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COMMUNICATION

Metal-free 1,3-dipolar cycloaddition polymerization *via* prearrangement of azide and alkyne in the solid state

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Metal-free 1,3-dipolar cycloaddition polymerization with controlled regioselectivity is achieved by pre-organizing azide and terminal alkyne functional groups in the solid state. Soluble polymers are obtained with monomers containing flexible tri- and tetra-ethylene glycol linkers.

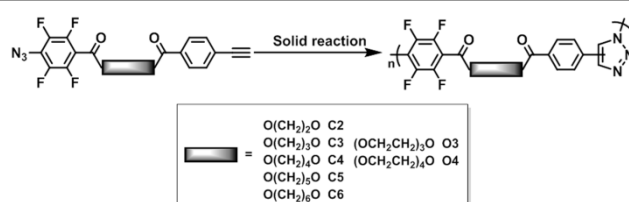
As efficient and environmental friendly protocols, solid-state organic reactions have become popular green methods to control the formation of covalent bonds¹. Such reactions mainly emerged as photoreactions² but have been extended to thermal, gas-solid, and solid-solid transformations.³ In the solid state, while molecules exhibit certain mobility allowing for chemical reactions, they are sufficiently constrained to realize optimal regioselectivity. Even special molecular geometries which are impossible occur in solutions may be adopted in the solid state.⁴ Recently, particular non-covalent interactions were introduced as helpful driving forces⁵ to arrange molecules in crystals favorably for chemical reactions.⁶ Hydrogen bonding, charge-transfer and arene-perfluoroarene interactions have been employed to realize [2+2] photodimerization^{4,7-9} Diels-Alder reaction,¹⁰ and polymerization of diacetylene.¹¹⁻¹⁴

The simple but effective 1,3-dipolar cycloaddition reaction between azide and alkyne was first discovered by Arthur Michael and further developed by Rolf Huisgen.¹⁵ 1,4- and 1,5-Disubstituted triazoles are usually obtained at a rough ratio of 1:1 in these reactions.¹⁶ A viable solution to optimal regioselectivity was accomplished by Sharpless¹⁷ and Meldal¹⁸, utilizing mild but efficient copper-catalyzed azide-alkyne cycloaddition (CuAAC) to give 1,4-triazoles products. Nonetheless, to circumvent the toxicity brought by copper ion, a greener azide-alkyne cycloaddition (AAC) reaction with high regioselectivity is urgently needed. We previously developed a metal-free 1,3-dipolar cycloaddition which proceeds in the solid state at room temperature. Regioselectivity was realized by pre-organization of the azide and alkyne functional groups by virtue of arene-perfluoroarene interactions in the crystalline state.¹⁹⁻²¹ Other groups also reported metal-free 1,3-dipolar cycloaddition methods, which were exploited for the syntheses of poly(bile acid)s^{22,23} and polysaccharide.²⁴⁻²⁶

Prearrangement of functionality in crystals is a pivotal factor for achieving regioselectivity.²⁷ Imaginably, different linker

structures between the alkyne and azide functionalities would cause significant changes in the molecular arrangements of crystals.²⁸ In this work, a series of molecules featuring different linkers joining aromatic and fluorinated aromatic moieties, carrying the azide and alkyne functionalities respectively, are designed and synthesized (Scheme 1). The solid-state reactions of all studied molecules show preferred regioselectivity for 1,4-triazole products, while fluctuation in the extent of selectivity is observed with different linker groups, as a result of varied arrangement of azide and alkyne groups. Particularly, molecule **C3** exhibiting an unusual “folding” conformation in the crystal shows the highest regioselectivity.

Furthermore, in most previously studied solid-state reactions, it was difficult to obtain soluble polymers.^{12,13,19} We further incorporated tri- and tetra-ethylene glycol linkers to improve the solubility of resultant polymers in organic solvents. We here report the series of soluble polymers prepared from metal-free AAC reactions with high regioselective control.



Scheme 1 Schematic representation of metal-free 1,3-dipolar cycloaddition polymerization.

