Stimuli-Responsive Azobenzene Micelles for Controlled Drug Release and MRI Monitoring

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INTRODUCTION

Current research on stimuli-sensitive systems for drug delivery and imaging highlights the relevance of azobenzene-based compounds[1]. In this work, we present the synthesis of an Azo-(Gd)-DOTA molecule based on 4-octyloxyazobenzene, functionalized with a PEG linker and complexed with Gd-DOTA. This compound forms micelles in aqueous media, undergoes stimuli-responsive isomerization upon UV exposure, and demonstrates MRI-relevant relaxivity, making it a promising candidate for dual-function imaging and stimuli-controlled drug release in cancer therapy.

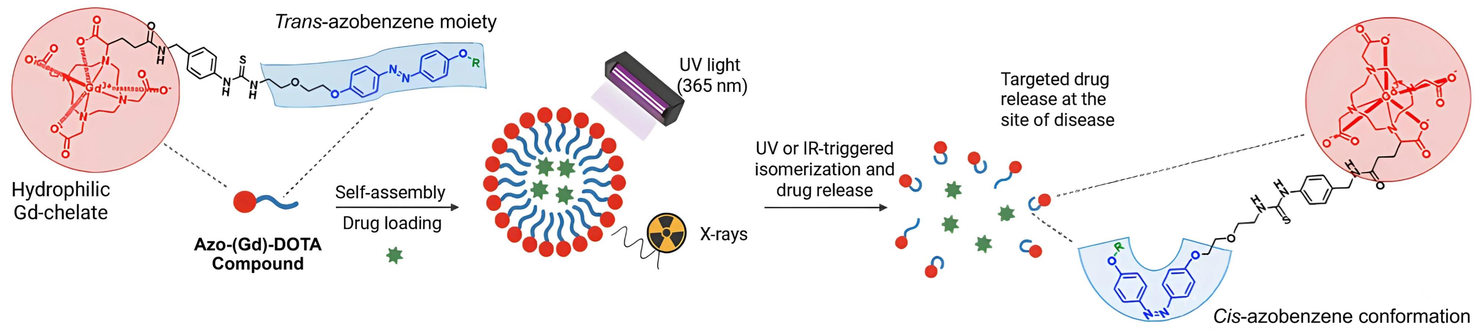
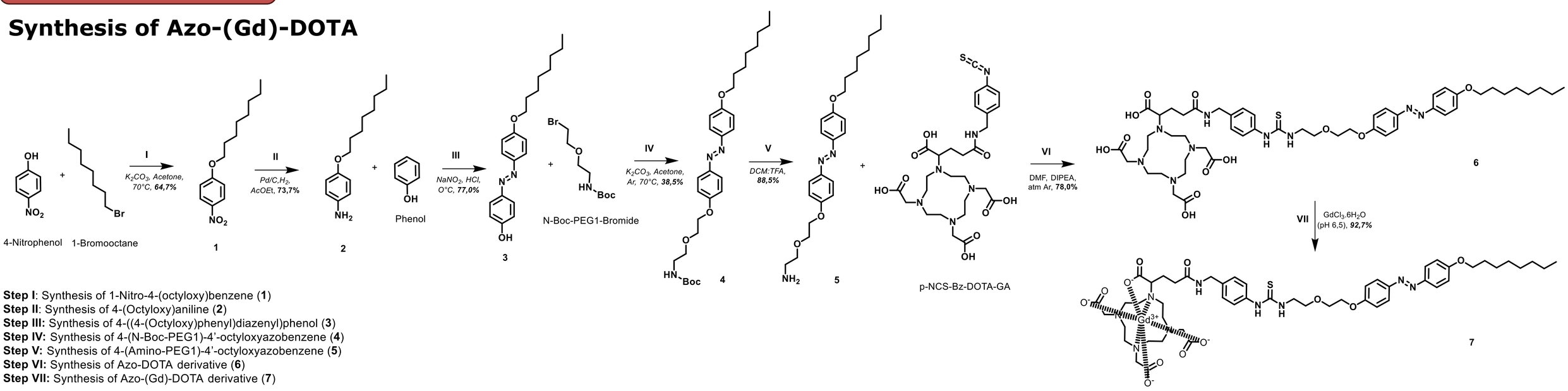


Figure 1. Schematic representation of an Azo-(Gd)-DOTA compound comprising (i) an ionizing radiation (IR)-responsive Gd chelate (red), (ii) a light-sensitive azobenzene photoswitch (blue), and (iii) variable hydrophobic chains (green, R). The diagram also illustrates micelle self-assembly and its disruption upon UV or X-ray exposure via azobenzene isomerization, triggering drug release.

