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Lanthanide Complex with Armed Crown Ether as Heterotopic Carrier of Hydrophilic Amino Acid Ester Salts

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Lanthanide complex with bipyridine-armed crown ether was first demonstrated to mediate effective transport of hydrophilic HisOMe and LysOEt salts via two-point binding.

Heterotopic receptors and carriers are recognized as a new class of host molecules which contain multiple binding sites complementary to the different functional groups present in guest species. In particular, crown ethers combined with macrocyclic polyamines, cyclophanes, cyclodextrins, and porphyrins have been reported to offer characteristic receptor and/or carrier activities.[1] Since their guest binding properties and subsequent chemical functions are remarkably dependent on the natures of binding subunits, attachment of a characteristic binding site to the crown ether system can be considered a useful strategy for receptor/carrier synthesis.

We report the unique cation binding and transport property of $Dy(fod)_3$[2] complexes with armed crown ethers which have two characteristic binding sites for amino acid ester salts (Fig. 1): 18-crown-6 ring holds primary ammonium cation and $Dy(fod)_3$ settled on a sidearm interacts with the ester group. We characterized various combinations of armed crown ethers and lanthanide reagents and found that some of them offered effective transport of uncommon amino acid ester salts. Although lanthanide reagents have been employed as NMR shift reagents and as organic reaction catalysts,[3] this is the first successful example of lanthanide complex exhibiting excellent receptor/carrier functions.

We synthesized monoaza-crown ethers (**1**-**3**) and diaza-crown ethers (**4**, **5**),[4] which had functionalized sidearms as the fixation sites for $Dy(fod)_3$ (Fig. 2). Transport experiment of amino acid ester salts across a

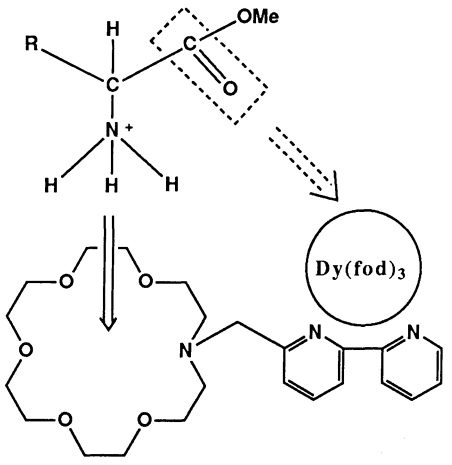

Fig. 1. Two-point binding model.

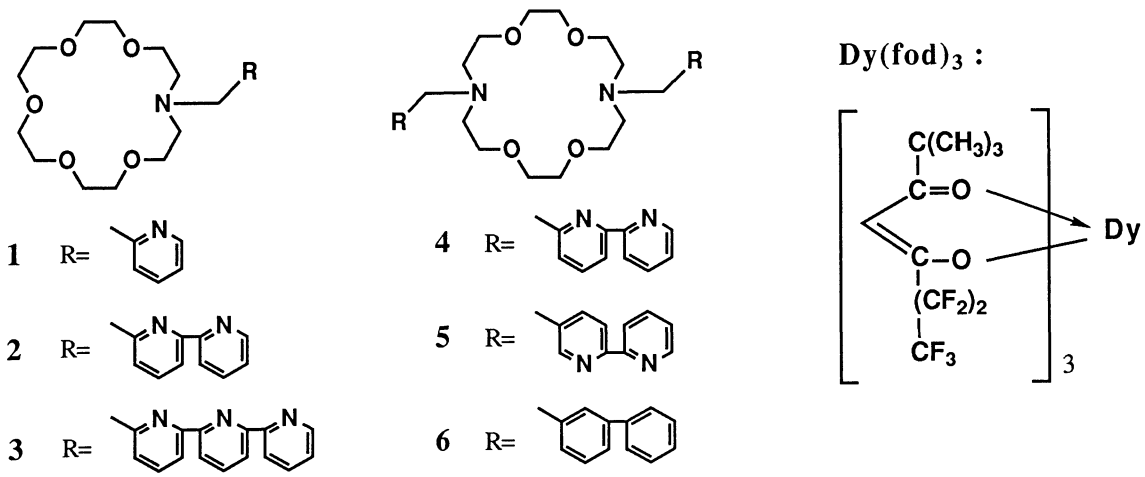

Fig. 2. Structures of armed crown ethers and $Dy(fod)_3$.