Molecules comprising phenylene and tetrafluorophenylene units joined by different alkyne linkers (**C2-C6**) and terminated by azide and alkyne groups were synthesized via two consecutive esterification reactions (Scheme S1). **C2**, **C3**, **C4**, and **C6** formed transparent crystals, while **C5** was a liquid at room temperature. In order to understand the relationship between the molecular arrangement in crystals and the regioselectivity in 1,3-dipolar cycloaddition, X-ray diffraction analyses were performed on the single crystals of **C2**, **C3**, **C4**, and **C6**, obtained by slow evaporation of solvents. The crystal structures revealed that molecules **C2**, **C3**, and **C6** displayed

brickwall, sandwich, and lamellar packing motifs respectively, all showing arene-perfluoroarene interactions, whereas **C4** uniquely adopted a brickwall packing, exhibiting stacking among perfluoroarene moieties *via* dipole-dipole interactions. Single crystal structures also unveiled differed orientations and distances between azide and alkyne groups in **C2-C6**, which were anticipated to induce disparate regioselectivity in AAC reactions.

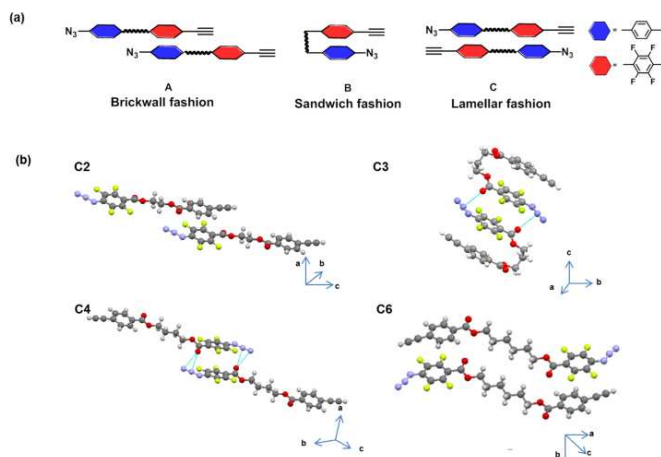


Fig. 1 (a) Schematic representation of possible arrangements of studied monomers exhibiting arene-perfluoroarene interactions in the solid state; (b) ORTEP drawings of the crystal structures of **C2**, **C3**, **C4**, and **C6**.

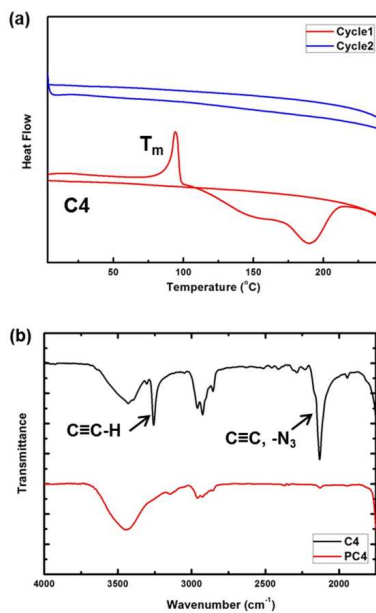


Fig. 2 (a) DSC thermograms of crystalline **C4** under N_2 atmosphere with a heating rate of $10\text{ }^\circ\text{C}\cdot\text{min}^{-1}$; (b) FTIR spectra of the monomer **C4** and polymer **PC4** from metal-free 1,3-dipolar cycloaddition polymerization.

Differential scanning calorimetry (DSC) analyses were first performed to monitor the 1,3-dipolar cycloaddition of **C2-C6**. **C4** exhibited a distinct endothermic peak indicating a melting point at about $97\text{ }^\circ\text{C}$ in the first heating scan (Fig. 2a), followed by broad exothermic peak starting at ca. $100\text{ }^\circ\text{C}$, which corresponded to the cycloaddition polymerization. It should be

noted that the polymerization barely took place before the phase transition. In the second heating-cooling cycle, no detectable exothermic or endothermic peak was observed, which suggested that 1,3-dipolar cycloaddition polymerization was completed in the first heating cycle. This conclusion was also confirmed by NMR data (Fig. S3-4).

