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Regulation of tryptophan transport via allosteric recognition of a pseudocrown ether

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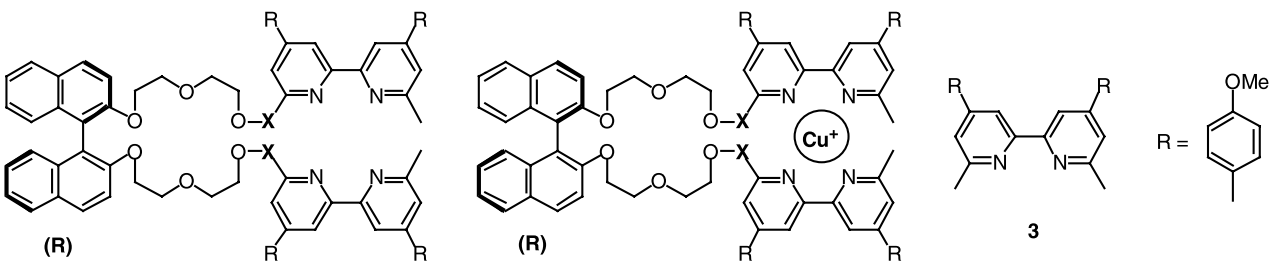
Abstract—Transport of zwitterionic tryptophan was enhanced by formation of a pseudocrown ether containing a Cu(I)·bipyridine complex, and cooperative binding of the macroring and the complex moiety to the guest was strongly suggested.

Regulation of molecular recognition by external stimulus is a current and important issue in host–guest chemistry.[1] Thus, we have designed artificial allosteric receptors bearing 2,2′-bipyridine moieties. Their function is controlled by utilizing a Cu(I) ion as an effector.[2] Complexation of the host with the Cu(I) ion quantitatively gave the corresponding metallo-host as a pseudomacrocycle. Multi-recognition strategy has been applied to a pseudomacrocycle in allosteric recognition of a more complicated guest.[3] In general, the framework of Cu(I) pseudocrown ethers possesses a macrocyclic polyether and a cationic Cu(I)–bipyridine moiety as potential binding sites for alkali metal ions and anionic species, respectively. Amino acids, therefore, are considered to be suitable guests for the pseudocrown ethers due to the zwitterionic character of the guests. A combination of several interactions should be useful to capture amino acids. In fact, many ditopic receptors for amino acids have been reported,[4] but there is no example for regulation of the recognition via external stimulus. Among a variety of amino acids, we chose tryptophan as a guest, because the uptake and transport of tryptophan play a very important role to synthesize neurotransmitters such as serotonin. Here we report allosteric regulation of the transport of tryptophan and the methyl ester hydrochloride through a liquid membrane using a Cu(I) ion as an effector.

Podands **1** and **2** consist of a binaphthyl skeleton and two polyether units bearing a bipyridine moiety.[5] They are converted quantitatively to the corresponding pseudocrown ethers upon the addition of Cu(I). The transport experiment was carried out by using a dual cylindrical cell[2] containing a source phase ([tryptophan]: 5.00×10^{-3} M, H_2O), a receiving phase (H_2O) and a liquid membrane ([host]:1.20×10^{-4} M, CH_2ClCH_2Cl).



1: **X** = $CH_2CH_2CH_2$
2: **X** = CH_2

1•Cu^+Cl^-: **X** = $CH_2CH_2CH_2$
2•Cu^+Cl^-: **X** = CH_2

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First, we examined tryptophan methyl ester hydrochloride as a guest in order to estimate the affinity of the pseudocrown ethers **1**·Cu(I) and **2**·Cu(I) to the ammonium moiety. The concentrations of the guest after 48 h in the receiving phase are summarized in Table 1. The Cu(I)-free hosts **1** and **2** exhibited nearly no transport ability for the L and D derivatives, because the amounts in the receiving phase were almost the same as those in the absence of the host. In the case of **1**·Cu(I), however, the transport was facilitated by a factor of 8 (positive allosteric effect), compared to **1**. Noteworthy is that much less enhancement of the transport was observed in **2**·Cu(I). Complex $\mathbf{3}_2$·Cu(I) without a polyether chain showed a similar transport efficiency to that of **2**·Cu(I). This means the macrocyclic moiety of **2**·Cu(I) did not work as a binding site for the ammonium group. These facts clearly indicate that the significant increase observed in **1**·Cu(I) is achieved by recognition of the ammonium group with the pseudocrown moiety. The difference in enhancement between **1**·Cu(I) and **2**·Cu(I) is probably caused by unfavorable electrostatic repulsion between the ammonium moiety and the cationic center of **2**·Cu(I) due to its shorter methylene linker than that of **1**·Cu(I). The binaphthyl moiety of **1**, **2** and their complexes did not discriminate the enantiomers, although the moiety is chiral (*R* configuration).

A very complicated ^{1}H NMR spectrum of **1**·Cu(I) in $CDCl_3$ was obtained in the presence of tryptophan methyl ester tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate. However, the signal of the central methylene protons in the trimethylene linker shifted downfield distinctly, and the tetrahedral geometry of the complex is proved to be maintained even in the presence of an excess amount of the guest. ^{1}H NMR titration using this change suggested 1:1 complexation of **1**·Cu(I) with the guest, although the association constant was not determined due to the high affinity and broadness of the signal.

