

# External stimulus responsive click reaction technology

## Controlling Inverse-Electron-Demand Diels–Alder Reaction with macrocyclic tetrazine

### Overview

Inverse-Electron-Demand Diels–Alder Reaction (IEDDA), a cyclization reaction between tetrazine and dienophile, is used in various fields from materials science to biological applications due to its fast reactivity and high selectivity. If this reactivity can be controlled, the application range is expected to expand dramatically. A method for controlling the reaction by oxidizing dihydrotetrazine to tetrazine, which is less reactive, has been reported, but there are problems such as the effect of natural oxidation and the inability to respond to stimuli other than oxidation.

The inventors found that the IEDDA reaction can be completely suppressed by derivatizing tetrazine to a macrocyclic structure, and that the reaction proceeds rapidly when the reaction is converted from a cyclic to an acyclic structure by stimulation. The stimuli in the present invention can be selected according to the application, such as light, heat, pH, enzymatic reaction, redox, etc. By using the present invention, it is expected to be applied to the in vivo synthesis of active pharmaceuticals, environmentally responsive drug delivery systems, chemical sensors, nuclear medicine diagnostics, etc.

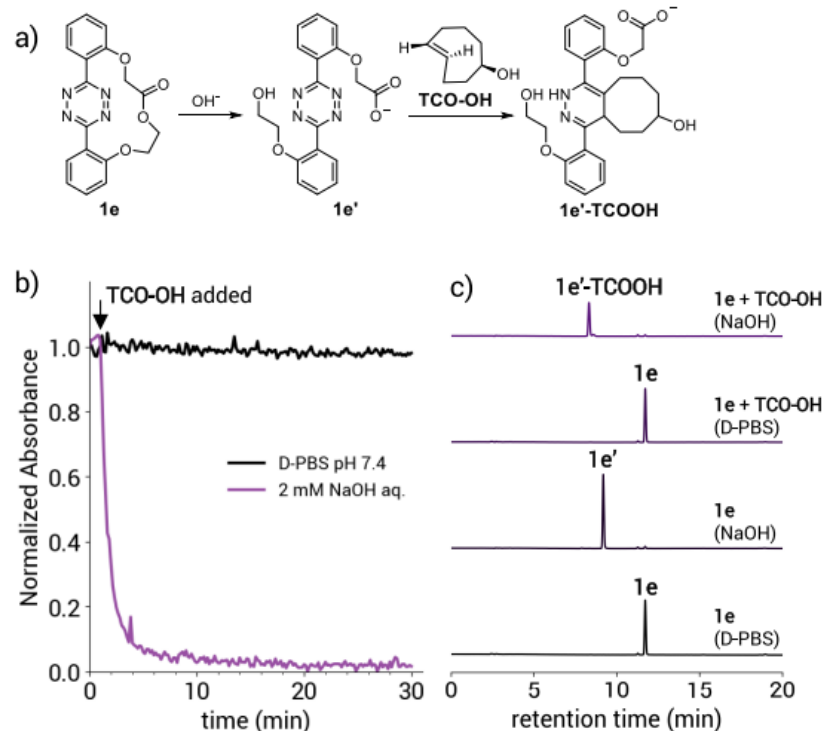
### Product Application

- ☐ In vivo synthesis of medicine
- ☐ Environment-responsive drug delivery system
- ☐ Chemical sensor
- ☐ Nuclear medicine diagnosis

### IP Data

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Ring is opened by stimulation and the reaction proceeds rapidly and specifically



- **Macrocyclization of tetrazine prevents cyclization**
- **The reaction proceeds by opening the ring under stimulus (pH in the figure above)**
- **In addition, click reaction control using light and enzymatic reactions has been achieved.**

### Related Works

I. Novianti, T. Kowada, and S. Mizukami. Clip to Click: Controlling Inverse Electron-Demand Diels–Alder Reactions with Macrocyclic Tetrazines. *Org. Lett.*, (2022) 24, 3223–3226.

### Contact