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Extraction and transport behaviour of aromatic amino acids by modified cyclodextrin

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The extraction efficiency together with the active transport assisted by the pH gradient through liquid membrane of some aromatic native and derivative amino acids by using heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin as extractant agent or carrier has been studied. The modified cyclodextrin extracted aromatic amino acids, native (L-tryptophane, L-phenylalanine, and L-tyrosine) and their methylester derivatives from aqueous phase into the organic phase. Moreover, the modified cyclodextrin exhibits the carrier abilities for amino acid methylesters through liquid membrane. In the case of transport processes involving liquid membranes, the physicochemical properties of the solvents play an important role in membrane stability. The results demonstrated that the inclusion properties of the investigated host are correlated with the structural properties of amino acids, and they also suggest further possibilities for optimal separation of amino acids derivatives.

Keywords: aromatic amino acid; modified cyclodextrin; solvent extraction; active membrane transport

Introduction

Cyclodextrins (CDs) are cyclic α (1–4)-linked oligosaccharides mainly consisting of 6, 7, or 8 glucose residues (α-, β-, and γ-CDs), respectively. The distribution of hydrophilic and hydrophobic groups of CDs confers them specific properties. Thus, the apolar cavity enables CDs to form inclusion complexes via non-covalent interactions with a large number of compounds in aqueous solution (*1–6*). The interactions involved in inclusion complexes of CDs (hydrogen bonding, van der Waals forces, release of conformational strain, charge-transfer, electrostatic and hydrophobic interactions) are known to play an important role in pharmaceutical science, biochemistry, immunochemistry, and also in separation chemistry (*7*). Moreover, the CDs inclusion complexation was considered a model mimicking the enzyme–substrate interactions (*8*).

A wide range of functional groups of known compounds were explored for improving the molecular properties of CDs and for opening new and exciting possibilities for applications (*9*, *10*). In the analytical field, CDs and their derivatives were extensively used in the separation of chemical and biochemical compounds by chromatographic or electrophoretic techniques (*11–14*). A more detailed study of charged cyclodextrin derivatives as chiral selectors for the enantioseparation in capillary electrophoresis was reported by Chankvetadze et al. (*15*). As compared with their use in some other applications, relatively few reports were published on the use of CDs in membrane separation. Ikeda et al. (*16*) reported the selective separation of a mixture of saccharides through liquid membrane using a cyclodextrin dimer as carrier. The system of liquid membrane was useful not only for separation of a mixture of saccharides, but also for clarifying the mechanism of action of saccharide transport through a biomembrane. In bulk liquid membranes, CDs were used for the determination of association constants of cyclodextrin–aromatic hydrocarbon complexes (*17*). The values of association constants for 1:1 complexes formed were in good agreement with those determined by other methods.

CDs were also used for selective extraction of lipophilic guest compounds from organic phase into aqueous phase (*18*, *19*).

The CDs and their derivatives form inclusion complexes with aromatic amino acids or their oligopeptides, it being well known that the aromatic amino acid residues are responsible for the interaction of proteins and peptides.

In our previously reported works, we investigated the formation of α-cyclodextrin complexes with alkylamines, amino acid and dipeptide in aqueous solutions by titration calorimetry (*20*, *21*). The complex formation of amino acid and dipeptide with α-cyclodextrin is mainly favoured by entropic contributions and characterised by hydrophobic interactions (*21*).

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Following our interest in the recognition and separation of biological compounds, we report herein a study on the solvent extraction from aqueous phase into chloroform phase and transport through liquid membrane of some native aromatic amino acids (L-tryptophane, L-phenylalanine and L-tyrosine) and their methylester derivatives, by using heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin as receptor.

Results and discussion

The yields value of extraction efficiency and transport through liquid membrane of native aromatic amino acid and methylesters obtained by using by heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin are presented in Figure 1.

Liquid–liquid extraction experiments performed using heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin as extractant show the following sequence of aromatic amino acid methylesters' extractability: L-TrpOMe (−1.16) > L-PheOMe (−1.45) > L-TyrOMe (−2.11) (*22*). The extractability yields vary between 17% (L-TyrOMe) and 50% (L-TrpOMe). The same sequence was observed in the case of native aromatic amino acids, but the yields of extractability are much lower ranging from 8% (L-Tyr) to 17% (L-Trp). Hence, there is a relationship between the extraction efficiency of amino acid methylesters carried out under experimental conditions and their hydrophobicity represented by log *P* (listed in parentheses), which is a quantitative indicator for the hydrophilic–lipophilic balance of corresponding amino acids (*22*). The modified cyclodextrin, heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin provided the highest affinity towards L-TrpOMe which bears the hydrophobic ester group and less towards L-Trp.

