Design and evaluation of azobenzene-functionalized macrocyclic peptoids as tunable molecular photoswitches

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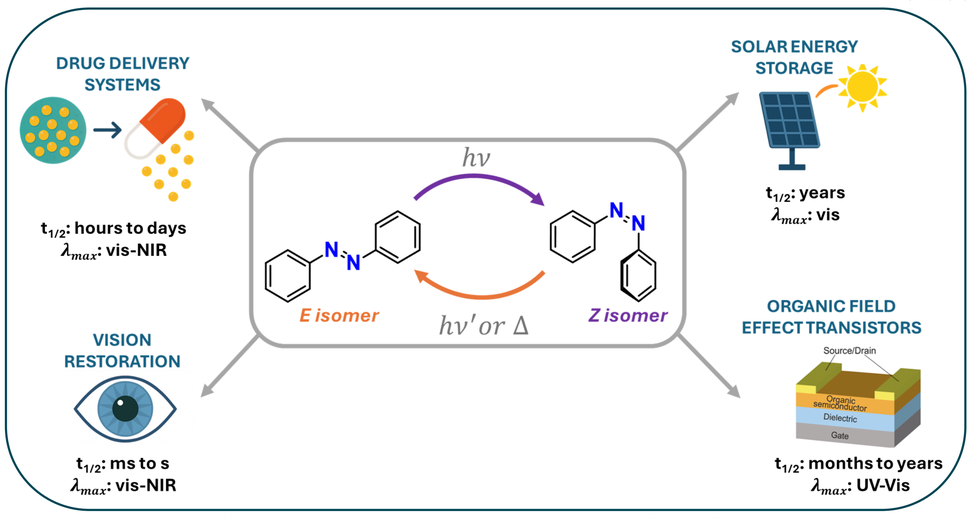
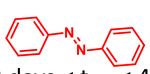


Figure 1. *Applications of azobenzene as photoswitchable compounds and the key properties to optimize [1], [2] .*

Introduction

Azobenzenes (AB) derivatives are a particularly interesting class of molecular photoswitches due to their capacity to reversibly photoisomerize between their trans and cis configurations. This property is exploited in fields such as solar energy storage, smart materials or pharmacology (**Figure 1**), depending on the photochemical properties such as the half-life ($t_{1/2}$) of the cis isomer and the absorption range of the trans isomer *[1], [2]*. Strategies used to modulate these properties include substituting azobenzenes or incorporating them as side chains onto a polymer backbone, including peptoids. Azobenzene derivatives have been previously incorporated all along a peptoid backbone with a strong impact on the photoswitching properties (**Figure 2**) *[2]*. Cyclization of peptoids by limiting their conformational flexibility should further affect the photoisomerization processes (**Figure 2**) *[3]*. In this context, the integration of azobenzenes into cyclic peptoids is promising for the design of new modular photosensitive molecular switches. Their unique structure would represent an ideal and versatile platform to tune the properties of azobenzene. This project explores the integration of a single azobenzene residue into a cyclic peptoid. The photoswitching properties of the obtained original molecules have been investigated using state of the art mass spectrometry methods.

Pristine azobenzene



- 2 days < $t_{1/2}$ < 4 days
- λ_{max} = 320 nm

Linear peptoid → **Cyclic peptoid**

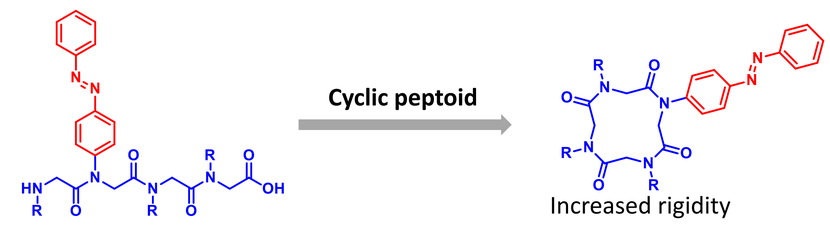


Figure 2. *Incorporating* azobenzenes into cyclic peptoids to design new photoreactive materials *[2], [3].*

Objectives

- Linear and cyclic peptoids synthesis
- Structural characterization (MS, MS/MS, LC-MS and LC-IMS-MS)
- Determination of $t_{1/2}$ (LC-MS)

