Selective Transport of Amino Acid Esters through a Chloroform Liquid Membrane by a Calix[6]arene-based Ester Carrier

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A liquid membrane containing the ethoxycarbonylmethyl derivative **1** of *p-tert*-butylcalix[6]arene exhibited pronounced transport selectivity towards ethyl esters of both phenylalanine and tryptophan over glycine, alanine and 4-aminobutyric acid (GABA).

Calixarenes are known to have attractive structural properties for construction of many biomimetic systems, and also have unique ionophoric properties towards various metal cations.[1] In spite of these interesting properties, few attempts have been made to use them in the selective recognition and separation of biologically important amino acids.[2] We have focused our attention on the use of a calixarene as a selective carrier for the separation of amino acids, and tried to elucidate the possible interaction between the carrier **1** and the ammonium moiety of amino esters.

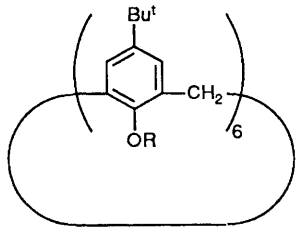
The ethyl ester **1** was prepared according to the reported procedure.[3] The transport of ethyl esters of amino acids in ammonium salt form was performed through a conventional U-tube (i.d. = 1.8 cm) type chloroform liquid membrane containing **1** as a carrier. Lithium perchlorate was added as a transport promoter. The amount of amino esters transported was determined by measuring the ion concentration of the co-transported perchlorate by using a perchlorate ion-selective electrode. Control experiments showed that no significant amount of lithium perchlorate was transported under identical conditions. All the experiments were performed at least in triplicate under steady-state conditions and the results obtained are summarized in Table 1.

Table 1 Transport rates of amino acid esters by carrier **1**[a]

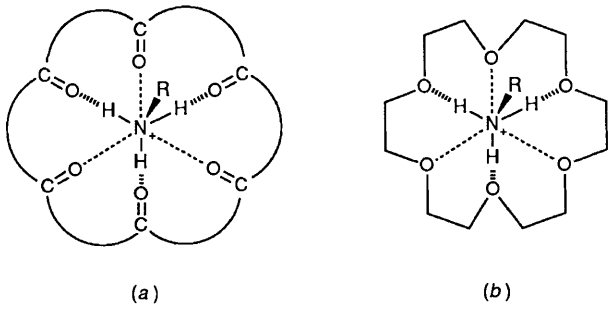
Amino acid ester	Transport rate × 10^7/ $dm^3\ mol^{-1}\ h^{-1}\ cm^{-2}$
Control	<0.3
Gly-OEt	4.2
Ala-OEt	7.6
β-Ala-OEt	8.7
GABA-OEt	14.9
Trp-OEt	89.3
Phe-OEt	98.5

[a] Source phase: hydrochloride salt of amino acid ethyl ester (0.5 mmol), $LiClO_4$ (1 mmol) in water (10 ml); membrane phase: carrier (0.05 mmol) in chloroform (15 ml); receiving phase: deionized water (10 ml). The membrane phase was magnetically stirred at 200 rpm at 25 °C.

As shown in Table 1, the transport rate of amino esters in the liquid membrane containing the carrier was facilitated markedly. It is known that the affinity of **1** for alkali metal cations increases with increasing size of the metal cations, *i.e.*, Cs^+ has the highest affinity for the hexaester.[3] The size of the ammonium ion (1.48 Å) is close to but slightly larger than that of K^+ (1.34 Å).[4] Therefore, it may be expected that the



1 R = CH_2CO_2Et



(a) (b)

Fig. 1 (*a*) Proposed binding mode in calixarene ester cavity; (*b*) binding mode in crown ethers

ammonium moiety of the amino esters, which might be a primary interacting part of the present host–guest system, could favourably interact with the binding site, the pseudocavity of the carrier. An examination of Corey–Pauling–Koltun (CPK) molecular models suggests that the ammonium moiety of the amino esters can be situated in the middle of the pseudocavity of the carrier, which consists of the oxygen atoms of ester carbonyl groups. Thus a plausible binding mode may be that in Fig. 1(*a*). The ammonium group of guest is anchored in the pseudocavity of the carrier both by the tripodal hydrogen bonding interaction N^+–H···O=C (carrier) and by the ion–dipole interaction N^+···O=C (carrier), which is reminiscent of the interaction found in many alkylammonium crown ether complex systems [Fig. 1(*b*)].[5]

The suggested binding mode was confirmed by UV and IR measurements. In the UV titration of n-butylammonium picrate with **1** in chloroform, the λ_{max} of the picrate shifted markedly from 342 to 378 nm with a clearcut titration break indicating 1 : 1 stoichiometry. The bathochromic shift to 378 nm indicates a solvent-separated state of the picrate ion resulting from the encapsulation of the ammonium moiety of the guest by the ligand.[6] Further evidence for the interaction mode is obtained from titration of the carrier with n-butylammonium chloride, when the IR absorption bands at 1750 (C=O) and 1180 cm^{-1} (–O– of ester) shifted to 1700 and 1205 cm^{-1}, respectively, upon complexation. Although determination of the structure of the complex unambiguously must await an X-ray study, these observations strongly support the suggested hydrogen bonding binding mode in the encapsulated state between the host and guest in the present system.

The trend of the transport efficiency was found to be closely related to the hydrophobicity[7] of the amino acids examined: Phe > Trp ≫ GABA > β-Ala > Ala > Gly; *i.e.* the carrier showed pronounced plateau selectivity towards phenylalanine and tryptophan over the other amino acids employed. This type of transport behaviour was also found in many experiments[8] including the transport of *N*-benzoyl amino acids in their carboxylate form employing **1** as a carrier.[9] Unfortunately, the transport of the ethyl ester of GABA, which is one of the most important neurotransmitters, is not particularly significant. The possibility of introducing a secondary interaction site and the use of the present carrier in the active transport of amino acids in zwitterionic form are being studied in our laboratories.

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References

1 C. D. Gutsche, *Calixarenes*, The Royal Society of Chemistry, Cambridge, 1989.
2 Y. Aoyama, M. Asakawa, A. Yamagishi, H. Toi and H. Ogoshi, *J. Am. Chem. Soc.*, 1990, **112**, 3145; J. Rebek, Jr., B. Askew, D. Nemeth and K. Parris, *J. Am. Chem. Soc.*, 1987, **109**, 2432.
3 F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M. J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.*, 1989, **111**, 8681; S.-K. Chang and I. Cho, *J. Chem. Soc., Perkin Trans. 1*, 1986, 211.
4 M. R. Truter, *Struct. Bonding (Berlin)*, 1973, **16**, 73.
5 I. O. Sutherland, *Chem. Soc. Rev.*, 1986, **15**, 63.
6 Y. Inoue, C. Fujiwara, K. Wada, A. Tai and T. Hakushi, *J. Chem. Soc., Chem. Commun.*, 1987, 393.
7 A. Radzicka and R. Wolfender, *Biochemistry*, 1988, **27**, 1664.
8 P. Scrimin, U. Tonellato and N. Zanta, *Tetrahedron Lett.*, 1988, **29**, 4967; J.-P. Behr and J.-M. Lehn, *J. Am. Chem. Soc.*, 1973, **95**, 6108; P. D. Wilson and K. P. Wheeler, *Biochem. Soc. Trans.*, 1973, **1**, 369.
9 S.-K. Chang, H.-J. Son, H.-S. Hwang and Y. S. Kang, *Bull. Korean Chem. Soc.*, 1990, **11**, 364.