C–I···π Halogen Bonding Driven Supramolecular Helix of Bilateral
N-Amidothioureas Bearing β-Turns

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ABSTRACT: We report the first example of C–I···π halogen bonding driven supramolecular helix in highly dilute solution
of micromolar concentration, using alanine based bilateral l-substituted N-amidothioureas that contain helical fragments,
the β-turn structures. The halogen bonding interactions afford head-to-tail linkages that help to propagate the helicity of
the helical fragments. In support of this action of the halogen bonding, chiral amplification was observed in the supra-
molecular helix formed in acetonitrile solution. The present
finding provides alternative tools in the design of self-assembling macromolecules.

INTRODUCTION

DNA double helix and protein α-helix represent two major
helical structures in Nature.1 Inter- and intrahelix hydrogen
bonding plays a key role in affording helical structures
constituted of chiral components. In the DNA double helix
π···π stacking between the base-pairs helps to form helical
structures. Despite several reports in the solid state of the
supramolecular helix driven by halogen bonding,2 mimicking
the natural helix in the solution phase remains highly
challenging since the supporting backup from the three-
dimensional solid matrix that accommodates the supra-
molecular helix does not exist in solutions, while the head-to-
tail linked interactions that lead to supramolecular helix have to
be strong enough to compete with other interactions that may
lead to the assembly of the formed helices. Pioneering work of
Moore et al. of Pd2+ coordination of foldable oligomers of m-
phenylene ethynylene bearing one or two meta-pyridine
terminal groups successfully led to supramolecular helices in
acetonitrile, when the oligomer was long enough for a positive
cooperativity to occur to promote the formation of the helix in
which intrahelix π···π stacking may have facilitated the folding
of the oligomeric ligand.3 Very recently Schmuck et al.
reported a supramolecular β-helix in pure water from
moderately hydrophobic, β-sheet forming alanine octamers
consisting of alternative D- and L-amino acids, which were
linked via triple hydrogen bonding and electrostatic interactions
between the guanidino-carbonylpyrrole group equipped at its
N-terminus and the carboxylate anion of another octapeptide.
The helix formed at the peptide concentration of 0.1 mM
underwent self-assembly into fibers upon aging.

Inspired by those highly instructive works and the recent
progress on halogen bonding in solution phase,4 in particular
the halogen bonding promoted formation of helical foldamers
of foldable oligomers,5 we set out to build a supramolecular
helix in solution phase by choosing helical fragments that are
expected to be held together by halogen bonds. We proposed
to design a helical fragment that exhibits fewer other
interactions between fragments, such as hydrogen bonding
and π···π stacking, in particular the latter, to prevent the
formation of staircase supramolecular polymers.6 Iodophenyl
groups are equipped at the two terminals of the helical
fragment, since the possible noncoplanar C–I···I–C or C–I···π
halogen bonding7 is expected to help propagate the helicity of
the constitutional helical fragments.

As our first attempt, we chose alanine based bilateral N-
amidothioureas with halogen atoms (F, Cl, Br, I) substituted at
para-position of the terminal phenyl rings (AXs, Scheme 1),
since we recently identified a β-turn structure in the dipeptide
based N-amidothioureas (Scheme 1).9 The β-turn is one of the

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secondary structural elements of proteins and peptides \(^{10}\) and can serve as a fragment of helical structures, exampled by the 3\text{10}-helix.\(^ {11}\) We chose thiourea derivatives also because of the weak intermolecular interactions such as hydrogen bonding between thiourea moieties.\(^ {12}\) Indeed, we found that the interfragment head-to-tail type C\(\cdots\)I\(\pi\) interaction\(^ {8}\) between the two terminal iodophenyl groups, a halogen bond with \(\pi\) system analogous to the C\(\cdots\)H\(\pi\) interaction,\(^ {13}\) acts to support the supramolecular helix of AL in the highly dilute solution of acetonitrile above 6 \(\mu\)M and in the solid state as well. To the best of our knowledge, this is the first observation of the halogen-bonding triggered supramolecular helix in solution.

