

Helicity Inversion in Responsive Foldamers Induced by Achiral Halide Ion Guests**

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Interest in foldamers^[1] and helically folding polymers^[2] has increased considerably over the past decade, reflecting the vast potential of this emerging field.^[3] One particularly attractive aspect is associated with the well-defined yet dynamic conformation of the backbone along with its responsiveness towards external stimuli that can be used to implement various functions for applications in targeting actuation,^[4,5] delivery,^[5] and sensing.^[6] In the latter case, the inherent chirality of the helical backbone makes it possible to conveniently monitor conformational changes by circular dichroism (CD) spectroscopy. Ideally the binding of various guests leads to the formation of an excess of one helical form, which is associated with an externally induced CD effect.^[7,8] The transfer of chirality to the usually achiral backbone is caused by interaction with a *chiral* guest,^[7,9] and as a result, the inversion of the (excess) helical twist sense^[10] is typically caused by the binding of the same guest but the other enantiomeric form.^[11] Further insights into the fundamentals of chirality transfer and amplification as one potential mechanism responsible for the homochirality in biomacromolecules^[12] will enable the design of new materials for chiral recognition, sensing, and separation as well as catalysis.^[13] For this purpose, the facile access to a responsive foldamer platform, which allows for convenient tuning of properties (even under abiotic conditions), is desirable. Here, we present our work on a novel family of responsive foldamers, so-called “clickamers”, and describe their efficient synthesis and investigations of their folding behavior under a variety of conditions. Importantly, we report on an unprecedented phenomenon of helix inversion^[11] observed in response to *achiral* guest molecules (halide ions).

Our foldamer design is inspired by the “helicity codon” approach developed by Lehn and co-workers that exploits the

strong preference of bipyridine and various aza-arenes for adopting an *anti* conformation to generate helical structures.^[14] We utilize the highly efficient Cu-catalyzed 1,3-dipolar cycloaddition reaction of aryl azides and aryl acetylenes, commonly referred to as the click reaction,^[15] to generate a backbone consisting of embedded helicogenic motifs based on alternating triazole and pyridine moieties. The resulting 2,6-bis(1,2,3-triazol-4-yl)pyridine structure has a strong preference for the *anti,anti* conformation,^[16a] and the preorganized kinked building blocks are connected by *meta*-phenylene hinges. Rotation about a minimal number of connecting bonds (at the *meta*-phenylene hinges) leads to folding into a helical conformation that is enthalpically stabilized by the resulting π - π stacking interactions (Figure 1). In an amphiphilic system, further stabilization can be induced by the solvophobic effect as well.^[17] Models of an oligomer bearing 17 (hetero)aromatic moieties illustrate another interesting structural feature of our clickamers as

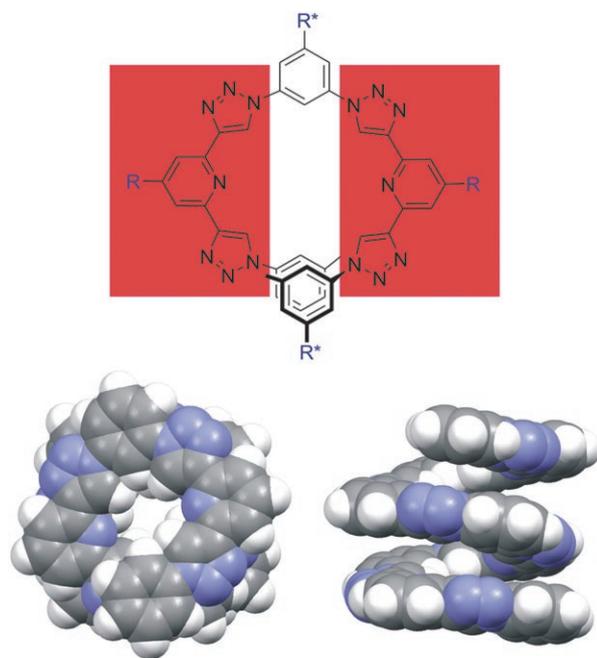


Figure 1. Concept of clickamers as foldamers prepared by click chemistry. Top: Helical folding is based on connecting preorganized 2,6-bis(1-aryl-1,2,3-triazol-4-yl)pyridine units (red) by *meta*-phenylene units (black) as well as π - π stacking interactions induced by solvophobic forces in polar solvents as a result of the amphiphilic structure (R and R* shown in blue represent polar side chains). Bottom: Top and side views of a space-filling model of the heptadecamer displaying two complete turns (van der Waals radii are shown and side chains are omitted for clarity).

