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Helix Persistence and Breakdown in Oligoureas of Metaphenylenediamine: Apparent Diastereotopicity as a Spectroscopic Marker of Helix Length in Solution

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Abstract: Oligomeric ureas derived from *m*-phenylenediamine with chain lengths of up to seven urea linkages were made by iterative synthetic pathways. Three families were synthesized: **4** and **20**, bearing a terminal chiral sulfinyl group; **24**, bearing a terminal rotationally restricted amide group, and **30** bearing a terminal achiral bromophenyl group. The distal end of the oligomers was capped with an *N*-benzyl group to act as a diastereotopic probe. With a terminal sulfinyl group, the ^{1}H NMR signals arising from the CH_2 group of the diastereotopic probe remained anisochronous even when separated from the stereogenic center by up to 24 bonds (in **20c)**. With a rotationally restricted amide, anisochronicity was no longer apparent beyond 17 bond lengths (in **24c**). No anisochronicity was observable with a terminal bromophenyl group. We interpret these results as indicating that the oligoureas of short lengths adopt a defined helical secondary structure in solution, but that in longer oligomers the helicity breaks down and transmission of chirality in these systems is limited to about 24 bond lengths. We propose that "apparent diastereotopicity" (anisochronicity) provides a general empirical method for identifying secondary structure in solution.

Introduction

The absolute control of the *configuration* of new stereogenic centers has been for several decades a central goal of synthetic chemistry.[1] Comparable stereochemical control over *conformation*, particularly of acyclic molecules, is a more nebulous aim toward which slow progress has been made in recent years.[2] Substitution patterns have been manipulated to induce defined conformational features in alkyl[3] and silyl[4] chains; methods have been developed for the control of slowly interconverting conformers (or atropisomers),[5−9] and the propagation of a chiral influence through global conformational control[10] has been exploited as a means of communicating stereochemical information over long (nanometer-scale) distances,[11,12] a chemical analogue of biological allostery. With respect to structurally repetitive compounds, numerous classes of foldamers—oligomers with a well-defined conformation—have been reported.[13,14]

Many classes of foldamers, even those made of achiral monomers, adopt well-defined, typically helical, conformations in the solid state.[13,15,16] Some of these have been proposed to retain helical conformations in solution as well, but determining the extent of

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helicity in solution in systems where conformational interconversion is rapid poses a significant challenge.[17] In some cases, these foldamers have been shown to adopt absolute helicity dependent only on stereochemistry present at one terminus.[18−21] An estimation of the fidelity with which such oligomers respond, in solution, to a terminal chiral influence is given by circular dichroism studies,[20−22] though generally only qualitative information about helicity is provided. Remotely stereoselective reactions[23] imply a degree of conformational control,[12,24] and the "chain length dependence test"[25] can give evidence of conformationally ordered structures. If diastereoisomeric conformers interconvert slowly on the NMR time scale direct measurement of conformational ratios may be possible.[19,21] However, when helix inversion is fast on the NMR time scale, it becomes difficult to establish (a) the extent to which the solution state conformation of the oligomer is helical and (b) the level of control obtained over the absolute helicity of the oligomer. (Absolute helicity (the adoption of specifically *M* or *P* helicity) most commonly results from chiral monomers which result in handed helices.[16] Cooperative effects mean that the "degree" of chirality required to provide a high level of helical control can be very small—even H vs D.[26] Likewise, not every monomer needs to be chiral for induction to be effective—the principle of "sergeants and soldiers" means that achiral monomers follow suit if chiral monomers are dispersed among them.[27])

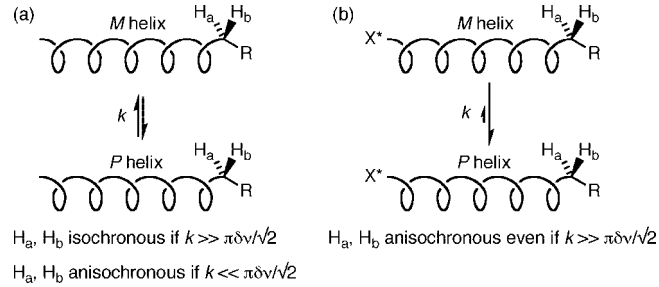

Figure 1. Fast and slow interconversion of enantiomeric and diastereoisomeric helices.

In this paper we propose that, even for oligomers undergoing fast conformational change, NMR methods can still provide a qualitative, empirical indication of the degree to which a molecule adopts a helical conformation in solution. Consider two enantiomeric interconverting helices carrying a pair of terminal protons H_a and H_b (Figure 1a) The protons are rendered diastereotopic by virtue of the chirality of the helix: slow (i.e., $k \ll \pi\Delta\nu/\sqrt{2}$, where $\Delta\nu$ is the chemical shift difference between H_a and H_b)[28] interconversion between the ***M*** and ***P*** helices will give rise to anisochronous signals (an AB system), as has been observed for example by Huc[29] and others. Fast interconversion (i.e., $k \gg \pi\Delta\nu/\sqrt{2}$) will however average the environments of H_a and H_b and these protons will appear isochronous (a 2H singlet).

Attaching a chiral controlling element X* to the terminus of the helix generates a diastereoisomeric pair of structures (Figure 1b). Now, even if the helices undergo fast interconversion, H_a and H_b remain diastereotopic by virtue of the presence of X*. However, the *apparent* diastereotopicity—the spectroscopically observed anisochronicity—of H_a and H_b due to the direct effect of X* will decrease rapidly as the oligomeric chain is lengthened, and direct interaction between X* and the geminal pair H_a, H_b is lost. Nonetheless, if X* is able to bias the equilibrium such that one of the diastereoisomeric helices ***M*** or ***P*** predominates, then H_a and H_b remain in diastereomeric environments due to the local influence of the unequally populated helix conformations: they remain anisochronous and will still appear as an AB system, in principle irrespective of the distance from X*, and irrespective of the rate of helix inversion. In practice of course anisochronicity will be under the control of a range of other factors,[30] but it can safely be assumed that persistence of apparent diastereotopicity significantly beyond the maximum range usually observed in acyclic systems (>8 bond lengths, say[31]) indicates a degree of helicity in the solution state conformation. If however, as the helix lengthens, the conformation becomes disordered such that X* can no longer control the local chiral environment of H_a and H_b via the helix, then the signal arising from the diastereotopic pair of protons will collapse to a 2H singlet. The chemical shift difference $\Delta\nu$ between H_a and H_b may thus be useful as a chain-length dependent[25] empirical measure of the distance over which the helicity of an oligomer persists in solution.

