Synopsis of Original Research Paper

Development of Carrier Molecules Capable of Transmembrane Permeation of Ascorbic Acid and Exploration of Its Mechanism

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We synthesized lipophilic cyclodextrins (CDs) having ionizable amino groups to investigate their abilities to form ion pair compounds with a biologically important reducing agent of ascorbic acid (vitamin C, AsA). Although per-methylation on the hydroxy groups of hydrophilic CD derivatives to make them lipophilic is unsuccessful, per-acetylation affords lipophilic CD derivatives having amino groups with excellent yields. The preliminary studies using hydrophilic amino-CDs revealed that the amino group introduced to the β-CD platform is able to form an ion pair with AsA. The binding constants of two monoamino-β-CDs, one of which has an amino group at the primary hydroxy side (1) and the other has it at the secondary hydroxy side (2), for AsA are 140 and 220 M−1, respectively, indicating the superiority of the secondary hydroxy side modification. β-CD itself may bind AsA, but the binding constant for the β-CD-AsA complex cannot be obtained spectroscopically. Guest binding studies with adenine nucleotides, which have similar negative charges support the ion pair formation between amino-CDs and AsA even in the highly polar aqueous solutions. Binding AsA by the amino-CDs is also supported by the retardation effect on the oxidative degradation of AsA. Ion pair formation between lipophilic CDs having amino groups and AsA is indicated by liquid-liquid extraction and liquid membrane transportation experiments. When the hydroxy groups of 1 and 2 are acetylated (Ac1 and Ac2, respectively) to make them lipophilic, they successfully extract AsA dissolved in aqueous phase into ethyl acetate phase where the lipophilic amino-CDs exist. The extraction abilities of Ac1 and Ac2 are greater than tetrabutylammnonium bromide, a well know ion pair agent, indicating that both amino group and CD framework are critical for the uptake of AsA from aqueous to organic phases. As the binding strength difference observed for the corresponding hydrophilic CDs, 1 and 2, the secondary hydroxy side modification is superior to the primary hydroxy side modification indicated by the greater extraction ability of Ac2. The results obtained in this study suggest that (1) lipophilic amino-CD derivatives may be useful in uptake of AsA across an organic layer, especially those which have amino groups at the secondary hydroxy side, and (2) the transmembrane permeation abilities of lipophilic CD derivatives for AsA may be estimated from simple binding studies in aqueous solutions using corresponding hydrophilic CD derivatives.