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Curcumin and its derivative optical study

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Abstract

Our research focuses on the distinct chemistry of curcumin to explain its disparate behaviour in various media. The structural structure of curcumin determines whether it behaves as an antioxidant or a pro-oxidant. Keto and enol are the two tautomeric derivatives of curcumin. Curcumin has antioxidant effects in its keto form. Degradation is possible with the enol form. Therefore, it is crucial to keep curcumin in keto form. While curcumin degrades in non-polar and basic media, it survives in keto form in polar and acidic environments. The mechanisms of curcumin degradation in various media are explored. In basic conditions, the hydroxyl group is attacked nucleophilically, while in non-polar situations, the free radical process is at work. Degradation under basic conditions leads to complete breaking of the molecule while under non-polar conditions; it proceeds via peroxide intermediate formation, clarifying the pro-oxidant effect of curcumin. In either of the cases, vanillin is the degradation product besides other degradation products. It is well known that curcumin can exist in at least two tautomeric forms; ketone and enol. With structural formula (1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E)) the curcumin structure contains a variety of functional groups including the β-diketo group, carbon–carbon double bonds and phenyl rings containing varying amounts of hydroxyl and methoxy substituents. Curcumin and its derivatives have similar structures with different functional groups, and □-electrons length extension two derivative were synthesized. The chemical structure of these molecules was investigated and characterized by UV–Vis, ^{1}H NMR, and IR spectroscopies. The obtained UV–Vis spectra indicated that the strong electron-donating groups on aryl rings of these molecules enhance the intensity of λmax and shift it toward the lower absorption energy. The conformation and structure of these molecules were investigated in solution and on the TiO_2 anatase surfaces. Accordingly, three conformations could be existed in the solution including Cis-Enol, Keto, and twisted (in nanoparticles). Also, these molecules anchor on the TiO_2 surface in a monodentate and bidentate chelating mode, depending on the TiO_2 surface sites.

Key words : curcumin, □-electrons extension, TiO_2.

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Introduction

Curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a natural dye, obtained from the rhizome of the Curcuma longa (turmeric). Curcumin is responsible for turmeric characteristic yellow color. It is widely used in foods as a food colorant and additive. Considering the potential importance of curcumin, structural aspects of it such as curcumin isomers in solutions and on surfaces of semiconductors are a matter of interest (Benassi, *et al*., 2008). Curcumin has two phenolic rings connected by an α,β-unsaturated-β-diketone, which the β-diketone structure undergoes Keto-Enol tautomerism in solutions (Patra & Barakat, 2011). In the crystal phase, it, however, exists preferably in enol configuration (Markov, 1984; Kawano, *et al*., 2013). α,β-unsaturated-β-diketone can exist in nine different isomers due to Keto-Enol tautomerism and cis–trans isomerism (Priyadarsini, 2013). The reported UV–Vis, fluorescence, and NMR spectra of curcumin indicated that three isomers of curcumin could exist in a solution (Payton, *et al*., 2007; Khopde, *et al*., 2000). Two of them could be assigned to the Keto and Enol isomers, and the structure of the last one is unknown. The isomer structure of curcumin in solution is an important subject in the medical application of curcumin. Each curcumin isomer has a specific symmetry, which influences the polarity and solubility of it. Also, for enhancing the solubility of curcumin by changing chemical structure, one needs to know all possible isomers of curcumin in solution.

In this study, the structure and conformation of curcumin and two curcumin derivative were studied in the solution and on the TiO_2 nanoparticles surface. The effects of functionalization of curcumin rings and extension of π conjugation length were investigated. Curcumin anchores on metal oxides surfaces such as TiO2 by –dikitone part. The anchoring mode and conformation of adsorbed curcumin properties such as its UV-Vis absorption (Adineh, *et al*., 2016). Appropriate interaction between curcumin and TiO_2 nanoparticles improves the device performance. Although, anchoring of the –dikitone to the anatase phase of TiO_2 was theoretically investigated (Mc Namara *et al*., 2008).

Experimental

Materials and methods

Acetylacetone, Benzaldehyde, p-Dimethylaminobenzaldehyde, p-Dimetylamin ocinnamaldehyde were purchased from Sigma-Aldrich and used without further purification. Ethyl acetate, Boron trioxide, Triethyl borate, buthylamine were purchased from Merck and used without further purification. Titanium chloride ($TiCl_4$) was purchased from Sigma-Aldrich. FTO glasses, TiO_2 scattering paste, and standard I^-/I_3^- electrolyte were purchased from Sharif Solar. All solvents were purchased from Merck. Solvents such as ethanol, acetonitrile, and DCM were dried over appropriate drying agents. All other solvents were used without further purification. NMR spectroscopy (Bruker Avance II 300 MHz), UV–Vis (SPECORD S-600 and Shimsdzu-2100), IR Spectroscopy Bomem-MB 102, Dynamic Light Scattering (SZ-100z Dynamic Light Scattering and Zeta potential analyzer, company: Horiba Jobin Jyovin), Solar Simulator (PROVA 8300 with an intensity of 1000 W/m^2), and IV Tracer (Sharif Solar IV-25) were used with the indicated instruments and conditions.