Oligoureas—Preliminary Study. We chose to apply this proposed technique to a series of oligomeric ureas of structures

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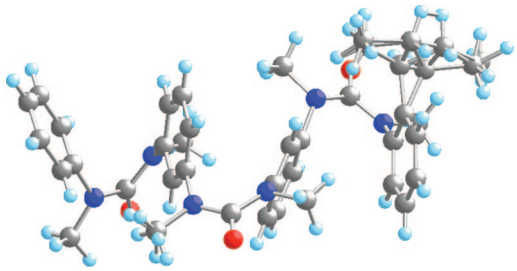


Figure 2. X-ray crystal structure of **1** [R^1 = H, R^2 = *s*-Bu].[36]

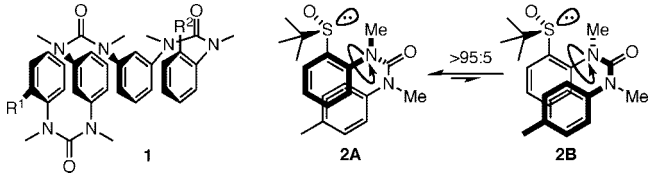
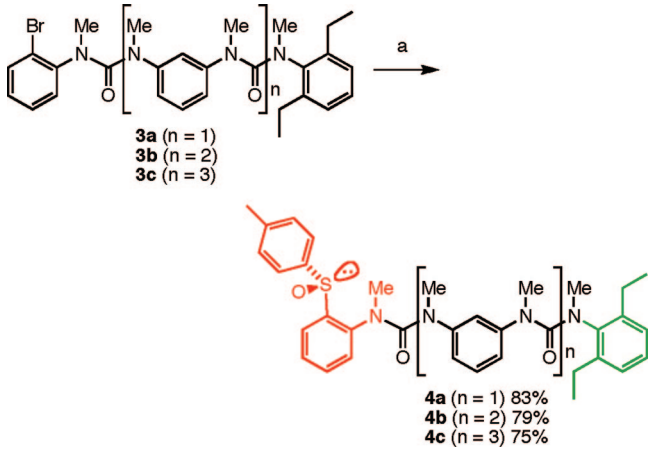


Figure 3. Conformational preferences in ureas.

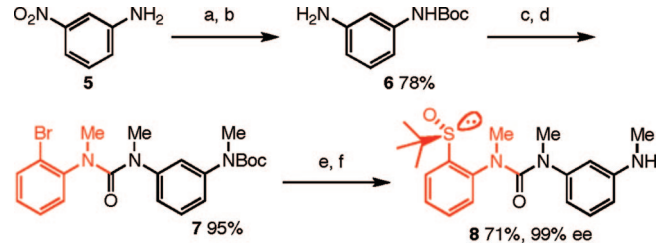
Scheme 1. Preliminary Synthesis of Three Sulfinyloligoureas[a]



[a] 1. *n*-BuLi, THF, −90 °C; 2. (1*S*, 2*R*, 5*S*)-(+)-menthyl-(R_S)-*p*-tolylsulfinate.

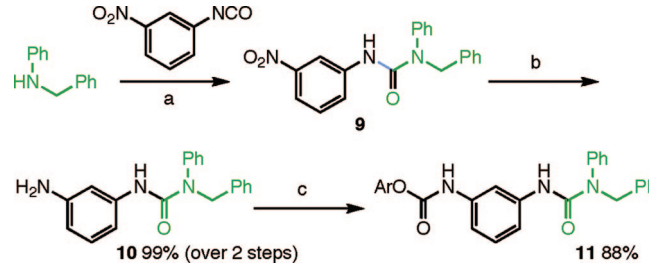
related to **1**. Fully *N*-substituted *N*,*N*′-diaryl ureas are known to adopt in general a conformation which places the aromatic rings close in space[32]—presumably due to π-stacking[33]—and kinetic and thermodynamic aspects of bond rotation in simple *N*,*N*′-diaryl ureas have been determined.[34,35] Oligomeric ureas of *N*,*N*-dimethyl-*m*-phenylenediamine (such as the triureas **1**, Figure 2) have been reported to adopt helical conformations in the solid state (Figure 2[36] shows the X-ray crystal structure of **1** [R^1 = H, R^2 = *s*-Bu]), and on the basis of upfield shifts in their NMR spectra, they have been assigned stacked, possibly helical conformations in solution.[36−38] In connection with attempts to use the propagation of a stereochemical influence within non-hydrogen bonded molecules to allow transmission of information in the form of stereochemistry,[10,12] we became interested in whether these oligo-ureas were indeed helical in solution, and if so whether their conformation could be controlled by a terminal chiral monomer.

Scheme 2. Synthesis of the Sulfoxide Terminus[a]



[a] (a) Boc_2O, THF, Δ 60 h; (b) H_2, Pd/C, THF, *i*-PrOH, rt, 16 h; (c) 2-BrC_6H_4NCO, CH_2Cl_2, rt, 14 h; (d) NaH, THF, 0 °C, 1 h; MeI rt, 60 h; (e) *n*-BuLi, THF, −90 °C, 1 min; (*R*)-*t*-BuSS(O)*t*-Bu, THF, −90 °C − rt, 18 h; (f) CF_3CO_2H, CH_2Cl_2, rt, 12 h.

Scheme 3. Synthesis of the N-Benzyl Terminus[a]



[a] (a) THF, rt, 16 h; (b) H_2, Pd/C, THF, *i*-PrOH, rt, 18 h; (c) *p*-$NO_2C_6H_4OCOCl$, py, THF, rt, 18 h.

