

The Click Triazolium Peptoid Side Chain: A Strong *cis*-Amide Inducer Enabling Chemical Diversity

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S Supporting Information

ABSTRACT: Access to homogeneous and discrete folded peptoid structures primarily depends on control of the *cis*/*trans* isomerism of backbone tertiary amides. This can be achieved by designing specific side chains capable of forming local interactions with the backbone. This is often undertaken at the expense of side-chain diversity, which is a key advantage of peptoids over other families of peptidomimetics. We report for the first time a positively charged triazolium-type side chain that does not compromise diversity and exhibits the best ability reported to date for inducing the *cis* conformation. The *cis*-directing effect was studied in *N*-acetamide dipeptoid model systems and evaluated in terms of $K_{cis/trans}$ using NMR spectroscopy in aprotic and protic solvents. Computational geometry optimization and natural bond orbital analysis in combination with NOESY experiments were consistent with a model in which $n \rightarrow \pi^*_{Ar}$ electronic delocalization [from carbonyl (O_{i-1}) to the antibonding orbital (π^*) of the triazolium motif on residue i] may be operative. In the computational model (gas-phase) and experimentally in $CDCl_3$, H-bonding between the triazolium C–H proton and the $C_i=O_i$ oxygen was also identified and may act cooperatively with the $n \rightarrow \pi^*_{Ar}$ delocalization, resulting in the absence of the *trans* rotamers in $CDCl_3$.

N-Substituted glycine oligoamides, termed peptoids, emerged in the early 1990s to answer the demand for large sets of compounds for high-throughput biological screening.^{1,2} They are very attractive peptidomimetics³ because of their ease of synthesis with huge side-chain diversity,^{4,5} and they possess other desirable advantages over peptides such as proteolytic stability and greater cell permeability.^{6,7} The major limitation of peptoids is their inherent flexibility due to the absence of internal hydrogen bonding, their achiral backbones, and above all, the low-energy rotameric *cis*/*trans* equilibrium of backbone tertiary amides. Interestingly, peptoids still retain a propensity to adopt stable secondary structures, provided that the *cis*/*trans* isomerism is optimally controlled. *N*-Aryl-substituted peptoids⁸ have been shown to fold into the naturally occurring polyproline type-II helix conformation (PPII) with *trans* amide bonds, and peptoids with α -chiral aromatic or aliphatic side chains can adopt the PPI-like conformation featuring only *cis* amide bonds.^{9,10} However, in the latter case, conformational heterogeneity originating from *cis*/*trans* interconversion is very often observed, and constructing peptoids in a discrete and

robust conformation still remains a major challenge. The stereoelectronic factors that may favor the *cis*-amide population have been scrutinized in the recent past. Importantly, Blackwell and co-workers have shown that $n \rightarrow \pi^*$ donation from a carbonyl oxygen (O_{i-1}) to the antibonding orbital (π^*) of an aromatic side chain on residue i (denoted as $n \rightarrow \pi^*_{Ar}$) stabilizes the *cis*-amide conformation in peptoids.^{11,12} Research from this group culminated in a recent publication providing firm evidence from solution and crystallographic studies that homooligomers composed of (*S*)-*N*-(1-naphthylethyl)glycine (*NsInpe*) form homogeneous and robust PPI peptoid helices but that steric interactions more than the $n \rightarrow \pi^*_{Ar}$ donation served as the primary cause for conformational restriction in 1-naphthylethylglycine oligomers.¹³ The *Inpe* and *4mpy* side chains (Figure 1) are the most efficient ones described to date in promoting the *cis* geometry in peptoids.

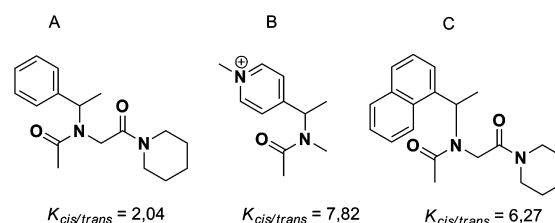


Figure 1. Literature peptoid models and corresponding *cis*/*trans* ratios in CD_3CN . Side chains: (A) phenylethyl (*pe*); (B) 4-methylpyridinium (*4mpy*); (C) 1-naphthylethyl (*Inpe*).

