $CHCl_3$ at 25 °C at equilibrium.

Results and Discussion

Quantification of Chiral Induction. Chiral induction in octamers **1**−**6**, which were prepared from commercial enantiomerically pure amines (ee > 99%), was demonstrated by circular dichroism spectroscopy (CD). In contrast with the silent CD spectra of helical oligomers bearing no chiral groups, or of those prepared as racemates (**7**−**9**), the spectra of chiral octamers **1**−**6** feature bands of variable intensities in the absorption region of the quinoline rings between 250 and 450 nm (Figure 1). In each of these compounds, the chiral group interacts differently with neighboring quinoline rings in the right-handed (P) or left-handed (M) helical conformers, leading to different stabilities of the P and M helices in solution, and thus to chiral induction. CD spectra show that the extent of chiral induction of helix handedness varies with the nature of the chiral group introduced at the end of the strand. The CD intensity at 385 nm reaches a maximum with chiral octamer **3** ($\Delta\epsilon = -113$ L mol^{-1} cm^{-1}), which bears a *R*-(+)-1-(1-naphthyl)ethylamino group. It is slightly lower for octamers **1**, **2**, **4**, and **6** ($\Delta\epsilon = -97$, -92, -82, and $+40$ L mol^{-1} cm^{-1}, respectively). Chiral induction of helix handedness appears to be the least efficient with a terminal L-phenylalanine methyl ester, as in octamer **5** ($\Delta\epsilon = -15$ L mol^{-1} cm^{-1}). The equilibrium that takes place between the right- and the left-handed conformers is shifted more or less according to the nature of the chiral group. The CD spectra of chiral octamers **1**−**5** all feature bands with the same negative of positive sign for any given wavelength, showing that the dominant handedness is the same in all five cases. The CD spectrum of octamer **6** shows bands with an inverted sign, suggesting a handedness opposite to that of **1**−**5**. Bands of opposite signs that might be interpreted as exciton couplets can be observed at between 230 and 280 nm and between 320 and 420 nm. The sign of these couplets would point to M helicity for **1**−**5** and P helicity for **6**. Assignment of helical handedness from the sign of CD bands on the basis of a complete exciton model analysis recently proved to be successful for *N*-alkylated poly(*p*-benzamide)s but was not attempted here.[19]

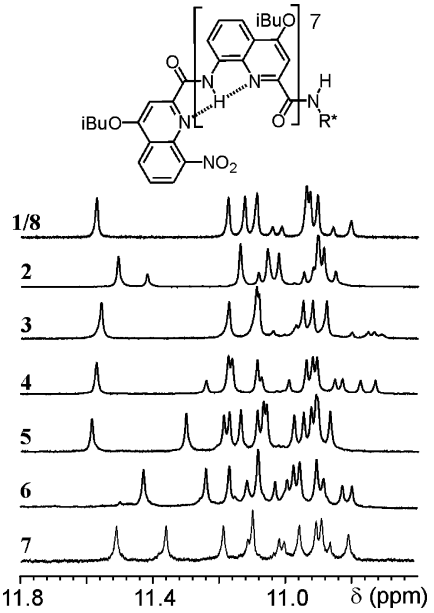


Figure 2. Parts of 400 MHz ^{1}H NMR spectra in $CDCl_3$ of compounds **1**−**8** showing the signals of the seven intramolecularly hydrogen-bonded amide protons at equilibrium at 25 °C. In each case, seven signals belong to the major stereomer(s), and seven signals belong to the minor stereomer(s).

The extent of chiral induction in chiral octamers **1**−**6** and also in racemic octamers **7** and **8** was evaluated by ^{1}H NMR spectroscopy (Figure 2). For an oligomer bearing, for example, an *R* asymmetric center, equilibrium takes place between two diastereomers, *R*-P and *R*-M. At 25 °C, the diastereomeric P and M helices of chiral octamers invert slowly on the NMR time scale and two sets of signals are observed,[31] one for the major diastereomer, and the other for the minor diastereomer. For a racemic compound, two independent equilibria take place between two pairs of diastereomers, *R*-P and *R*-M, and *S*-P and *S*-M. However, the overall spectrum of an *R*/*S* racemic mixture is identical to that of a single *R* or *S* enantiomer. Integration of the major and minor species allowed one to calculate the diastereomeric excesses reported in Table 1. These de values are consistent with those calculated from CD intensities at 385 nm (Table 1). Indeed, chiral induction is again found to be the strongest with an *R*-(+)-1-(1-naphthyl)ethylamino group in **3** (de = 83%), and the weakest with an L-phenylalanine methyl ester group in chiral octamer **5** (de = 9%). Some discrepancies between the de values estimated from NMR and CD spectra

(31) This exchange is fast on the NMR time scale at 25 °C for tetramer **9**.