Previous work[9] had shown that an enantiomerically pure arylsulfinyl or *t*-butylsulfinyl group placed adjacent to the ArC-N bond of an *N*-arylurea is able to exert powerful control over the orientation of the urea function (Figure 3). Alignment of dipoles and steric effects combine to ensure that **2**, for example, adopts the conformation **2A** in preference to **2B** with >95:5 selectivity (Figure 3). (For related examples of the use of sulfinyl groups to control bond orientation, see refs 5, 8, and 39.) We hoped that this conformational controlling effect, combined with the known preference for helicity in oligoureas, would allow the sulfinyl group to control the helicity of the urea in solution. Sulfinyl groups have proved to be widely effective in remotely stereocontrolled reactions.[40]

We had to hand[36] three oligoureas **3a**−**c** bearing a terminal 2,6-diethylphenyl group, and a simple halogen metal exchange followed by quench with (1*S*, 2*R*, 5*S*)-(+)-menthyl-(R_S)-*p*-tolylsulfinate[41] converted the bromo substituent to a tolylsulfinyl group (Scheme 1). We used the sulfoxides **4a**−**c** as a "proof of principle" before embarking on a more elaborate synthesis of a larger set of oligoureas. Because of slow rotation in the 2,6-diethylphenyl ring, the two ethyl groups of **3** may be rendered diastereotopic by virtue of the chirality of the helix. However, in **3** they appear as a single set of peaks, either because of fast helix interconversion or because of the lack of ordered

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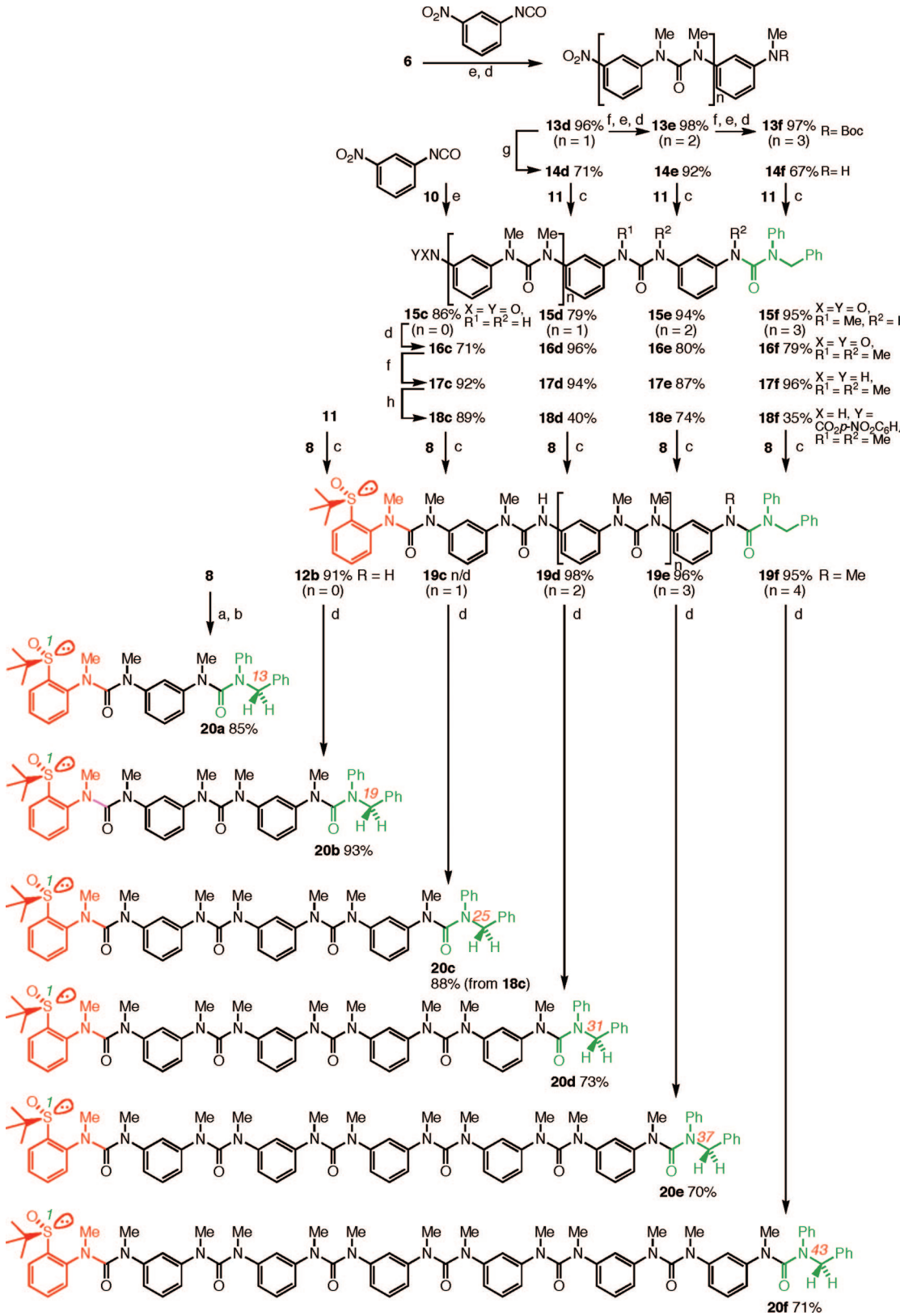
Scheme 4. Construction of Oligoureas[a]



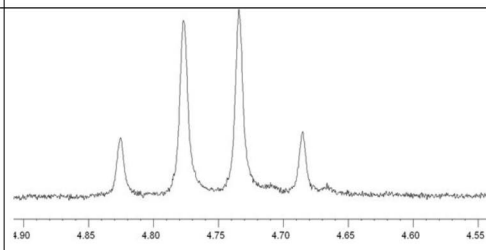
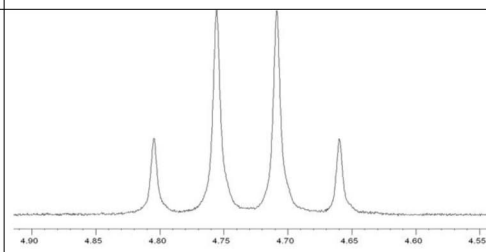
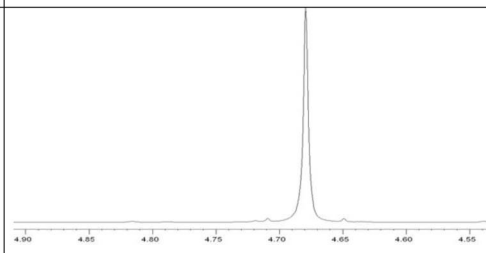
[a] (a) PhNCO, THF, rt, 14 h; (b) NaH, THF, 0 °C, 1 h; BnBr, rt, 10 h; (c) **8** and/or **11**, DMAP, THF, rt, 16 h; (d) NaH, THF, 0 °C, 1 h; MeI, rt, 14 h; (e) THF, rt, 18 h (32 h with **10**); (f) H_2, Pd/C, *i*-PrOH, THF, rt, 18 h; (g) CF_3CO_2H, CH_2Cl_2, rt, 15 h; (h) *p*-$NO_2C_6H_4OCOCl$, py, THF, rt, 18 h. Note that compounds are represented here for clarity—no assumptions about true solution conformations are implied.

conformation. In **4** however, diastereotopicity is evident in the ethyl groups of **4a** (the two terminal methyl triplets differ in chemical shift by 0.09 ppm) but for **4b** and **4c** peak separation between these triplets is essentially zero.