To ensure that polymerization of the monomers took place in the solid state rather than the melting phase, the crystalline **C4** was heated at $85\text{ }^\circ\text{C}$, below its melting point (T_m). According to the FT-IR spectroscopy, monomer **C4** exhibited strong bands at 3280 cm^{-1} and 2120 cm^{-1} assignable to the stretching vibrations of $(C\equiv)C-H$ and $C\equiv C/N\equiv N$ groups, respectively. After 10 hours' thermal treatment, these bands were significantly reduced (Fig. 2b). The residual peaks were attributed to the small amounts of unreacted azide and alkyne groups. Similar DSC thermograms and FT-IR results were obtained for **C2**, **C3**, and **C6** (see the ESI).

Table 1 Reaction conditions and regioselectivity of monomers **C2-C6**.

	T_m^a ($^\circ\text{C}$)	Reaction Temperature ($^\circ\text{C}$)	Reaction Time (h)	$F_{1,4}^b$ (%)
C2	97	85	10	59
C3	58	45	10	84
C4	97	85	10	64
C6	55	45	10	73

^aEstimated by DSC thermograms under N_2 atmosphere with a heating rate of $10\text{ }^\circ\text{C}\cdot\text{min}^{-1}$. ^bFraction of 1,4-regioisomers determined by ^1H NMR in $\text{DMSO-}d_6$.

Molecules **C2**, **C3**, **C4**, and **C6** could all dissolve in common organic solvents such as CHCl_3 , DMSO , THF and acetone. After thermal treatment, the solubility of resultant polymers was however very poor in these solvents, corroborating that cycloaddition polymerization occurred. For the purpose of getting quantitative information about the regioselectivity, the solid-state reaction time was reduced to 2 hours, to obtain more soluble oligomers. Under otherwise identical reaction conditions, it was reasonable to assume that the selectivity of oligomers was similar to that of polymers. The ratios of 1,4- and 1,5-disubstituted triazoles were calculated based on the ^1H NMR spectra of product polymers in $\text{DMSO-}d_6$. It was found that the fraction of 1,4-triazoles in **PC2**, **PC3**, **PC4**, and **PC6** ranged from 59% to 84% (Table 1).

In order to exclude the influence of electronic effects of tetrafluorophenyl group²⁹ on the regioselectivity and also conveniently characterize the products, we designed two control molecules, containing azide and alkyne groups respectively but not linked together. The 1,3-dipolar cycloaddition between these monofunctional molecules conducted in $\text{DMSO-}d_6$ at $100\text{ }^\circ\text{C}$ for 10 hours, and the fraction of 1,4-triazoles was 52%. Namely, the 1,4- and 1,5- isomer ratio was roughly 1:1 (Figure S2-32).

Moreover, although **C5** was a liquid at room temperature, upon heating at $100\text{ }^\circ\text{C}$ for 10 hours under solvent- and metal-free conditions, the fraction of 1,4-triazoles in **PC5** was 69%. The slightly preferred 1,4- selectivity suggested the presence of certain prearrangement of azide and alkyne groups in the melted phase of **C5**.

To gain further insight into the origin of varied regioselectivity in the polymerizations of **C2-C6**, the distances and orientations of azide and alkyne groups in the crystal structures were compared in details (ESI). The difference in the distances between azide and alkyne groups to give 1,4- and the 1,5-regioisomers was one of the decisive factors that influenced the regioselectivity¹⁹. For **C2**, to offer 1,4-regioisomers the

proper distances between azide and alkyne groups were 7.202 Å and 7.008 Å, similar to the distances (8.519 and 6.084 Å) to give 1,5-regioisomers (**Figure S4-1**). This result may explain the poor regioselectivity observed with **C2**. On the contrary, for **C3** the shortest distances between the alkyne carbons and 1-/3-nitrogen atoms of azide group were 3.646 Å and 4.645 Å (**Figure S4-2**), which were found intramolecularly. Although the two reacting groups were close to each other within the same molecule, the ring strain may have disfavored the intramolecular reaction to offer 1,5-triazole product. Furthermore, the distances between the reactive groups from neighboring columns were similarly short, at 3.982 and 3.931 Å. Thus, **C3** could easily react intermolecularly to give 1,4-triazole product with high selectivity.