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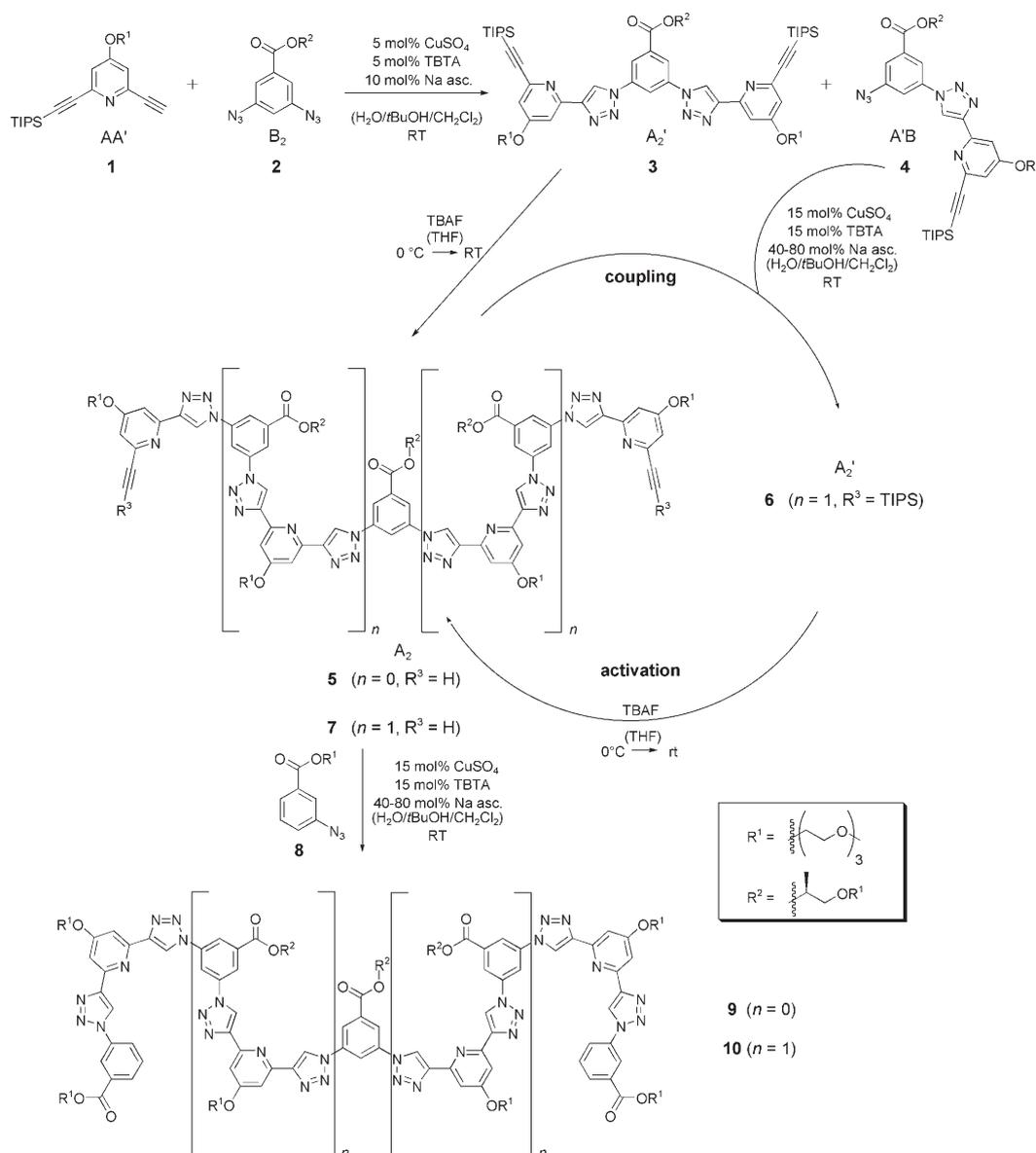
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they exhibit a rather unusual fourfold symmetry relative to the number of side chains per turn.^[14c,d,18]