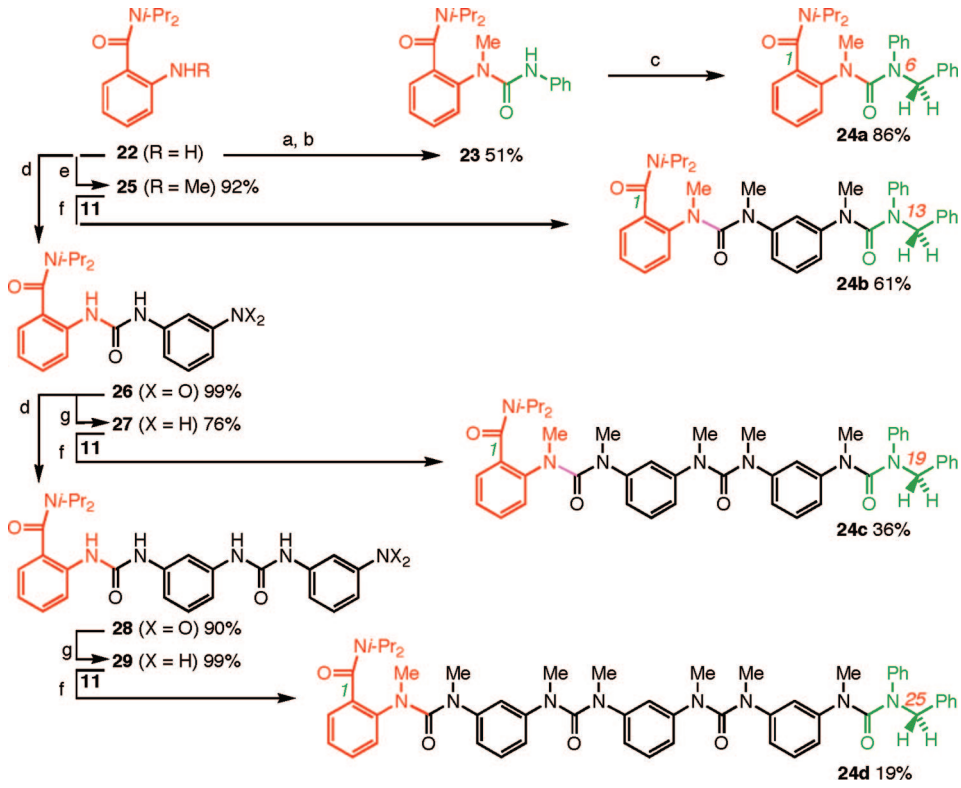
To investigate in more detail the effects of structure and chain length on apparent diastereotopicity we chose to simplify the diastereotopic probe to an *N*-benzyl group and also to make two further changes to **4**: first, we were concerned that the particularly bulky 2,6-diethylphenyl group might perturb π-stacking of the terminal ring of the oligomer.[35] Second, it had previously been noted that in some situations *t*-butylsulfinyl groups exert significantly greater conformational controlling effects than arylsulfinyl groups.[9]

We set out therefore to build oligoureas **20a**−**f** carrying at one terminus a *t*-butylsulfoxide substituent, and at the other a diastereotopic reporter group in the form of an *N*-phenyl-*N*-benzyl urea. Two obstacles meant that the route needed to be more elaborate than the iterative chain extension previously used for simple unfunctionalised compounds. First, oligoureas containing multiple NH groups tended to be intractable,[36] necessitating gradual N-methylation during the synthesis of the oligomers rather than global methylation at the end of the synthesis. Second, incompatibilities between (a) the (acidic,[42] toward BuLi) *N*-benzyl diastereotopic marker group and the (basic) conditions required for the introduction of the sulfoxide substituent, and (b) between the sulfoxide and the reductive hydrogenation conditions required during the chain extension (reduction of nitro to amino groups), meant that the two termini of the oligomers had to be separately synthesized before a late coupling step.

Table 1. Apparent Diastereotopicity in the NCH_aH_bPh Signal of Sulfinylureas **20**

compound	Separation of diastereotopic probe from stereogenic centre	Appearance of NCH_aH_bPh signal	$\Delta\delta$ (ppm x 10^{-3})
20a	1,13	 [C_6D_6, 300 MHz]	80 (C_6D_6) 0 $CDCl_3$)
20b	1,19	 [$CDCl_3$, 300 MHz]	83 ($CDCl_3$)
20c	1,25	 [$CDCl_3$, 500 MHz]	10 ($CDCl_3$, −90 to +23 °C)) 0 (other solvents)
20d	1,31	2 H singlet	0 (various solvents, +23 and −50 °C)
20e	1,37	2 H singlet	0 (various solvents, +23 and −50 °C)
20f	1,43	2 H singlet	0 (various solvents, +23 and −50 °C)
12b	1,19	2 H singlet	0 (various solvents, +23 and −50 °C)

Scheme 5. Synthesis of Amidoureas[a]



[a] (a) PhNCO, THF, rt, 14 h; (b) NaH (1.2 equiv.), THF, rt, 20 min; MeI (1.5 eqiuv.), rt, 16 h; (c) NaH, THF, rt, 20 min; BnBr, rt, 16 h; (d) *m*-$NO_2C_6H_4NCO$, THF, rt, 18 h; (e) Boc_2O, THF, Δ, 14 h; NaH, MeI, rt, 10 h; CF_3CO_2H, CH_2Cl_2, rt, 2 h; (f) **11**, DMAP, THF, Δ, 12 h; NaH, THF, MeI, rt, 16 h (g) H_2, Pd/C, MeOH, THF, rt, 18 h.