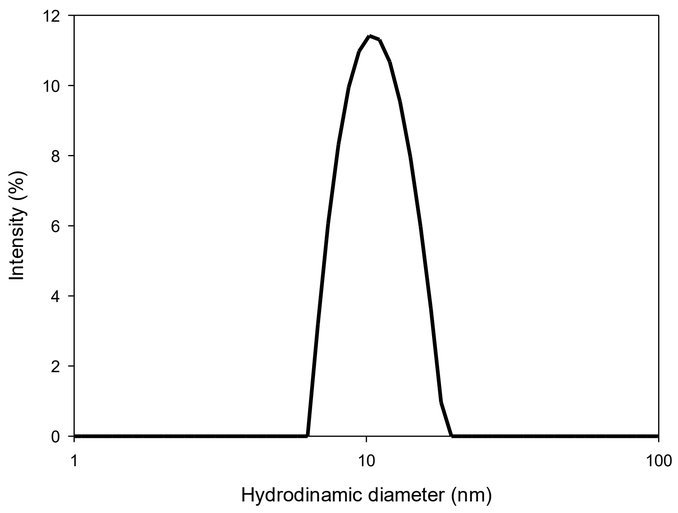
RESULTS

Synthesis of Azo-(Gd)-DOTA



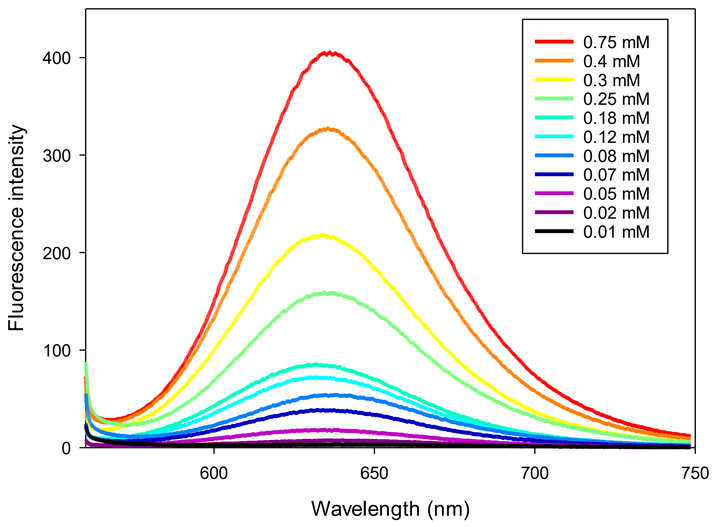
Step I: Synthesis of 1-Nitro-4-(octyloxy)benzene (**1**)
Step II: Synthesis of 4-(Octyloxy)aniline (**2**)
Step III: Synthesis of 4-((4-(Octyloxy)phenyl)diazenyl)phenol (**3**)
Step IV: Synthesis of 4-(N-Boc-PEG1)-4'-octyloxyazobenzene (**4**)
Step V: Synthesis of 4-(Amino-PEG1)-4'-octyloxyazobenzene (**5**)
Step VI: Synthesis of Azo-DOTA derivative (**6**)
Step VII: Synthesis of Azo-(Gd)-DOTA derivative (**7**)

Micelle Formation Characterized by DLS



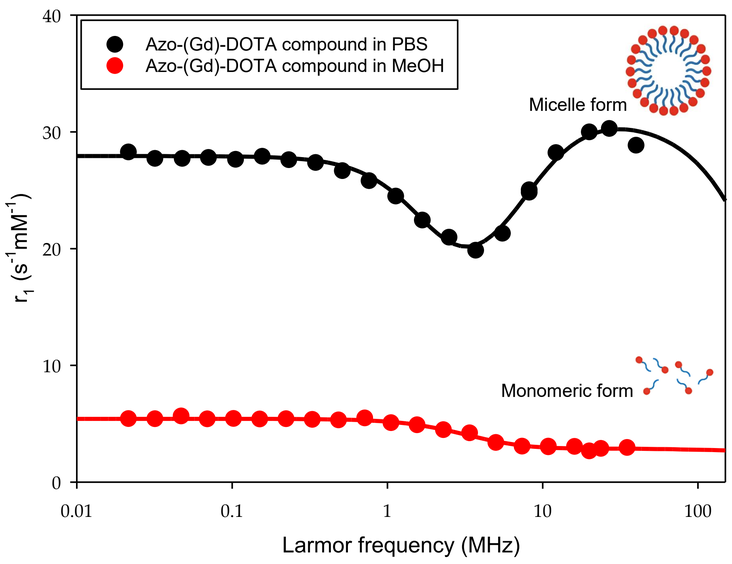
Dynamic Light Scattering (DLS) analysis of the micelles in PBS at 25°C shows a hydrodynamic diameter of **11.1 nm** (PDI: 5.96%).