The oligomer strands were prepared by a repetitive bidirectional synthesis in which the click reaction served as the coupling step and protidesilylation was the activation step (Scheme 1).^[16a,19] Initially, the starting building blocks pyridine bisacetylene **1** (AA' monomer) and phenyl bisazide **2** (B₂) were coupled to afford the protected central core building block **3** (A₂') as well as the extended core building block **4** (A'B) as well as the unprotected core **5** (or a higher homologue such as **7**) was coupled with monomer **4** and the product then deprotected to afford the next higher oligomer. This sequence was repeated to extend the oligomers to overall eight (hetero)aromatic repeat units per sequence and was finally terminated by reaction with monofunctional azide **8** to afford nonamer **9** and heptadecamer **10**.^[20] High overall yields

were achieved by carefully optimizing the conditions for the click reaction, for example, by use of tris(benzyltriazolylmethyl)amine (TBTA) as a Cu^I-stabilizing ligand^[16a,21] and the choice of the triisopropylsilyl (TIPS) moiety as an orthogonal protecting group.^[16a] Polar oligo(ethyleneglycol) side chains were attached to the nonpolar (hetero)aromatic backbone to provide a further driving force for folding based on the solvophobic effect operating in the resulting amphiphilic structure.^[17] Furthermore, the side chains ensure good solubility in various solvents and incorporation of chiral centers at every *meta*-phenylene unit enables the use of CD spectroscopy to investigate the conformational behavior in solution.

After successful synthesis and standard characterization, the conformational behavior of clickamer **10**, which displays two complete turns and hence a significant number of



Scheme 1. Synthesis of clickamers **9** and **10** by means of a bidirectional growth approach based on repetitive sequences of 1) coupling with elongated A'B monomer **4** and 2) deprotection followed by capping of the backbone termini. Na asc. = sodium ascorbate, TBAF = tetra-*n*-butylammonium fluoride, TBTA = tris(benzyltriazolylmethyl)amine, TIPS = triisopropylsilyl.

stabilizing π - π stacking contacts, was investigated in dilute solution by various optical spectroscopy techniques. As the optical spectra of **10** in acetonitrile did not deviate substantially from those in chloroform solution,^[18b] the addition of significant amounts of water was necessary to enhance the solvophobic driving force of folding.^[17] The UV/Vis absorption spectra of **10** (Figure 2, top) show a hypochromic and

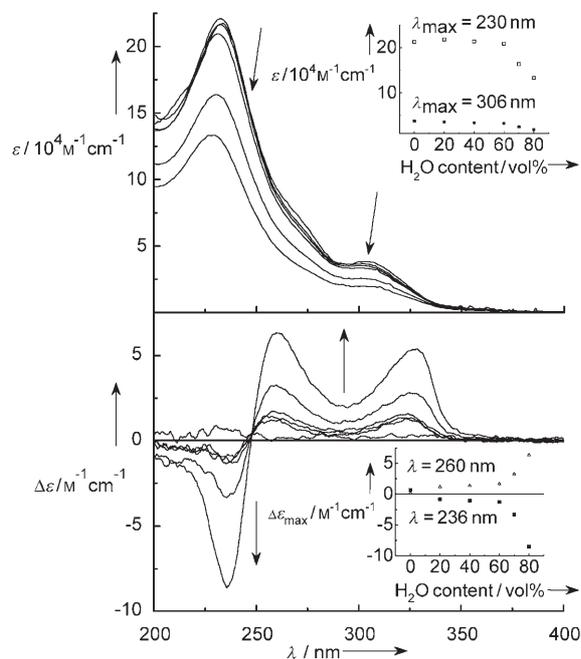


Figure 2. Optical spectra of clickamer **10** (5×10^{-6} M) in acetonitrile with increasing water content at 25 °C. Top: UV/Vis absorption spectra. Bottom: CD spectra.

bathochromic shifts of the bands at 230 nm and 306 nm, respectively, indicating stacked chromophores with increasing water content. At higher water content, the more intense short-wavelength absorption maximum of the clickamer backbone is associated with an intense bisignate signal exhibiting positive exciton chirality^[22] and zero-crossing at 246 nm as well as another bathochromically shifted, positive signal at 260 nm (Figure 2, bottom). This indicates the population of a helical conformation with excess helicity as a result of chirality transfer from the chiral side chains to the backbone (chiral anisotropy factor $g = 0.0006$ in 80 vol% water).^[19] The folding transition at higher water content is also reflected in the fluorescence spectra, which show a transition from a sharp monomerlike emission at 373 nm to a broad, excimerlike emission centered around 409 nm, which is characteristic of stacked chromophores (in a helical conformation).^[19] The folding transition is particularly effective above a threshold amount of 60 vol% water in acetonitrile, as indicated by the nonlinear relationship of each optical signature as a function of the water content (insets in Figure 2). Aggregation as another potentially contributing factor can be excluded since dilution experiments showed a linear response over the relevant concentration range, and no aggregates were detected in dynamic light-scattering meas-