Synthesis of the Sulfinyloligoureas. The sulfoxide terminus was constructed as shown in Scheme 2. The monoprotected diamine **6** was converted into bromourea **7**. Halogen-lithium exchange required very low temperature to avoid decomposition; quenching with Ellman's di-*tert*-butylthiosulfinate[43] gave the sulfoxide in enantiomerically pure form (by HPLC) which was deprotected to yield aniline **8**.

The *N*-benzyl terminus required for all but the simplest member of the series **20a** was made as shown in Scheme 3. Urea formation from *N*-benzylaniline and 3-nitrophenyl isocyanate gave **9** which was reduced to aniline **10** and converted to reactive carbamate **11** by acylation with *p*-nitrophenyl carbamyl chloride.

The diurea **20a** was made simply by addition of sulfinylaniline **8** to phenylisocyanate and N-benzylation of the product (Scheme 4). The next member of the series, triurea **20b** was made by acylation of the same sulfinylaniline **8** with the benzylated reactive carbamate **11**, followed by N-methylation of the resulting urea **12b**.

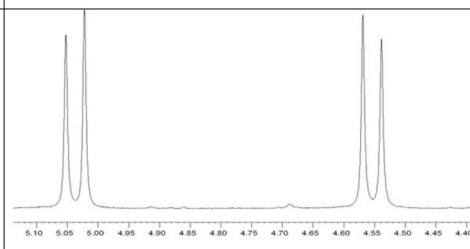
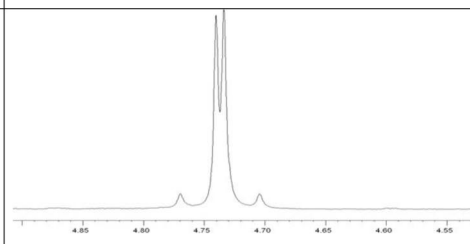
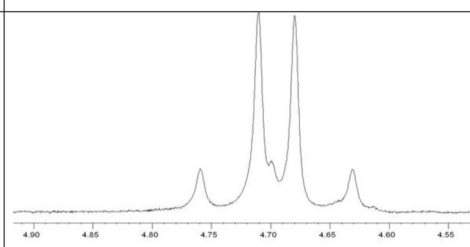
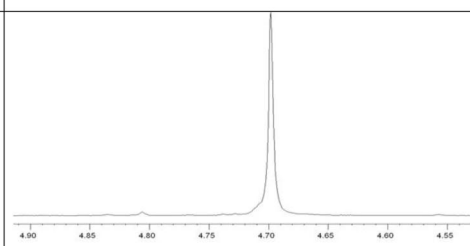
For the remaining members of the series it was necessary to synthesize separately a central oligourea section **14**, which was then sequentially capped with the *N*-benzyl terminus to yield **16** and the sulfoxide terminus to yield **19** and hence **20**. Scheme 4 shows how this central section was built up for various chain lengths. First, monoprotected *m*-phenylendiamine **6** was added to 3-nitrophenyl isocyanate to yield, after methylation, **13d**. Monourea **13d** was then treated under our published urea chain extension conditions[36] to yield the diurea **13d** and the triurea **13e**. Oligoureas bearing multiple NH groups soon become intractable, insoluble powders, so with each chain growth step the ureas **13** were methylated. Deprotection of each member of the series **13** yielded anilines **14d**−**f**. At this stage, the N-benzyl terminus was introduced: acylation of the mono-, di- and triureas **14d**−**f** with reactive carbamate **11** yielded tri-, tetra- and pentaureas **15d**−**f**. An analogous diurea member of this series **15c** was obtained by chain extension of **10** with *m*-nitrophenylisocyanate **9**. Again, for ease of handling it was necessary to methylate the remaining nonalkylated urea nitrogens of **15**, yielding fully methylated di-, tri-, tetra- and pentaureas **16c**−**f**.

These ureas were prepared for capping with the sulfoxide terminus by reduction to the amines **17** followed by formation of the reactive carbamates **18**. Acylation of sulfinyl aniline **8** by **18c**−**f** yielded tetra-, penta-, hexa- and heptaureas **19c**−**f**. A final methylation yielded the remaining members of the family of oligoureas **20**: tetraurea **20c**, pentaurea **20d**, hexaurea **20e** and heptaurea **20f**.

NMR Studies of Sulfinylureas. ^{1}H NMR spectra of the sulfinylureas **20a**−**f** were obtained at either 300 or 500 MHz at a concentration of ca. 10 mg mL^{-1} in deuterated chloroform, benzene, toluene, methanol or DMSO at 23 °C. The form of the NCH_aH_bPh signal at ca. δ 4.9−4.6 was examined, and representative examples are illustrated shown in Table 1, which also tabulates the chemical shift difference, $\Delta\delta$, in ppb, between the two anisochronous signals, which was established by modeling the AB system using the commercial software gNMR. When diastereotopicity was apparent, the signal took the form of an AB system, J = 14.7 Hz. In other cases, a 2 H singlet was observed.

Clear AB systems were evident for the diurea **20a** and the triurea **20b** (though surprisingly **20a** displays a 2H singlet in chloroform). In tetraurea **20c** the diastereotopic probe lies 24 bond-lengths from the sulfinyl group, and in most solvents appeared as a 2 H singlet. Nonetheless, in $CDCl_3$, a clear, very

Table 2. Apparent Diastereotopicity in the NCH_aH_bPh Signal of Amidoureas **24**[a]

compound	Separation of diastereotopic probe from stereogenic axis	NCH_aH_bPh signal	$\Delta\delta$ (ppm x 10^{-3})
24a	1,6	 [$CDCl_3$, 500 MHz] [not to same scale]	484 ($CDCl_3$)
24b	1,13	 [$CDCl_3$, 500 MHz]	20 ($CDCl_3$)
24c	1,19	 [$CDCl_3$, 300 MHz]	65 ($CDCl_3$)
24d	1,25	 [$CDCl_3$, 500 MHz]	0 (various solvents, +23 and –50 °C)

[a] Minor peaks visible in the NMR spectra are due to small amounts of inseparable impurities.

strongly coupled, AB system is evident. The outer lines of the AB system are clearly located ca. 15 Hz from the central line, clearly distinguishable from the natural abundance ^{13}C coupled doublet with $^1J_{CH} = 138$ Hz. The form of the AB signal remained essentially unchanged over a range of temperatures from −90 to +23 °C. It was also independent of concentration, appearing the same at 1/2, 1/4, and 1/8 dilutions of the original concentration.

