An Artificial Oligomer Carrier for Transport of Organic Substrates[1]

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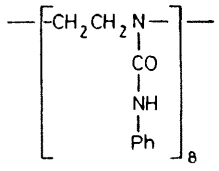
Summary A new type of lipophilic host oligomer, $[CH_2CH_2N(CONHPh)]_8$, efficiently transported biologically important adenine, amino-acid, and catechol amine salts as well as simple amine derivatives

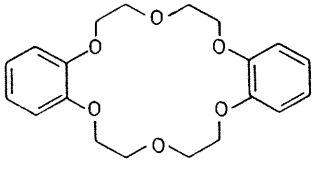
BIOLOGICAL transport of organic substrates including nucleotides, amino-acids, catechol amines, and others, plays a most important role in life processes Since some crown ethers[2] and surfactants[3] aided the transport of

organic salts through artificial membranes, various modifications have been made to their basic structures,[4] enabling successful optical resolution of racemic substrates to be performed.[5] Such synthetic carriers, which may be easily synthesized, offer the possibility of efficient and selective transport of specific organic substrates. The discovery of a new class of carrier having novel structural features is a challenging target.

Here we report a new type of lipophilic host oligomer which specifically binds and transports biologically important adenine, amino-acid, and catechol amine salts as well as simple amine salts. The carrier (**1**) is a linear octamer having the structure $[CH_2CH_2N(CONHPh)]_8$. This was prepared by ring-opening oligomerization of 1-(*N*-phenylcarbamoyl)aziridine,[6] and consists of three functionalized regions: (a) a binding site (>NCONH-) that can undergo hydrogen-bonding or dipolar interactions, (b) a recognition site (Ph) that can produce a hydrophobic environment and participate in discrimination processes, and (c) a flexible polyethyleneamine chain which leads to molecular flexibility, but also ensures that the binding sites remain connected. These structural features of the carrier (**1**) are quite different from those of the usual carriers such as crown ethers, cyclic peptides, and others.



(1)



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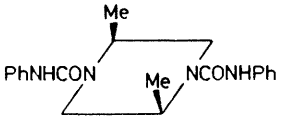

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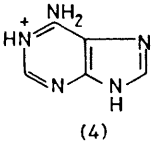

(4)

Recently we have demonstrated that (**1**) acts as a selective Cu^{2+} ion carrier; its copper complex acts as a carrier for various anionic substrates.[7] The hydrophilic metal ion could be encapsulated in the hydrophobic domain formed by carrier residues, and transported through a hydrophobic membrane. We now report the application of the carrier (**1**) to the transport of organic cationic salts.

The binding properties of the carrier (**1**) and, for comparison, dibenzo-18-crown-6 (**2**) for a variety of organic cationic substrates were studied by the liquid extraction method. An aqueous sulphuric acid solution (3 ml) of the organic substrate (0·01 M) and sodium perchlorate (0·5 M) was shaken at *ca.* 15 °C with a methylene chloride solution (3 ml) of the carrier (**1**) or dibenzo-18-crown-6 (**2**) (0·7 mol. equiv.). The concentrations of substrates remaining in the aqueous phase were determined by u.v. spectroscopy or gas chromatography. Extraction percentages of substrates from the aqueous to the organic phase are listed in the Table.

The carrier (**1**) exhibited some characteristic extraction properties which were quite different from those of the conventional crown ether (**2**). (a) It extracted salts of some aromatic amines (aniline, *p*-toluidine, *p*-anisidine, and *p*-chloroaniline), highly selectively compared with aliphatic amine salts (α- and β-phenethylamine, and cyclohexylamine). In contrast, the crown ether (**2**), which is known to be an effective host molecule[2] for organic ammonium cations, showed a stronger binding power for a variety of amine salts, and could not discriminate between salts of aromatic and aliphatic amines. (b) The amidinium cation derived from adenine was extracted by the carrier (**1**), whereas it seems to be an unfavourable guest for the crown ether (**2**).† (c) Compound (**1**) also showed binding properties towards tyrosine derivatives. Since phenylalanine ethyl ester was hardly extracted by (**1**), the phenol moiety in tyrosine ethyl ester seemed to be essential for its binding to (**1**). These extraction experiments clearly indicate that

TABLE. Extraction and transport of organic cation salts.