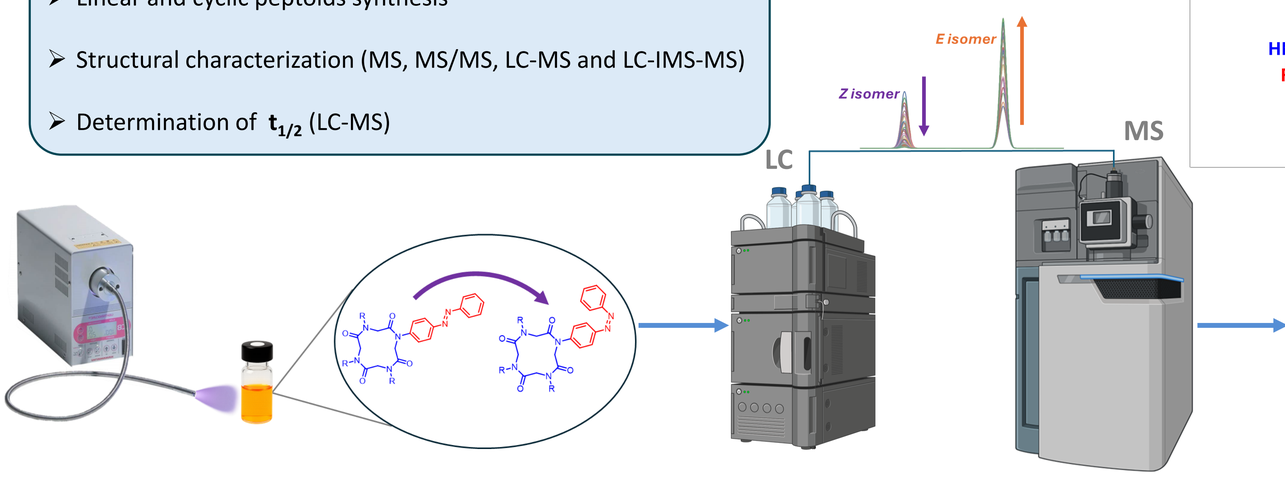


Figure 3. Experimental procedure and setup for determining the half-life of the cis isomer by LC-MS. C_{18} Agilent Eclipse plus column; H_2O (0.01 % HCOOH) / ACN gradient.

Synthetic pathway

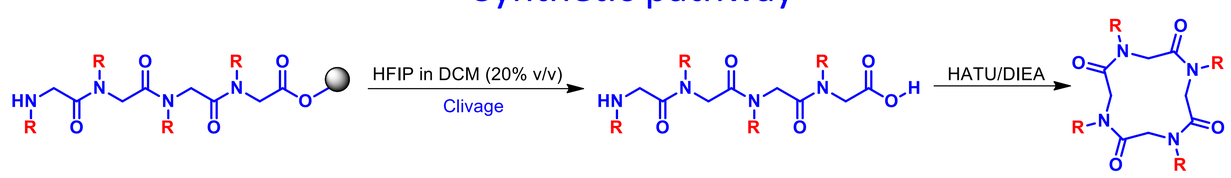
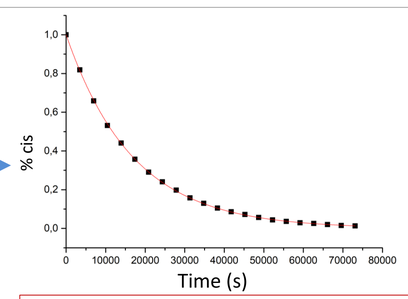
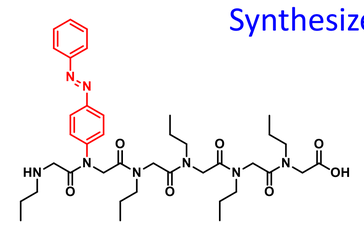