Urea **12b** is the incompletely methylated analogue of **20b** and in contrast with **20b** its NCH_aH_bPh signal is a 2H singlet.

Penta-, hexa- and heptaureas **20d**−**f** displayed no apparent diastereotopicity in their NCH_aH_bPh signals in a variety of solvents and at a variety of temperatures. A number of attempts were made to detect the presence of unresolved chemical shift differences between coupled protons in these compounds by using homonuclear INADEQUATE experiments with very long (up to 1 s) evolution delays. Long evolution delays are needed because the effect of strong coupling is to shift the optimum delay for double quantum excitation to longer times;[44] in the limit of very strong coupling the optimum total delay is of the order of T_2. In principle this is a very sensitive test, capable of detecting very small shift differences, since double quantum coherence between two spins can only be created if they are distinguishable. Unfortunately the detection of intramolecular double quantum coherence, which requires that the two spins involved have (slightly) different chemical shifts, is confounded by the potential presence of intermolecular double quantum coherence arising from the very weak long-range dipolar

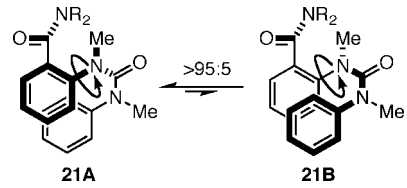
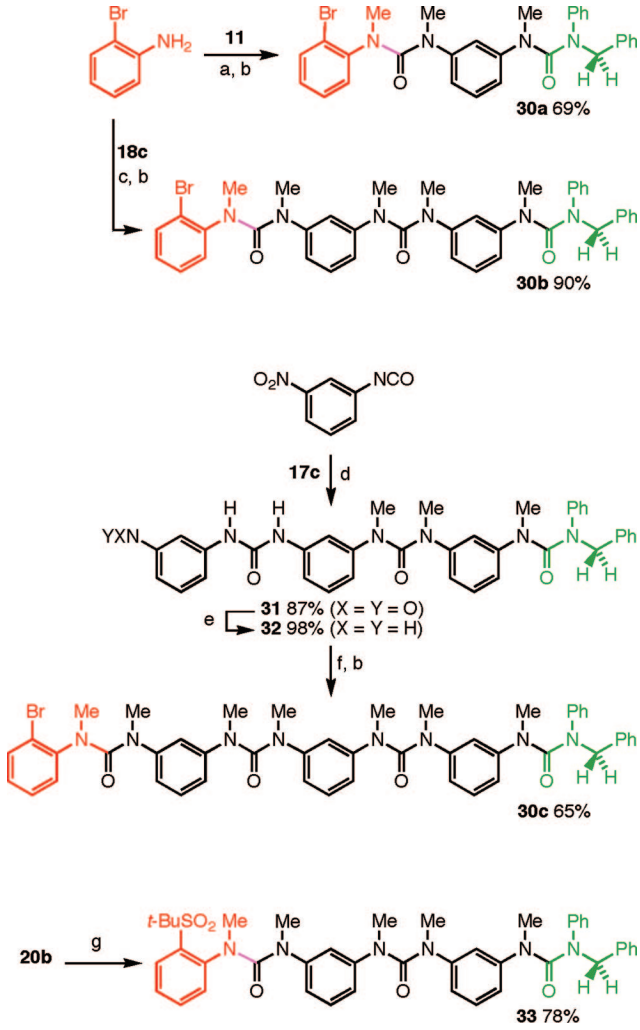


Figure 4. Conformation of an amido urea.

Scheme 6. Synthesis of Bromoureas and a Sulfonyl Urea[a]



[a] (a) **11**, DMAP, THF, rt, 12 h; (b) NaH, THF, 0 °C, 1 h; MeI, rt, 15 h; (c) **18c**, DMAP, THF, rt, 12 h; (d) **17c**, THF, rt, 16 h; (e) H_2, Pd/C, THF, *i*-PrOH, rt, 16 h; (f) 2-BrC_6H_4NCO, THF, rt, 16 h; (g) *m*-CPBA, CH_2Cl_2, rt, 12 h.

interaction between blocks of spins in different spatial regions of the sample.[45] Such effects are most commonly seen in very concentrated samples, typically in protiated solvents such as H_2O, but can be detected at much lower concentrations if, as here, suitably sensitive methods are employed. A diagnostic difference between intra- and intermolecular coherence is that the amplitudes of signals deriving from the former scale linearly with concentration, and those for signals deriving from the latter scale quadratically; a more direct solution to the problem would be the use of magic angle gradient pulses.

Synthesis of Amidooligoureas. Unlike circular dichroism, apparent diastereotopicity is independent of homochirality and must apply equally to both enantiomerically enriched and to racemic samples. Furthermore, just as NMR will detect transiently chiral conformations provided enantiomeric conformers interconvert slowly on the NMR time scale, so even achiral molecules adopting transient helical conformations may be studied by our method. In order to explore this feature, we made a series of oligoureas **24** terminated simply by a "conformational anchor"—an amide group whose bond rotation is slow on the NMR time scale[5,46] and which therefore prevents rapid helix inversion.

Amidourea **21** and its congeners have been shown to adopt a single relative conformation **21A** in solution (Figure 4),[9] and in the solid state the amide and the urea dipoles are orientated *anti* to one another as shown.[9] Based on previous studies,[6,46] we expected the rate of interconversion at ambient temperature of the two enantiomeric *anti* conformations of **21** to be too fast for **21** to be considered a chiral molecule, but slow enough for the NMR spectrum of **21** to lie in the slow exchange regime. *N*-Benzyl urea **24a** was made from **22** by regioselective methylation followed by benzylation (Scheme 5). The signal for the NCH_2Ph group of **24a** was evident as a clear AB system, an observation fully consistent with slow ($t_{1/2}$ > ca. 0.01 s) Ar-CO rotation.

A further series of amidooligoureas **24** based on this structure were built up as shown in Scheme 5. Amine **25** was acylated with **11** to give the diurea **24b**. The stability of the amide substituent meant that a simple series of homologations[36] of amine **22** using 3-nitrophenylisocyanate, followed by reduction, gave unsubstituted ureas **27** and **29**, each of which was acylated with **11** and globally methylated to yield triurea **24c** and tetraurea **24d**. For the simplicity of the route, global methylation was reserved until the final step. However, the intractability of the intermediate ureas meant that overall yields were low.

