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Empirical, thermodynamic and quantum-chemical investigations of inclusion complexation between flavanones and (2-hydroxypropyl)-cyclodextrins

Benguo Liu [a], Wei Li [b], Tien An Nguyen [c], Jian Zhao [c,*]

[a] School of Food Science, Henan Institute of Science and Technology, Xinxiang 453003, PR China
[b] College of Biological Engineering, Hubei University of Technology, Wuhan 430068, PR China
[c] School of Chemical Engineering, The University of New South Wales, Sydney, NSW 2052, Australia

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ABSTRACT

The inclusion complexation of (2-hydroxypropyl)-cyclodextrins with flavanones was investigated by phase solubility measurements, as well as thermodynamic and quantum chemical methods. Inclusion complexes were formed between (2-hydroxypropyl)-α-cyclodextrin (HP-α-CD), (2-hydroxypropyl)-β-cyclodextrin (HP-β-CD), (2-hydroxypropyl)-γ-cyclodextrin (HP-γ-CD) and β-cyclodextrin (β-CD) and four flavanones (naringenin, naringin, hesperetin and dihydromyricetin) in aqueous solutions and their phase solubility was determined. For all the flavanones, the stability constants of their complexes formed with different CDs followed the rank order: HP-β-CD (MW 1540) > HP-β-CD (MW 1460) > HP-β-CD (MW 1380) > β-CD > HP-γ-CD > HP-α-CD. Experimental results and quantum chemical calculations showed that the ability of flavanones to form inclusion complex with (2-hydroxypropyl)-cyclodextrins was determined by both the steric effect and hydrophobicity of the flavanones. For flavanones that have similar molecular volumes, the hydrophobicity of the molecule was the main determining factor of its ability to form inclusion complexes with HP-β-CD, and the hydrophobicity parameter Log *P* is highly correlated with the stability constant of the complexes. Results of thermodynamic study demonstrated that hydrophobic interaction is the main driving force for the formation process of the flavanone–CD inclusion complexes. Quantum chemical analysis of the most active hydroxyl groups and HOMO (the highest occupied molecular orbital) showed that the B ring of the flavanones was most likely involved in hydrogen bonding with the side groups in the cavity of the CDs, through which the inclusion complex was stabilised.

1. Introduction

Flavonoids are a large and diverse group of polyphenolic compounds that can be divided into subgroups, including anthocyanidins, flavonols, flavones, flavanols, flavanones and isoflavones (Erlund, 2004). They are widely distributed in the leaves, flowers and fruits of plants as secondary metabolites (Kim, Kim, & Jung, 2008) and constitute a natural part of our diet. In the last two decades, the biological activities of flavonoids have attracted an enormous amount of study, which has shown that flavonoids possess a number of beneficial properties, including antioxidant, antimicrobial, anti-inflammatory and anticarcinogenic activities (Galati & O'Brien, 2004; Hertog, Feskens, & Kromhout, 1997). Epidemiological studies indicate that intakes of flavonoid-rich foods in sufficient quantity may improve heart health, reduce the risk of certain cancers and slow down the aging process (Erlund, 2004). Many flavonoids are the active principals of medicinal plants and exhibit pharmaceutical effects. As a result, there is a growing interest in applying flavonoids in food products to enhance their health functions, as well as in developing flavonoid-based nutraceutical and pharmaceutical products. However, flavonoids are poorly soluble in water, which severally restricts their application in these products.

Formation of supramolecular complexes with cyclodextrins could be one way to improve the water solubility of flavonoids. Cyclodextrins are cyclic oligosaccharides consisting of six (α-cyclodextrin), seven (β-cyclodextrin), eight (γ-cyclodextrin) or more glucopyranose units linked by α-(1,4) bonds and adopting a truncated cone structure with hydrophobic cavity (Del Valle, 2004). The nonpolarity of the interior cavity of cyclodextrins makes them ideal for solubilising nonpolar solutes, whereas the polarity of their exterior enables them and the guest to become soluble in water (Astray, Gonzalez-Barreiro, Mejuto, Rial-Otero, & Simal-Gándara, 2009; Del Valle, 2004). Hydroxylpropyl–cyclodextrin (HP–CD), a hydroxyalkyl derivative of cyclodextrin, is an alternative to α-, β- and γ-cyclodextrin, with improved water solubility. FDA has approved the application of HP-β-CD in food, agriculture and pharmaceutical products (Yuan, Jin, Xu, Zhuang, & Shen, 2008a).

