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Development of a new class of photochromic peptides by using diarylethene-based non-natural amino acids

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ABSTRACT

We synthesized novel photochromic non-natural amino acids based on diarylethene skeletons. The non-natural amino acids can be introduced at any positions in various types of peptides by solid/solution phase synthesis. In this study, linear and cyclic peptides including the diarylethene residues were prepared. Their peptides showed photochromism peculiar to original diarylethenes.

1. Introduction

Diarylethene is the most representative photochromic molecule, showing high performance in the photoisomerization: effective isomerization, fastness against repeating isomerization, and thermal stability (Fig. 1). Therefore, many researchers have been developing a variety of diarylethene derivatives and been exploring their properties from the view point of materials science.[1] On the other hand, diarylethenes have been scarcely applied to biomimetic chemistry and chemical biology because their photoisomerization accompanies relatively small structural changes as compared with those of other conventional photochromic compounds, such as azobenzenes and spiropyrans.[2,3] Recently, we have reported photoswitchable, DNA-binding helical peptides cross-linked with diarylethene skeletons.[4] The photochromic peptides consist of diarylethene-bridged and DNA-binding regions at their N- and C-termini, respectively. When the diarylethene moieties adopted the open form on the peptides, the secondary structures were induced to stable α-helices. Upon UV irradiation, the open form was transformed to the closed one to destabilize the helical structures. The interaction of the photochromic peptides to DNAs was photoregulated, which was observed by Quartz crystal microbalance. Even the relatively small structural changes in the diarylethene photoisomerization were enough for regulating the peptide structures because a bit of the hydrogen bonds of the helical peptides are broken by the structural change to collapse the whole helicity like dominoes. This finding encourages us to utilize diarylethene photochromism to other biological applications. Therefore, the development of new diarylethenes capable of being incorporated into peptide main chains will yield a more effective regulation of the secondary structures of the peptides. Here, diarylethene-based non-natural amino acids were developed to incorporate diarylethene units into peptide backbones, and photochromic peptides were prepared using them.[5]

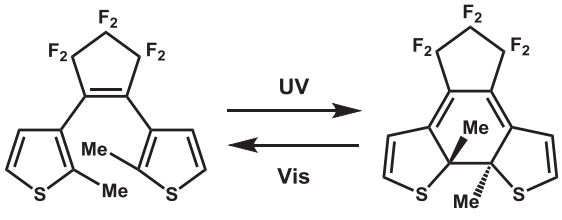

Fig. 1. Diarylethene photoisomerization.

2. Results and discussion

The 5 positions of thiophene rings in diarylethene skeletons can be easily modified with various functional groups.[1] In our previous

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paper, synthesized were diarylethene cross-linking agents possessing dioxopyrrolidin-1-yloxycarbonyl groups at the positions.[4] We envisaged that diarylethene-based non-natural amino acids (Daa) could be build up by introducing carboxy and aminomethyl groups at each of the 5 positions. The closed-Daa possess a dihedral angle of ca. 24° between the two substituent groups at the positions. When they are introduced at the loop and turn regions on peptides of biological importance and into cyclic peptides as peptide backbones (Fig. 2), the former peptides are expected to photoregulate biological interactions and the latter ones can be a new class of photochromic host molecules for biologically important chemical species.

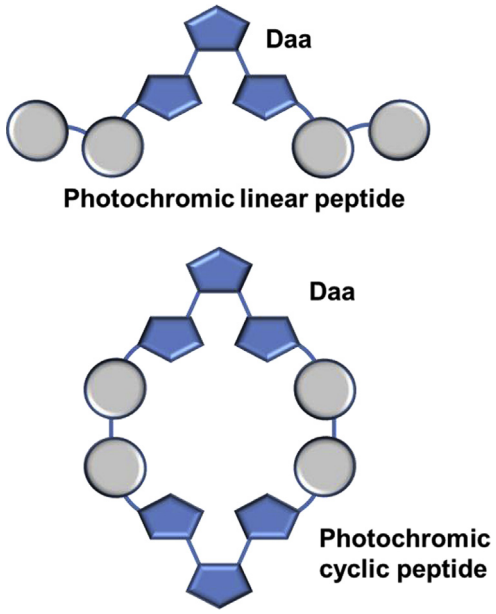
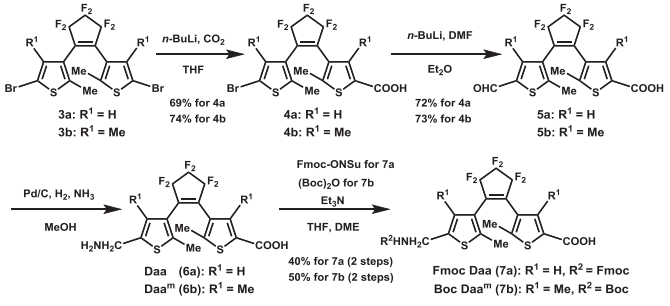


Fig. 2. Photochromic peptides including Daa residues.

