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Luteolin organic solvent interactions. A molecular dynamics simulation analysis

Khadidja Smail [a], Noureddine Tchouar [b,c], Mohammed Barj [d], Bogdan Marekha [d], A. Idrissi [d,*]

[a] Département de Biotechnologie, Faculté SNV, Université des Sciences et de la Technologie d'Oran-Mohamed Boudiaf (USTO-MB), BP 1505 El M'naouer, Oran 31000, Algeria
[b] Laboratoire de Modélisation et Optimisation des Systèmes Industriels (LAMOSI), Université des Sciences et de la Technologie d'Oran- Mohamed Boudiaf (USTO-MB), BP 1505 El M'naouer, Oran 31000, Algeria
[c] Département de Chimie Physique, Faculté de Chimie, USTO-MB, BP 1505, Oran 31000, Algeria
[d] LASIR UMR 8516, Université Lille 1 Sciences et Technologies, UFR de Chimie Bât C8, Villeneuve d'Ascq59650,France

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ABSTRACT

Molecular dynamics (MD) simulations have been performed on Luteolin (Lut) dissolved in various solvents (methanol, 1-propanol, 2-propanol, 1-butanol, dimethylsulfoxide, acetone and hexane) with the purpose to characterize the local structure around the hydroxyl (OH)[1] and carbonyl (C═O) moieties and to correlate the findings with the experimental vibrational spectroscopy and NMR results. The local structure is analyzed through the calculation of the radial distribution functions (RDF), the nearest neighbor radial and orientation distribution functions as well as the distribution of the dihedral angle involving the C═O and the adjacent (OH)[1] atoms. Our results show that the C═O moiety is interacting in a similar way with the protic solvents while the intra molecular hydrogen bond between this moiety and the (OH)[1] hydroxyl group is weakened in favor of the intermolecular hydrogen bond between the (OH)[1] and the protic and aprotic solvents.

1. Introduction

Flavonoids are one of the most studied classes of phenolic molecules that exhibit biological activity and photochemical reactivity. Indeed, they are involved in anti-inflammatory effect through the inhibition of the corresponding enzyme and protein activity and they have an anti-oxidant activity through the scavenging of the reactive oxygen species, the chelation of transition metals and they are cancer chemo-protective agents by combining the anti-oxidant and anti-inflammatory properties and by reducing the alteration of DNA. Detailed information on these effects can be found in the following references [1–6]. This biological activity is the basis of their medical relevance. There is a convergence in the literature that the structural properties that are related to this biological activity are the presence of the OH groups at various positions, the double bonds between certain carbon atoms of the rings that make the electron conjugation effective and, finally, the presence of the carbonyl group is also mentioned as associated with these biological actions. Indeed, it has been clearly proved that the gamma-pyrobenzene ring called the B-ring (see Fig. 1) is the most important site for H-transfer and consequently for the anti oxidant capacity [7–9]. This is particularly true when the B-ring is a catechol moiety as in Luteolin [10]. The torsion angle of ring B with the rest of the molecule is correlated with the scavenging activity, due to the increased conjugation offered by the planarity. The anti-inflammatory activity was associated with the presence of the hydroxyl in the benzene ring called the A ring [11].

In addition to the presence of the above mentioned structural elements of the flavonoids, their biological activity is strongly affected by the environment (polar or non-polar solvent, cellular environment…) [5,12–16]. The study of solvation of flavonoids in molecular solvents is an important step to understand their interactions with large biological systems such as proteins, nucleic acids or membranes [10,16–18]. Indeed, a previous work pointed to the modulation of the antioxidant activity of flavonoids by non-covalent interactions (intra- and inter-molecular hydrogen bond) and it was outlined that the anti-oxidant behavior of the flavonoids cannot be fully rationalized unless the interactions with the surrounding medium are carefully considered. Furthermore, in another work, it has been shown that there is a correlation between the different patterns of the local structure around the OH moieties of quercetin and its solubility in various solvent such as chloroform, water, acetone and ter-butanol [19].