Curcumin synthesis

Two derivative of curcumin were synthesized base on Pabon pathways that modified by Thomas Erker (Pabon, 1964; Handler, *et al*., 2007). In a three-necked flask, acetylacetone (5 mmol, 0.51 ml) and boron oxide (3.5 mmol, 0.244 g) were solved in 5 ml absolute ethyl acetate and heated to 75 °C for 1 h. The corresponding benzaldehyde (10 mmol) and tributyl borate (10 mmol, 2.4 ml) were mixed with ethyl acetate, stirred for 45 min and then added to the solution. The mixture was heated to 100°C for 1h. Then n-butylamine was solved in 5 ml ethyl acetate, and 3.85 ml of this solution were added drop-by-drop throughout 90 min. The reaction was stirred for 20 h at 85°C and then cooled to 60°C. Then 5 ml of an HCl solution (10%) were heated to 50 °C, added, and the mixture was stirred at 60°C for 1h. The solution was extracted three times with ethyl acetate, the organic layers were dried over Na_2SO_4, and the solvent reduced to 7–8 ml. Two and a half milliliters of ethanol were added, the solution was cooled overnight, then the precipitate was filtered off and recrystallized to obtain the purified desired product.

Synthesis of 1,7-diphenyl-1,6-heptadiene-3,5-dione (A1)

0.5 g of acetylacetone and 0.24 g boric acid were dissolved in 10 ml ethyl acetate, and the solution was stirred for 30 min at 40°C. To the resulting solution, 1.06 g benzaldehyde and 2.4 ml triethyl borate were added and left for 30 min. To this mixture, a solution of 4 drops of buthylamine in 4ml ethyl acetate was added dropwise in 1 min interval and refluxed for 24 h. Then 5 ml HCl 10% added to the reaction vessel and let it stay at 60 °C for 1h more. The mixture was transferred to the separatory funnel, and the ethyl acetate phase was washed with distilled water, and the organic phase was dried by $MgSO_4$. The resulting solution was precipitated by the addition of methanol, and the precipitate was filtered and washed by methanol, yield 20%. ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 7.6(m, 6H), 7.4(m,6H), 6.7(d, 2H), 5.8 (s,1H), IR: 3082, 3053 and 1620 cm^{-1}.

Synthesis of 1,7-bis(4-dimethylaminophenyl)-1,6-heptadi-ene-3,5-dione (A3)

The synthetic procedure for A3 was the same as A1, but 1.5 g of p-dimethylaminobenzaldehyde was used instead of benzaldehyde. A3: yield 30%. ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 7.6 (d,2H), 7.5 (d,4H), 6.7 (d,4H), 6.5 (d,2H), 5.7 (s,1H), 3.0 (s.12H), IR: 3031, 2897, 2815, 1586, 1361 cm^{-1}.

Result and discussion

Curcumin derivatives were synthesized from the reaction of acetylacetone with related aldehydes in the presence of tri-alkyl borate and butylamine as catalysts (Pabon, 1964; Handler, *et al*., 2007). Structures of the synthesized molecules and the extracted curcumin from Turmeric are displayed in Fig.-1. These molecules were characterized by ^{1}HNMR and FTIR spectroscopies. The obtained spectra from the extracted curcumin are matched with the reported data in the literature (Peng, *et al*., 2014). In fact, curcumin is the major component of three curcuminoids, which exist in the rhizome of the perennial herb Curcuma longa (Aggarwal, *et al*., 2006). Demethoxycurcumin (DMC) is another one in which one -OMe functionality at the outer phenol rings are removed. The observed singlet peak at δ3.9 without any peak at δ3.8 indicated that the curcumin is effectively separated from DMC by the method. Also, the integration of this peak reveals that the near 98% of

the extracted dyes are the curcumin (with one methoxy in each ring).