In this study, two types of Daas were synthesized in relatively high yields (Scheme 1). The difference is in the presence of Me groups at the 4 positions of thiophene rings in the diarylethene skeletons. The Me groups were reported to be effective against photo-degradation for repeating diarylethene isomerization between the open and closed forms.[1] A key intermediates **3** were prepared according to the synthetic procedure published previously.[6,7] The precursors **6** for peptide synthesis were obtained by adding carboxy and aminomethyl groups in order at the 4 positions of the thiophene rings in **3**. To perform peptide synthesis using **6**, the amino groups of **6** were modified with Fmoc and Boc protecting groups to afford **7a** and **7b**, respectively.[8]



Scheme 1. Synthesis of diarylethene-based non-natural amino acid derivatives for peptide synthesis.

Photochromic linear peptides including a single Daa residue were synthesized using **7a** by solid phase peptide synthesis (SPPS).[4,9] It was found that **6** could be installed at any positions, including N- and C-termini, of the linear peptides by SPPS (not shown), promising that the diarylethene moiety can be inserted into the turn regions of helix–turn–helix motifs. In this study, peptide **1** of 7 *mer* was used to examine the photochromic property of linear peptides. The sequence of **1** contains a single Daa at its middle position considered to be most effective for photoregulating peptide structures (Fig. 3), being a model sequence for helix–turn–helix motifs.

Peptide **1**: Ac-Ala-Lys-Ala-Daa-Ala-Glu-Ala-NH_2

Peptide **2**: cyclo(Daa^m-Gly-Gly-Daa^m-Gly-Gly)

Fig. 3. Amino acid sequences of photochromic peptides **1** and **2**. Daa and Daa^m denote the residues of **6a** and **6b**, respectively.

Fig. 4 shows the UV/vis spectra of the peptide **1** in a phosphate buffer, in which an absorption band characteristic for the diarylethene-open form was observed around 260 nm before UV irradiation. Upon irradiation with a UV lamp of 4 W at 254 nm for 1 min, the absorption band decreased, and two new ones appeared around 360 and 552 nm. This spectral change indicates that the open form of the Daa residue isomerized to the closed one.[1] The conversion yield of the cyclization reaction was determined to be 96% on the basis of the HPLC profiles of **1** (Fig. S1 in the Supplementary data). To re-isomerize the closed form to the open one, visible light (>480 nm) was irradiated to the peptide solution by using a high-pressure mercury lamp of 100 W with a cut filter for 5 min, resulting in returning almost to the original spectrum; the conversion yield of the ring-opening reaction was 92%. Thus, the Daa residue was found to behave like conventional diarylethenes in the linear peptides in a buffer solution.

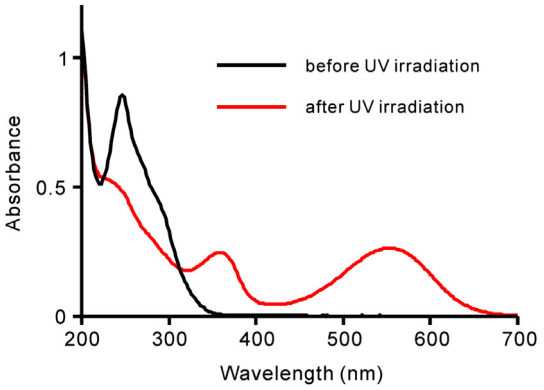


Fig. 4. UV/vis spectra of **1** (2.1×10^{-4} M) before and after UV irradiation in a phosphate buffer (pH 6.5) at 25 °C.

To evaluate the secondary structures of **1** before and after the photoirradiation, its CD spectra were measured under the same condition as in the above UV/vis spectra (Fig. 5). UV irradiation induced the following spectral change; a negative CD at 195 nm was enhanced and another one at 227 nm was weakened. Although it is hard to assign these CDs to the secondary structures of **1** before and after UV irradiation, the structural variation would be caused by the diarylethene photoisomerization.[10] This finding suggests that Daa-introduced peptides of biological importance might be useful for photoregulating biomolecular interactions.

Repeating photoirradiation to **1** was performed to explore the photo-stability of the Daa residue against the experimental