Chiral sensing for amino acid derivative based on a [2]rotaxane composed of an asymmetric rotor and an asymmetric axle†

Naohiro Kameta,*[a] Yoshinobu Nagawa,[a] Michinori Karikomi[b] and Kazuhisa Hiratani*[b]

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A racemic [2]rotaxane, composed of an asymmetric rotor and an asymmetric axle, formed a diastereomer with an amino acid derivative, and showed an optical response for the chiral recognition.

Interlocked and topological molecules such as rotaxanes, catenanes, and knots have been of interest in the development of nanotechnology, especially, molecular devices, memories and machines, since those supramolecular systems show molecular movements, such as the shuttling and rotating of rotor moieties, which are able to be controlled by various stimuli.[1] Control of the molecular movement has been achieved by metal coordination, oxidation/reduction of metal ions, variation of the MLCT (metal to ligand charge transfer) excited state, protonation/deprotonation, electrochemical oxidation/reduction, photoisomerization and artificial biological reactions.[2] More recently, interlocked and topological molecules have been noted also in the fields of analytical chemistry[3] and organic chemistry[4] because of the specific cavity and the molecular-recognition space constructed cooperatively by both rotor and axle. Optical- and electrochemical-sensors for anions[3a,b] and biological compounds[3c–e] based on rotaxanes and pseudo rotaxanes have been reported so far. We have succeeded in the development of highly selective alkaline metal ion sensors based on [1], [2], and [3]rotaxanes bearing plural metal-binding sites on both rotor and axle.[5] Unique molecular chiralities of rotaxanes and catenanes composed of asymmetric rotors and asymmetric axles which are achiral themselves, and helicities of knots, also have been reported to be attractive chiral architectures.[6] Those corresponding racemates could be separated into each enantiomer using an HPLC system equipped with commercially available chiral columns,[7,8] and were able to form diastereomers with chiral-shift reagents.[9]

In this work, to construct a fluorescence-sensing system of chiral recognition for amino acid derivatives based on [2]rotaxane composed of an asymmetric rotor and an asymmetric axle without chiral carbon atoms, we designed and synthesized novel [2]rotaxanes having molecular chirality and the property of fluorescence *via* energy transfer from a donor moiety in the rotor to an acceptor moiety in the axle. Chiral recognition and sensing abilities of the rotaxanes in organic solvent were investigated using ^{1}H NMR and fluorescence spectroscopies.

Rotaxane racemates composed of an asymmetric rotor and an asymmetric axle were effectively synthesized *via* our original method.[8]† The difference in structure between rotaxane **1** and **2** is in only the asymmetric rotor moiety, in which the 26-membered crownophane has naphthyl, polyether, hydroxy and amide groups and the 25-membered crownophane has naphthyl, benzyl, polyether, and hydroxy groups for rotaxane **1** and **2**, respectively (Fig. 1).

Synthesized rotaxanes possess plural proton donor and acceptor moieties such as hydroxy groups, amide groups and ether oxygens, and therefore were expected to interact with various amino acid derivatives through hydrogen-bond formation, and to recognize their chirality depending on the specific three-dimensional cavity constructed from the rotor and axle. Binding and chiral recognition abilities of rotaxanes toward amino acid derivatives were investigated using a ^{1}H NMR titration method. The ^{1}H NMR spectrum of rotaxane **1** racemate in the presence of over 0.5 equivalents of L-phenylalaninol gave two completely separate peaks for the protons numbered in Fig. 1, while the protons expressed by asterisks in Fig. 1, especially those in the carbazole moiety, were not separated (spectra are shown in the ESI†). For the protons without a number in Fig. 1, the assignment and the justification of peak separation and shift was too difficult because those peaks overlapped complexly with each other, even though we confirmed that the shape of the overlapped peaks changed on the addition of L-phenylalaninol. One of the separated peaks was similar to that of the rotaxane **1** in the absence of L-phenylalaninol, and the other indicated a different chemical shift as shown in

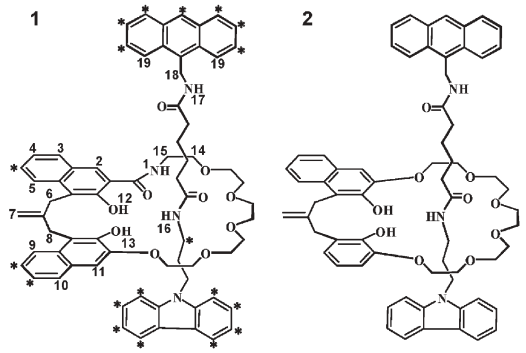

Fig. 1 [2]Rotaxanes composed of an asymmetric rotor and an asymmetric axle.