Table 1. Proportions of the Two Diastereomers for Octamers **1**−**7** and Calculated Diastereomeric Excess (de) on the Basis of NMR and CD Data[a]

oligomer	proportions	de (NMR[b]) (%)	de (CD[c]) (%)
1	10:1	82	82 (ref)
2	10:3	54	78
3	10:0.9	83	95
4	10:3.3	50	70
5	12:10	9	13
6	10:5	33	33
7	10:5	33	

[a] For de values calculated from CD spectra, the de measured by NMR for **1** was used as a reference. [b] Error ranges for de values measured from integration of NMR signals are estimated to be ±12%. [c] Error ranges for de values calculated from CD intensities relative to that of **1** are estimated to be <1%.

may be attributed to incertitude in NMR signal integration, especially when signals overlap, and also to possible deviations from an assumed linear increase of $\Delta\epsilon$ with the de, for example, if a chromophore at the chiral moiety contributes to the CD signal at this wavelength.

As expected, NMR spectra of octamers **1** and **8** are identical. Results obtained with octamer **7** are almost the same as for octamer **6**, which suggests that phenylglycine amide and phenylglycine methyl ester groups interact in the same way with neighboring quinoline rings in the right-handed or left-handed helix. For compound **8**, the same de values were measured in others solvents such as DMSO-d_6 and toluene-d_8, showing that neither helix stability nor chiral induction is affected by the polarity of the environment. The diastereomeric excess was found to vary almost negligibly with temperature between −30 and 80 °C.

On the basis of NMR measurements, the half-life of helix inversion of chiral octamer **1** at 25 °C was previously calculated at 154 ± 13 min.[29] We hypothesized that this helix inversion rate might be slow enough to allow a chromatographic separation of the diastereomers. Indeed, for the phenylalanine derivative **5**, the two diastereomers possess (surprisingly) different retention coefficients and appear as distinct spots on TLC. The preparative chromatographic separation of the two diastereomers *S*-P and *S*-M of **5** could be achieved on silica gel at 0 °C. NMR spectra were recorded just after separation for both diastereomers and allow one to attribute all of the signals of the diastereomeric mixture to one or the other diastereomer (Figure 3). After the temperature was raised to 25 °C, each diastereomer progressively interconverts into the other one and equilibrium is reached after approximately 1 day in both cases. The CD spectra follow the same trend. Intense signals can be measured for each diastereomer just after their separation. The intensity of each CD band then decreases, and, in one case, the sign of the bands eventually inverts, to reach the same equilibrium value after approximately 1 day (Figure 4).

Assignment of Chiral Induction. Our efforts to assign the handedness of the major and minor diastereomeric helices for each chiral oligomer **1**−**6** are primarily based on X-ray crystallography. Our initial hope was to crystallize the major P or M diastereomeric form of an enantiomerically pure oligomer. Using a mixture as biased as possible in favor of one handedness and, assuming that both diastereomers should have similar solubility, it was expected that the major diastereomer should reach its solubility limit and crystallize first, eventually shifting the equilibrium in its favor. However, it was observed that the

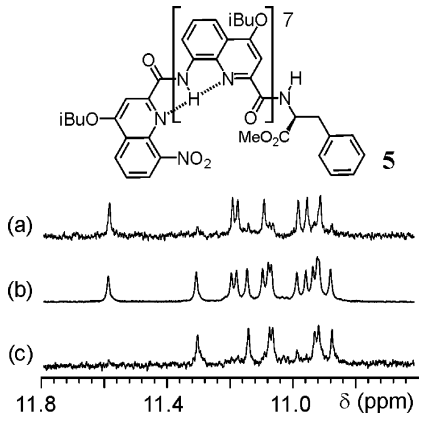


Figure 3. Parts of 400 MHz ^{1}H NMR spectra of compound **5** in $CDCl_3$ showing the resonances of the seven intramolecularly hydrogen-bonded amide protons (a) of diastereomer P-**5** just after separation; (b) at equilibrium at 25 °C; and (c) of diastereomer M-**5** just after separation. The assignment of the M and P helices is described in the text.