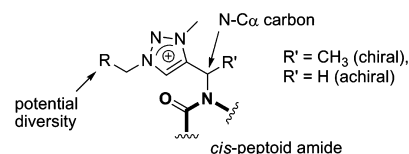


Figure 2. Structure of *cis*-directing triazolium-type peptoid side chains.

A desirable side chain should not only predispose a peptoid to adopt a specific conformation but also allow the introduction of a wide variety of substituents to facilitate foldamer applications.¹⁴ Here we show that triazolium-type side chains (Figure 2) provide a solution to this challenge. The triazolium motif is easily formed using Cu-catalyzed azide–alkyne

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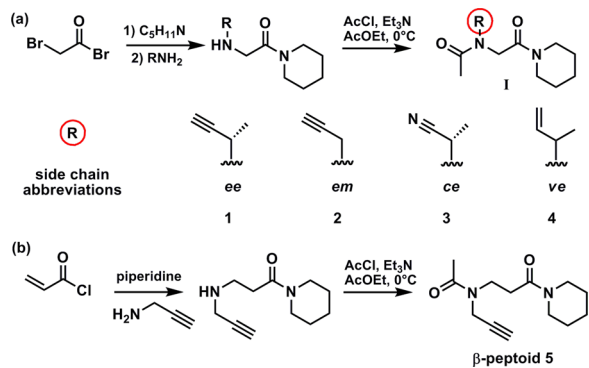
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cycloaddition (CuAAC) “click” postmodification of *N*-propargyl side chains¹⁵ and subsequent methylation. The effect of triazolium side chains was studied using **I**, an acetamide peptoid model capped as a piperidinyl amide at the C-terminus (Scheme 1).

The model proposed by Blackwell and co-workers¹² was very well suited for predicting the proportions of *cis*- and *trans*-amides in peptoid oligomers. Its use also ensured a direct comparison of our results to literature data. Two versions of the triazolium side chain were envisaged to probe the contribution of steric and electronic factors: *N*- α -branched and unsubstituted at *N*- α (*N*- α -methylene).¹⁶ The *cis/trans* ratios ($K_{cis/trans}$) were measured from ¹H NMR spectra in various aprotic and protic solvents. We found the electron-deficient triazolium motif to be the most effective peptoid *cis*-amide inducer reported to date. The high values of $K_{cis/trans}$ even for the noncrowded *N*- α -methylene triazolium side chains gave strong evidence that the origin of the effect of the triazolium side chain is not steric in nature. Here we show that an $n \rightarrow \pi^*$ triazolium interaction contributes to stabilization of the *cis*-amide geometry. This was supported by molecular calculations and solution conformational studies using nuclear Overhauser effect spectroscopy (NOESY). Only aromatic groups (phenyl, naphthyl) and carbonyl amides have been studied as acceptors in backbone–side-chain $n \rightarrow \pi^*$ interactions.^{11,12} We also report the significant effect on the amide *cis/trans* equilibrium due to a cyano-containing side chain in comparison with alkyne and alkene side chains of comparable steric bulk.

Compounds **1**–**4** were prepared by methods similar to those of Blackwell and co-workers¹¹ [Scheme 1a; see the Supporting

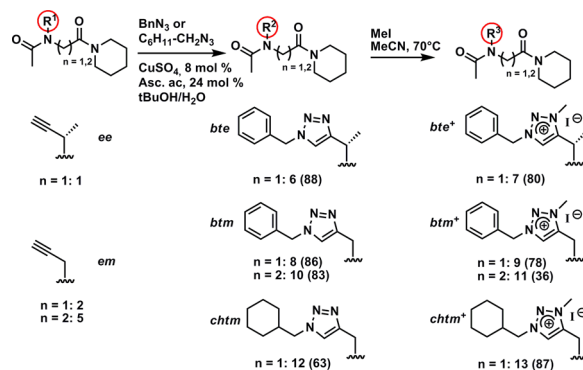
Scheme 1. Synthesis of α - and β -Peptoid Models^a



^aLetters in italics are side-chain abbreviations: *ee*, 1-(ethynyl)ethyl; *em*, ethynylmethyl; *ce*, 1-(cyano)ethyl; *ve*, 1-(vinyl)ethyl.