[a]*Nanoarchitectonics Research Center, National Institute of Advanced Industrial Science and Technology, Tsukuba Central 5, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan. E-mail: n-kameta@aist.go.jp; Fax: +81-(0)29-861-4545; Tel: +81-(0)29-861-4615*
[b]*Department of Applied Chemistry, Faculty of Engineering, Utsunomiya University, 7-1-2 Youtou, Utsunomiya 321-8585, Japan. E-mail: hiratani@cc.utsunomiya-u.ac.jp; Fax: +81-(0)28-689-6146; Tel: +81-(0)28-689-6146*

† Electronic supplementary information (ESI) available: Synthesis and NMR, IR, MS data of **1**. ^{1}H NMR spectra of **1** in the presence and absence of L-phenylalaninol in $CDCl_3$. Enantiomeric separation of **1** *via* HPLC. See DOI: 10.1039/b607251h

Table 1 Chemical shifts of rotaxane **1** in the presence and absence of L-phenylalaninol in $CDCl_3$ at 25 °C[a]

Position of ^{1}H	Chemical shift/ppm			Position of ^{1}H	Chemical shift/ppm		
	Absence	Presence			Absence	Presence	
1 (NH)	8.74 (br, 1H)	8.74 (br, 0.5H)	8.72 (br, 0.5H)	10 (Naphthalene)	7.53 (t, 1H)	7.53 (t, 0.5H)	7.54 (t, 0.5H)
2 (Naphthalene)	8.46 (s, 1H)	8.46 (s, 0.5H)	8.45 (s, 0.5H)	11 (Naphthalene)	6.78 (s, 1H)	6.78 (s, 0.5H)	6.80 (s, 0.5H)
3 (Naphthalene)	7.70 (d, 1H)	7.70 (d, 0.5H)	7.72 (d, 0.5H)	12 (OH)	10.15 (s, 1H)	10.15 (s, 0.5H)	10.22 (s, 0.5H)
4 (Naphthalene)	7.50 (d, 1H)	7.50 (d, 0.5H)	7.53 (d, 0.5H)	13 (OH)	7.73 (s, 1H)	7.73 (s, 0.5H)	7.79 (s, 0.5H)
5 (Naphthalene)	7.80 (d, 1H)	7.80 (d, 0.5H)	7.79 (d, 0.5H)	14 (Methylene)	1.42 (d, 2H)	1.42 (d, 1H)	1.36 (d, 1H)
6 (Isobutenyl)	3.45 (s, 2H)	3.45 (s, 1H)	3.51 (s, 1H)	15 (Methylene)	2.04 (t, 2H)	2.04 (t, 1H)	2.06 (t, 1H)
7 (Isobutenyl)	4.59 (s, 1H)	4.59 (s, 0.5H)	4.52 (s, 0.5H)	16 (NH)	6.06 (br, 1H)	6.06 (br, 0.5H)	6.11 (br, 1H)
	4.36 (s, 1H)	4.36 (s, 1H)	4.40 (s, 0.5H)	17 (NH)	6.87 (br, 1H)	6.87 (br, 0.5H)	6.92 (br, 1H)
8 (Isobutenyl)	3.16 (s, 1H)	3.16 (s, 0.5H)	3.11 (s, 0.5H)	18 (Methylene)	5.29 (m, 1H)	5.29 (m, 0.5H)	5.30 (m, 0.5H)
9 (Naphthalene)	7.87 (d, 1H)	7.87 (d, 0.5H)	7.89 (d, 0.5H)		5.32 (m, 1H)	5.32 (m, 0.5H)	5.31 (m, 0.5H)
				19 (Anthracene)	8.24 (d, 2H)	8.24 (d, 1H)	8.27 (d, 1H)

[a] Position of ^{1}H corresponds to the number displayed on rotaxane **1** in Fig. 1. (Spectra are shown in the ESI.)

