



Highly selective recognition of tryptophan in water by a poorly water-soluble scandium compound



Nobuyuki Hayashi^{a,*}, Shigeki Jin^b, Tomomi Ujihara^c

^a National Food Research Institute, National Agriculture and Food Research Organization (NARO), 2-1-12 Kannondai, Tsukuba, Ibaraki 305-8642, Japan

^b Faculty of Health Science, Hokkaido University, Kita 12, Nishi 5, Kita-ku, Sapporo, Hokkaido 060-0812, Japan

^c National Agriculture and Food Research Organization (NARO), 3-1-1 Kannondai, Tsukuba, Ibaraki 305-8642, Japan

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ABSTRACT

In order to recognize aromatic α -amino acids in water using a poorly water-soluble artificial receptor, a new scandium compound was synthesized. This receptor had high affinities for tryptophan (Trp) and lysine (Lys). Due to a rate difference in the complex formation process, high selectivity for Trp was achieved. Geometry optimizations using ω B97XD density functional theory (DFT) calculations revealed that Trp was thoroughly included in the receptor with intermolecular forces of the Sc/O coordination bond, aromatic/aromatic interactions, and NH/O interaction in addition to the hydrophobic effect and van der Waals attractive force. In the complex between Lys and the receptor compound, the Sc/O coordination bond, ionic NH/O interactions, CH/ π interaction, and NH/ π interactions were found along with the hydrophobic effect and van der Waals attractive force.

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Molecular recognition in aqueous solutions is an attractive research area in supramolecular chemistry because chemical events in water are connected to many biological reactions and are considered green chemistry. To achieve recognition in aqueous solutions, organic and supramolecular chemists have created many unique host molecules^{1–3} based on structures such as cyclodextrins,^{4,5} arene systems,^{6–15} and cucurbiturils^{16–21} and other systems.^{22–26} However, there are many challenges in developing artificial receptors (host molecules) that function in aqueous solution as intended. It is inherently difficult to synthesize water-soluble host molecules, because the introduction of polar functional groups onto organic compounds for obtaining water solubility often prevents the construction of complicated molecular structures. Additionally, molecular recognition in water is difficult to achieve because intermolecular interactions attributed in large part to electrostatic factors such as hydrogen bonds between heteroatoms and hydrogen atoms, which are potent tools for recognition in low-polar solvents, are usually weakened in aqueous solution.²⁷

Recently, we approached these problems from a novel angle using ‘poorly water-soluble’ substances (e.g., **1–3** in Fig. 1) as host molecules in water, which were easily synthesized by coordinating two ligands with two sulfonate groups per molecule onto a trivalent scandium ion.²⁸ Since scandium compounds generally retain

Lewis acidity in aqueous solutions in contrast to many Lewis acids,²⁹ it was expected that compounds **1–3** would have both Lewis acidic and basic portions in a single molecule as illustrated in Figure 1. These receptors possessed the ability to recognize the acidic amino acids [aspartic acid (Asp) and glutamic acid (Glu)] and/or the basic amino acids [arginine (Arg), histidine (His), and lysine (Lys)] in water. However, even though the ligands of **1–3** were constructed of aromatic rings, **1–3** had little affinity for neutral amino acids with aromatic groups on the side chains such as phenylalanine (Phe), tyrosine (Tyr), or tryptophan (Trp) except for modest removal of Trp by **2**. These results surprised us, because interactions between aromatic rings are generally useful as a binding force in aqueous media, are often found in biological recognition,^{30,31} and in fact have been used to capture aromatic amino acids.^{32–39}

Our further explorations into poorly water-soluble scandium compounds resulted in the discovery of a receptor that was able to selectively recognize an aromatic amino acid. In this Letter, the highly selective removal phenomenon of Trp in water by means of the new receptor compound is reported. Moreover, complex structures between the receptor and the amino acids are discussed on the basis of DFT calculations.

The new ligand and scandium compound were synthesized in a similar manner to the previous case (Scheme 1). To an aqueous solution of the ligand compound (**6**) prepared from isophthaloyl chloride (**4**) and aminonaphthalenesulfonic acid (**5**), an aqueous scandium trifluoromethanesulfonate solution was added at

* Corresponding author.

E-mail address: hayn@affrc.go.jp (N. Hayashi).

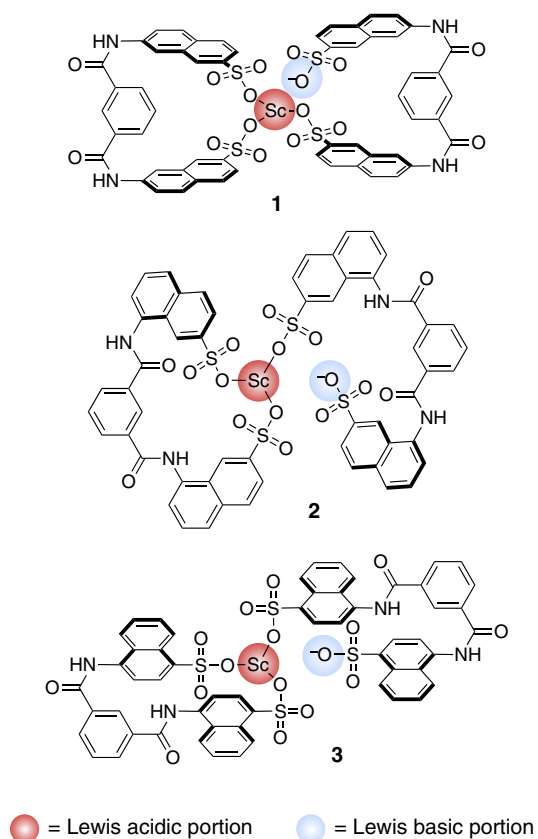
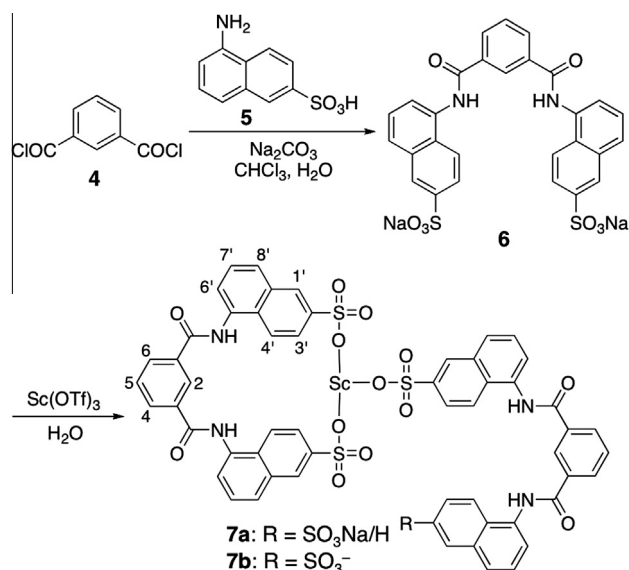