The experiments continued with the transport of native aromatic amino acids and methylesters through chloroform liquid membrane using heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin as carrier. In Figure 1, the transport efficiency of aromatic amino acid methylesters through chloroform liquid membrane with heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin is displayed. As in the extraction experiments, heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin exhibited a high transport ability towards L-tryptophane methylester. The sequence of decreasing transport yields of amino acids using heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin as carrier was the following: L-TrpOMe > L-PheOMe > L-TyrOMe, with the yields varying between 20 and 96% for L-TyrOMe and L-TrpOMe, respectively. The transport yields differ significantly for the same aromatic amino acids in native form. These values are between 9% L-Tyr and 12% for L-Trp, respectively.

The differences in the transport yields of aromatic amino acid native and methylesters with modified

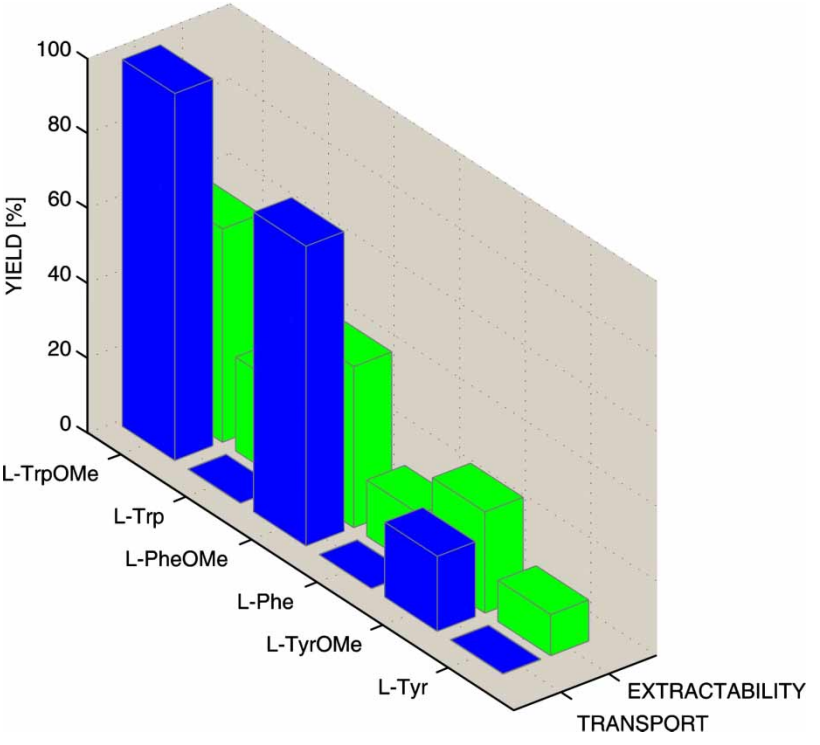

Figure 1. Experimental data of the extractability from aqueous phase into chloroform phase and transport through chloroform liquid membrane of some native aromatic amino acids native and methylesters by heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin at $T = 298.15$ K.

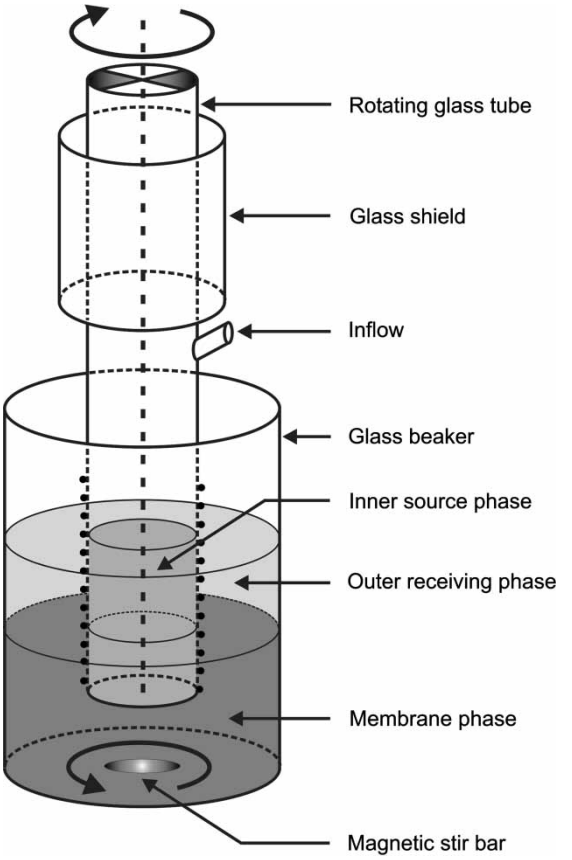

Figure 2. The device employed in amino acids transport through chloroform liquid membrane.

cyclodextrin used in the experiments may be attributed to the structural characteristics, especially to the hydrophobicity of the amino acids.

The results pointed out that the hydrophobicity of the amino acids is an important parameter, which has to be considered in both the extraction and transport experiments. Further studies on this topic are in progress.

Experimental

All of the native aromatic amino acids L-tryptophane (L-Trp), L-phenylalanine (L-Phe) and L-tyrosine (L-Tyr) and their derivatives L-tryptophane methylester hydrochloride (L-TrpOMe), L-phenylalanine methylester hydrochloride (L-PheOMe) and L-tyrosine methylester hydrochloride (L-TyrOMe) were purchased from Fluka (Poole, Dorset, UK) at the highest purity commercially available (Chart 1).

The heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin was obtained from Ciclolab (Budapest, Hungary) and used without further purification (Chart 1). Distilled and deionised water was used throughout the experiments. The organic solvent chloroform (dielectric constant $\varepsilon_r = 4.81$ (*23*)) was distilled before use.

The spectrophotometric measurements were carried out using JASCO V-530 UV–vis spectrophotometer. The pH was measured by a digital MV-870 pracitronic pH-meter with glass electrode and saturated calomel electrode.

Liquid–liquid extraction

Equal volumes (10 mL) of aqueous solution of amino acid native or methylester (5.0×10^{-4} M), at pH 5.5 and chloroform solution (10 mL) of heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin (10^{-3} M) were mixed and shaken for 30 min at $T = 298.15$ K. Chloroform and water were saturated with each other to prevent volume change during extraction. The pH of the aqueous solutions was adjusted by adding hydrochloric acid. The extraction measurements of amino acid methylesters from aqueous phase into chloroform were performed according to Pedersen's procedure (*24*). The extraction efficiency was calculated as $E\ [\%] = (A_0 - A)/(A_0) \times 100$, where A_0 and A are the absorbances of the aqueous phases before and after the extraction with cyclodextrin, respectively. Each experiment was performed five times.

Liquid membrane transport

The transport experiments were carried out using a device (Figure 2, (*25*)) consisting of two concentric tubes: the inner one contained the source phase, 5 mL of amino acid aqueous solution (5.0×10^{-4} M) which also acted as a stirrer, whereas the aqueous receiving phase 5 mL (pH 1.5), together with the membrane phase 35 mL of heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin (10^{-3} M) in chloroform, was introduced into the outer tube. The phases were stirred at 180 rpm for 24 h. Each experiment was repeated three times and reproducibility was ±10%. Similar transport experiments were performed for reference in the absence of a carrier.

Conclusions

The extraction abilities and the transport through chloroform liquid membrane of heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin upon some aromatic amino acid native and methylesters (L-tryptophane, L-phenylalanine, L-tyrosine and their methylester derivatives) were investigated. The experimental results suggested that aromatic amino acid native and methylesters are extracted from aqueous phase (pH 5.5) into organic phase and transported through chloroform liquid membrane by heptakis (2,3,6-tri-*O*-acetyl)-β-cyclodextrin by an active transport assisted by pH gradient. The extractability and the transport were proved to be essentially controlled by the structure of amino acid. The results suggested further

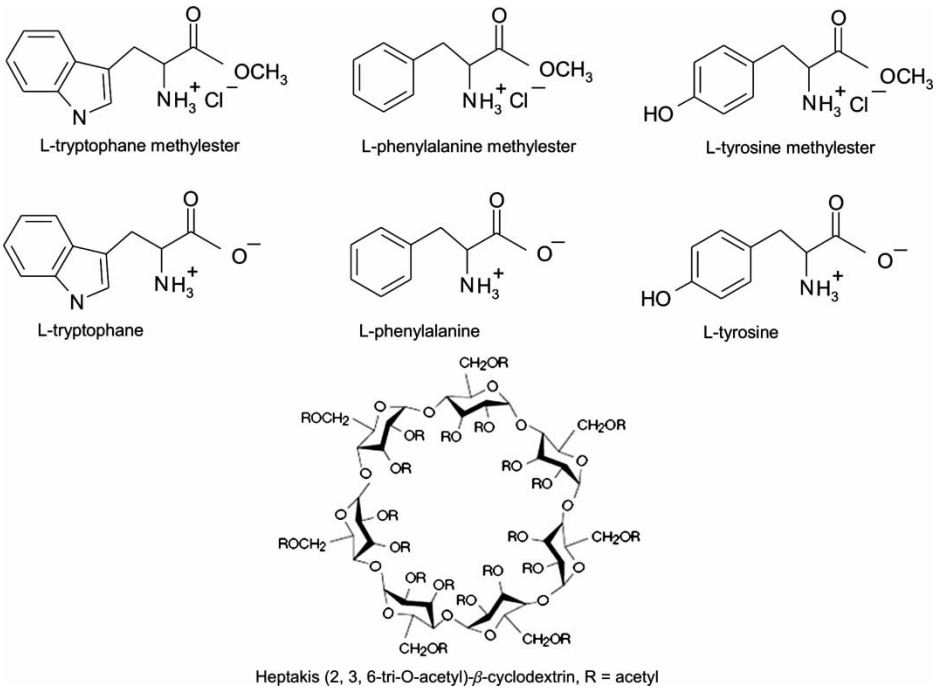

Chart 1. The chemical structure of compounds used throughout the experiments.

possibilities for optimal separation of native amino acids and derivatives and other biological species by means of derivative CDs.

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