Figure 3. *Pathway for the cyclization of peptoids from linear precursors [3].*

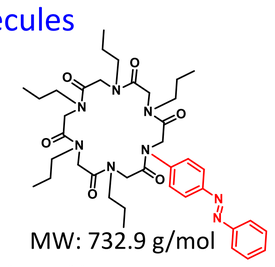


$$k = \frac{k_B T}{h} e^{-E_a/RT} \leftrightarrow t_{1/2} = \frac{\ln 2}{k}$$

Synthesized molecules



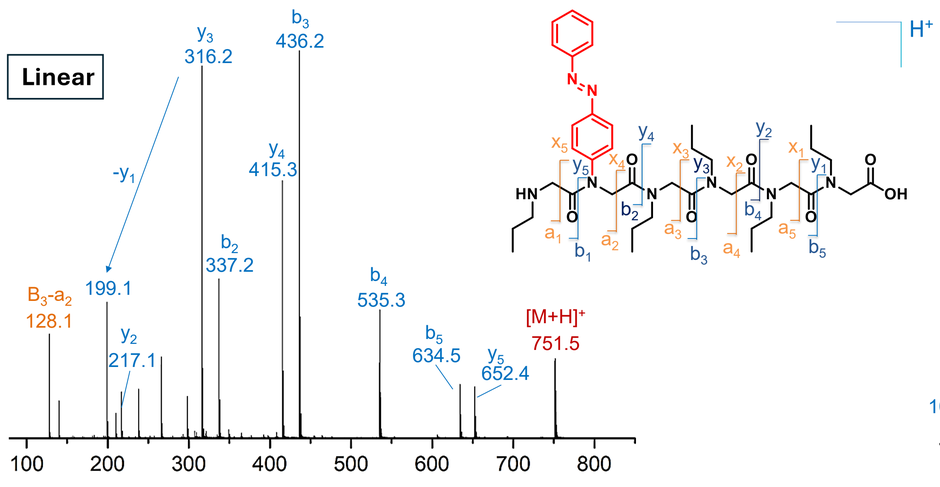
MW: 750.9 g/mol



MW: 732.9 g/mol

NproNazoNproNproNproNpro

Structural analysis (MS/MS)



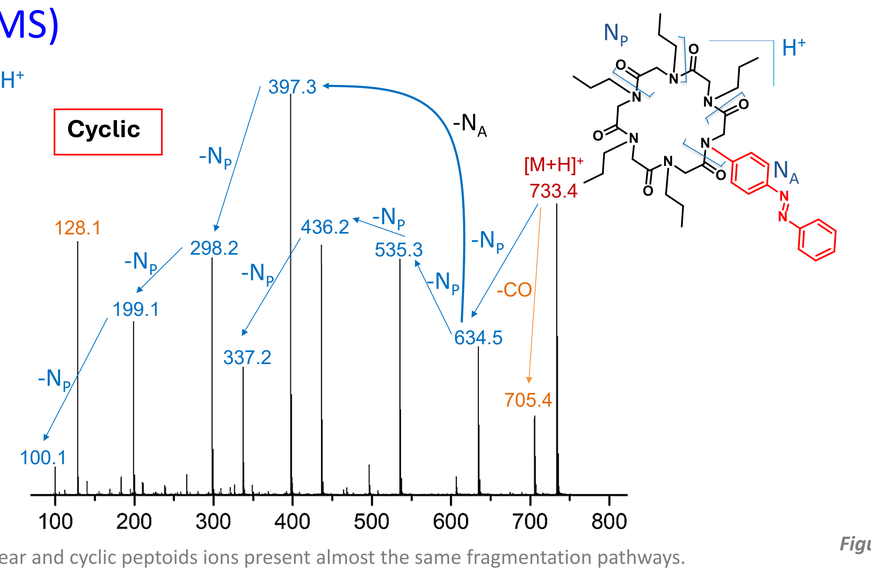


Figure 4. MS/MS spectra of linear and cyclic peptoid ions as $[M+H]^+$ ions . Collision energy: 25 eV. Linear and cyclic peptoids ions present almost the same fragmentation pathways.

Survival yield (LC-MS/MS)