### RESULTS AND DISCUSSION

Alanine based bilateral N-amidothioureas (L,L- and D,D-AX, X = H, F, Cl, Br, and I, Scheme 1) were synthesized via procedures given in Scheme S1. AH, AF, ACI, and ABr exhibited similar absorption and CD spectra in CH\(_3\)CN (Figure 1), in which the Cotton effect at 228 nm is assigned to the alanine residues and amide bonds,\(^ {14}\) while that beyond 253 nm is attributed to the achiral phenylthiourea chromophore embraced within the \(\beta\)-turn.\(^ {9}\) AL differs very much in its absorption and CD spectra from those of AH, AF, ACI, and ABr, showing red-shifted absorption and sign-reversed and dramatically enhanced CD signals (g factor of \(-3 \times 10^{-3}\) at 272 nm, Figure S1). Dynamic light scattering (DLS, Figure S2) showed the existence of species of diameters of ca. 10\(^2\) nm in the CH\(_3\)CN solution of AL, likely the supramolecular polymeric species\(^ {15}\) since the I-substituent in AL could afford halogen bonding to link the AL molecules.\(^ {8}\) CD spectra of AL in CH\(_3\)CN underwent a nonlinear enhancement upon raising its concentration (Figure S3), while the CD signal dropped dramatically when the solution was heated (Figure S4), both in line with the formation of supramolecular polymeric species\(^ {15}\) that may form beyond a critical aggregation concentration of ca. 6 \(\mu\)M (Figure S3). In contrast, CD signals of AH, AF, ACI, or ABr vary linearly with their concentrations (Figures S5 and S6) and are insensitive to the change in solution temperature (Figure S7), implying their existence in monomer form in CH\(_3\)CN.

To better understand these intriguing observations made with AL in solutions, crystals of L,L-AL were grown in CH\(_3\)CN/DMSO (4:1, v/v) at room temperature and subject to X-ray crystallography. \(\beta\)-Turn structures were identified at two sides of the L,L-AL molecule (Figure 2a).\(^ {3}\) L,L-AL molecules in the crystal were found to exist in two forms according to the parameters of the \(\beta\)-turns, labeled as P (with \(\beta_1\) and \(\beta_2\)) and Q (with \(\beta_3\) and \(\beta_4\)) (Figure S8 and Table S2), respectively. Meanwhile, \(\beta\)-turns at two sides of the same L,L-AL molecule differ too, despite the same L-configuration of the alanine

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**Figure 1.** Absorption (a) and CD (b) spectra of L,L-AX (X = H, F, Cl, Br, I) in CH\(_3\)CN. [L,L-AX] = 20 \(\mu\)M.

**Figure 2.** (a) X-ray crystal structure of L,L-AL with \(\beta\)-turn at each side. Dashed green lines highlight the HBs while the \(\beta\)-turn structures are labeled as \(\beta_1\) and \(\beta_2\). (b) The C\(\cdots\)I\(\pi\) interaction, in which Cg is the centroid of benzene ring. (c) Intermolecular C\(\cdots\)I\(\pi\) interactions linking alternative P and Q molecules of L,L-AL. Dashed black lines indicate C\(\cdots\)I\(\pi\) interactions. (d) Single-stranded left-handed helix in the crystal packing of L,L-AL.
since its distance (4.10 Å, Table 1) is out of the cut-off parameter for C–I···π (Figure 2b,c). These C–I···π interactions can be divided into two kinds, according to their structural parameters. For C–I$_2$···π (Figure 2b), the distance of iodine atom to the centroid of benzene ring C$_G$, $d_2$, is 3.44 Å, and the angle $\theta$ is 148.1°, while those for C–I$_3$···π are 3.48 Å and 154.6°, respectively (Table 1), within the criteria for C–I···π interactions.$^8$ In the Table 1. Geometrical Parameters and Calculated Energies of C–I···π Halogen Bonding Interactions Based on Crystal Structure of L,L-AI

<table>
<thead>
<tr>
<th>C–I···π</th>
<th>$d_2$ (Å)$^a$</th>
<th>$\theta$ (deg)</th>
<th>$\Delta E$ (kJ mol$^{-1}$)</th>
<th>$\Delta C$ (kJ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C–I$_1$···π</td>
<td>3.625</td>
<td>152.8</td>
<td>−40.6</td>
<td>−32.5</td>
</tr>
<tr>
<td>C–I$_2$···π</td>
<td>3.445</td>
<td>148.1</td>
<td>−28.8</td>
<td>−22.4</td>
</tr>
<tr>
<td>C–I$_3$···π</td>
<td>3.488</td>
<td>154.6</td>
<td>−34.8</td>
<td>−28.6</td>
</tr>
<tr>
<td>C–I$_4$···π</td>
<td>4.100</td>
<td>155.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Distance of iodine to the centroid of benzene ring C$_G$. $^b$Calculated in gas phase. $^c$Calculated in CH$_3$CN solution. Method: MO62X DFT with the 6-311G** basis set for C, H, LANL2DZ for I atoms, and D3 empirical dispersion correction.

same AI molecule, the iodophenyl group at one side (i.e., Ph–I$_1$ in P) acts as the donor of the C–I···π halogen bond (halogen atom), while that at the other side (i.e., Ph–I$_2$ in P) is the acceptor (π system). Dihedral angles of 66.57° (Ph–I$_2$ and Ph–I$_4$) and 76.48° (Ph–I$_1$ and Ph–I$_4$) were measured between two adjacent molecules that may help to propagate the helicity of the β-turn structures. Indeed, repeating intermolecular C–I···π interactions between alternative P and Q molecules lead to zigzag-like linear arrangement (Figure S9a). Thus, the formed structures from L,L-AI display zigzag-like linear arrangement (Figure S9b), differing much from the helical structure of its L,L-AI counterpart (Figure 2d).

