Lipophilic Lanthanide Complexes: a New Class of Carriers for Extraction and Transport of Potassium Benzyloxycarbonylamino Acidates

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Lipophilic lanthanide complexes co-ordinated by fluorinated β-diketone ligands [M(OCRCHCR′O)$_3$] (M = Eu, Pr, Dy or Yb; R = Bu^t, R′ = C$_3$F$_7$ or CF$_3$) were demonstrated to act as neutral carriers for efficient extraction and rapid transport of potassium benzyloxycarbonylamino acidates. They formed 1 : 1 complexes with the organic anions and exhibited different anion-extraction and transport behaviours from those of common anion carriers.

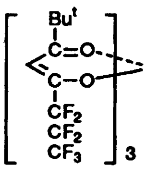
The binding and transport of amino acids and organic anions play an important role in many biological processes and considerable effort has been devoted to the development of synthetic anion-complexing agents.[1] Although a variety of elegant examples has been reported,[2–5] the number of systems capable of effecting anion extraction and transport remains quite limited.[6] These are based upon ammonium surfactants,[7,8] lipophilic metal complexes,[9,10] rigid receptors containing positively charged subunits[11,12] and macrocyclic polyammonium cations.[13] Here, we demonstrate that several lanthanide tris(β-diketonates) effectively extract potassium salts of benzyloxycarbonylamino acids and rapidly transport them across a liquid membrane. These complexes have frequently been employed as shift reagents in NMR spectroscopy and catalysts in organic synthesis, but this is the first successful application in extraction and transport processes of organic anions.[14]

Lanthanide tris(β-diketonates) have the potential to co-ordinate to an anionic group of one or more substrates,[15,16] though they are electrically neutralized by the three β-diketone ligands. Since fluorinated β-diketonates with lanthanide ions have suitable lipophilicity, these can serve as neutral carriers for extraction and transport of anionic substrates. We found that the lanthanide tris(β-diketonates) offered unique anion-receptor and -carrier activities.

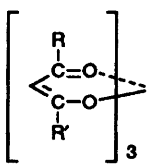
Results and Discussion

Lipophilic Lanthanide Complexes.—We examined three kinds of lanthanide tris(β-diketonates) as carriers of organic anions: those of fluorinated ligands (**1a**–**1d** and **2**), of non-fluorinated ligands (**3** and **4**) and the chiral complex **5**. The copper bis(β-diketonate) **6** was also employed to elucidate the effect of the central metal cation on anion binding and transport phenomena. We previously reported that several crown ethers transported organic anions together with alkali-metal cations,[17] and dibenzo-18-crown-6 (6,7,9,10,17,18,20,21-octahydrodibenzo[*b*,*k*][1,4,7,10,13,16]hexaoxacycloctadecine) was chosen as a typical example.

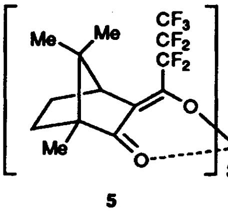
Transport of Potassium Amino Acidates.—Anion-transport experiments were performed using a CH$_2$Cl$_2$ liquid membrane cell as described.[18] Scheme 1 illustrates transport systems involving lanthanide complexes and crown ethers. When a lipophilic lanthanide complex is employed as a carrier, a highly co-ordinated complex is formed with the benzyloxycarbonylamino acid anion at the left-hand side of the membrane and the K$^+$ cation is extracted as a counter cation. The resulting complex moves across the membrane. At the right-hand side of the membrane the guest anion is released into the receiving aqueous phase together with the K$^+$ cation. A crown ether also transports the amino acid anion and K$^+$ cation in the same direction, but it binds the K$^+$ cation rather than the anionic substrate. Thus, these two carrier systems have different binding modes for the potassium amino acidates and appear to exhibit different anion recognition and transport abilities.



