INCLUSION COMPLEXES OF FLAVONOLS WITH β- AND γ-CYCLODEXTRINS: A MOLECULAR DOCKING STUDY

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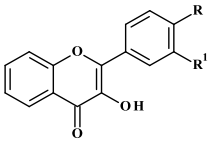
Cyclodextrins (CDs) have widely been used as food products, textiles, and pharmaceutics due to their ability to incorporate or adsorb the guest molecules into their central hydrophobic cavity. In recent years, CDs have also attracted growing interest as drug-delivery carriers because of their good biocompatibility, low toxicity, and easy functionalization. Moreover, encapsulation of aromatic guest molecules into CDs increases their solubility in water, expanding their scope and applications. Commonly used CDs contain six-to-eight glucopyranose units, classified as α-, β- and γ-CDs, respectively. Molecular docking is a promising tool for rapid screening of favorable 3D structures formed between a CD host and a guest molecule. However, a crucial limitation of commonly used molecular docking approaches is that, while allowing extensive sampling of guest conformations, they keep a rigid structure of a CD macrocycle.

Here we utilize molecular docking to study the structure and energetics of inclusion complexes of some flavonol derivatives (Table 1) with α-, β- and γ-cyclodextrins using AutoDock Vina 1.1.2 tools. We found that all studied flavonols were not able to insert into a small cavity of α-CD host molecule. In contrast, they all formed stable complexes with the larger size β- and γ-CDs. The binding affinity towards β- and γ-CDs depends on the nature of peripheral substituents R and R^1 located in the 4`-aryl ring of the flavonols, as well as on the size of the CD macrocycle, as summarized in (Table 1).

Table 1. Studied flavonol derivatives and their molecular docking binding affinity (kcal/mol) towards β- and γ-CD host molecules

guest molecules	R	R^1	β-CD		γ-CD	
			rigid	flexible	rigid	flexible
	H	H	-6.1	-6.3	-5.9	-8.5
	OCH_3	H	-6.1	-6.3	-5.9	-8.6
	OH	H	-6.0	-6.2	-5.8	-8.7
	NO_2	H	-6.2	-6.8	-6	-9.2
	$N(CH_3)_2$	H	-6.1	-6.5	-6.1	-8.6
	$COOCH_3$	H	-6.1	-6.6	-6	-9.1
	COOH	H	-6.1	-6.6	-5.9	-9.1
	CN	H	-6.4	-6.7	-6.2	-9.0
	F	H	-6.1	-6.3	-6.0	-8.6
	Cl	H	-6.1	-6.4	-6.0	-8.6
	Br	H	-6.1	-6.4	-6.0	-8.6
	I	H	-6.1	-6.4	-6.0	-8.5
	OBn	H	-7.1	-7.6	-6.8	-9.5
	OBn	OBn	-6.4	-6.7	-6.6	-9.6

We first utilized the rigid CD model and found that the binding affinity varies in a range from -6.0 up to -7.1 kcal/mol. Next, we developed the flexible docking model allowing torsion sampling of the primary and secondary hydroxyl groups of the CD macrocycles. The use of the flexible CD models significantly improves the interaction between the guest flavonols and the host CD molecules, so that the binding affinity increases additionally up to -3.2 kcal/mol (Table 1). These findings open up a promising opportunity for a better understanding of guest-CD complexes at the molecular level.