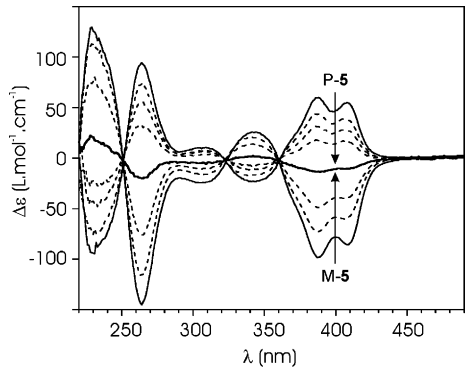


Figure 4. CD spectra of both diastereomers P-**5** and M-**5** in $CDCl_3$: at 0 °C just after their separation (solid lines), and at 25 °C, respectively, 30, 60, and 90 min after chromatographic separation for P-**5**, and 120 and 180 min after chromatographic separation for M-**5** (dashed lines). Equilibrium (bold line) is reached after approximately 1 day.

two diastereomeric helices prefer instead to cocrystallize despite the fact that the initial solution is enriched in one of the components. Thus, chiral induction as observed in solution is eventually canceled in the solid state. This was initially shown for octamer **1**,[29] and was repeated for octamers **2** and **6** (see below). In each case, the asymmetric unit contains one right-handed and one left-handed helical diastereomer both with an *R* stereocenter. It came as a surprise because examples of cocrystals of diastereomers are rare[32] and have even more rarely been observed in the context of chiral induction. A related phenomena was reported for isotactic poly-(*S*-4-methyl-1-hexene), the crystals of which apparently contain an equal number of right- and left-handed helices even though one handedness is favored in solution.[33] Enantiomeric helices, as other mixtures of enantiomers,[34] tend to crystallize as racemates

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(34) About 90−95% of racemic solutions produce racemic crystals, and at most 5−10% spontaneously resolve in crystals containing exclusively one or the other enantiomer (conglomerate). See: Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*, 3rd ed.; Krieger Publishing Co.: Malabar, FL, 1994.

instead of forming conglomerates. This trend is followed by the P and M enantiomeric conformers of helical aromatic oligoamides not bearing any asymmetric centers, which all crystallize in centrosymmetric space groups.[26,27,35,36] In the case of **1**, **2**, and **6**, the two diastereomeric helices behave as pseudo-enantiomers even though they are diastereomers. It seems that in the process of forming a pseudoracemic crystal, helical chirality "weighs" more than the stereogenic center.

The cocrystallization of two interconverting helical diastereomers appears even more remarkable when one considers the energetic parameters involved. In the case of **1**, the proportions between the major and the minor helices in solution at 25 °C amount to 10:1 reflecting an energy difference of 5.7 kJ/mol. On the other hand, the half-life of helix inversion of 154 min reflects an energy barrier of interconversion at 25 °C of about 18 kJ/mol. That the 10:1 solution mixture is completely shifted to a 1:1 mixture in the solid state requires that crystal growth be slower than helix handedness inversion. Indeed, cocrystals of diastereomers of **1**, **2**, or **6** always grow over several days. Attempts to accelerate crystallization led to precipitates.

As discussed below, a positive aspect of these results is that they show, at once, the structure of both the major and the minor diastereomeric helices. However, as for Pauling's α-helix,[1−3] it is not at all obvious to decide which is which. Occasionally, we have obtained crystals that indeed contained only the major diastereomer, as could be established upon redissolving them and measuring the NMR spectrum.[29] However, none of these was close to be suitable for a single crystal X-ray diffraction analysis, and their aspect was more related to a crystalline powder. We finally could lift these difficulties precisely by using the strong tendency of racemates to cocrystallize that had been problematic with **1**, **2**, and **6**.

When using racemic compounds **8** and **9**, which both bear a (±)-phenethylamino group, crystals grown upon diffusion of *n*-hexane into a toluene solution were analyzed by X-ray diffraction and show, in both cases, that only one pair of enantiomers cocrystallize as a true racemate (Figure 5, Table 2). Both structures belong to the centrosymmetric space group *P*-1. As expected, each unit cell thus contains one right-handed and one left-handed helix. At the chiral center, the terminal phenyl group points away from the helix, the methyl group is aligned with the helical backbone, and the proton points toward the helix. Most importantly, in these crystals, *S* asymmetric centers are always associated with right-handed helicity and *R* asymmetric centers are associated with left-handed helicity.