	M
1a	Eu
1b	Pr
1c	Dy
1d	Yb



2 R = Bu^t, R = CF$_3$
3 R = R′ = Bu^t
4 R = R′ = Me



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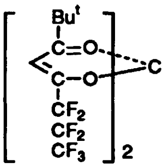

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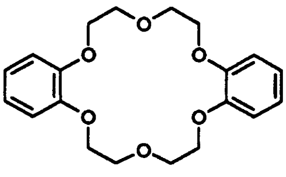
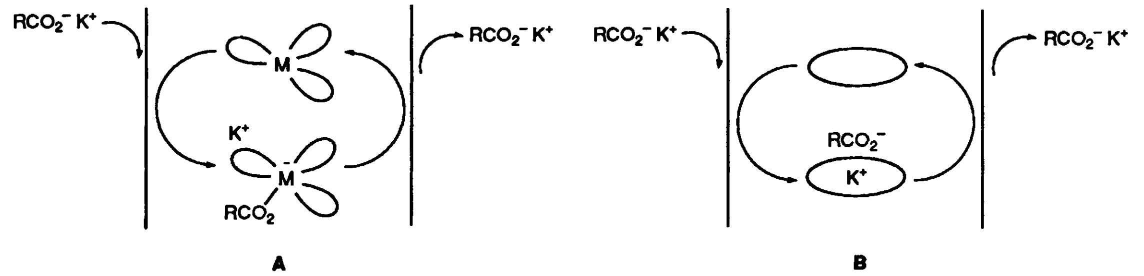


Table 1 summarizes the transport properties of lanthanide complexes **1a**–**1d** and **5**, copper complex **6** and dibenzo-18-crown-6. Since corresponding amounts of K$^+$ cation were moved into the receiving aqueous phase, the transport

Table 1 Transport rates of potassium benzyloxycarbonylamino acidates by lanthanide complexes

	10^6 Transport rate/mol h^{-1}						
Acidate	**1a**	**1b**	**1c**	**1d**	**5**	**6**	Dibenzo-18-crown-6
Glycinate	3.4[a]	1.0[a]	3.5[a]	1.9[a]	—	0.7	1.9
Alaninate	6.2	4.3	4.1	3.1	4.3 (4.3)[b]	0.4	2.3
β-Alaninate	4.4	2.9	4.2	2.7	—	0.3	1.3
Valinate	8.3	6.1	9.6	6.4	6.3 (6.1)[c]	0.2	3.8
Leucinate	7.7	4.7	7.8	8.0	5.8 (5.8)[b]	0.1	5.7
Phenylalaninate	4.9	3.4	6.0	5.5	6.1 (6.8)[b]	0.1	7.6

[a] Membrane phase was not clear. [b] Transport rates for D isomers in parentheses; others were rates for L isomers. [c] Racemic mixture was employed.



Scheme 1 Schematic illustrations of transport mechanisms of potassium amino acidates. **A** = Lanthanide complex carrier; **B** = crown ether carrier

mechanisms shown in Scheme 1 were supported in each case. All lanthanide complexes examined transported the amino acid anions, but their transport profiles were different from those with the crown ether: lanthanide complexes transported the anions of benzyloxycarbonyl-valinate and -leucinate more effectively than the corresponding phenylalaninate, while the crown ether favoured the latter. The nature of the lanthanide metal cation had a great influence on the tranport profiles. For example, the europium and dysprosium complexes **1a** and **1c** exhibited higher carrier activities than those of the praseodymium and ytterbium complexes **1b** and **1d**. Since the copper complex **6** was an ineffective carrier, anion co-ordination to the lanthanide metal centre is significantly involved. We also compared the carrier activities of four europium complexes **1a** and **2**–**4** having different ligands. When potassium benzyloxycarbonylvalinate was a guest, the fluorinated β-diketonate complexes **1a** and **2** mediated effective membrane transport, while complexes **3** and **4** did not act as carriers. Relative transport rates were estimated as 8.3 for **1a**, 5.4 for **2** and 0 for **3** and **4**, respectively. As pointed out for NMR shift reagent systems,[19] electronegative fluorinated ligands promote anion co-ordination and enhance carrier activity of lanthanide tris(β-diketonates). Therefore, this type of lanthanide complex showed interesting anion-transport abilities based on the unique anion co-ordination, which could be adjusted by the choice of a combination of the central metal and ligand.

The chiral europium complex **5** was employed as a carrier for enantiomer-selective membrane transport. It effectively transported several potassium benzyloxycarbonylamino acidates, but showed almost the same transport rate for each pair of enantiomers. The complex has been used as a chiral shift reagent in the determination of the optical purities of various chiral substrates,[20] but chiral recognition of the potassium amino acidates was rarely observed in the liquid-membrane transport.