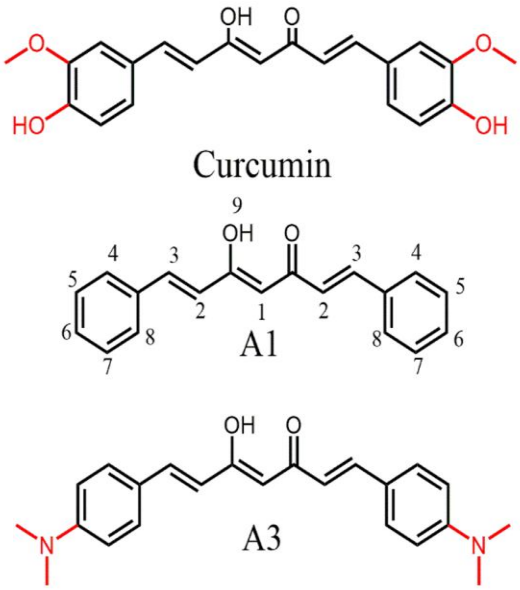

Fig.-1: Structures of curcumin and synthesized curcumin derivatives were highlighted

The H1 hydrogen signal (Fig.-1) was observed in the 5.5–6 ppm range for all samples, indicating that the enol-keto tautomer is the dominant tautomer (for keto-keto, this peak appears in 4.5–5 ppm) (Yanagisawa, *et al*., 2010). These results also support the fact that the enol form is the major isomer of these compounds in the $CDCl_3$ solution (Khopde, *et al*., 2000). Actually electron donor groups and low polar solvent (such as $CDCl_3$) improve the enol form of the □–dicarboxyl structure. The NMR spectra of A1 shows a single peak for the H1 hydrogen while other shows two peaks in this region. This observation can be related to stereoisomers of these molecules. These stereoisomer forms can be generated by the inter or intramolecular hydrogen bonding, twisted conformation, cis–trans isomerization, and intermolecular interaction, influencing the resonance, electron density and hydrogen bonding in the β-dicarbonyl position.

The H9 hydrogen in the A3 dye was detected in 16ppm, which could give important information about the structure of this molecule in the $CDCl_3$ solution. This result reveals that the

H9 hydrogen is placed in the β-dicarbonyl position but not on the amine groups. Also, the methyl hydrogens of the dimethylamine groups were observed in the 3 ppm, which matches with the unprotonated form of the dimethylamine groups. Accordingly, these data indicated that the A3 molecule is not in zwitterion form in $CDCl_3$ solution. These keto-enol forms could be stabilized by a strong hydrogen bond where the hydrogen atom is symmetrically located between the two oxygen atom. Single crystal studies of curcumin conform that the keto-enol form is the favoured isomer in the crystal and amorphous structure of curcumin (Paramita et al., 2007).

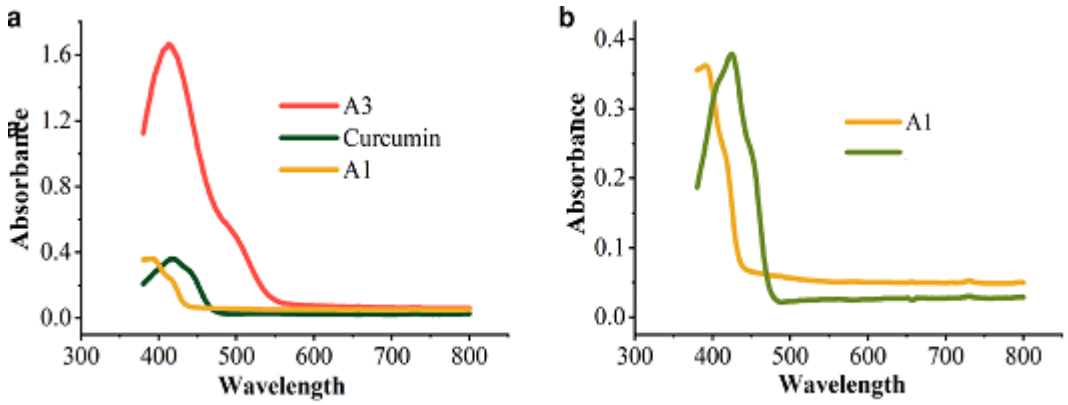

Figure-2: UV-Vis spectra of 0.01 mM curcumin and curcumin derivative in dichloromethane

Figure-2a shows the UV–Vis spectra of the A1, A3, and extracted curcumin. The A1 derivative, without any electron donor groups at the aryl rings, displayed the lowest λ_{max} (389 nm) and intensity. Modifying the A1 structure with electron donor groups such as methoxy (curcumin) and dimethyl-amine (A3) caused λ_{max} shifts to the 416 and 414 nm regions, respectively. Although the absorption intensity was not significantly changed by the methoxy group, the intensity was considerably enhanced by adding the dimethylamine group by a factor of 4. It is presumably due to the better intramolecular charge transfer (ICT) characteristics of this electron donor group, which promotes electronic absorption (Park, *et al*., 2015; Canard, *et al*., 2015). Consequently, adding the electron donor groups on the aryl rings has resulted in a red shift of the λ_{max} and an improvement of the intensity.