Racemic crystals of **8** and **9** could be obtained much more easily than crystals of **1**−**6** containing exclusively a right- or a left-handed helix from a homochiral oligomer. We think that these results bear some general value, and attempts to crystallize racemates of helices might be useful in cases where homochiral helices do not crystallize as for numerous helical β-peptides.[10,11,37] The tendency of peptide racemates to crystallize has actually been widely used in the past to quantify racemization in peptide coupling reactions as in the Young test[38] and the Anderson test.[39]

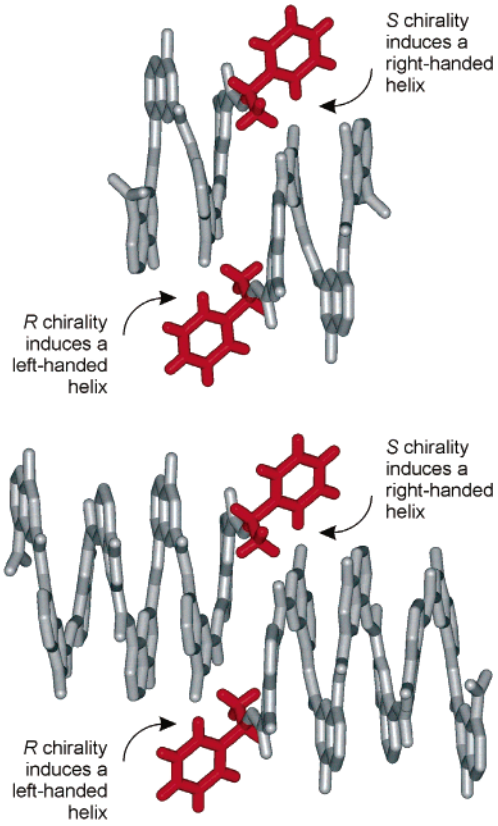

Figure 5. Crystal structures of octamer **8** and tetramer **9**. The entire unit cells are shown. Included toluene solvent molecules, isobutyl side chains, and backbone hydrogens have been omitted for clarity.

The crystal structures of **8** and **9** show that one configuration of the stereogenic center is always associated with the same handedness of the helix. However, to unambiguously assign the handedness of the major and minor diastereomers in solution, it remained to determine whether the pair of enantiomers *S*-P, *R*-M observed in the solid state corresponds to the major or to the minor species in solution. This was achieved by measuring NMR spectra of freshly dissolved crystals of **8**, taking advantage of the low helix inversion rates.[31] As shown in Figure 6, the NMR spectrum of freshly dissolved crystals of racemic octamer **8** at −30 °C shows essentially one set of signals belonging to the racemic mixture of *S*-P and *R*-M helices, thus reflecting the composition of the crystal. Only trace amounts of the other racemic pair can be detected. After the temperature was raised to 25 °C, the chemical shift values allow one to unambiguously assign these signals to the major diastereomer observed in solution (Figure 6b). A second set of signals progressively builds up, corresponding to the other pair of enantiomers, *R*-P and *S*-M, and equilibrium is reached after 1 day (Figure 6c). An NMR spectrum of the equilibrium solution at −30 °C allows one to check that equilibrium shift is not due to temperature change (Figure 6d).

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Table 2. Crystallographic Data for **2**, **6**, **8**, and **9**