Determination of CMC



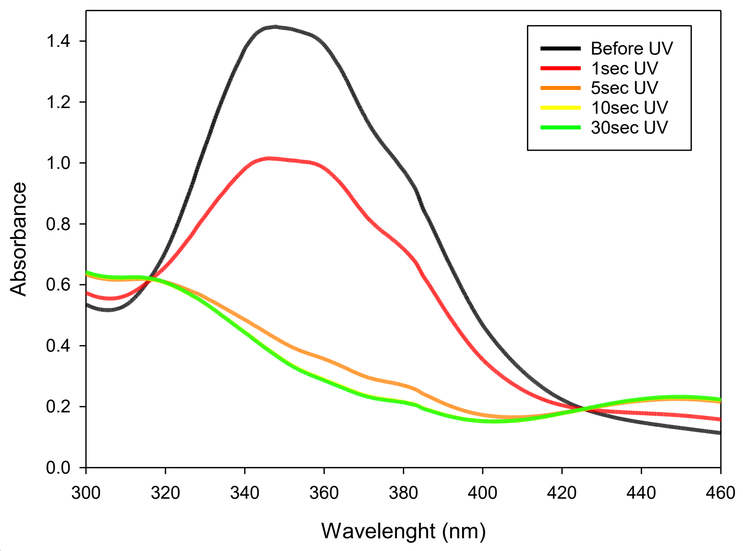
Critical Micelle Concentration (CMC) was determined using a fluorescence-based method with Nile Red as a hydrophobic probe. The critical micelle concentration was calculated to be **0.20 mM**.

NMRD Profile and Relaxivity Enhancement

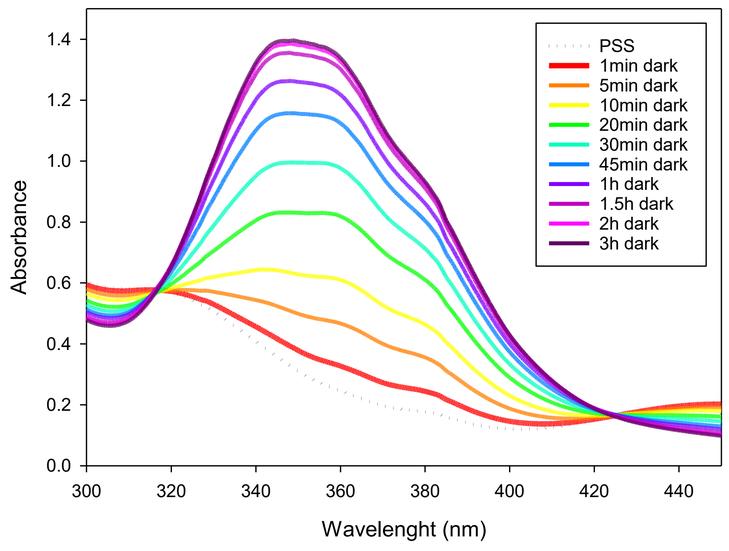


NMRD analysis showed increased **relaxivity** in aqueous media, attributed to micelle-induced rotational restriction. Our compound offers enhanced contrast properties compared to its monomeric form in methanol.

Light-Induced Isomerization



Thermal Back-Isomerization



Azobenzene-(Gd)-DOTA compound underwent efficient **trans-to-cis isomerization** upon UV irradiation, monitored by UV–Vis spectroscopy.
After reaching the **photostationary state** (PSS), thermal back-isomerization at 37°C followed a one-phase exponential model, with a **cis-isomer half-life** of **29 minutes.**
These results confirm the reversible and controllable behavior of the Azo-(Gd)-DOTA.

CONCLUSION

Azo-(Gd)-DOTA molecule was successfully synthesized and characterized. It forms stable micelles in aqueous media, responds to light via reversible isomerization, and enhances MRI relaxivity.
These properties support its potential as a dual-function system for stimuli-responsive drug delivery and MRI-guided cancer therapy.

References: 1- A. Guesdon-Vennerie, P. Couvreur, F. Ali et al. Nat Commun, 2022, 13, 4102.
Acknowledgments: this work was performed with the financial support of the F.R.S.-FNRS – Télévie.

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