Substrate		Extraction (%)[a] (**1**)	(**2**)		Transport rate × 10^6/(mol/h)[b] (**1**)	(**2**)	(**3**)
$PhNH_3^+$	[A]	36	52	[C]	5·17	3·50	3·50
				[D]	2·83	6·83	0·76
p-$MeC_6H_4NH_3^+$	[A]	33	54	[C]	7·17	9·17	5·50
p-$MeOC_6H_4NH_3^+$	[A]	10	50	[C]	1·83	7·17	2·16
p-$ClC_6H_4NH_3^+$	[A]	10	53	[D]	3·63	14·21	0
$PhCHMeNH_3^+$	[A]	1	64	[C]	0	5·00	0
$PhCH_2CH_2NH_3^+$	[A]	3	65	[C]	0	1·67	0
Cyclohexyl-NH_3^+	[A]	2	64	[C]	0	3·83	0
(**4**)	[B]	18	2	[D]	0·90[c]	0·30[c]	0·40[c]
$PhCH_2CH(CO_2Et)NH_3^+$	[B]	1	49		[d]	[d]	[d]
p-$HOC_6H_4CH_2CH(CO_2Et)NH_3^+$	[B]	16	10	[D]	9·62	6·83	0·31
m,p-$(HO)_2C_6H_3CH_2CH_2NH_3^+$	[B]	11	7	[D]	1·00	0·96	0

[a] Extraction conditions: Organic phase; carrier (0·021 mmol.) in CH_2Cl_2 (3 ml); aqueous phase: [A] free amine (0·030 mmol.), $NaClO_4$ (1·50 mmol.) in 0·05 M H_2SO_4 (3ml); [B] free amine (0·030 mmol.), $NaClO_4$ (1·50 mmol.) in 0·005 M H_2SO_4 (3 ml). Negligible amounts of amine salts were extracted in the absence of carriers (**1**) or (**2**). [b] Transport conditions: aqueous phase I: free amine (0·4 mmol.), KSCN [C] or $LiClO_4$[D] (2·00 mmol.) in 0·05 M H_2SO_4 (4 ml); membrane: carrier (0·019 mmol.) in CH_2Cl_2 (8 ml); aqueous phase II; distilled water (10 ml). Transport rate was obtained from the rate of appearance of substrate in aqueous phase II: reproducibility, ± 10% or better. [c] The initial amount of this substrate in aqueous phase I was 0·2 mmol. The values given were normalized. [d] Under the conditions employed ([C] or [D]), leakage of phenylalanine ethyl ester was too large to enable the transport rate to be calculated with any degree of accuracy.

† Recently, promising host molecules for related substrates such as imidazolium and guanidinium cations have been reported,[8] but their application as transporting agents has not yet been reported.

the substance (**1**) binds organic substrates containing NH_2 and OH groups as well as the NH_3^+ group, in contrast crown ether (**2**) is well known to bind compounds having NH_3^+ and $-N^+\equiv N$ groups The oligomer (**1**) may well form complexes with organic substrates in a different manner from (**2**), (**1**) has a regular array of hydrogen-bonding sites (-CONH-) and hydrophobic moieties (Ph), resulting in a cavity able to accommodate aromatic substrates

These binding properties of carrier (**1**) enable it to exhibit important and unique transport phenomena The transport experiments were performed in a system consisting of a stirred methylene chloride membrane separating two aqueous phases I and II Aqueous phase I contained substrate (0 4 mmol) in aqueous 0 05 M sulphuric acid solution (**4** ml) Aqueous phase II consisted of distilled water (10 ml) The methylene chloride membrane (8 ml) containing carrier (0 019 mmol) bridged them, and was stirred magnetically Typical results are summarized in the Table

When carrier (**1**) was added to the membrane, aniline and its derivatives (*p*-toluidine, *p*-anisidine, and *p*-chloroaniline) were taken up and transported through the liquid membrane with high efficiencies For example, (**1**) transported the aniline salt in an amount equal to 31% of the total after 24 h ‡ under the conditions stated On the other hand, this carrier scarcely carried aliphatic amine salts (α- and β-phenethylamine and cyclohexylamine) In marked contrast, the crown ether (**2**) transported both aromatic and aliphatic amine salts The transport selectivities of both carriers examined almost parallel those observed in the extraction experiments

As expected the carrier (**1**) successfully transported biologically important substrates such as adenine tyramine, tyrosine, and dopamine derivatives Facilitated transport of adenosine, AMP, and ADP was also attempted using this carrier, but it failed Since their larger hydrophilic parts could not be encapsulated in this oligomer, they require a more elaborate carrier having a larger hydrophobic domain

The dimer (**3**) having the urea structure was examined for comparison This showed almost the same trends in transport properties to those of the octameric carrier (**1**), but its rates were largely suppressed As we pointed out previously,[1] more recurring >NCONHPh units are needed for better carriers

(*Received, 27th August* 1980, *Com* 932)

‡ The corresponding amount of counter anion (in this case SCN^-) was also transported, this was determined by use of Methylene Blue [9]

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