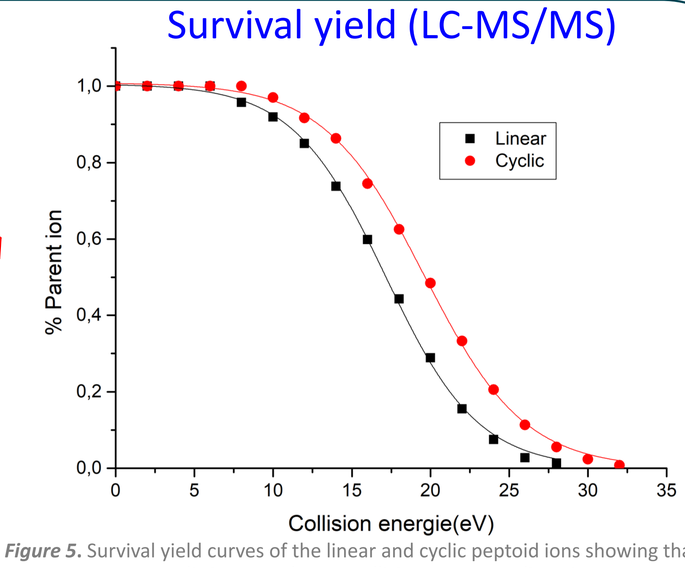
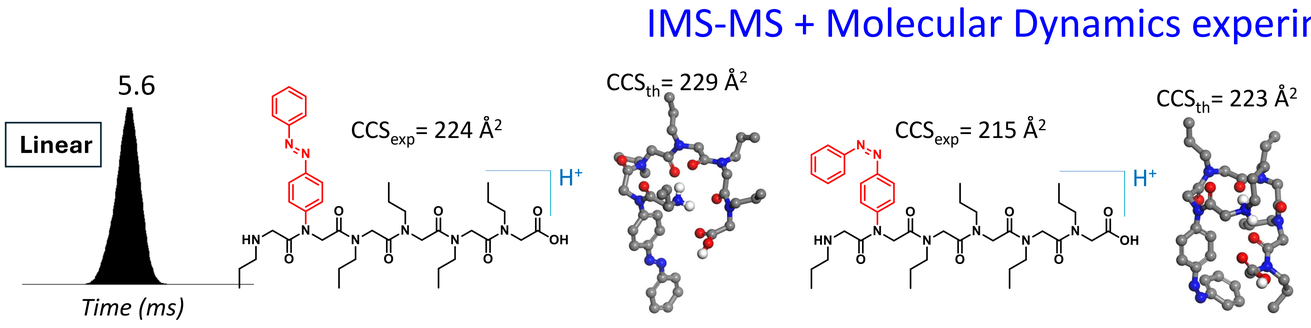


Figure 5. Survival yield curves of the linear and cyclic peptoid ions showing that the cyclic ions need more collision energy to dissociate.

IMS-MS + Molecular Dynamics experiments, including CCS determination



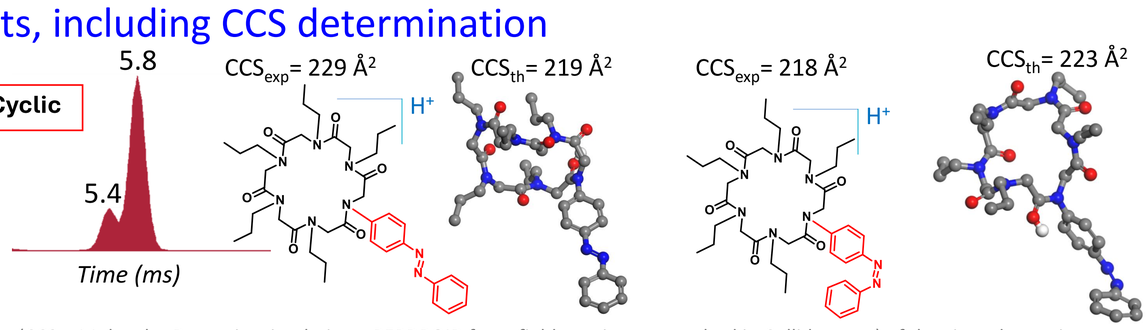


Figure 6. IMS mobilograms of linear and cyclic peptoid ions (HW: 40V; VW: 800 m/s), along with the experimental and theoretical collision cross sections (CCS – Molecular Dynamics simulations, PEPDROID force field + trajectory method in Collidoscope) of the cis and trans isomers.

LC-MS analysis

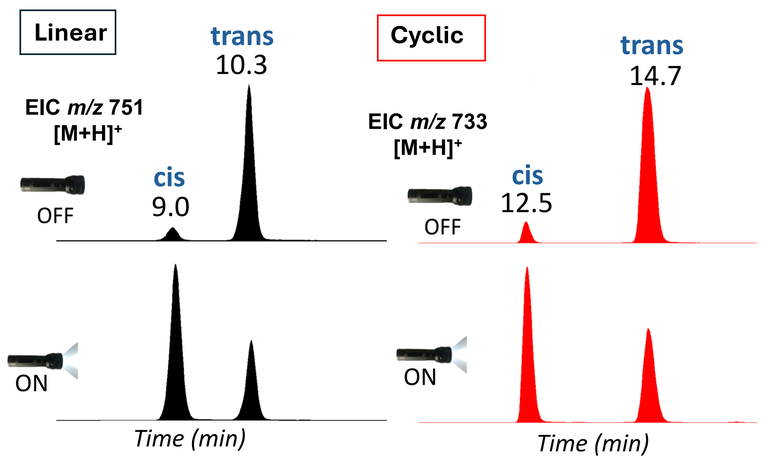


Figure 7. LC-MS analyses : *EIC of linear and cyclic peptoid ions before and after UV light irradiation* (lightningcure LC8 L9588-02A lamp (ca. 220 - 400 nm).