Information (SI) for details]. The alkyne functions of the ethynylethyl (*ee*) and ethynylmethyl (*em*) side chains in **1** and **2** were converted into triazoles by CuAAC using benzylazide or cyclohexylmethylazide partners, affording **6**, **8** and **12**;¹⁷ subsequent methylation¹⁸ gave **7**, **9**, and **13** with triazolium side chains (Scheme 2). β -Peptoid¹⁹ model **5** with the pendant *N*-propargyl side chain was also prepared (Scheme 1b) and converted into the corresponding triazole and triazolium compounds **10** and **11** (Scheme 2). ¹H NMR spectra of these peptoid models (with side chains R¹–R³) were then recorded in CDCl₃, CD₃CN, MeOD, and D₂O at 15 mM concentration, and $K_{cis/trans}$ values for the *N*-terminal acetamides were obtained by integration of characteristic signals (Table 1).

Scheme 2. Post-Side-Chain Modifications of **1**, **2**, and **5**^{a,b}



^aNumbers inside parentheses denote unoptimized isolated yields.

^bLetters in italics denote side chain abbreviations: *bte*, 1-(benzyltriazolyl)ethyl; *btm*, benzyltriazolylmethyl; *chtm*, cyclohexylmethyltriazolylmethyl; *bte*⁺, 1-(benzyltriazolium)ethyl; *btm*⁺, benzyltriazoliummethyl; *chtm*⁺, cyclohexylmethyltriazoliummethyl.

Remarkably high values of $K_{cis/trans}$ (>19) were observed for compounds **7**, **9**, and **13** in CDCl₃, indicating complete suppression of the *trans* rotamers. It is worth noting that the population of *cis*-amides remained exceptionally high in CD₃CN (>90%) and protic solvents (~90% in MeOD and 85% in D₂O). The efficiency of the *bte*⁺ triazolium side chain of **7** in inducing the *cis* geometry is higher than that for the previously reported positively charged *N*- α -chiral pyridinium (*4mpy*) side chain,¹¹ which could be considered as the best one reported to date (*bte*⁺ $K_{cis/trans}$ 11.7 vs *4mpy* $K_{cis/trans}$ = 7.8 in CD₃CN).²⁰ Even the *N*- α -methylene *btm*⁺ side chain in **9** was able to suppress the *trans* rotamer completely in CDCl₃ and to a great extent in the other solvents examined. It is particularly important to notice that in protic solvents, $K_{cis/trans}$ for **9** is comparable to that for peptoid model **7**. $K_{cis/trans}$ for **13** (*chtm*⁺) is in the same range as for **9** (*btm*⁺), suggesting that the results are not influenced by the nature of the substituent on the triazolium motif and in particular by aromatic groups. The effect of the achiral triazolium side chain was also assessed using **11**, the β -peptoid homologue of **9**. Despite a decrease in $K_{cis/trans}$ (by 30% on average) relative to **9**, the population of *cis*-acetamide was still exceptionally high for this flexible backbone.

Relative to the triazolium peptoid models discussed above, the triazole precursors **6**, **8**, **10**, and **12** showed a dramatic decrease in $K_{cis/trans}$, which was in the range 1–2 rather than >19. This trend could be anticipated if an $n \rightarrow \pi^*$ interaction is operative in these systems, as the efficiency of the $n \rightarrow \pi^*$ interaction can be correlated with the electron-deficient character of the Ar motif. Unsurprisingly, the *N*- α -branched *bte* triazole side chain in **6** slightly increased the *cis*-amide population relative to the achiral *btm* (**8**) and *chtm* (**12**) analogues. The influence of the *bte* side chain was on the same order of magnitude as that of the *pe* side chain (see Figure 1) in model peptoid **I** (*bte* $K_{cis/trans}$ = 1.45 vs *pe* $K_{cis/trans}$ = 1.26 in CD₃OD and *bte* $K_{cis/trans}$ = 1.99 vs *pe* $K_{cis/trans}$ = 2.04 in CD₃CN).¹² In view of the large dipole moment of the triazole ring (~5 D),²¹ this shows that dipole–dipole interactions do not have any significant impact on $K_{cis/trans}$. The same conclusion can be drawn a priori for the triazolium ring, which is characterized by a small intrinsic dipole moment (~1.2 D; see the SI).