Table 1. A similar phenomenon was also observed in the presence of D-phenylalaninol. In the presence of alaninol, prolinol, and tryptophanol, the peak separation and the shift of rotaxane **1** racemate were not observed even if an excess of those amino acid derivatives was added. These results show that each enantiomer of rotaxane **1** racemate can, not only selectively interact with L- or D-phenylalaninol, respectively among four amino acid derivatives, but also recognize the chirality of phenylalaninol. Of course, the enantiomer of **1** that interacts with L-phenylalaninol is the mirror image of the enantiomer of **1** that interacts with that D-phenylalaninol. The peak separation as shown in Table 1 means that a diastereomer of rotaxane **1** (one enantiomer) with L-phenylalaninol and free rotaxane (another enantiomer) coexist in the solution. The binding and chiral recognition abilities of rotaxane **2** toward the above amino acid derivatives was also investigated. However, the ^{1}H NMR spectrum of rotaxane **2** racemate was unchanged in all cases.

When rotaxane **1** selectively formed a diastereomer with L- or D-phenylalaninol, the optical response of rotaxane **1**, having fluorophores such as anthracene and carbazole in the axle and naphthalene in the rotor which act as fluorescence-acceptor and -donor moieties,[10] was investigated in detail. We have already found that a [1]rotaxane composed of a rotor having naphthalene and an axle having anthracene, emits strong fluorescence from the anthracene due to the energy transfer from an excited naphthalene in the rotor to the anthracene in the axle.[5a] Fig. 2a indicates the fluorescence spectra of rotaxane **1** racemate, the rotor, and the axle moieties measured by irradiation at 285 nm which corresponds to the maximum-absorption band of naphthalene. In the case of only rotor, a fluorescence band was ordinarily observed at about 340 nm, based on the naphthalene. On the other hand, there is no naphthalene fluorescence in the case of rotaxane **1**. The fluorescence band consisted of three sharp peaks (395, 416 and 440 nm) and one broad peak (470 nm) based on anthracene in the axle appearing instead of fluorescence based on naphthalene in the rotor. The fluorescence band derived from carbazole located at the other end position of the axle was also observed at 358 and 369 nm, in which the fluorescence intensity was smaller than that of anthracene. These phenomena strongly suggested the occurrence of the energy transfer from the excited naphthalene in the rotor to anthracene (and carbazole) in the axle, since the irradiation at 285 nm was not able to directly excite the anthracene and the carbazole moieties. In fact, the fluorescence intensity of only the axle moiety measured by the irradiation at 285 nm was very small as shown in Fig. 2a. The proper excitation wavelengths of anthracene and carbazole moieties are more than 350 nm according to the absorption bands of those moieties.

Fig. 2b shows the fluorescence spectra of rotaxane **1** racemate in the presence and absence of L-phenylalaninol. The fluorescence intensity of anthracene decreased with an increase in the concentration of L-phenylalaninol, and alternately the fluorescence intensity of carbazole gradually increased. A fluorescence spectral change did not occur on the addition of other amino acid derivatives, such as alaninol, prolinol, and tryptophanol, as can be