Détermination of the half-lives at 40°C: LC-MS

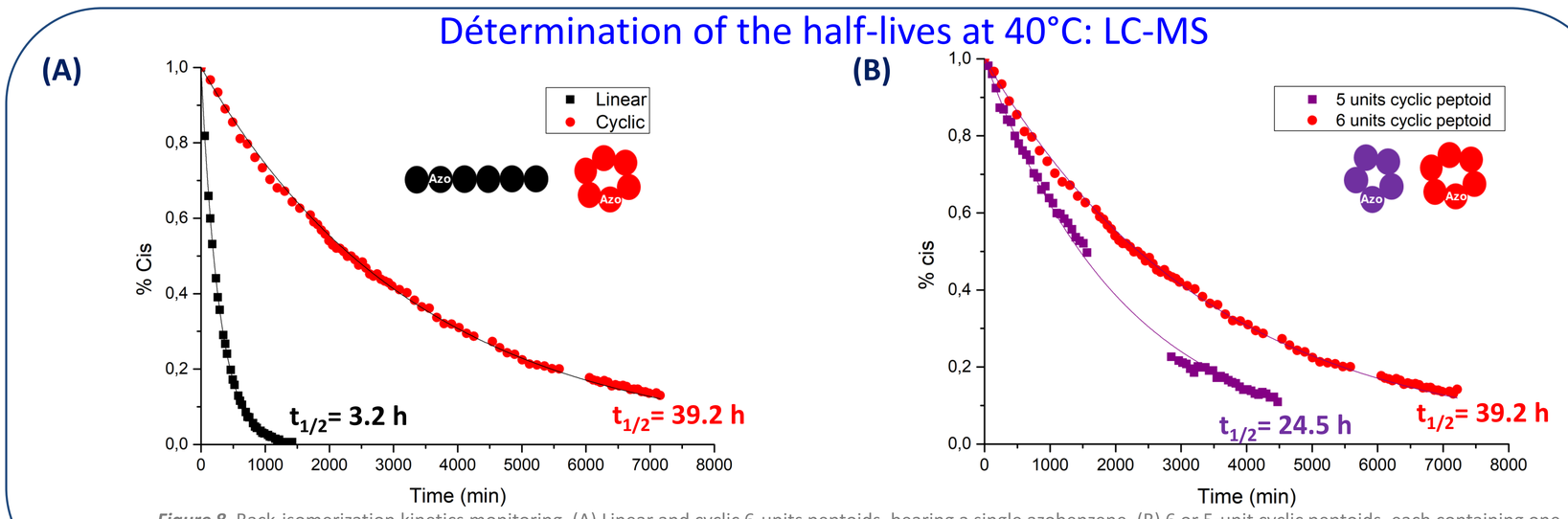


Figure 8. Back-isomerization kinetics monitoring. (A) Linear and cyclic 6-units peptoids, bearing a single azobenzene. (B) 6 or 5-unit cyclic peptoids, each containing one azobenzene. In both cases, the remaining side chains are propyl. The results indicate that cyclization increases the half-life of the cis isomer and that ring size further modulates this parameter.

Conclusions

This work combines mass spectrometry techniques (MS, MS/MS, and IMS-MS) with theoretical investigations. Theoretical chemistry helped to determine the structures of linear and cyclic peptoids ions containing a single azobenzene residue. An LC-MS method was used to study the back-isomerization kinetics of the Z-stereoisomers. The results demonstrate that both cyclization and ring size have a significant effect on the back-isomerization.

Acknowledgments

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References

[1] J. Zhu *et al.*; J. Control. Release., 325, 475-493 (2023).
[2] B. Tassignonet *al.*; Chem. Eur. J., 29, (2023).
[3] A. D'Amato *et al.*; J. Org. Chem., 88, 6588-6598 (2023).

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