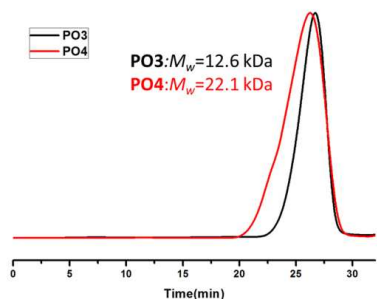


Fig. 3 GPC traces of the obtained **PO3** and **PO4** from metal-free 1,3-dipolar cycloaddition polymerization.

In view of the limited solubility of **PC2-PC6** in common solvents, new monomers **O3** and **O4** were designed and synthesized, in which tri- and tetra-ethylene glycol were introduced as linkers to improve solubility of the product polymers. Due to the flexible ethylene glycol linkers in monomers **O3** and **O4**, it was unable to get their single crystals, but soluble polymers with high molecular weight and regioselectivity were achieved in the absence of solvents and catalysts. When the monomers were heated at 100 °C for 10 hours, the 1,3-dipolar cycloaddition polymerization took place and as expected the solubility of the resultant polymers **PO3** and **PO4** was very good in common organic solvents. Thus, we were able to characterize those polymers with traditional methods, such as gel permeation chromatography (GPC). The weight-average molecule weights of **PO3** and **PO4** were up to 12.6 and 22.1 kDa, respectively (Table S3-1), and the fractions of 1,4-triazoles were 78%, and 89%, respectively. This is a rare examples²² of soluble polymers with triazoles and aromatic moieties as repeating unit.

Conclusions

In summary, we designed and synthesized a series of molecules with different linkers between aromatic and fluorinated aromatic moieties carrying azide and alkyne functionalities. Influenced by arene-perfluoroarene interactions, different molecular arrangements were achieved when using different linkers. The metal-free polymerization was conducted by heating these monomers in the solid state. The regioselectivity of polymerization reaction was attributed to the prearrangement of monomers in crystals. Among them, **C3** with an unusual folding fashion offered the highest regioselectivity. Furthermore, molecules with tri- and tetra-ethylene glycol as linkers were introduced to improve polymers' solubility in

common organic solvents, and we were able to characterize the resultant polymers by GPC. We believe that the metal-free AAC can be applied in the syntheses of functional molecules with ethylene glycol and triazole motifs.³⁰⁻³⁴ The on-going research is focusing on functionalization of materials synthesized through this green method.

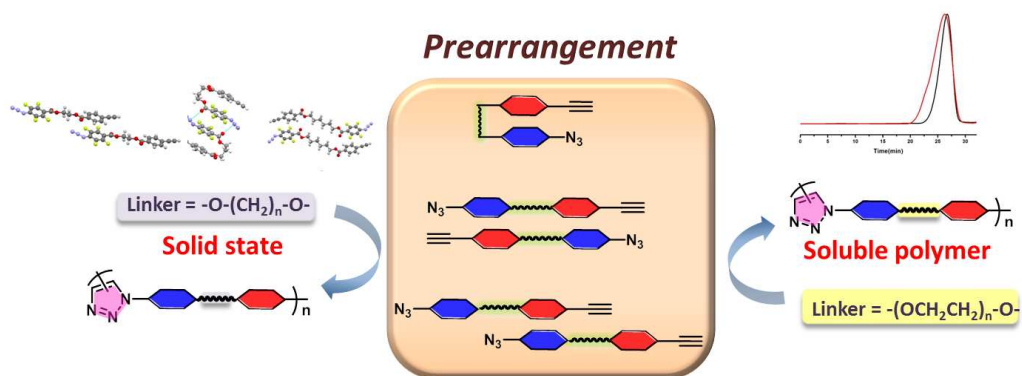
Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, details of spectroscopic and analytical data. See DOI: 10.1039/b000000x/

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