NMR Studies of Amidoureas. As with the sulfinylureas, ^1H NMR spectra of the amidoureas **24a**−**d** were obtained at either 300 or 500 MHz at a concentration of ca. 10 mg mL^{-1} in deuterated chloroform or other solvents at 23 °C. Representative examples of the form of the NCH_aH_bPh signal at ca. δ 4.9−4.6 are illustrated in Table 2, which also tabulates the chemical shift difference, $\Delta\delta$, in ppb, between the two anisochronous signals.

In the monourea **24a**, with only a 5-bond separation between the diastereotopic probe and the rotationally restricted amide, an AB system ($J = -14.7$ Hz) with peak separation of nearly 0.5 ppm was observed. This separation dropped to 20 ppb in the diurea **24b** (13 bonds from amide to probe) but interestingly rose again to 65 ppb in the triurea **24c**, possibly because the influences of the amide and the helix on the relative chemical shifts of H_a and H_b are opposed in sign. In the tetraurea **24d**, in every solvent tried, and at low temperature in $CDCl_3$, toluene or deuteromethanol, a 2 H singlet was observed.

Synthesis of Bromooligoureas. As a further control, we synthesized a series of three oligoureas devoid of a terminal chiral group of any type, namely bromooligoureas **30a**−**c**. (Ar−N bond rotation in related simple 2-bromoureas takes place with a barrier of around 55 kJ $mol^{-1}$and a half-life for bond rotation of around 5 ms at 25 °C.[24,35]) Diurea and triurea **30a** and **30b** were made by addition of 2-bromoaniline to **11** and **18c**, respectively, followed by global methylation; tetraurea **30c**

(42) Clayden, J.; Dufour, J. *Tetrahedron Lett.* **2006**, *47*, 6945.
(43) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317.
(44) Freeman, R.; Bax, A. *J. Magn. Reson.* **1980**, *41*, 507.
(45) (a) Levitt, M. H. *Concepts Magn. Res.* **1995**, *8*, 77. (b) Warren, W. S.; Richter, W.; Reotti, A. H.; Farmer, B. T. *Science* **1993**, *262*, 2005.
(46) Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.

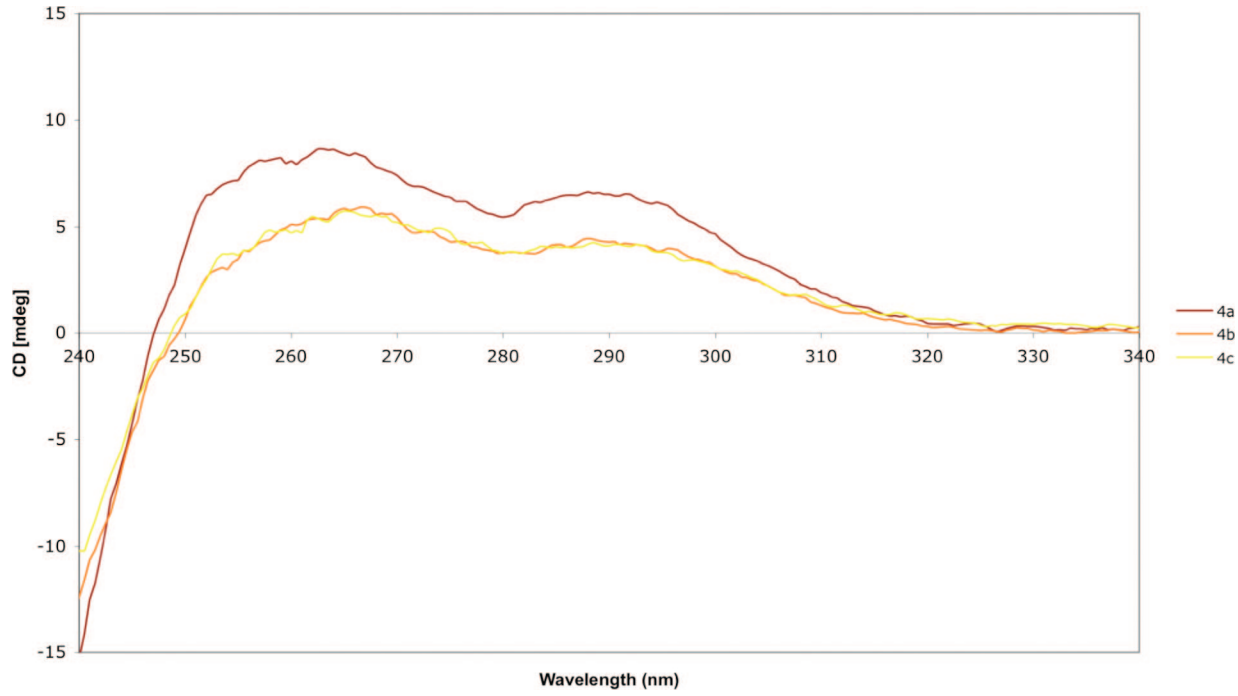


Figure 5. CD spectra of **4a**−**c**.