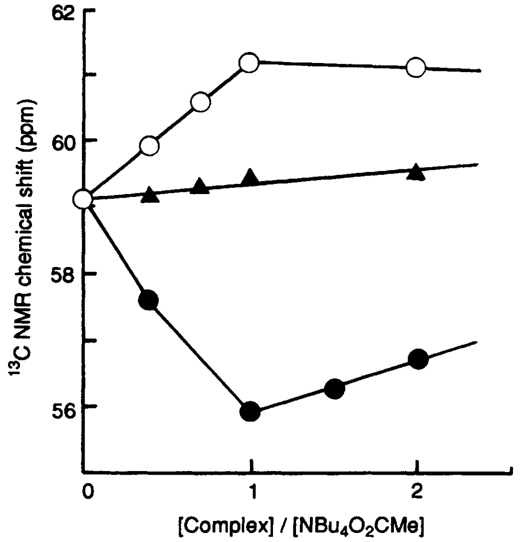


Fig. 1 Metal complex-induced changes in the ^{13}C NMR chemical shifts of $[NBu_4][O_2CMe]$: (○) europium complex **1a**, (▲) copper complex **6** and (●) praseodymium complex **1b**

Anion Co-ordination Properties of the Lanthanide Complexes.—Anion bindings of the complex carriers were characterized using ^{13}C NMR spectroscopy. Fig. 1 illustrates metal complex-induced changes in the carbon signal of the tetrabutylammonium acetate. Lanthanide complexes **1a** and **1b** formed highly co-ordinated complexes with acetate anion, while the corresponding copper complex **6** hardly bound it. Indeed, addition of the europium complex **1a** resulted in significant shifts of the carbon signal $NCH_2CH_2CH_2CH_3$, while the carbon signals of the acetate anion were broadened and disappeared. The observed titration curve had a sharp bend in the presence of equimolar complex **1a**, indicating 1 : 1 complexation between **1a** and the guest acetate anion. The log K value was estimated as larger than 3.7. When the praseodymium complex **1b** was employed the carbon signal shifted in the opposite direction, but 1 : 1 complexation was demonstrated. Thus, benzyloxycarbonylamino acidates may similarly form 1 : 1 complexes with the lanthanide complexes.

Table 2 summarizes the results of ^{13}C NMR binding studies for several lanthanide and copper complexes toward tetrabutylammonium acetate. Although the shifts and directions are probably dependent both on the physical properties and anion-binding abilities of the lanthanide metal cations, the lanthanide complexes **1a**, **1b**, **1d**, **2**, **3** and **5** were demonstrated to interact with acetate anion. The europium complex **5** induced similar shifts to those produced by the other europium complexes **1a**, **2** and **3**, and its bulky ligand derived from camphor [(1*R*)-1,7,7-

Table 2 Induced changes in ^{13}C NMR chemical shifts of tetrabutylammonium acetate

	δ			
Carrier	$N^+C^1H_2$	C^2H_2	C^3H_2	C^4H_3
None	59.10	24.27	19.86	13.67
1a	61.18	25.63	20.76	14.10
1b	55.93	21.78	18.03	12.47
1d	65.83	26.58	23.34	15.49
2	61.66	25.88	20.73	14.13
3	60.96	25.51	20.59	14.06
5	61.42	25.93	19.81	14.30
6	59.45	24.44	19.66	13.54

Conditions: carrier, 0.05 mmol; $[NBu_4][O_2CMe]$, 0.05 mmol; $CDCl_3$, 1 cm^3.

trimethylbicyclo[2.2.1]heptan-2-one] rarely disturbed the co-ordination of the small acetate anion. The present study suggests that a variety of lanthanide complexes may be promising candidates for anion receptors and carriers.

Extraction of Potassium Amino Acidates.—The anion-binding abilities of several lanthanide complexes were further assessed by liquid–liquid extraction of potassium benzyloxycarbonylamino acidates. Three lanthanide complexes **1a**, **1c** and **5** were compared with dibenzo-18-crown-6. The extraction percentage, *i.e.* the percentage of amino acidate extracted into the organic phase, was calculated from the acidate concentration in the aqueous phase which was spectroscopically determined.

