Article 8 - Effect of backbone flexibility on covalent template-directed synthesis of linear oligomers

Núñez-Villanueva, D.; Hunter, C. A. Effect of Backbone Flexibility on Covalent Template-Directed Synthesis of Linear Oligomers. *Organic & Biomolecular Chemistry* **2022**, 20 (42), 8285–8292. https://doi.org/10.1039/d2ob01627c.

Figure 3:

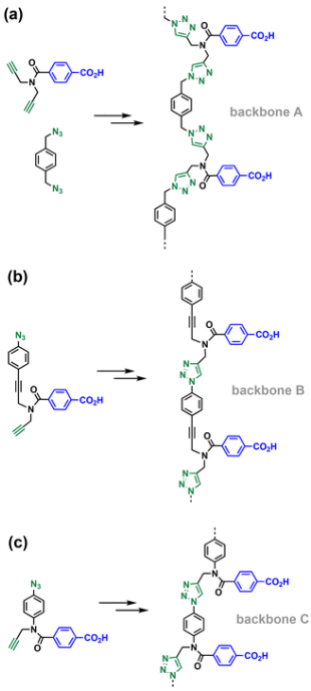

Fig. 3 : Three different backbones synthesised by CuAAC oligomerisation of the corresponding building blocks. (a) 1,4-Bis(triazolyl)methylbenzene (A). (b) p-Triazolylethynylbenzene (B). (c) p-Triazolylaniline (C).

Synopsis:

The construction of specific molecular structures is a key focus in modern chemistry, particularly when creating chains of molecules, known as oligomers, from smaller building blocks called monomers. In their study "Effect of Backbone Flexibility on Covalent Template-Directed Synthesis of Linear Oligomers," researchers Diego Núñez-Villanueva and Christopher A. Hunter investigate how the flexibility of a monomer's backbone influences the efficiency and outcome of this process. Understanding these effects is crucial for designing effective synthetic strategies that minimize unwanted by-products and optimize yield.

Template-directed synthesis is a method in which a template molecule acts as a scaffold, guiding monomers to connect in a predetermined order. This approach is widely used to ensure

precision in constructing complex molecular architectures. However, not all monomers behave the same during this process, and their structural characteristics, particularly backbone flexibility, can significantly influence the resulting products. The study explores this phenomenon by comparing monomers with varying degrees of flexibility and examining the types of products formed.

The researchers observed that monomers with highly flexible backbones tend to produce a mix of two types of products: linear oligomers and ring-shaped structures known as macrocycles. These macrocycles form when the ends of a growing chain connect to create a closed loop, rather than continuing to extend linearly. Conversely, monomers with rigid backbones predominantly form linear oligomers, with minimal macrocycle formation. This distinction suggests that backbone flexibility plays a pivotal role in determining the structural outcome of the synthesis process.

To delve deeper into this behavior, the team analyzed the energy associated with forming ring structures, a concept known as ring strain. Ring strain measures how much energy is required to bend a molecule into a ring, with higher values indicating greater difficulty in forming the structure. Their calculations revealed that products with low ring strain, typically in the range of 20–30 kJ/mol, form easily and quickly. In contrast, structures with high ring strain, exceeding 100 kJ/mol, are much less likely to form. This finding helps explain why rigid monomers are less prone to forming macrocycles—they create rings with higher strain, making the process energetically unfavorable.

The study highlights the importance of balancing flexibility in monomer design. Monomers must be rigid enough to discourage unwanted macrocycle formation but sufficiently flexible to allow efficient linear assembly along the template. This balance ensures that the desired product, a linear oligomer, is obtained with minimal by-product formation. Furthermore, the researchers propose that molecular mechanics calculations of ring strain can serve as a valuable tool for evaluating monomer suitability before synthesis, providing a predictive framework to guide experimental design.

The article's key figure (Figure 3) visually captures these findings by illustrating the relationship between backbone flexibility and product distribution. It shows the transition from macrocycle-dominated outcomes in highly flexible monomers to linear oligomer predominance as backbone rigidity increases. This visual representation underscores the nuanced interplay between molecular structure and synthetic outcomes, providing a clear and accessible summary of the study’s conclusions.

This research contributes significantly to the field of synthetic chemistry, offering practical insights for designing more efficient and precise molecular assembly processes. By demonstrating the impact of backbone flexibility on product formation and proposing a predictive approach using ring strain analysis, the study sets a foundation for future advancements in template-directed synthesis. This work is particularly relevant for applications requiring highly

specific molecular structures, such as materials science, drug development, and nanotechnology.