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# LIPOPHILIC MACROCYCLIC TETRAMINE AS SPECIFIC CARRIER OF AMINO ACID AND RELATED ANIONS[1]

Hiroshi Tsukube

Department of Chemistry, College of Liberal Arts and Science,
Okayama University, Okayama 700, Japan.

Lipophilic macrocyclic polyamine **1**, 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane, was firstly demonstrated to mediate specific transport of amino acid and related anions, especially dicarboxylates.

Some naturally occurring polyamine derivatives are well-known to play important roles in biological recognition and transportation of anionic and cationic species.[2] As interesting model compounds, macrocyclic polyamines have been drawing much interest. They form much more stable and selective complexes with various transition metals than do open chain analogues.[3] Recently their protonated forms, macrocyclic polyammonium cations, have also been reported to complex some kinds of anionic species.[4] Since their cation- and anion-binding properties can be significantly controlled by size and shape of macrocyclic systems, introduction of macrocyclic polyamine moiety into the carrier molecules may lead to the specific transport of a given species "at will".

Here we report that some lipophilic macrocyclic polyamine derivative can mediate specific transport of amino acid and related anions, especially dicarboxylate anions. Our examined macrocyclic tetramine **1**, 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane, was easily prepared from N-benzylaziridine,[5] and provides several important features as pH-sensitive and specific carrier: (i) **1** bears two protons at neutral pH conditions;[6] (ii) The protonated macrocycle may act as highly densed diammonium cation, showing interesting anion-

binding properties; (iii) Its four benzyl groups offer high hydrophobicity enough to be partitioned into liquid membrane phase.[7] Although Kimura et al. and Lehn et al. have claimed the possible use,[4] this is the first application of macrocyclic polyamine compound to the anion transport process.

Liquid membrane transport experiments were performed by using an U-shaped glass cell (2.0 cm, i.d.) as described before[8] (see Figure 1). After a period of 12 h, the transported amounts of guest anions into the receiving phase were determined spectroscopically. Three types of carriers were examined below (Figure 2): macrocyclic tetramine **1**, macrocyclic polyether **2**, and quaternary ammonium cation **3**.[9] Typical results of anion transport experiments are shown in Table.

Figure 1. Anion Transport Mediated by Macrocyclic Polyamine Carrier.

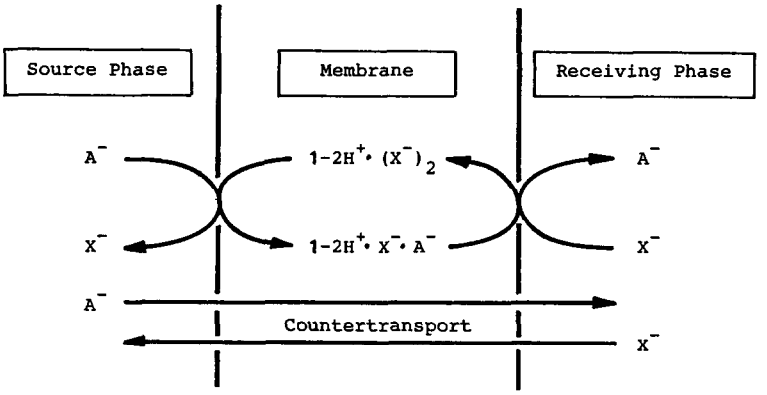


Figure 2. Synthetic Carriers

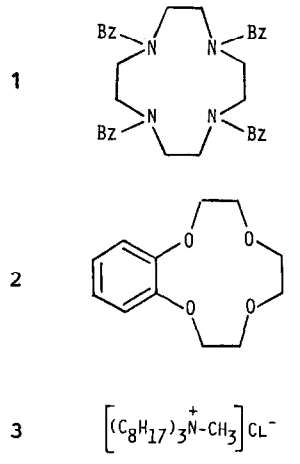


Table shows that 12-membered macrocyclic tetramine **1** is a pH-sensitive and specific carrier of amino acid and related anions. Its transport rates for monocarboxylate anions (Z-Asn, Z-Gln, and Z-Gly) were clearly influenced by pH conditions of source phases, and increasing pH values was found to decrease the transport rates. Probably, under the neutral and acidic conditions (pH values of source phases: 4 - 6 ), the carrier **1** can accomodate two protons into the cavity, and the formed lipophilic diammonium cation may act as anion-carrier like as the carrier **3** (Figure 1). On the other hand, the carrier **3**

