外　国　語　要　旨

学位論文題目　Development of the sensor molecules based on the dynamic conformational property

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Conformational property of functional molecules is one of the most important factors to display their functions such as bioactivity, molecular recognition, and supramolecule formation. Design of the functional molecules requires molecular architecture with control of the steric structure and dynamic behavior. Recently, molecules that change their structures by external stimuli such as photoirradiation are applied to development of functional molecule including molecular machine or molecular switch. For example, azobenzene changes the structure from trans to cis by UV irradiation and are used as optical functional molecular switch. Generally, most of the switching units in these functional molecules have enough energy gap between two structural states. On the other hands, I considered that the molecules having small energy gap between two structural states also can be applied to the switching units, by changing the equilibrium induced by various external stimuli. From this consideration, I focused on amide cis/trans isomerization (Fig.1a) and helical right/left handed structures (Fig.1b) as key switching structures of novel molecular sensors with dynamic conformational behavior.

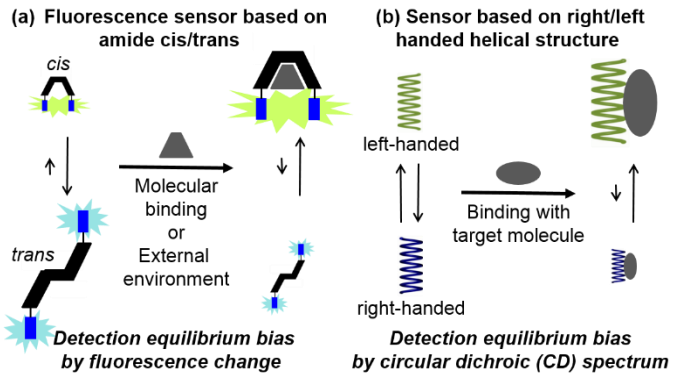

Fig. 1. Design concepts of sensor molecules based on the dynamic conformational property.

<u>Development of florescence sensor molecule based on the solvent-dependent conformational transformation of hydroxamic acid derivative</u>

Amide C-N bonds have partial double-bond character, and show conformational behavior with moderate rigidness and softness. Especially, several aromatic amide derivatives change the cis/trans equilibrium bias depending on external environment, such as pH and solvent. Section 2 aims to develop the molecular sensor based on the amide conformational transformation. From the previous studies on the stereochemistry of aromatic amides by our group, I selected solvent-dependent *N*-phenylbenzhydroxamic acid as the cis/trans switching system, designed, and synthesized **II-3** bearing two pyrene moieties (Fig. 2). The ratio of cis/trans conformers of **II-3** determined by ^{1}H NMR at low temperature changed depending on the solvent. The ratio of the excimer fluorescence to monomer fluorescence also changed depending on the solvent,

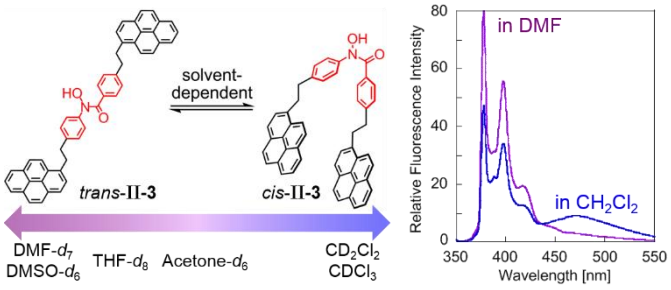

Fig. 2. Solvent-dependent fluorescence sensor molecule.

and the order agreed well with that of the ratio of cis/trans conformers. Thus, **II-3** exhibited solvent-dependent conformational alteration with change of fluorescence properties. To date, several types of aromatic amides that exhibit conformational change in response to various environmental changes such as pH and redox state have been reported. The strategy shown in this research could be applied to fluorescent sensors for various environmental conditions.

Surface recognition of α-helices by quinoline oligoamide foldamer

Protein-protein interactions are significant for various physiological and pharmacological processes. Therefore, it is important to elucidate the interactions of protein surfaces at atomic and molecular levels, and to develop novel modulators of such interactions. Thus, I proposed that the surface recognition of peptidic α-helix that is one of most significant structures in protein-protein interactions, by quinoline oligoamide foldamer with helical structure. I assumed that the interaction between α-helix and quinoline oligoamide can be detected by the biased handedness of the helical oligoamides by using CD spectra (Fig. 3a), and designed the helix-helix interactions between the quinoline oligoamide **III-1** having hydroxyl groups (Fig. 3b) and the target peptides having polar non-charged amino acids (Fig. 3c) via multipoint hydrogen bonds. **III-1** existed in the helical structures both in solution and in the crystal. Soluble peptides **Bz-P2**~**4** showed high α-helicity in non-polar solvent. Further, the chiral inductions of **III-1** via intermolecular interaction with peptides were illustrated by CD signals around 350-450 nm peculiar to quinoline oligoamide foldamers (Fig. 3d). The results suggested that **III-1** maintains the helical structure and changed the ratio of right-handed and left-handed helices by the interaction with peptides on the surface.

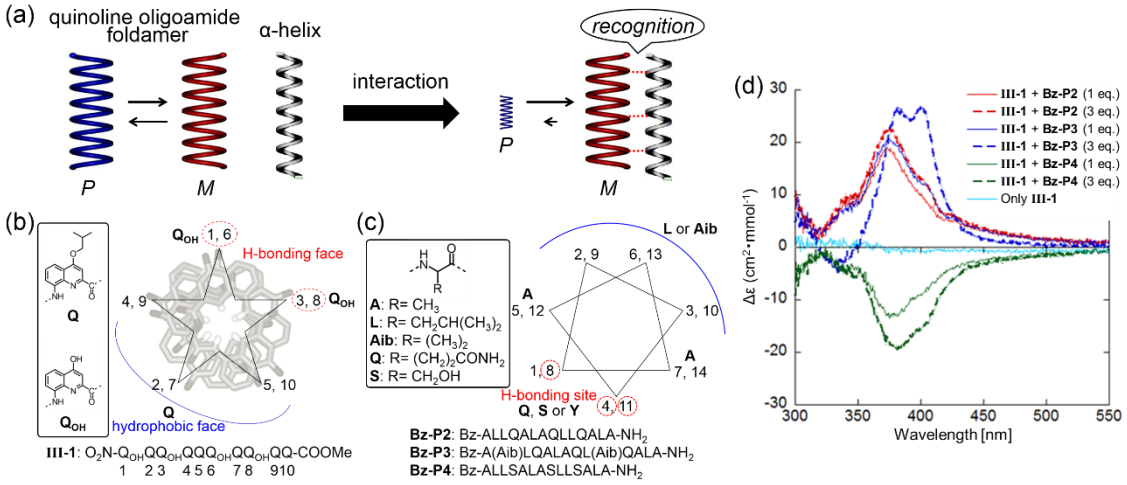

Fig. 3. (a) Surface recognition of peptidic α-helix and chiral induction, (b) Molecular design of quinoline oligoamide foldamer **III-1** (Top view), (c) Molecular design of peptides (Top view), (d) CD spectra of **III-1** in the presence of peptides.

Two sensing systems based on the change of the equilibrium by weak external perturbation were developed. The dynamic conformational changes depending on external environment or binding to target molecules were converted into spectroscopic signals such as fluorescence and CD. The results indicated the possible application of the dynamic conformational properties to develop the sensing molecules.