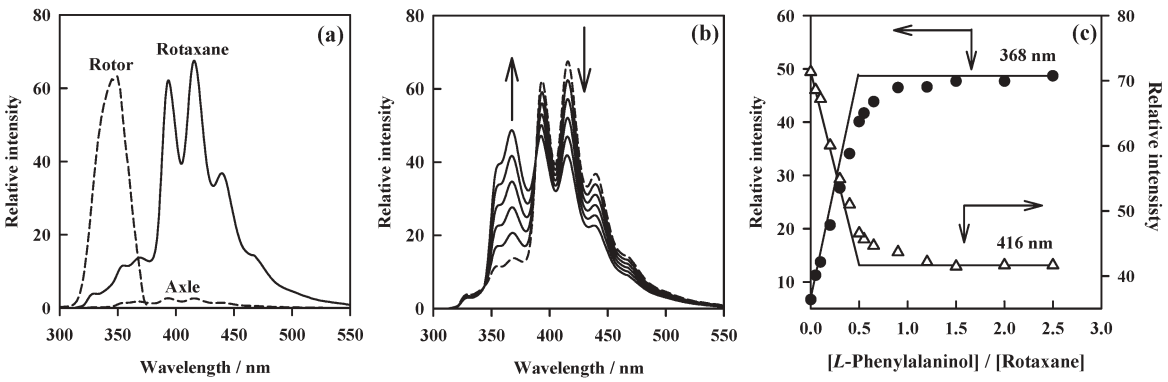

Fig. 2 (a) Fluorescence spectra of 1.0×10^{-7} M rotaxane **1** racemate, the rotor, and the axle in $CHCl_3$. (b) Fluorescence spectra of 1.0×10^{-7} M rotaxane **1** racemate, in the presence and absence of 1.0×10^{-8}–2.5×10^{-7} M L-phenylalaninol in $CHCl_3$. (c) Relationship between the variation of the apparent fluorescence intensity and the molar ratio of L-phenylalaninol to rotaxane **1** racemate. (Excitation wavelength: 285 nm).

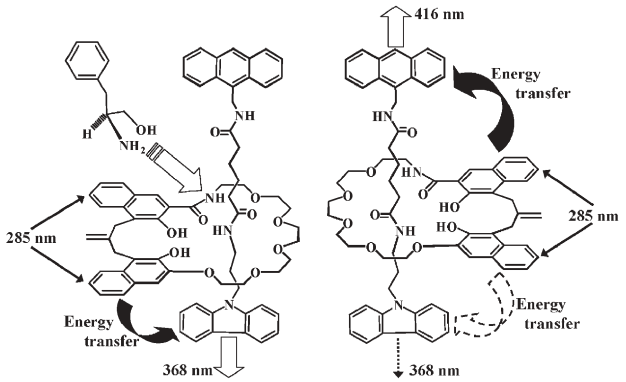

Fig. 3 Optical response of rotaxane **1** on the chiral recognition toward phenylalaninol.

expected by inspection of the above ^{1}H NMR titration experiments. The relationship between the variation of the fluorescence intensities at 368 and 416 nm and the molar ratio of L-phenylalaninol to rotaxane **1** racemate is shown in Fig. 2c. Both plots fit well with two straight lines having an intersection at [L-phenylalaninol]/[Rotaxane **1** racemate] = 0.5, which corresponds to a 1:1 stoichiometry because only one enantiomer was able to form a diastereomer with L-phenylalaninol. We confirmed that the absorption band of L-phenylalaninol is below 260 nm, and therefore L-phenylalaninol itself shows no fluorescence by irradiation at 285 nm. Variation of the fluorescence intensity was ascribable to the formation of a diastereomer.

Rotaxane **1**, composed of an asymmetric rotor and an asymmetric axle, was able to recognize the chirality of phenylalaninol due to the selective diastereomer formation, while it showed no interaction toward other amino acid derivatives such as alaninol, prolinol, and tryptophanol. At the same time, rotaxane **1** could also indicate a fluorescence response on the chiral recognition as shown in Fig. 3. The structure of the diastereomer between rotaxane **1** and phenylalaninol was still not found in this work. However, the larger 26-membered rotor and the more strongly acidic hydroxy group attached near the carbonyl group of the rotor in rotaxane **1**, together with the amide group in the axle must be important factors for the diastereomer formation, because rotaxane **2**, having a 25-membered rotor without a carbonyl group, could not interact with phenylalaninol and other amino acid derivatives. Diastereomer formation will be ascribable to the complex interactions, such as multiple hydrogen bonds and $\pi-\pi$ interactions, between rotaxane **1**, having plural hydrogen bonding sites (hydroxy and amide groups, ether oxygens) and aromatic rings (naphthalene, anthracene, carbazole) and phenylalaninol. As the result, diastereomer formation will influence the distance between the naphthalene in the rotor as donor and the anthracene (and carbazole) in the axle as acceptor, since the efficiency of the energy transfer has been widely known to be dependent on the donor–acceptor distance.[11]

We have succeeded in the development of a highly selective optical sensor for chiral recognition based on an interlocked molecule, rotaxane. Although chiral recognition using receptors without any chiral carbon atom is nowadays commonplace, receptors based on chiral rotaxanes are unique. Rotaxane **1** racemate can be completely separated into its enantiomers by HPLC equipped with chiral column,† therefore, the chiral rotaxane reported here could be applicable not only to the chiral separation of various compounds but also to the directional controlling of molecular movements such as the rotating and shuttling of rotor and axle in rotaxanes.

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