CH_2Cl_2 membrane was performed using a U-tube glass cell (2.0 cm, i.d.),[5] and the transported amounts of amine salts were determined by colorimetry.

$Dy(fod)_3$ complexes with armed crown ethers **1-4** exhibited greatly different transport abilities toward amino acid ester salts from those observed with their

Table 1. Transport Rates of Organic Ammonium Cations[a]

Carrier	Transport rate × 10^6 (mol/h)			
	GlyOMe·H+	HisOMe·2H+	Histamine·2H+	LysOEt·2H+
1	3.2	<0.3	<0.3	<0.3
1+$Dy(fod)_3$	4.0	1.0	0.4	1.3
2	4.3	<0.3	<0.3	<0.3
2+$Dy(fod)_3$	5.6	1.7	<0.3	1.3
3	3.9	<0.3	<0.3	<0.3
3+$Dy(fod)_3$	5.0	0.8	<0.3	0.4
4	8.5	<0.3	<0.3	0.3
4+$Dy(fod)_3$	12.0	4.2	0.5	2.7
5	7.9	<0.3	<0.3	0.3
5+$Dy(fod)_3$	(2.2)	(<0.3)	<0.3	(<0.3)
6	9.4	<0.3	<0.3	<0.3
6+$Dy(fod)_3$+Bipy	9.5	<0.3	<0.3	0.5

a) Conditions: Aq.1: Amine·HCl, 0.5 mmol. $Mg(ClO_4)_2$, 0.5 mmol. Water, 5 ml; Membrane: Crown ether, 0.0372 mmol. $Dy(fod)_3$, 0.0372 mmol for **1-3** or 0.0744 mmol for **4-6**. CH_2Cl_2, 12 ml; Aq. 2: Water, 5 ml. ( ): Precipitate appeared in these cases. Bipy: 2,2'-bipyridine (0.0744 mmol). Experimental errors were confirmed as <15%. The limit of detection was 0.3.

parent crown ethers (Table 1). Typically, **2**+Dy(fod)$_3$ complex effectively mediated transport of HisOMe·2H$^+$ and LysOEt·2H$^+$ cations, while the parent crown ether **2** could not transport these hydrophilic dications. An enhanced transport rate was not observed for histamine·2H$^+$ cation but was for GlyOMe·H$^+$ cation. Dy(fod)$_3$ acted as an effective co-factor in crown ether-mediated transport, especially of amino acid ester salts. **4**+Dy(fod)$_3$ complex offered the largest transport rates for GlyOMe·H$^+$, HisOMe·2H$^+$, and LysOEt·2H$^+$ cations. Two Dy(fod)$_3$ units fixed on the sidearms of the crown ether **4** offered a statistical advantage for clasping ester moieties, whereas the parent diaza-18-crown-6 ring bound organic ammonium cations more strongly than aza-18-crown-6 ring. Interestingly, transport of $^+NH_3(CH_2)_nCO_2Me$ cation (n=2 or 3) was not enhanced, indicating that α-amino acid ester salt could be recognized by this carrier system. Diaza-18-crown-6 **5** with bipyridine units at a remote position exhibited a marked contrast. Its Dy(fod)$_3$ complex rarely transported HisOMe·2H$^+$ or LysOEt·2H$^+$ cation and showed a reduced transport rate for GlyOMe·H$^+$ cation. Since **6**+Dy(fod)$_3$+bipyridine system was ineffective, spatial arrangement of 18-crown-6 ring and Dy(fod)$_3$ unit must be essential for cooperative action. The nature of lanthanide reagent also influenced the transport profile. Transport rates of HisOMe·2H$^+$ cation were measured as 4.2 for **4**+Dy(fod)$_3$, 3.2 for **4**+Yb(fod)$_3$, 2.2 for **4**+Eu(fod)$_3$, and 0.4 for **4**+Pr(fod)$_3$.[6] The combination of crown ether and lanthanide reagent should be chosen carefully in designing carriers of this type.[7]