Figure 1. The scandium compounds reported previously.

ambient temperature to obtain poorly water-soluble solid (**7a**). ^1H and ^{45}Sc NMR spectra in $\text{DMSO}-d_6$ confirmed that the solid consisted of the ligand molecules and scandium atom.⁴⁰ The absence of resonance signals in the ^{19}F NMR spectra indicated that sulfonate ligands had replaced the triflates on the scandium ion. In the MALDI-TOF-MS spectrum, the negative ion signal of the complex was detected at m/z 1193, and its composition was determined to be two ligands and one scandium ion by high-resolution



Scheme 1. Synthesis of the poorly water-soluble scandium compound (**7a**).

analysis. Elemental analysis revealed that this scandium compound was a heptahydrate and the counter ion ratio of the sulfonate group was $\text{Na}^+/\text{H}^+ = 37/63$.

To evaluate the ability of the scandium compound **7b** to recognize α -amino acids in water, the removal ratio of the α -amino acids in suspensions of compound **7a** was investigated. This evaluation method is reasonable because compound **7a** is poorly water-soluble. To each 2.00 mM deuterium oxide solution (0.700 mL) of α -amino acid in a 2-mL microcentrifuge tube, **7b** (1.28 μmol , 91 mol %) was added, and the resulting suspensions were stirred by a microtube mixer for 30 min at ambient temperature. After centrifugation, the amount of the amino acid remaining in the supernatant was determined by integration of the ^1H NMR spectrum. The bar graphs in Figure 2 illustrates the removal ratios of the α -amino acids in the supernatants. Only Trp and Lys of the twenty essential amino acids were removed from the water phase at high ratios, 93% and 57%, respectively. The neutral aromatic amino acids except Trp were not removed. Although prolongation of stirring time in the removal experiments did not affect the removal ratio of Trp, that of Lys was increased to 83% by an extension of 30 min. However, even with further extension of the stirring time, an increase in the removal ratio of Lys was not observed. From these results, it was speculated that the removal of Trp by **7b** was a faster process than that of Lys.

After the recovered solid in the Trp removal experiment was suspended in pure water and spun down, the ESI-Orbitrap-MS analysis of the supernatant detected negative ion signals at m/z 698 [charge number of the ion (z) = 2], which fitted [**7b** + Trp – H^+] (Calcd for $\text{C}_{67}\text{H}_{47}\text{N}_6\text{O}_{18}\text{S}_4\text{Sc}$ 698.0700. Found 698.0704). In the case of Lys, [**7b** + Lys] (z = 1, Calcd for $\text{C}_{62}\text{H}_{50}\text{N}_6\text{O}_{18}\text{S}_4\text{Sc}$ 1339.1629. Found 1339.1653) was detected in the mass spectrum.

In order to investigate the influence of the coexisting amino acids on the Trp removal, aqueous solutions including Trp, the other amino acids, and compound **7b** in a 1:1:0.91 molar ratio were treated for 30 min at ambient temperature. As shown in Figure 3, high selectivity for Trp was maintained in all cases. Although pH values of the supernatants differed slightly between the single systems (Fig. 2) and the mixed systems (Fig. 3), the abundance ratio of the chemical species of each amino acid does not change significantly due to these pH variations. In these pH regions most chemical species are α -carboxylate and α -ammonium forms, and the polar groups on the side-chains of Asp, Glu, Arg, His, and Lys are protonated. Interestingly, in the system including both Trp and Lys, the removal ratio of Lys was inhibited to 6%. It was speculated that the selective ratio of Trp/Lys = 10:1 was attributed to the faster complexation of compound **7b** with Trp compared to the case of Lys as described above.

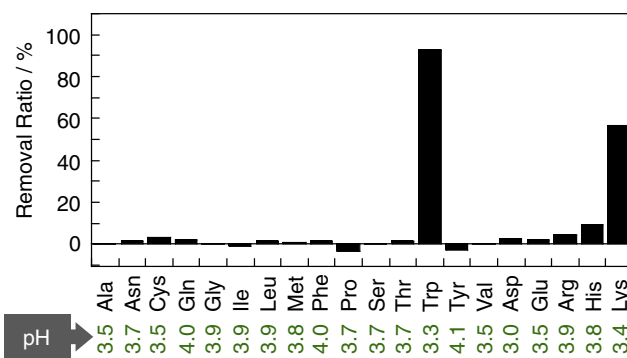


Figure 2. Removal ratio of the essential amino acids from water by the scandium compound (**7b**). The bottom numbers represent the supernatant pH values indicated on a pH meter.

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