Positive enhancement of the tryptophan transport was also achieved by this system (Table 2). The source aqueous phase contains tryptophan as a zwitterion, because pH of the phase is 6.2. In the cases of **1** and **2** and in the absence of the host, comparable amounts of the guest moved to the receiving phase. Compared to the free hosts **1** and **2**, the corresponding Cu(I) complexes transported the L-isomer 4.7 and 4.3 times (D-isomer: 5.8 and 4.2 times) faster after 144 h, respectively. Very interestingly, addition of Cu(I) into the transport system after 62 h caused abrupt increase of the transport rate (Fig. 1). $\mathbf{3}_2$·Cu(I) showed a higher ability of the transport of the guests by a factor of 3∼4 than **1** and **2**. Thus, electrostatic interaction between the cationic center of the bipyridine–Cu(I) complexes and the anionic carboxylate group of the guest in the outer coordination sphere is strongly suggested.[6] The higher efficiency of the transport in **1**·Cu(I) (or **2**·Cu(I)) than in $\mathbf{3}_2$·Cu(I) is ascribed to interaction between the ammonium group of the guest and the pseudocrown ring. Less transport of the guest by **2**·Cu(I) than **1**·Cu(I) indicates less binding affinity of the pseudocrown ring in **2**·Cu(I) toward the ammonium group, as seen in the

Table 1. Transport[a] of tryptophan methyl ester hydrochloride through a liquid membrane

Carrier	L-Tryptophan methyl ester hydrochloride (10^{-5} M)[b]	D-Tryptophan methyl ester hydrochloride (10^{-5} M)[b]
1·Cu^+Cl^-	10.40±0.02	11.53±0.14
2·Cu^+Cl^-	3.05±0.02	2.71±0.11
1	1.37±0.03	1.49±0.07
2	1.39±0.02	1.44±0.02
$\mathbf{3}_2$·Cu^+Cl^-	2.36±0.07	2.30±0.02
Blank	1.07	1.14±0.07

[a] Source phase (dist. H_2O) 4 ml: [tryptophan methyl ester hydrochloride] = 5.0×10^{-3} M, receiving phase (dist. H_2O) 40 ml, org. phase (CH_2ClCH_2Cl) 50 ml: [Host·Cu^+Cl^-] = 1.2×10^{-4} M (CuCl = 1.1 equiv.), stirred at 200 rpm, 25°C.
[b] Concentration of tryptophan methyl ester hydrochloride in the receiving phase after 48 h.

Table 2. Transport[a] of tryptophan through a liquid membrane

Carrier	L-Tryptophan (10^{-6} M)[b]	D-Tryptophan (10^{-6} M)[b]
1·Cu^+Cl^-	9.4±0.7	9.3±0.3
2·Cu^+Cl^-	6.5	7.2±0.2
1	2.0	1.6
2	1.5±0.1	1.7±0.1
$\mathbf{3}_2$·Cu^+Cl^-	5.8±0.4	5.4
Blank	1.2±0.2	1.3±0.3

[a] Source phase (dist. H_2O) 4 ml: [tryptophan] = 5.0×10^{-3} M, receiving phase (dist. H_2O) 40 ml, org. phase (CH_2ClCH_2Cl) 50 ml: [Host·Cu^+Cl^-] = 1.2×10^{-4} M (CuCl = 1.1 equiv.), stirred at 200 rpm, 25°C.
[b] Concentration of tryptophan in the receiving phase after 144 h.

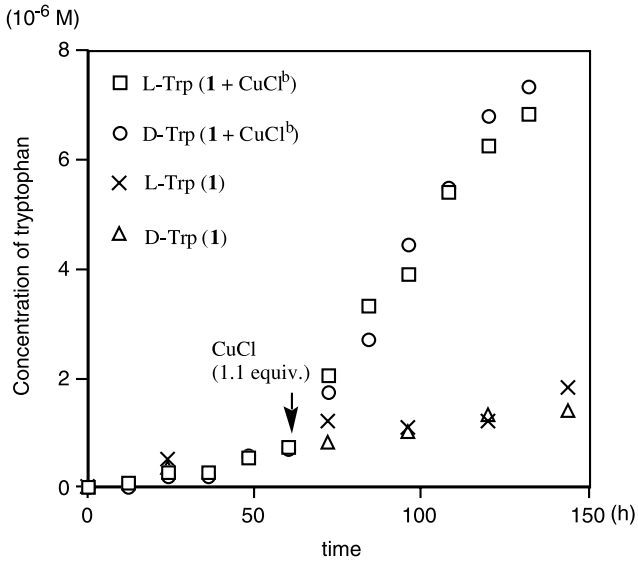

Figure 1. Effect of CuCl on transport[a] of tryptophan by **1**. [a]Source phase (dist. H_2O) 4 ml: [tryptophan] = 5.0×10^{-3} M, receiving phase (dist. H_2O) 40 ml, org. phase (CH_2ClCH_2Cl) 50 ml: [**1**] = 1.2×10^{-4} M, stirred at 200 rpm, 25°C.
[b]1.1 equiv. of CuCl was added after 62 h.

transport of the methyl ester. Consequently, the enhancement of the transport in the cases of **1**·Cu(I) and **2**·Cu(I) is considered to result from synergistic interaction of the pseudocrown moiety and the Cu(I) complex moiety with tryptophan.

Chiral differentiation is the next objective of our study and will be probably performed by introduction of a side chain interactive with amino acids into the framework of **1** and **2**. We are now investigating such modification to enhance interaction of the host with chiral zwitterionic guests.

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5. For the synthesis and characterization of **1** and **1**·Cu(I), see: Nabeshima, T.; Hashiguchi, A.; Saiki, T.; Akine, S. *Angew. Chem., Int. Ed. Engl.*, in press.
6. The interaction in the inner coordination sphere can be ruled out, because the absorption spectrum ($MeCN:H_2O = 3:1$, v/v) of the **1**·Cu(I) complex around the MLCT region characteristic of the tetrahedral geometry does not change in the presence of 2 equiv. of tryptophan.