	2	6	8	9
solvent/precipitant	toluene/hexane	toluene/hexane	toluene/hexane	toluene/hexane
formula	$(C_{120}H_{127}N_{17}O_{18})_2$	$(C_{121}H_{121}N_{17}O_{20})_2$	$C_{120}H_{121}N_{17}O_{18}$	$C_{64}H_{65}N_9O_{10}$
(asymmetric unit)	$(H_2O)_4$	$(C_7H_8)_2$	$(C_7H_8)_2-(C_6H_{14})$	$(C_7H_8)_{0.5}-(C_6H_{14})_{0.5}$
dimensions (mm)	0.10 × 0.15 × 0.20	0.15 × 0.15 × 0.20	0.25 × 0.20 × 0.15	0.45 × 0.45 × 0.40
aspect	yellow prisms	yellow prisms	yellow prisms	yellow prisms
cryst. syst.	triclinic	triclinic	triclinic	triclinic
space group	*P*1	*P*1	*P*-1	*P*-1
Z	1	1	2	2
unit cell params.				
a (Å)	17.353(1)	17.126(1)	17.8823(8)	13.271(1)
b (Å)	18.956(1)	19.100(1)	17.9987(8)	14.131(1)
c (Å)	19.884(1)	20.095(1)	21.8143(9)	20.652(1)
α (deg)	99.42	74.62	86.313(3)	90.15(1)
β (deg)	100.11(1)	78.47(1)	69.151(3)	104.04(1)
γ (deg)	93.68	84.68	74.408(3)	117.10(1)
temp (K)	133(2)	133(2)	153(2)	296(2)
volume (Å^3)	6323.2(6)	6204.4(6)	6316.1(5)	3315.9(4)
Fw (g mol^{-1})	4262.85	4450.96	2359.78	1209.40
ρ (g cm^{-3})	1.117	1.191	1.241	1.211
radiation	Cu Kα	Cu Kα	Cu Kα	Mo Kα
λ (Å)	1.54178	1.54178	1.54178	0.71073
θ measured	$11.12 \le \theta \le 57.56$	$11.13 \le \theta \le 56.12$	$6.52 \le \theta \le 72.11$	$2.94 \le \theta \le 24.98$
refl. mesured	30 941	56 001	21 837	20 134
refl. unique	18 089	25 876	21 837	11 531
GOF	1.251	1.252	1.029	1.034
R_1 ($I > 2\sigma(I)$)	0.1398	0.1484	0.1132	0.0837
wR_2 (all data)	0.3802	0.4119	0.4161	0.2883

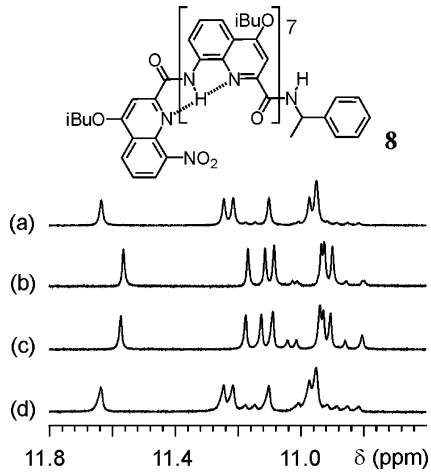


Figure 6. Parts of 400 MHz ^{1}H NMR spectra of racemic compound **8** in $CDCl_3$ showing the signals of the seven intramolecularly hydrogen-bonded amide protons (a) at −30 °C just after dissolving crystals grown from toluene, (b) after 1 h at 25 °C, (c) at equilibrium at 25 °C after 3 days, and (d) at equilibrium at −30 °C.

Thus, ^{1}H NMR spectra definitely confirm that the species observed in the solid state are indeed the major diastereomers in solution. For octamer **1**, which bears an *R* phenethylamino group, left-handed helicity is thus favored. By comparison of the sign of the CD bands of octamer **1** and of octamers **2**−**6** (Figure 1), assignment of the screw sense favored by the stereogenic center for each chiral compound can be deduced. For **1**−**5**, M helicity is favored, while P helicity is favored for **6**.

Role of Steric Effects. Chiral induction of helix handedness in **1**−**7** is highly variable in amplitude, and the favored handedness does not simply relate to the absolute configuration of the asymmetric center. As mentioned above, crystal structures of **1**,[29] **2**, and **6** could be obtained where both the major and the minor diastereomers have cocrystallized (Figure 7, Table 2). In these structures, the right- and left-handed helices are related by a pseudo-center of inversion, and they differ only by the position of two substituents at the asymmetric carbon. In **1** and **2**, the hydrogen and the methyl group are either pointing toward or away from the helix in the right- and left-handed forms, and the phenyl and cyclohexyl residues are always found aligned with the helical backbone, stacked face-to-face with the second quinoline ring of the sequence. In the case of **6**, the hydrogen is always found pointing toward the helix and the phenyl and methyl ester groups are either aligned with the helical backbone or pointing away from it.

In each of these three structures, both helices can be assigned to the major and minor diastereomer observed in solution on the basis of the combined X-ray, NMR, and CD data collected with compound **8**. However, even with this assignment at hand, it is not simple to explain why M-**1**, M-**2**, and P-**6** are more abundant in solution than P-**1**, P-**2**, and M-**6**, respectively. Given the size of the various substituents at the stereogenic centers in **1**−**7**, we suspected that steric hindrance between the terminal residues and the helix might play a role. One might for example point to the fact that the chiral carbon of **1**−**4**, for which chiral induction of helix handedness is the strongest, bears one proton, one methyl, and a group much larger than a methyl group (phenyl, cyclohexyl, or naphthyl). When chiral induction is weak (as in **5**−**7**), the chiral carbon bears one proton and two residues, the sizes of which do not differ too much (ester/amide and phenyl, or ester and benzyl).