It was expected that in polar solvents such as CH$_3$CN, intermolecular hydrogen bonding between L,L-AI molecules might not be strong enough to hold molecules together,$^{15}$ leaving ACI molecules in their monomer forms. This is indeed what was experimentally observed from the spectral behavior of L,L-AX in CH$_3$CN (X ≠ I, Figure 1). The highest efficiency of C–X···π interaction of the I-substituent$^8$ affords halogen bonding between AI molecules so that AI remains in its polymeric form in CH$_3$CN.

It is interesting to emphasize that DFT calculations confirmed that the C–I···π interaction occurs between two iodobenzene structural units both in gas phase and in CH$_3$CN solutions, giving a bonding strength of ca. 15.2 kJ mol$^{-1}$ (Figure S10 and Table S4). However, for other halogenated benzenes, similar C–X···π halogen bonding was not shown, agreeing with that noted in the crystal structure of L,L-AI and the monomeric form of them in CH$_3$CN. In addition, according to the crystal structure of L,L-AI, the calculated energies for the intrahaloexch C–I···π interactions are 22.4 kJ mol$^{-1}$ (C–I$_2$···π) and 28.6 kJ mol$^{-1}$ (C–I$_3$···π) in CH$_3$CN solutions (Table 1), which are stronger than the C–I···π interaction between two iodobenzene molecules (15.2 kJ mol$^{-1}$, Table S4). These energies are also more significant than the C–I···π interactions in solution phase between 2-C$_3$F$_7$I or 1-C$_3$F$_7$I and toluene-$d_8$, with strength of ca. 6.4 or 5.4 kJ mol$^{-1}$ and C–H···π interactions that are weaker than 4.0 kJ mol$^{-1}$. Because of the weak inductive effect of para-thiourea group in AI molecule,$^{19}$ the stronger C–I···π interaction between AI molecules than that between iodobenzene molecules is attributed to the formation of supramolecular helix from the helical fragments in AI molecules that facilitates the halogen bonding in CH$_3$CN, a cooperativity that could also be seen in the sigmoidal dependence of the CD signal on the concentration of AI (Figure S3).

To correlate the solid and the solution phase structures, AI was subject to solid-state CD measurements. We found that the solid-state CD spectra were similar to those obtained in CH$_3$CN solutions (Figure 4a). Therefore, similar stacking modes were assumed for AI molecules in the solid state and in the solution. For other AXs (X ≠ I), their CD spectra in the solid state and solution phase differ very much in both signs and positions (Figure S11), suggesting that the existing forms are not the same in the solid state as in the CH$_3$CN solutions.
Those solution samples of AI for spectral measurements were also characterized by scanning electron microscopy (SEM). The observed left-handed helicity of the L,L-AI fibers (Figure 4b) agrees with that obtained from the crystal structure (Figures 2d and 3) and the CD spectra (Figure 1b). These helical fibers were approximately 100 nm in pitch and 40 nm in diameter and some of them were tangled together. Right-handed helices were found in the SEMs taken from samples of D,D-AI (Figure S12), confirming that the helicity of the supramolecular helix is dictated by the absolute configuration of the chiral alanine residues, which is again supported by the mirror-imaged CD spectra of L,L-AI and D,D-AI in both solid state and CH3CN solutions (Figure 4a). In contrast, SEM images of AH, AF, ACl, and ABr only show block or amorphous aggregates (Figure S13), demonstrating the critical importance of I-substituent in AI in terms of affording the C–I−⋯π halogen bonding.