Table 3 summarizes the anion-extraction properties of the three lanthanide complexes and the crown ether. Complexes **1a**, **1c** and **5** showed much higher extraction abilities for the amino acidate salts than those of the crown ether. Their extraction abilities were significantly influenced by the nature of the lanthanide metal and the ligand. Interestingly, the europium complex **1a** exhibited more effective anion-complexing ability for the hydrophilic benzyloxycarbonyl-glycinate and -alaninate anions than did the dysprosium complex **1c** and the chiral europium complex **5**. The europium metal centre acted as a potential anion-binding site, but the steric repulsion between the bulky ligand and amino acid residues seemed to decrease the extraction efficiency. As observed in the transport experiments (see Table 1), enantiomer recognition was not achieved by complex **5** in the extraction experiments.

We have demonstrated the unique and effective anion-binding and transport abilities of lanthanide tris(β-diketonates). Their unique co-ordination properties enabled both effective extraction and fast membrane transport of anionic organic substrates. To the best of our knowledge, this is the first example of lanthanide complexes acting as extraction and transport agents for organic anions.

Experimental

Materials.—Lanthanide complexes were obtained from Aldrich Chemical, Fluka Chemie and Gelest; benzyloxycarbonylamino acids were from Tokyo Chemical Industry and used without additional purification.

Transport Experiments.—Transport experiments were performed at room temperature (*ca.* 16 °C) in a U-tube glass cell (internal diameter 2.0 cm). The lanthanide tris(β-diketonate), dissolved in CH_2Cl_2 (0.0372 mmol per 12 cm^3), was placed in the base of the U-tube, and two aqueous phases, I and II, were placed in the tube arms which were floating on the CH_2Cl_2 membrane; I was an aqueous solution of the benzyloxycarbonylamino acid (0.500 mmol per 5 cm^3), while II was pure water (5 cm^3). Phase I was initially adjusted to pH 5.6–6.6 by adding KOH; potassium chloride was added so that the total K^+ concentration was 0.2 mol dm^{-3}. Although the free benzyloxycarbonylamino acid (acid form) is partially soluble in CH_2Cl_2, we confirmed that no transport occurred at the employed pH range (5.6–6.6) in the absence of carrier. The transport rates in Table 1 were calculated from the initial rates of appearance of the amino acid in phase II, which were determined spectroscopically. The corresponding amount of K^+ transported was detected by atomic absorption spectroscopy (carried out at Exlan Technical Center, Okayama). Reproducibilities were confirmed as ± 15% or better.

Table 3 Extraction percentages of potassium benzyloxycarbonylamino acidates by lanthanide complexes

	Extraction percentage			
Substrate	**1a**	**1c**	**5**	Dibenzo-18-crown-6
Glycinate	21[a]	8	—	4
Alaninate	24	10	14 (13)[b]	3
Valinate	44	27	28 (27)[c]	16
Leucinate	53	37	41 (41)[b]	14
Phenylalaninate	47	36	48 (47)[b]	15

[a] Organic phase was not clear. [b] Values for D isomers in parentheses; others were those for L isomers. [c] Racemic mixture was employed.

NMR Binding Experiments.—Carbon-13 NMR studies were carried out with a JEOL 90A spectrometer. The chemical shifts were determined using the central peak of the $CDCl_3$ carbon (δ 77.10) as reference. The salt $[NBu_4][O_2CMe]$ was dissolved in $CDCl_3$ at a concentration of 0.05 mol dm^{-3}.

Extraction Experiments.—Extraction experiments (Table 3) were carried out by adding a CH_2Cl_2 solution of the carrier molecule (0.015 mmol per 1.5 cm^3) to an aqueous solution (1.5 cm^3) of the benzyloxycarbonylamino acid. This was prepared by 10-fold dilution of phase I used in the transport experiments. After the mixture had been stirred for 2.5 h the aqueous phase was separated, and the concentrations of the benzyloxycarbonylamino acidates were determined spectroscopically.

Acknowledgements

This research was supported in part by a Grant (No. 06241253) from the Ministry of Education, Science and Culture, Japan.

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Received 8*th August* 1994; *Paper* 4/04851B