* Corresponding author. Tel.: +61 2 9385 4304; fax: +61 2 9385 5966.
E-mail address: jian.zhao@unsw.edu.au (J. Zhao).

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There are some reports on the formation of supramolecular inclusion complexes between HP-β-CD and flavonoids such as baicalein and quercetin (Jullian, Moyano, Yanez, & Lea-Azar, 2007; Liu, Qiu, Gao, & Jin, 2006; Wen, Liu, Yuan, Ma, & Zhu, 2010). These studies, however, are empirical in nature and limited to the characterisation of the inclusion complexes formed between HP-β-CD and one or two individual flavonoids and their bioactivities. The influences of molecular properties of both the CD and flavonoids, such as the relative size of flavonoid molecules to the interior cavity of the CD molecules and hydrophobicity, on the formation of the supramolecules have not been reported. Consequently, the mechanism unpinning the complexation process between flavonoids and HP-CDs remains to be elucidated.

Here we report a systemic investigation of the inclusion complexation between five different HP–CDs and β-CD and four flavanones, namely naringenin, naringin, hesperetin, dihydromyricetin (Fig. 1), with different molecular sizes and substitution groups on ring B using empirical, as well as thermodynamic and quantum-chemical methods. The objective of the study was to obtain a better understanding of the complexation process, including the thermodynamic forces driving the formation of complexes between HP-CDs and flavanones, as well as the quantum chemical parameters controlling the stability of the formed supramolecules.

2. Materials and methods

2.1. Materials and chemicals

β-cyclodextrin (MW1134.98), (2-hydroxypropyl)-α-cyclodextrin (average MW 1180), (2-hydroxypropyl)-β-cyclodextrins (average MW 1380, 1460 and 1540) and (2-hydroxypropyl)-γ-cyclodextrin (average MW 1580) were obtained from Sigma (St. Louis, MO). Naringenin, naringin and hesperetin were purchased from Shaanxi Huike Botanical Development Co., Ltd., (Xi'an, China). Dihydromyricetin was extracted and purified from *Ampelopsis grossedentata* leaves in our laboratory following the procedure published previously (Liu, Du, Zeng, Chen, & Niu, 2009). The purity of all the flavanones was checked by high performance liquid chromatography (HPLC) to be greater than 99%. HPLC grade methanol was purchased from Burdick & Jackson (Morristown, NJ). Ultrapure water from a Millipore Milli-Q laboratory water system (Billerica, MA) was used throughout the experiments. All other chemicals were of analytical grade unless stated otherwise.

2.2. Phase solubility studies

Phase solubility study of inclusion complexation with cyclodextrin is the quantitative determination of the solubility of a guest substance at various concentrations of cyclodextrin, which yields a solubility diagram of the dissolved guest substance against different concentrations of cyclodextrin. Phase solubility studies were carried out according to the method described by Higuchi and Connors (Higuchi & Connors, 1965). An excess amount of each flavanone (about 80 mg) was added to a series of test tubes each containing 5 ml cyclodextrin solutions at concentrations ranging from 0 to 10 mM, and the mixture was vortexed for 2 min to disperse the flavanone. The test tubes were shaken in a rotary water bath (150 rpm) set at 20–40 °C for 72 h. After that, the mixture was filtered through a 0.45 μm nylon filter and appropriately diluted. The concentration of the dissolved flavanone in the solution was determined by HPLC, and the cyclodextrin present did not interfere with the HPLC measurements. The apparent stability