Surprisingly, the *N*- α -chiral *ee* side chain in **1** slightly promotes the *cis* rotamer of model peptoid **I**, particularly in

Table 1. Cis/Trans Ratios $K_{\text{cis/trans}}^{a,b}$ and Corresponding Free Energy Differences ΔG^c for 1–13 in Various Solvents (15 mM)

| peptoid | side chain | CDCl ₃ | | CD ₃ CN | | MeOD | | D ₂ O | | $K_{\text{cis/trans}}^{\text{avg}}$ (% cis) |
|---------|-------------------|------------------------|----------------|------------------------|------------|------------------------|------------|------------------------|------------|---|
| | | $K_{\text{cis/trans}}$ | ΔG | $K_{\text{cis/trans}}$ | ΔG | $K_{\text{cis/trans}}$ | ΔG | $K_{\text{cis/trans}}$ | ΔG | |
| 1 | ee | 1.55 | -0.26 | 3.04 | -0.66 | 1.90 | -0.38 | 1.36 | -0.18 | 2.51 (72) |
| 2 | em | 0.54 | 0.36 | 1.31 | -0.16 | 0.78 | 0.15 | 1.00 | 0.00 | 0.96 (49) |
| 3 | ce | 4.34 | -0.87 | 8.22 | -1.24 | 3.71 | -0.77 | 2.92 | -0.63 | 5.37 (84) |
| 4 | ve | 0.56 | 0.34 | 1.41 | -0.20 | 0.83 | 0.11 | 0.69 | 0.22 | 1.06 (51) |
| 5 | em | 0.63 | 0.27 | 1.38 | -0.19 | 0.73 | 0.19 | 1.24 | -0.12 | 1.01 (50) |
| 6 | bte | 2.06 | -0.43 | 1.99 | -0.41 | 1.45 | -0.22 | 1.34 | -0.17 | 1.76 (64) |
| 7 | bte ⁺ | >19 ^d | - ^d | 11.73 | -1.46 | 11.12 | -1.42 | 5.52 | -1.01 | >14.20 (93) |
| 8 | btm | 1.10 | -0.06 | 1.11 | -0.06 | 1.03 | -0.02 | 1.07 | -0.04 | 1.08 (52) |
| 9 | btm ⁺ | >19 ^d | - ^d | 10.92 | -1.41 | 8.67 | -1.27 | 5.86 | -1.04 | >12.01 (92) |
| 10 | btm | 1.56 | -0.26 | 1.20 | -0.11 | 1.04 | -0.02 | 1.27 | -0.14 | 1.23 (55) |
| 11 | btm ⁺ | 18.03 | -1.71 | 7.89 | -1.22 | 6.27 | -1.08 | 4.05 | -0.83 | 8.22 (89) |
| 12 | chtm | 1.12 | -0.07 | 1.09 | -0.05 | 1.00 | 0.00 | 1.06 | -0.03 | 1.06 (51) |
| 13 | chtm ⁺ | >19 ^d | - ^d | 10.54 | -1.39 | 9.03 | -1.30 | 4.94 | -0.94 | >10.94 (92) |

^aDetermined by integrating and averaging several (typically 3–4) ¹H NMR signals. ^bStandard deviations for $K_{\text{cis/trans}}$ were $\leq 10\%$. ^c $\Delta G = -RT \ln K_{\text{cis/trans}}$. Values are given in kcal/mol. ^dTrans-amide rotamers were not detected; ΔG not measurable.