The effect of sterics can be rationalized using a nomenclature different from the *R*/*S* notation to describe the stereochemistry of the asymmetric carbon in **1**−**6**. If one defines a R^s/S^s nomenclature where the four substituents are not ranked according to the Cahn−Ingold−Prelog rules but according to decreasing sizes (helix > naphthyl > phenyl > benzyl > ester > methyl > hydrogen), the configuration is R^s for **1**−**5** and S^s for **6**. Using this description, a left-handed helix is favored when

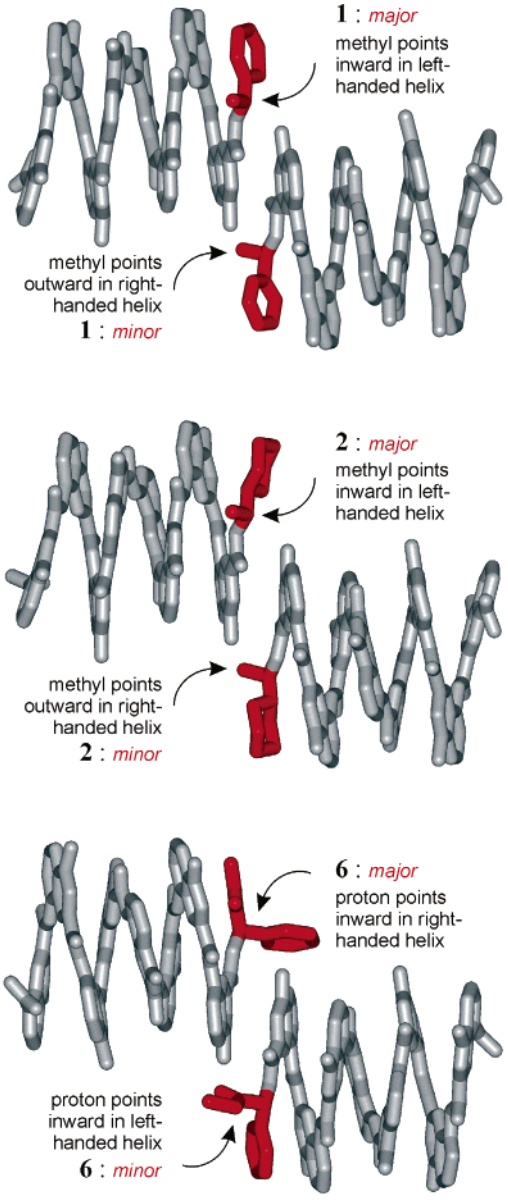


Figure 7. Crystal structures of chiral octamers **1**,[29] **2**, and **6** (asymmetric units) showing both right- and left-handed diastereomers. Included toluene solvent molecules, isobutyl side chains, and hydrogens have been omitted for clarity.

the configuration is R^s and a right-handed helix is favored when the configuration is S^s. This model applies even if the size difference is weak as in **5** and **6**. It is also consistent with a larger chiral induction in **3** than in **4** (1-naphthyl > 2-naphthyl). However, some discrepancies also show that sterics are not the only effects involved. For example, one might have expected larger chiral inductions in **2** and **4** than in **1** (cyclohexyl and 2-naphthyl > phenyl), but the reverse is observed.

Conformational Behavior at the Stereogenic Center. To understand how sterics and other effects might operate, we examined more carefully the possible conformations at the chiral center in each helix. For **1**,[29] **2**, and **6**, the crystal structures shown in Figure 7 display two possible conformations at the chiral center. Moreover, the conformations of the phenethylamino group in the right-handed and the left-handed helices of **1** (Figure 7) differ from its conformation in the crystals of **8** and **9** (Figure 5). In the former, the phenyl group lies stacked