NMR was next applied to investigate the structural characteristics of AXs in solution phase. Protons Hx and Hy were assigned by 2D NOESY spectra taken in DMSO-δ6/CD3CN in which AXs exist in monomer forms (Figure S14). 1H NMR of L,L-AX in the binary solvents verified the existence of the β-turn structure featuring an IHB, since the resonance of the thiourea NH proton involved in this IHB does not change very much when the competitive component DMSO-δ6 was added (Figures S15 and S16). 2D To bring in direct evidence for C−I−⋯π halogen bonding in solution, 3H NMRs of AXs (20 μM) in CD3CN were recorded on an 850 MHz NMR equipment. Under the same conditions, 1H NMR signals of AI were approximately 13 times weaker than those of ACl (Figure S17). This can be explained in terms of the formation of supramolecular helix of AI in CD3CN, which is invisible by the solution NMR technique due to signal broadening. Interestingly, two sets of sharp 3H NMR peaks are observed for AI but only one set for other AXs (X ≠ I, Figures S17 and S18). The stronger ones are those of the monomers, while the weaker ones are assigned to the small helical oligomers of AI, on the basis of the concentration-dependent 1H NMR spectra (Figures S19 and S20). The upfield shift of the proton signals on iodophenyl rings (Hx and Hy) in the helical oligomers is consistent with their participation in the C−I−⋯π halogen bonding. Meanwhile, the larger shifts observed in the signals of Hx (0.186 ppm) and Hy (0.046 ppm) than that of Hg (0.014 ppm) support their direct involvement in the intermolecular halogen bonding. 2D NMR experiments were next performed. For ACI, observation of obvious NOE peaks between Hx and Hy but not for Hg−Hx (Figure 5a) agrees with their distances identified in the crystal structure of L,L-ACI (3.189 Å for Hg−Hx and 4.348 Å for Hx−Hg). Despite the low solubility and the existence of helices of varying sizes, NOE peaks in AI were observed (Figure 5b). The obvious contact between Hx and Hy indicates the interconversion of monomers and the helical structures. The intramolecular distance between Hx and Hy (4.550 Å) is longer than that of Hg−Hx (3.106 Å), yet NOE signals of Hg−Hx were observed but not for Hg−Hx opposite to those of L,L-ACI (Figure 5a). Both COSY and ROESY spectra of AI (Figures S21 and S22) confirmed these NOEs. These Hx−Hx couplings therefore result from intermolecular coupling because of the halogen bonding. Indeed, the crystal structure shows that the distance between Hx (Hx) and Hy (Hy) of the two adjacent L,L-AI molecules is 2.368 Å and that of Hg(Hg)−Hg(Hg) is 3.686 Å. Therefore, 2D NMR studies confirm the intermolecular C−I−⋯π halogen bonding between AI molecules in CD3CN solutions.

Influence of solvent of varying basicity provides further support for the halogen bonding. With increasing volume fraction of the electron-donating solvent THF, the CD spectrum of AI in CH3CN converted slowly to one similar to that of ACl, whereas it remained unchanged when CHCl3 of low basicity was added into CH3CN (Figures S23–S25), supporting the halogen bonding nature of the interactions between AI molecules in CH3CN. Meanwhile, the CD spectrum of ACI in CH3CN showed no response to those added solvents, implying that the added solvents do not break the intramolecular β-turn structures. It was also found that the absorption and CD spectra of AI in CH3CN responded more strongly to I− than to Cl− (Figures S26–S28), while the responses of ACI to I− and Cl− were both negligible (Figures S29–S31). The former is attributed to the stronger affinity of halogen bonding of I− than Cl− to compete with the C−I−⋯π halogen bonding between AI molecules, while the latter is a reflection of the weak binding of the thiourea moiety with I− and Cl− anions. It was therefore concluded that the C−I−⋯π halogen bonding between AI molecules drives the formation of the supramolecular helix of AI in solution.

In order to confirm the role of β-turn structures designed in the AI molecule, we synthesized a peptide counterpart of L,L-AI,
halogen bonding. This single-stranded supramolecular helix solutions.24 We therefore examined if this occurred with our bonding that holds AI molecules together.

β-amidothioureas that bear two iodophenyl groups equipped at two terminals of the compound as the donor and acceptor of the C−I···π halogen bonding except this “head-to-tail” intrahelix bonding. This single-stranded supramolecular helix exhibits substantially enhanced CD signals, with for example a high value of g-factor (−3 × 103) at 272 nm and a chiral amplification. These findings open a new avenue toward the rational design of building blocks to create functional supramolecular helices driven by halogen bonding.

ASSOCIATED CONTENT

Supporting Information

Detailed synthetic procedures, characterization, crystal data, spectral analysis and others (PDF)
Crystalllographic information for l,l-AI (CCDC 1484798) (CIF)
Crystalllographic information for l,l-ACl (CCDC 1484799) (CIF)

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The authors declare no competing financial interest.

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REFERENCES


Figure 6. Plots of CD signals at 238 and 272 nm of AI in CH3CN against ee. [l,l-AI] + [d,d-AI] = 20 μM. Black lines represent the situation without any chiral amplification.


