Highly Efficient Transport of Amino Acids through Liquid Membranes via Three-Component Supramolecules

Manfred T. Reetz,* Jürgen Huff, Joachim Rudolph, Karl Töllner, Alfred Deege, and Richard Goddard

Max-Planck-Institut für Kohlenforschung Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, FRG

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The transport of molecules across biomembranes constitutes a fundamentally important process in biological systems.[1] A case in point concerns the transport of amino acids and peptides, a process that has been studied in natural[1,2] and abiotic systems.[3] Lehn first reported the use of ammonium salts as carriers for the transport of amino acids and dipeptides through a bulk toluene membrane separating two aqueous phases.[4] Later other carriers were reported, including crown ethers, merocyanine dyes, cyclodextrins, and hydrophobic metal complexes.[5] A highly effective carrier system was described by Rebek, who employed a derivative of Kemp's acid which incorporates ionic, hydrophobic, and aromatic domains.[6]

We envisioned a different way to stabilize and to lipophilize the dipolar form of amino acids **1** necessary for transport through organic media. Accordingly, arylboronic acids **2** and donor molecules **3** such as crown ethers function as a cooperative binary carrier system in which the arylboronic acid undergoes novel hydrogen bonding with the carboxylate anion (cf. **4**).

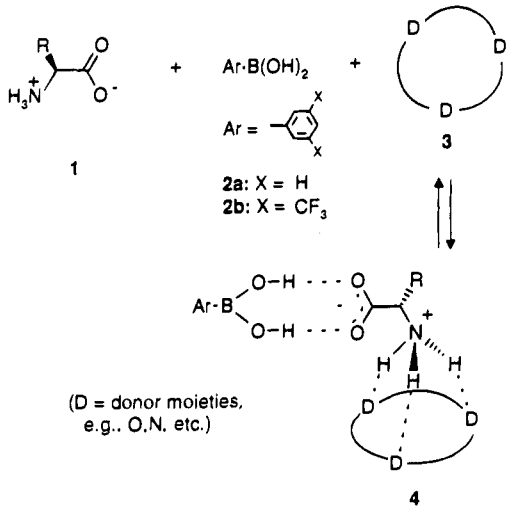

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Table 1. Transport of L-Phenylalanine through $HCCl_3$

carrier	rel transport rate	enhancement factor due to presence of arylboronic acid
–	1	
2a	2.6	
2b	13.1	
5a	1.1	
5a, 2a	2.4	2.1
5b	6.3	
5b, 2a	33	5.2
5c	170	
5c, 2a	720	4.2
5c, 2b	1270	7.4
9	1.9	
10a	33	
10b	352	
6	34	
6, 2a	360	10.6
6, 2b	1190	35
7	4.3	
7, 2a	31	7.2
7, 2b	630	150
8	201	
8, 2a	1026	5.1
8, 2b	912	4.5
TOMA	4.5	
TOMA, **2a**	15	3.3
TOMA, **2b**	14	3.1

Although there is ample precedence for ammonium salts RN^+H_3 binding to crown ethers,[3] we are not aware of structural data concerning hydrogen bonding between arylboronic acids and anions such as carboxylates. It is also important to note that the zwitterionic forms of amino acids bind only weakly to crown ethers.[3]

Using a "glass cylinder" apparatus as described by Izatt,[7] we measured the transport rate of phenylalanine (**1**, R = $PhCH_2$) through chloroform. Arylboronic acids **2a** and **2b** in combination with 12-crown-4 (**5a**), 15-crown-5 (**5b**), 18-crown-6 (**5c**), benzo-18-crown-6 (**6**), dibenzo-18-crown-6 (**7**), or 1,6-pyrido-18-crown-6 (**8**) as well as crown ether modified arylboronic acids[8] **9** and **10** served as carriers.

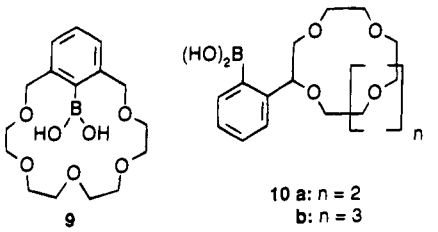

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Table 1 and Figure 1 show that the relative transport rates are dependent on the type of crown ether and the nature of the arylboronic acid, and that the two carrier components function synergistically. The proper combination, viz., **2b/5c**, constitutes one of the most efficient abiotic pH-neutral transport systems for amino acids currently known.[6] In addition to the bonding interactions described in **4**, the transport rates are also influenced by the distribution of the carrier molecules between the two phases. In general, hydrophobic crown ethers exhibit lower transport rates than more hydrophilic analogs. However, if a crown ether itself is very soluble in water, the complex with the amino acid should also be very soluble in water, thus leading

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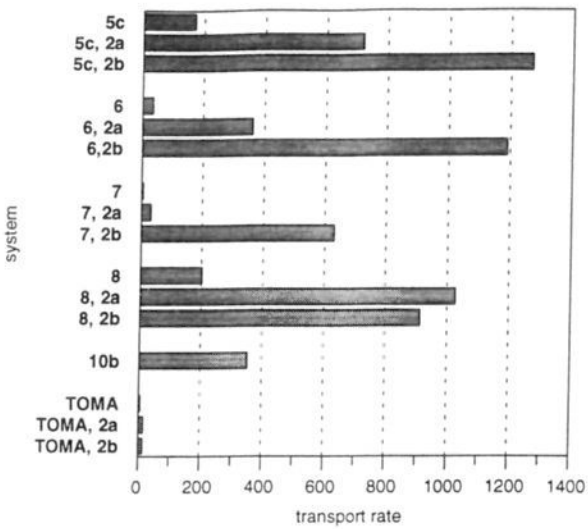


Figure 1. Transport of L-phenylalanine through $HCCl_3$.