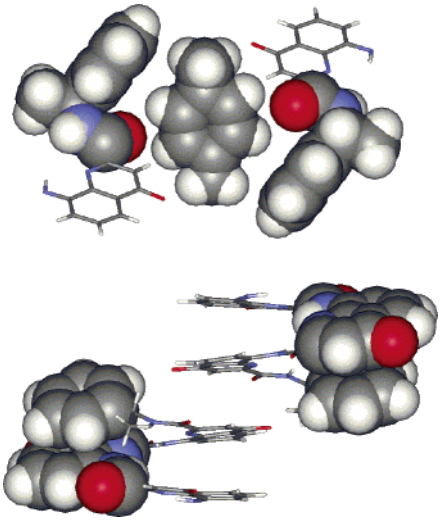


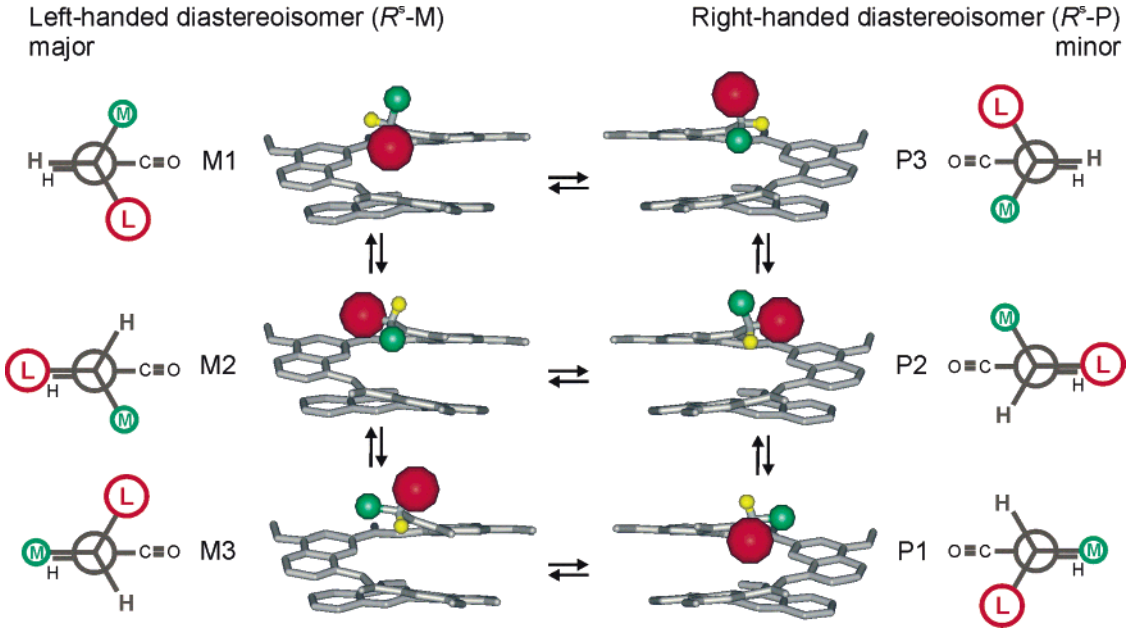
Figure 8. Parts of the crystal structures of racemic tetramer **9** (top) and chiral octamer **1** (bottom), showing different packing modes at the stereogenic center. In **9**, the phenyl groups are involved in edge-to-face aromatic stacking with a toluene molecule (the toluene occupies statistically two possible positions, which gives it the aspect of a *p*-xylene molecule with two "half-methyl" groups). In **1**, the phenyl groups are stacked face-to-face on the second quinoline ring in the helix sequence, and the first quinoline rings of different helices also stack face-to-face; no specific interactions with included toluene molecules are observed.

on the helix, while in the latter it points away from it. This difference might originate in packing arrangements in the crystal and from interactions with included solvent molecules as shown in Figure 8. The conformations in the crystal are not necessarily representative of the conformations in solution. The crystal structures nevertheless reveal that the stereogenic centers may be involved in a variety of conformations.

From the various conformations observed in the solid state, it can be proposed that each of the three substituents (besides the helix itself) of the chiral carbons in **1**−**6** can be in any of three positions: pointing toward the helix, or away from it, or aligned with the helical backbone. Considering a helix bearing for instance an R^s asymmetric center (see above for a definition of R^s), each diastereomer R^s-P (minor) and R^s-M (major) may undergo an equilibrium between three different conformers, M1, M2, M3, generated by 120° rotations of the chiral group about the HN−C* bond (Scheme 1). In these conformers, the substituent on the chiral carbon that is aligned with the helical backbone is in an eclipsed conformation with the amide proton, so as to minimize steric hindrance with the amide carbonyl. Steric hindrance is also expected to prevent the bulkiest substituent from pointing toward the helix, which should not be possible without bringing significant perturbations to the helix. Indeed, in no case conformers such as M1 and P1 (Scheme 1) were observed in the solid state, and it seems reasonable to assume that these two conformers are not significant in solution. When the second largest group is larger than a methyl group, as for methyl ester **6**, it may be assumed that this group may not point toward the helix as well; conformers M2 and P3 are also highly disfavored by steric hindrance. Thus, the two conformers in the crystal structure of **6**, corresponding to M3 and P2,[40] are probably the only conformers present in solution for this compound. The conformer that is favored among these

(40) In fact, it is their/its mirror image(s) because **6** bears an S^s chiral group, whereas Scheme 1 illustrates the case of an R^s chiral group.