CD₃CN and MeOD ($K_{\text{cis/trans}} = 3.04$ and 1.90 , respectively). Steric effects undoubtedly play a critical role in this result, as shown by a comparison with **2** ($K_{\text{cis/trans}} = 1.31$ in CD₃CN and 0.78 in MeOD), but we also suspected an $n \rightarrow \pi^*_{\text{C}\equiv\text{C}}$ interaction between the acetamide carbonyl O and the alkyne π^* orbital. This was supported by a comparison of the $K_{\text{cis/trans}}$ values for alkyne **1** and alkene **4** side chains of comparable steric bulk. The marked decrease in $K_{\text{cis/trans}}$ for **ee** relative to **ve** may be explained by the higher tendency of alkynes to accept lone-pair electrons due to their lower LUMO energies relative to alkenes. It was also supported by the remarkable effect of the **ce** side chain in **3** containing the electron-withdrawing nitrile group, which gave a high proportion of *cis*-amide (89% in CD₃CN, 79% in MeOD, and 75% in D₂O). These values are in the same range as for the very sterically hindered *Inpe* side chain, which recently allowed Blackwell's group to build homogeneous, robust PPI-type helices.¹³

To understand better the *cis*-directing effect of triazolium side chains, the potential energy surface of peptoid model **II** (Figure 3), with the acetamide in the *cis* conformation, was determined at the B3LYP/6-31G+* level using systematic variation of the torsion angles χ_1 and χ_2 by intervals of 20°. As expected for an achiral molecule, the Ramachandran-type plots for this peptoid model system show two centrosymmetric minima: a deep one centered around (60°, 60°) and its mirror

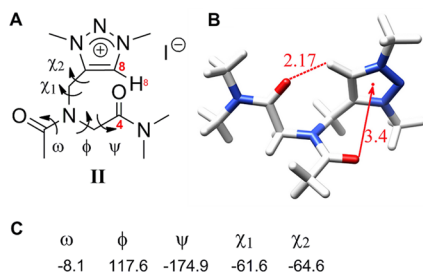


Figure 3. Computational study of peptoid model **II**. (A) Definition of the dihedral angles and labels of selected atoms. (B) Low-energy conformation calculated at the B3LYP/6-31G+* level. The $n \rightarrow \pi^*_{\text{Ar}}$ interaction is shown by the red arrow and the H-bond by the dotted line; the associated distances are also shown. (C) Dihedral angles for one of the two centrosymmetric lowest-energy conformations.

image near (-60°, -60°) (see the SI). The geometrical requirements for $n \rightarrow \pi^*_{\text{Ar}}$ overlap²² (distance of 2.8–3.8 Å between the carbonyl O atom and the ring centroid; dihedral angle of $\sim 90^\circ$ between the O=CX₂ and aromatic ring planes) are respected in the lowest-energy conformations: the O–centroid distance is 3.4 Å, and the dihedral angle is 87°.

The energy of this interaction was estimated as 1.11 kcal/mol using second-order perturbation theory as implemented in Natural Bond Orbital 5.9 (NBO 5.9); this value has the same order of magnitude as those evaluated for carbonyl–carbonyl interactions in proteins.^{23,24} Importantly, the conformationally optimized model **II** (Figure 4) also revealed the presence of H-

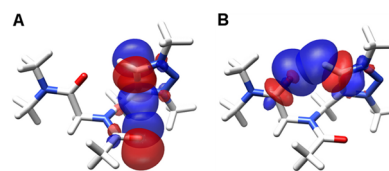


Figure 4. Orbital overlaps stabilizing the preferred conformation of **II**: (A) $n \rightarrow \pi^*_{\text{Ar}}$ delocalization; (B) H-bonding interaction ($n \rightarrow \sigma^*$).

bonding between the carbonyl O of the *N,N*-dimethylamide and the triazolium proton ($d_{\text{C-H}\cdots\text{O4}} = 2.17$ Å; C4–O4–H8 = 152°). The dihedral angles (ϕ, ψ) = (117°, -175°), associated with (χ_1, χ_2) = (-61°, -64°), roughly correspond to the known *cis* α_D conformation (ϕ and ψ clustered around $\pm 90^\circ$ and 180° , respectively).²⁵ The slight deviation for ϕ (117° vs 90° on average) may be due to a conformational adjustment arising from the formation of the H-bond.