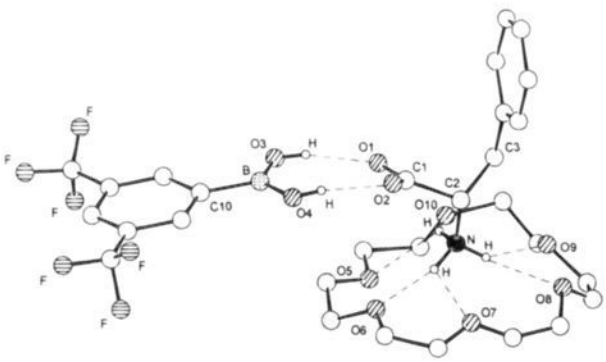
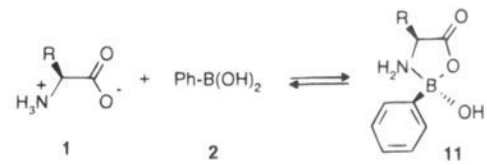


Figure 2. Molecular structure of the complex [**1**(R = $PhCH_2$)/**2b**/**5c**]. Selected interatomic distances (Å) and angles (deg): O1···O3 2.67-(2), O2···O4 2.64(2), N···O5 2.96(2), N···O6 2.86(3), N···O7 2.90-(4), N···O8 2.96(3), N···O9 3.00(3), N···O10 2.89(3), C1−O1 1.24(2), C1−O2 1.24(3), C1−C2 1.53(2), C2−N 1.51(2), C2−C3 1.51(2), B−O3 1.34(3), B−O4 1.35(3), B−C10 1.56(2), O3−B−O4 126(2). H atoms in calculated positions.

to low extractability. Such opposing effects also need to be considered in the optimal choice of the boronic acid. We therefore determined the partitition coefficients[9] $D = [C(\text{org})]/[C(H_2O)]$ for the distribution of the two boronic acids **2a**,**b** in $HCCl_3/H_2O$ at 25 °C. Whereas the D value for **2a** turned out to be 0.37, the bis(trifluoromethyl) derivative **2b** was found to be essentially only in the chloroform phase ($D = 35$).

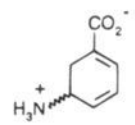
All observations are compatible with our model **4**. In order to gain further support, the X-ray structure analysis of crystals obtained by mixing **1** (R = $PhCH_2$), **2b**, and **5c** was carried out. The molecular structure shows the presence of a novel supramolecular species consisting of three molecules held together by hydrogen bonding, exactly as postulated in **4** (Figure 2). Thus, the synergistic role of the two carrier components is documented structurally.

Recently, Czarnik reported the use of phenylboronic acid/trioctylmethylammonium bromide (**2a**/TOMA) as a carrier of amino acids through a $ClCH_2CH_2Cl$ phase.[10] Accordingly, reversible borate complex formation, **11**, was postulated. We have tested this system and include the results in Table 1 and Figure 1. In all cases arylboronic acids/crown ethers are much more effective than **2a**/TOMA.



1 **2** **11**

Our results are not readily explained by the chelation model **11**. A final piece of evidence for the supramolecular model **4** and against the chelation model emerged upon studying the transport of the naturally occurring amino acid (±)-gabaculine (**12**). Since this amino acid cannot form a chelate due to geometric reasons, the chelation model (cf. **11**) would predict little or no transport, whereas a reasonable transport rate would be expected on the basis of model **4**. Upon using our carrier system **2a**/**5c**, a relative transport rate of 630 was observed (with respect to a "blank" experiment in the absence of a carrier). Here again the presence of the phenylboronic acid imparts a clear synergistic effect (18-fold enhancement). In contrast, the Czarnik carrier **2a**/TOMA[10] transports (±)-gabaculine much less efficiently, the relative transport rate being 17 (TOMA alone leads to a value of 9.5). Thus, in this case the two transport systems differ by a factor of 37.



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In summary, we have devised a new and highly efficient carrier system for the transport of amino acids from neutral aqueous solutions across organic media. It is based on the synergistic action of arylboronic acids/crown ethers, which bind to the carboxylate and ammonium moieties, respectively, the zwitterionic form of amino acids being lipophilized by formation of novel three-component supramolecular species. Studies directed toward enantioselective transport are underway.

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Supplementary Material Available: Full details of the transport experiments and complete X-ray data of **1** (R = $PhCH_2$)/**2b**/**5c**, including tables of fractional atomic coordinates, thermal parameters, and bond distances and angles (9 pages); tables of observed and calculated structure factors (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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