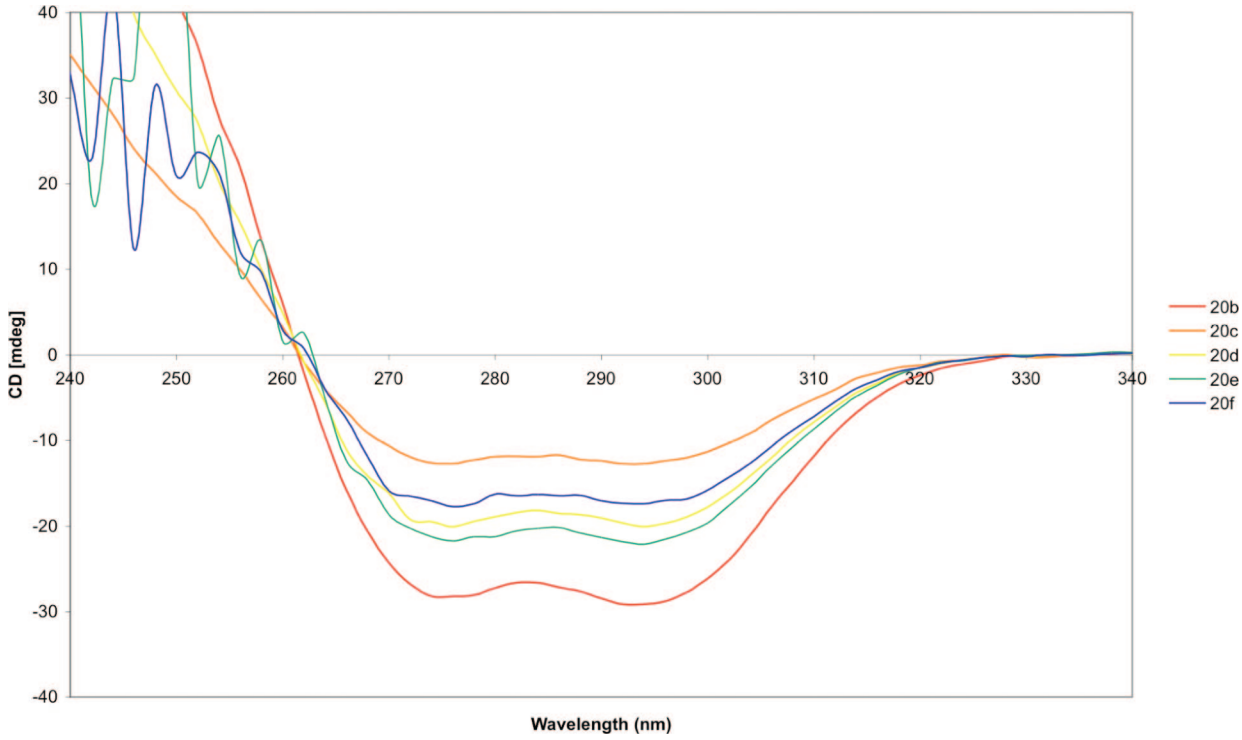


Figure 6. CD spectra of **20a**−**f**.

was synthesized as shown in Scheme 6: aminodiurea **17c** was chain-extended with *m*-nitrophenyl isocyanate, reduced to the amine, added to 2-bromophenyl isocyanate and methylated. A further oligourea devoid of chirality was made by oxidizing the sulfoxide **20b** to sulfone **33**.

NMR Studies of Bromooligoureas 30. The NCH_2Ph groups of all three bromoureas **30a**−**c** displayed singlets in their ^1H NMR spectra in various solvents at ambient temperature and at −90 °C. This signal in the spectrum of sulfone **33** however, while appearing as a singlet at room temperature, decoalesced to an AB system of peak separation 75 ppb at −50 °C, presumably because Ar−N bond rotation becomes slow at this temperature. 2-Substituted ureas adopt twisted conformations,[34,35] and the helicity of **33** at low temperature may be governed by the resulting transient Ar−N axis.

Circular Dichroism Spectroscopy. CD spectra were obtained for the sulfinyl ureas **4a**−**c** and **20a**−**f** in solution in chloroform (Figures 5 and 6). All show distinctive features in the region 250−350 nm which we take to indicate opposite helicity induced by the R_S sulfoxide of **4** and the S_S sulfoxide of **20**. In both

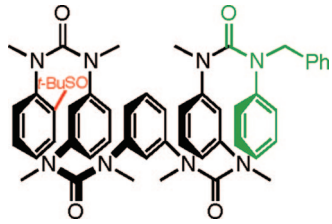


Figure 7. Stacked, helical conformation proposed for **20c**.

series there is a general trend toward less intense CD bands as the helix lengthens, in agreement with our assumption that there is a loss of helicity in longer oligomers.

Discussion

The NMR data from sulfinylureas **20** and amidoureas **24** show that the diastereotopic probe remains under the influence of the terminal substituent even when separated by up to about 24 bond lengths. In the absence of secondary structure within the oligomer, this would be an unprecedentedly remote effect for an acyclic molecule, and the distance over which the environmental influence of the chiral group is projected makes it clear that the ureas adopt a well-defined structure over these lengths. The lack of observable diastereotopicity in **30** discounts the possibility that diastereotopicity arises because of the oligourea structure alone. We also rule out the possibility that the apparent diastereotopicity arises from an intermolecular (head-to-tail, say) interaction for two reasons. First, the apparent diastereotopicity remained constant with decreasing concentration. Second, mixing together equimolar amounts of achiral triurea **30b** and chiral triurea **20b** did not induce anisochronicity in the NMR signal arising from the NCH_2Ph group of **30b**.

Solid state evidence and previous observations of upfield chemical shifts suggesting Ar−Ar stacking,[36,37] lead us to conclude that such *N*-alkylated aromatic oligoureas of up to four stacked rings adopt a chiral secondary structure—presumably a helix—in solution, and that this helix may have its relative stereochemistry (and absolute stereochemistry in the case of the sulfoxides) determined by a terminal sulfinyl or amido group. The stacked helical structure we propose for **20c** is illustrated in Figure 7. Unmethylated ureas adopt "open" (*exo*) conformations,[35] and the lack of apparent diastereotopicity in **12b** (Table 1) is consistent with disruption of the helix in this type of unalkylated structure. Beyond four or five stacked rings, it seems that entropic effects take over and disorder within the secondary structure—in other words, the presence of further rapidly interconverting alternative conformers—dilutes the effect of the chiral terminus to the point where only singlets are observed. We discount as unlikely the possibility that the helix persists but that $\Delta\delta$ is zero by chance, since singlets were observed in a wide variety of solvents and at a variety of temperatures.

It is interesting to note the way that apparent diastereotopicity in the sulfoxides **20** and amides **24** drops off markedly from 484 ppb in the monourea **24a** to between 20 and 85 ppb in all of the di- and triureas **20a**,**b** and **24b**,**c**. It seems possible that this degree of anisochronicity represents the local influence of the helix, while the greater degree of anisochronicity observed in **24a** is a result of the diastereotopic probe falling into the direct local influence of the amide group itself. Anisochronicity appears to be only weakly dependent on solvent, in accord with the suggestion that order in these structures arises from π-π stacking interactions.

Conclusion

Inclusion of a terminal diastereotopic probe remote from a chiral influence can give qualitative information about ordered chiral secondary structure in solution. When applied to oligoureas built from *m*-phenylenediamine monomers, the technique suggests order persists for oligomer lengths of up to about four or five monomer units. We are currently seeking to apply the technique more widely to the functional application of foldamer conformation in solution.

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Supporting Information Available: Experimental procedures and characterization data for all compounds reported in this paper. This information is available free of charge via the Internet at http://pubs.acs.org.

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