Table. Artificial Transport of Amino Acid and Related Anions.

| Guest Anion* | Countertransported Anion | Transport Rate $x10^6$(mol/h) 1 | 2 | 3 |
|---|---|---|---|---|
| Z-Asn(pH=11.3) | $Cl^-$ | 0.3 | 0 | 9.8 |
| (pH=5.6) | $Cl^-$ | 0.8 | 0 | 9.0 |
| (pH=4.7) | $Cl^-$ | 4.9 | 0 | 8.8 |
| Z-Gln(pH=4.3) | $Cl^-$ | 7.8 | 0 | 10.2 |
| Z-Gly(pH=4.8) | $Cl^-$ | 2.4 | 0 | 7.9 |
| Z-Asp(pH=9.2) | $Cl^-$ | 0 | 0 | 1.9 |
| (pH=5.9) | $Cl^-$ | 2.2 | 0 | 2.0 |
| (pH=4.7) | $Cl^-$ | 5.4 | 0 | 4.3 |
| | $ClO_4^-$ | 5.0 | 0 | 4.6 |
| | None | 0 | 0 | 0 |
| Z-Glu(pH=4.0) | $Cl^-$ | 7.6 | 0 | 5.9 |
| p-phthalate(pH=5.5) | $Cl^-$ | 0 | 0 | 1.4 |
| m-phthalate(pH=5.4) | $Cl^-$ | 0.1 | 0 | 1.5 |
| o-phthalate(pH=5.4) | $Cl^-$ | 5.2 | 0 | 3.7 |

Initial concentrations: Source phase; Guest anion salt, 0.250 mmol/aq. NaOH, 5 ml. Membrane phase; Carrier, 0.0557 mmol/$CHCl_3$, 12 ml. Receiving phase; Countertransported anion salt, 2.5 mmol/$H_2O$, 5 ml.

* The values indicated in parentheses were pH values of "Source phase".

exhibited constantly high transport efficiencies for monocarboxylate anions under the employed conditions (pH values of source phases: 4 -11). Since macrocyclic polyether **2** was confirmed to hardly mediate such an anion transport, these results indicate that macrocyclic polyamine-mediated transport system was coupled with protonation of macrocycle **1**, and significantly regulated by proton concentrations of source phase.

The nature of countertransported anion was also essential factor in determining the transport efficiencies (see Table). When KCl or $NaClO_4$ was added into the receiving phase as source of countertransported anion, guest anions were effectively transported by the aids of carrier **1**. Since no diffusion was detected in the absence of countertransported anion, the concentration gradient of countertransported anion could drive the effective anion transport.

The present carrier **1** offered higher transport rates and selectivities for dicarboxylate anions (Z-Glu, Z-Asp, and phthalate anions), compared with the conventional quaternary ammonium cation carrier **3**. When the carrier **1** was employed, o-phthalate anion was rapidly transported, while m- and p-phthalate anions were hardly transported. A similar transport trend was attained by using the carrier **3**, but its transport selectivity was much lower than the carrier **1**. As reported before,[4] large-sized macrocyclic pentamine and hexamine derivatives could specifically bind a variety of polyanions in the aqueous solution. Although the details of this anion transport system is complicated,[10] our obtained results demonstrate that small-sized macrocyclic tetramine **1** is suitable for specific binding of dicarboxylate anions in the transport process.

## References and Notes


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