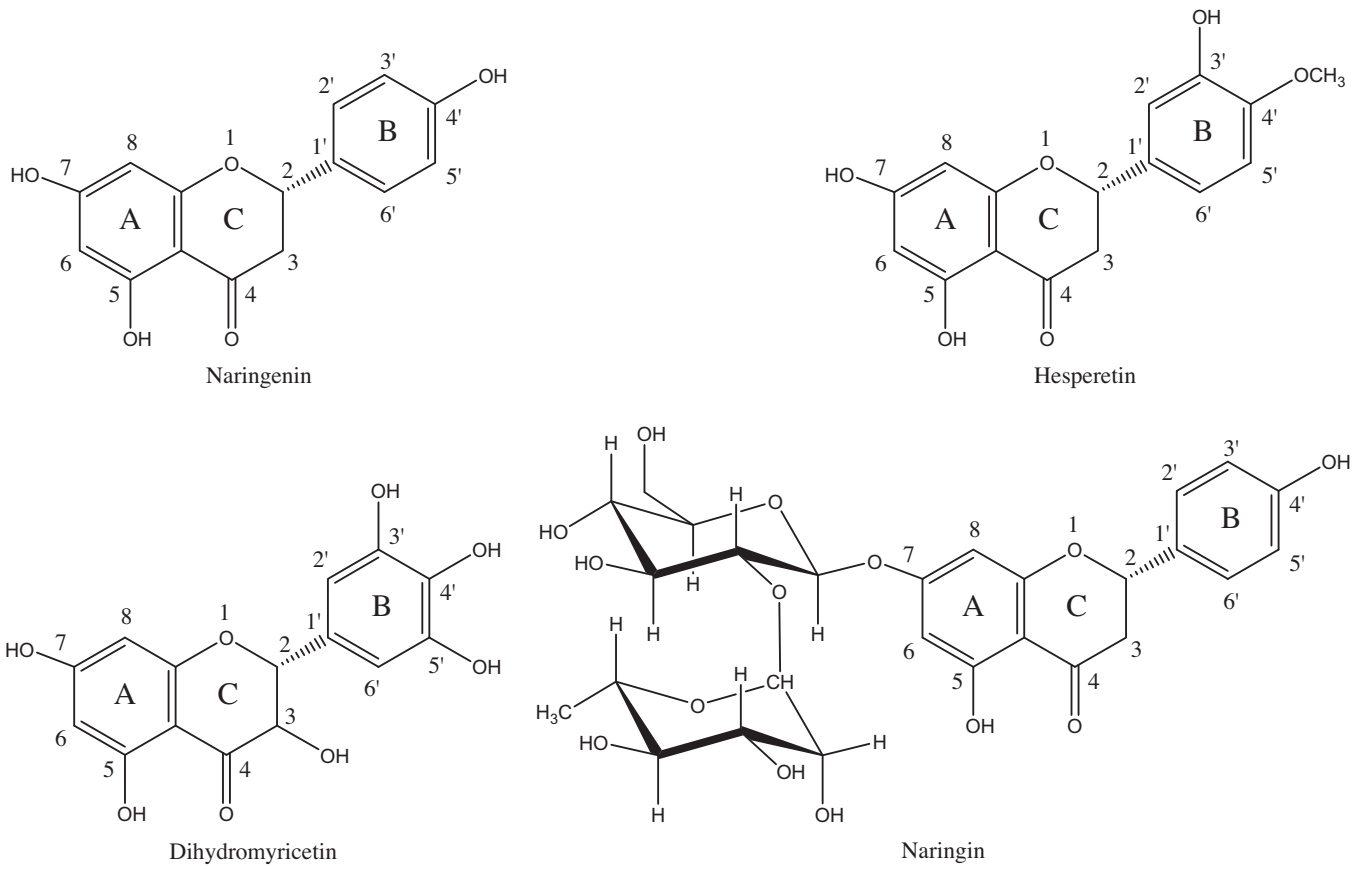

Fig. 1. Chemical structures of naringenin, naringin, dihydromyricetin and hesperetin.