Guest-binding behavior of the Dy(fod)$_3$ complexes was investigated by ^{13}C-NMR

Table 2. Induced Change in ^{13}C-NMR Chemical Shifts of GlyOMe·HCl[a]

Additive	Induced chemical shift (ppm) $^+NH_3—\underline{C}H_2—\underline{C}O—O—\underline{C}H_3$		
Bipy+Dy(fod)$_3$	-0.4	-0.4	-0.2
2	+0.2	+0.3	<-0.1
2+Dy(fod)$_3$	-2.4	-2.3	-0.7
4	+0.3	-0.6	-0.1
4+Dy(fod)$_3$	-3.8	-3.8	-1.1
5	+0.2	+0.4	<-0.1
5+Dy(fod)$_3$	-1.1	-0.8	-0.5
Diaza-18-crown-6+ Bipy+Dy(fod)$_3$	-1.2	-0.8	-0.6

a) Conditions: GlyOMe·HCl, 0.06 mmol. Dy(fod)$_3$, 0.01 mmol. Bipy, 0.01 mmol. **2**, 0.01 mmol. **4** , **5**, or Diaza-18-crown-6, 0.005 mmol in MeOH-CDCl$_3$ (1:2) 0.6 ml. Positive is downfield shift.

spectroscopy (Table 2). $Dy(fod)_3$ is a typical NMR shift reagent and coordinates with the ester group of a guest.[3] Indeed, addition of bipyridine+$Dy(fod)_3$ complex to a solution of GlyOMe·HCl caused definite shifts of the signals for CH_2 and CO carbons. Further remarkable spectral changes were induced when **2**+$Dy(fod)_3$ complex was added. The shifted values for all the carbon signals of GlyOMe·H^+ were much larger than those observed with either bipyridine+$Dy(fod)_3$ complex or crown ether **2** alone. **2**+$Dy(fod)_3$ complex was suggested to bind GlyOMe·H^+ cation effectively via two-point interaction as shown in Fig. 1. **4**+$Dy(fod)_3$ complex offered larger shifts than **2**+$Dy(fod)_3$ complex, indicating that the former carried GlyOMe·H^+ cation more strongly and efficiently than the latter. Cooperative action of crown ring and lanthanide reagent may allow effective extraction and transport of hydrophilic HisOMe·$2H^+$ and LysOEt·$2H^+$ dications. ^{13}C-NMR spectrum of the GlyOMe·HCl was modestly changed in the presence of **5**+$Dy(fod)_3$ complex. This showed similar induced values observed with unsubstituted diaza-18-crown-6+bipyridine+$Dy(fod)_3$ system. Thus, lanthanide complex with armed crown ether can act as an effective receptor/carrier of amino acid ester salts if in the proper geometrical arrangement.

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6) This transport trend is parallel to that in NMR binding studies (conditions, same as those in Table 2): **4**+$Dy(fod)_3$ offered the largest shifted values of GlyOMe·HCl signals, while spectral changes were rarely recorded in the presence of **4**+$Pr(fod)_3$.

7) Transport rate of HisOMe·$2H^+$ cation also depended on $Dy(fod)_3$/crown ratio. Transport rate $\times 10^6$ mol/h [$Dy(fod)_3$/crown **2**]: 0.9 [0.5]; 1.7 [1]; 1.8 [2]. Transport rate $\times 10^6$ mol/h [$Dy(fod)_3$/crown **4**]: 2.1 [1]; 4.2 [2]; 4.3 [3].

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