Scheme 1. Schematic Structures and Newman Projections of Three Left-Handed Conformers (M1, M2, M3) and Three Right-Handed Conformers (P1, P2, P3) of a Helix Bearing a R^s Chiral Center[a]



[a] M1, M2, and M3 (respectively, P1, P2, and P3) are interconverted by 120° rotations about the HN−C* bond. M2 and P2, M1 and P3, and M3 and P1 are interconverted by helix handedness inversion. The substituents of the chiral group are represented by balls of different sizes (medium = M and large = L), according to their bulkiness. The largest substituent points to the helix in M1 and P1, is aligned with the helical backbone in M2 and P2, and points away from the helix in M3 and P3.

two then determines the preferred handedness of the helix. In the case of **6**, it is remarkable that the preferred conformer is the one where the large substituent (phenyl) points away from the helix and the medium size substituent (methyl ester) is aligned with the helical backbone (equivalent to M3[40]). This apparently supports the idea that steric repulsion between the large phenyl group and the helix overcomes favorable face-to-face aromatic stacking between the phenyl group and the helix as observed in the minor diastereomer (Figure 7).

When the second largest group is a methyl, conformations such as M2, where this group protrudes toward the helix, have been observed in the crystal structures of **1** and **2** (Figure 7). In fact, for compound **1**, M2, P2, and M3 conformers have all been observed in the solid state, and only P3 has not. The helix handedness is then determined by the ratio between the population [M2 + M3] (favored) and [P2 + P3] (unfavored). Assuming that steric effects rule the conformation at the stereocenter, the bulkiest group should preferentially point away from the helix, the second largest group should be aligned with the helix backbone, and the smallest should point to the helix. Thus, in **1** and **2**, conformer M3 should be more stable than P2 and P3. However, conformer M2 should be less stable than P2 and P3. The most stable conformer does have the preferred handedness, and this may be enough to drive the equilibrium in its favor. However, given the relatively small effects reported in Table 1, this preliminary analysis needs to be refined by a more quantitative approach, using ab initio calculation or molecular dynamics, so as to estimate the contributions of factors other than sterics.

Conclusion

We have shown that chiral groups attached to the end of quinoline-derived oligoamide foldamers give rise to chiral helical induction in solution. Chiral induction was first demonstrated by circular dichroism spectroscopy and was quantified using NMR spectroscopy. Despite the fact that the observed chiral inductions are relatively weak and that diastereomeric helices coexist and interconvert in solution, the right-handed or left-handed helical sense favored by the terminal chiral group could be determined unambiguously using X-ray crystallography. Assignment of chiral induction was performed in an original way using the strong tendency of racemates to cocrystallize, and taking advantage of slow helix inversion rates, which allowed one to establish that the stereomers observed in the crystals do correspond to the major stereomers in solution. We think that these results bear some general value, and attempts to crystallize racemates of helices might be useful in cases where homochiral helices do not crystallize. The sense of chiral helical induction was rationalized on the basis of sterics. Upon assigning an R^s or S^s chirality to the stereogenic center using a nomenclature where the four substituents are ranked according to decreasing sizes, it is observed that R^s asymmetric centers always favor left-handed helicity (M) and S^s asymmetric centers favor right-handed helicity (P). X-ray structures shed some light on the role of sterics in the mechanism of chiral induction. The preferred conformation at the stereocenter is apparently one where the bulkiest group should preferentially point away from the helix, the second largest group should be aligned with the helix backbone, and the smallest should point to the helix. However, some discrepancies also show that sterics are not the only effects involved. It will be interesting to refine this preliminary qualitative analysis by a more quantitative approach, using ab initio calculation or molecular dynamics, so as to incorporate others factors than sterics. Future developments also include the use of chiral elements other than simple stereogenic

centers to induce helical chirality in quinoline-derived oligoamide foldamers, as, for example, various types of helical peptides.

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Supporting Information Available: Crystallographic data in CIF format, and characterization of compounds **2**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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