Prediction and Verification of the Solubility of Flavonoids in Ionic Liquids - A Priori Design of the Green Routes for Efficient Enzymatic Synthesis of Lipophilic Flavonoid Derivatives

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The effectiveness and absorption of many drugs are largely controled by their low solubility, therefore, modification of drugs and producing so-called prodrug is a useful method to obtain improved properities. Flavonoids are limited in function by their low solubility and unavailability. Lipophilisation of flavonoids into fatty acid esters has been proven to an efficient way to expand their functionality and applications in human nutrition. However, the attempts to establish an efficient enzymatic esterification of flavonoids with fatty acids in conventional solvents have been seriously upset by their low solubility. As neoteric green media, ionic liquids offer enormous opportunities to design efficient reaction system by judiciously selecting cation, substituents and anions. A model-assistant prescreening and evaluation on the contribution of the moiety of ionic liquids on the properties constitutes the crucial step for tailoring a desired structure from accessible ionic liquids numbered in trillions. In this work, rutin and esculin were selected as representative flavonoids to examine their solubility in ionic liquids. 52 cations and 33 anions with over 1700 combinations, including imidazolium, pyridinium, tetraphosphonium and tetraammonium etc, were employed for COSMO-RS (Conductor-like Screening Model for Real Solvents) calculation, based on molecular simulation by Turbomole. The solubilities of fatty acids in these ionic liquids were also predicted following similar procedure. The solvation properties between solutes and ILs were characterized by comparison of their respective polarity interaction, H-bonding interaction and van der vaals interaction. The resulted showed that the solubilities of flavonoids in ILs are strongly anion-dependent, while the solubility of long chain fatty acids depends largely on the nature of cation part. In the same type of ILs, the solubilities of fatty acids increase with the decrease of chain length of fatty acids and the increase of unsaturation degree of fatty acids. Investigation of the intrinsic reasons revealed that strong H-bonding interaction and misfit interaction are important for a higher solubility of flavonoids, however, van der vaals interaction plays more crucial role in promotion of fatty acid dissolving. Accordingly, based on solubility difference of flavonoids, ILs can be categorized into three groups.

To validate the predictions, the solubilities of flavonoids in 12 types of ILs paired different anions were measured using HPLC-ELSD analysis. The results indicated that the measured data agree well with the predicted results, essentially reflecting the practical capacity of ILs to dissolve flavonoids. This work demonstrated that COSMO-RS-assistant prescreening of IL structures could provide fundamental knowledges and deep understanding of structure-property relationship, which is of paramount importance for designing an efficient reaction system.