The presence of the carbonyl group in the gamma-pyrobenzene ring close to an OH group is associated with the photochemical properties of flavonoids. One of the important issues in the study of the photochemistry of flavonoids is to rationalize to what extent the nature of the solvent determines their photochemistry [20]. Indeed, it has been shown that flavonoids can form electronically excited states capable of undergoing rapid isomerization to a tautomeric form which is influenced by solvent and temperature. These tautomeric forms can be involved in

* Corresponding author.
E-mail address: nacer.idrissi@univ-lille1.fr (A. Idrissi).

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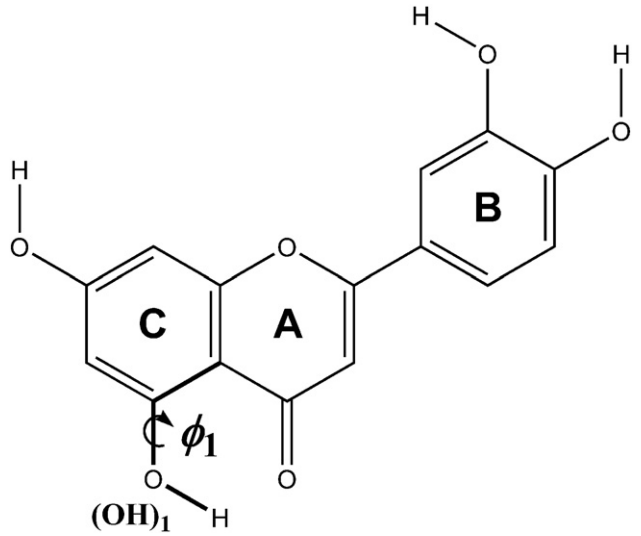

Fig. 1. Chemical structure of luteolin (5,7,3′,4′-tetrahydroxyflavone). The intra molecular dihedral angle ϕ_1.

rapid excited state intra-molecular proton transfer (ESIPT). This property has been proposed to be important in the mode of action of flavonoids in many oxidative–reductive enzyme systems. The dynamics of the excited state of a flavonoid is controlled by the nature of its interactions with the solvent molecules in the fundamental state. Indeed, experimental results indicate that the slow observed ESIPT of 3-hydroxyflavone (3HF) solvated in acetonitrile is mediated by solute–solvent interaction *via* a hydrogen bond with the hydroxyl group of the 3HF [21]. Both experimental[20–22] and computational studies[18,23–25] have highlighted the key role of the intra-molecular hydrogen bond between the hydroxyl OH and the C═O carbonyl moieties in determining the ESIPT reaction.