urements. In addition, the CD spectra do not change significantly within the accessible temperature range (5–75 °C), suggesting that chirality induction is indeed based on intramolecular chirality transfer and not formation of aggregates.^[23] While these experiments provide strong evidence that clickamer **10** adopts a helical conformation in water/acetonitrile mixtures, the corresponding spectroscopic measurements with the shorter oligomer **9** indicate only a slight population of the helical conformation.

Isolated 2,6-bis(1-aryl-1,2,3-triazol-4-yl)pyridines undergo a dramatic structural change from the kinked *anti,anti* conformation to an extended *syn,syn* conformation upon either metal ion complexation or simply protonation.^[16a] Therefore, we studied the response of clickamer **10**, which incorporates four such switchable subunits, towards protonation (Figure 3). Surprisingly, the addition of HCl did not result

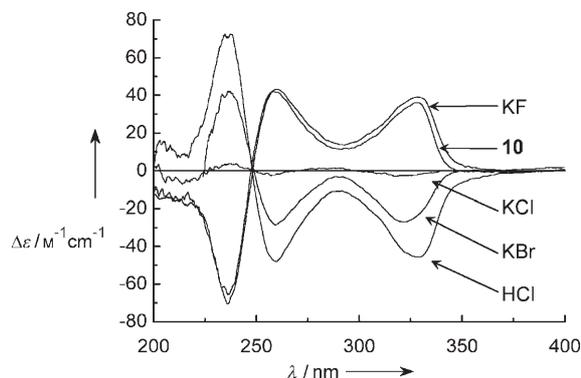


Figure 3. Optical response of clickamer **10** (8×10^{-6} M, 75 vol% water in acetonitrile, 25 °C) to various halide ions: KF, KCl, and KBr (all at neutral pH) as well as HCl.

in denaturation of the helical conformation but rather an exact inversion of the CD signal. To examine the involvement of the counterion in the recognition process, the effect of various halide anions on the CD spectra was investigated at neutral pH. Whereas addition of fluoride ions led to a slight increase in CD intensity relative to the neat oligomer **10**, the presence of chloride ions caused an inverted signature of small intensity, and finally addition of bromide ions gave an inverted CD spectrum of higher intensity. It is important to note that all CD spectra display an isodichroic point at 248 nm and that the positions and relative intensities remain constant, reflecting an inversion of the same helical conformation; in other words, only the helical twist sense is altered without other structural changes.

To the best of our knowledge, this represents the first example of a helix inversion^[10] in response to an achiral stimulus.^[11] Furthermore, this finding is remarkable in light of the observed selectivity for various halide anions since anions are notoriously difficult to recognize, in particular in aqueous systems.^[24] Although we can only speculate about the mechanism of anion recognition, clearly the size of the halide anion plays an important role for the interaction with the helix. Although decreasing the pH seems to enhance the effect, the accompanying counteraction is most likely not

involved in the recognition process as complexation of the potassium ions with [18]crown-6 did not alter the CD signal.^[19] In view of the clean inversion to the helix mirror image, even at neutral pH, it seems likely that the halide ions interact with the oligo(ethylene glycol) side chains, thereby altering intramolecular^[25] chirality transfer to the (hetero)-aromatic backbone. It is remarkable that a rather subtle interaction with the halide ion(s) is translated into such significant observed changes in the CD spectra, reflecting the bias of the equilibrium between the left- and right-handed helices.

In summary, we have introduced clickamers as a new promising family of foldamers with unique folding and recognition behavior in aqueous systems. In addition to their straightforward and efficient synthesis, these clickamers display an unprecedented helix inversion in response to achiral halide ions. Ongoing work in our laboratories is concerned with elucidating the structural basis for halide recognition and extension to the recognition of transition-metal cations.^[16] Furthermore, the influence of the nature of the monomer building blocks, which determine the preorganization and strength of π - π stacking, on the folding behavior are currently under investigation.^[26]

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