Experimentally, involvement of the triazolium proton in H-bonding was strongly suggested by NMR downfield chemical shifts of the triazolium proton (H8) and carbon (C8). For **7** in CDCl₃, $\delta_{\text{H8}} = 10.18$ ppm and $\delta_{\text{C8}} = 131.4$ ppm. These values are shifted significantly downfield relative to standard values reported in the literature for 1,2,3-triazolium motifs not involved in H-bonding (typically $\delta_{\text{H}} = 9.10$ – 9.80 and $\delta_{\text{C}} = 127$ – 129 ppm).²⁶ Moreover, increasing the temperature did not change δ_{H8} in CDCl₃ (see the SI). The correlations observed in the 2D NOESY spectrum of **7** in CDCl₃ were consistent with the correct orientation of the triazolium moiety to form the H-bond with the carbonyl of the piperidinylamide. In this conformation (Figure 5), the geometrical criteria

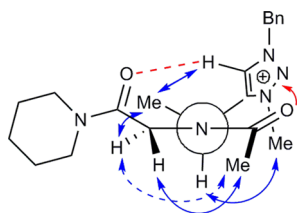


Figure 5. Newman projection of the most populated conformation of **7** in CDCl_3 as deduced by NOESY. Strong and medium NOEs (solid and dashed blue arrows, respectively), the $n \rightarrow \pi^*_{\text{Ar}}$ interaction (red arrow), and the intramolecular H-bond (red dashed line) are shown.

necessary for an $n \rightarrow \pi^*_{\text{Ar}}$ interaction are met. In CD_3CN , $\delta_{\text{H8}} = 8.57$ ppm was observed, suggesting from the relevant literature²⁷ the absence of an intramolecular H-bond. Nevertheless, the same NOEs were observed in CD_3CN and CDCl_3 , indicating again the spatial proximity of the triazolium and acetamide groups, enabling a possible $n \rightarrow \pi^*_{\text{Ar}}$ delocalization.

The $n \rightarrow \pi^*_{\text{Ar}}$ delocalization and intramolecular H-bond may act cooperatively. The H-bond not only would restrict the conformational freedom (ϕ , ψ) but also may assist the carbonyl (acetamide) and triazolium ring to adopt the proper orientation to maximize the $n \rightarrow \pi^*_{\text{Ar}}$ delocalization. This cooperative effect would explain why the trans rotamers are completely suppressed in CDCl_3 regardless of the side-chain type (N - $\text{C}\alpha$ -branched or unsubstituted at N - $\text{C}\alpha$).

In conclusion, we have proposed a new type of peptoid side chain containing a triazolium moiety capable of controlling the amide isomerism in α - and β -peptoid model systems while maintaining the potential for side-chain diversity. This type of side chain should facilitate the understanding of how β -peptoids fold. To our knowledge, the triazolium motif represents the best *cis*-amide control conceived to date both in aprotic and protic solvents. We have shown that its ability to promote the *cis*-amide geometry is not steric in nature. The conformation found in CDCl_3 and CD_3CN is consistent with an attractive interaction arising from a backbone–side-chain $n \rightarrow \pi^*_{\text{Ar}}$ electronic delocalization. These results are supported by DFT and NBO analysis. It is obvious that other types of noncovalent interactions (e.g., electrostatic dipole–dipole or charge–charge interactions) may influence $K_{\text{cis/trans}}$. In protic solvents, particularly in water, solvation of the triazolium H-bonding motif certainly accounts for the strong decrease in $K_{\text{cis/trans}}$. This work has also shown for the first time the remarkable effect of the nitrile group in stabilizing the *cis*-amide conformation in peptoids. Work on syntheses and conformational studies of peptoid oligomers with various sequence patterns of triazolium side chains are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and additional data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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