In our recent work[25], we have studied Luteolin (Lut) (see Fig. 1 for the chemical structure and atom numbering) dissolved in methanol, propanol, butanol and DMSO solvents. The main result we obtained is that the position of the C═O vibration mode was not affected by the nature of the solvent. This result seems to be specific for Lut since in the case of the 3HF, the C═O vibration mode is strongly dependent on the nature of the solvent. The C═O vibration mode of Lut is influenced by both the intra and inter molecular hydrogen bond interactions. The former involves the C═O and the closest OH moiety and the later involves its interaction with the solvent. It should be mentioned that the intra molecular interactions are also indirectly affected by the inter molecular interactions between the $(OH)^1$ moiety and the solvents. Unfortunately, using Raman spectroscopy, it was not possible to extract the information on the solvation of the OH groups in general and specifically on the $(OH)^1$ that is close to the C═O group. Indeed, because of the low solubility of Lut and the overlap between the spectral contribution of the $(OH)^1$ and that of the protic solvents, it was not possible to quantify the change in the position of the OH vibration mode of Lut [25]. However, in previous works, [26,27] the information on the solvation state of the $(OH)^1$ moiety of Lut was quantified through the ^1H proton NMR shielding and particularly by using the temperature coefficient, $(\Delta\delta / \Delta T)$ that measures the effect of increasing the temperature, T, on the chemical shift, δ. The values of this coefficient for the $(OH)^1$ hydroxyl group close to the C═O moiety were −2.3, −1.8 and 0.5 ppb/K, for Lut dissolved in acetone-d_6, DMSO-d_6 and methanol-d_3, respectively. This means that, by increasing the temperature, the intra- and inter-molecular hydrogen bonding interactions involving this $(OH)^1$ moiety are strong because of the small values of the $(\Delta\delta / \Delta T)$ coefficient and that they are broken more easily in acetone-d_6 than in DMSO-d_6 and in methanol-d_3. However, in both cited studies it was not possible to assess the contribution of the intra- and inter-molecular HB interactions to the observed $(\Delta\delta / \Delta T)$ coefficient variations. As a consequence, in order to disentangle between these interactions, we carried out molecular dynamics (MD) simulations. The connection between the MD simulations and the results obtained by vibrational spectroscopy experiment (or any other experiment probing the local microenvironment such as NMR, UV…) is based on the hypothesis that the nearest neighboring molecules are considered to exert a stronger influence on each other than on any of the other molecules. One then can expect that the behavior of the frequency position associated with a particular mode of a probe molecule (Lut in our case) is mainly determined by the nearest neighboring molecule distribution (local structure). In characterizing the local structure, the radial distribution function (rdf) between the C═O and $(OH)^1$ moieties and the solvent can provide useful information. This function represents the probability of finding solvent molecules at a distance r from a specific solute atom. We may thus compare the solvation of the C═O and OH moieties of Lut in various solvents. Furthermore, we showed in our recent works that more insight in the local structure is gained when the rdf analysis is complemented by the statistical analysis of the nearest neighbor radial distribution functions (nnrdf) of the solvent molecules located around the solute atoms [28–30]. The main idea then is to evaluate smoothed distribution functions over a physically small volume. Thus we calculated from our MD simulations, the nnrdf of the first nearest neighbor atoms X of the solvent molecules around atoms of the C═O and O–H groups of Lut molecule. In this approach, the atoms of the solvent that are present in the solvation shell of the C═O and O–H groups of Lut molecule are sorted by distance into the first neighbors; second neighbors *etc*. Separate nearest neighbor radial distribution functions, $p_{i-j}(r, n)$ may be defined for each set of nearest neighbor atoms j (indicated by n), and at a distance r from the central atom i. It is obvious to mention that an average is done over all choices of central atom and that the corresponding rdf $g_{i-j}(r)$ is equal to the sum over n of the $p_{i-j}(r, n)$. These functions do not contain bulk contribution and thus contain more information than the corresponding $g_{i-j}(r)$. Based on these nearest neighbor distributions, we can estimate the average radial distance and the corresponding fluctuations using the following equations:

$$\langle r_{i-j}(n)\rangle = \int_0^\infty dr' r' p_{j-j}(r', n) \tag{1}$$

$$\Delta r_{i-j} = \left(\left\langle r_{i-j}^2\right\rangle - \langle r_{i-j}\rangle^2\right)^{\frac{1}{2}}. \tag{2}$$

A short average distance indicates the strong interactions (hydrogen bond) and the values of the corresponding fluctuation give information on how diffuse/rigid is the position of the nearest neighbor atom. Also, it is possible to use the same approach to get information on the orientation between the reference $(OH)^1$ moiety and the OH, C═O, S═O bonds of the nearest neighbor solvent molecules.

The paper is organized as follows: Section 2 describes the studied systems, and Section 3 describes the MD simulation as well as the potential model used in our simulations. Section 4 describes the main findings and, finally, concluding remarks are given.

2. Luteolin and solvents

The studied flavonoid designated as Luteolin (5,7-dihydroxy-2-(3,4-dihydroxyphenyl)-chromen-4-one, Lut), was chosen as a prototype in this study because it possesses both carbonyl and hydroxyl groups. This flavonoid is ubiquitous in plants and has a beneficial impact on human health (anti-inflammatory and anti-oxidant activity, decrease of the risk of cardiovascular diseases, cancer *etc.*) as reported in the literature [2]. The structure of Lut is given in Fig. 1.

Four protic and polar solvents methanol, 1-propanol, 2-propanol, and 1-butanol referenced here after as MeOH, 1-PrOH, 2-PrOH and