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Figure-2b shows the effect of the π-conjugation length on the UV–Vis absorption band. The absorption intensity of the A3 structure is similar to that of A1, but the λ_{max} of it shifted to the red region. Generally, the bandgap of a molecule is reduced by improving π-conjugation length (Roncali, 2007). This improvement in A3 dye decreased the required energy for the π-π* transition compared with that of A1 dye. The effects of the large alkoxy groups on the ortho position of the aryl rings (A3 molecule) are shown in Fig.-2c. These large alkoxy groups have no considerable effect on the λ_{max} position compared with the extracted curcumin.

Solvent effects on the curcumin electronic transition were investigated, and obtained spectra are shown in Fig.-3a. A slight red shift was observed for the solvents that have high dielectric constant such as ethanol (24.5), DMF (36.7), and acetonitrile (37.5). The lower λ_{max} was observed in the low dielectric constant solvents such as dichloromethane (8.93) and ethyl acetate (22.3). This behavior is common in the π-π* electronic transition, in which a high dielectric solvent reduces the energy of the π-π* transition (Brubaker, 1966). Patra and Barakat (2011) observed similar behavior for curcumin dye in different solvents indicating an interaction between the ground state of this kind of dyes with the polar solvents. Furthermore, the absorption intensity of the curcumin is affected by the nature of the solvent. According to Fig.-3a, the low polar solvent increases the absorption intensity of the dye. This could be related to better solubility of the curcumin in the low polarity solvents. The shoulder, that was observed around 400 nm, could be assigned to the keto-keto tautomer of curcumin.

Figure-3 also shows the UV–Vis spectra of the A3 molecules in different solvents. The absorption intensity of the A3 in the polar solvents (such as DMF) increased compared with the low polar solvent (such as ethyl acetate). It could be depending on the presence of the amin groups in A3 molecule, which increases the solubility of A3 in the polar solvents. Also, the peak of the keto-keto form of the A3 cannot be seen in any solvents, it means that the concentration of the Keto-Keto tautomer is low, or covered with enol-cis broad peak.

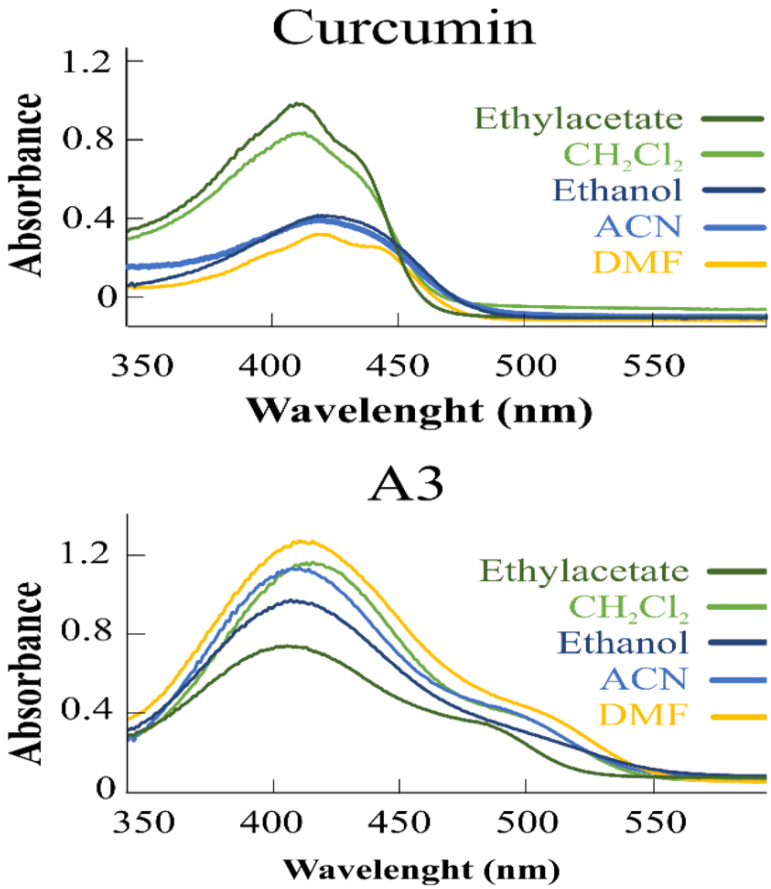

Figure-3: UV-Vis spectra of curcumin (top) and A3 (bottom) in the different solvents

According to the above discussion, we assume that the middle peak, which was observed in the UV–Vis spectra of curcumin and their derivative, could be assigned to the twisted molecules in the nano-particles. The self-assembled nano-particles of curcumin and their derivative (in a wide range of solvents) indicated that these molecules have strong intermolecular interaction. Considering that there is a high tendency for intermolecular interaction, it is remarkable to study the interaction of them with other materials such as TiO_2.

However, the carbonyl peak for the adsorbed curcumin on the surface of the TiO_2 has shifted toward higher energy (1665 cm^{-1}). This result shows that electron density in the C=O bond increased and electrons in the β-dicarbonyl position are more localized (double bond) compared with curcumin powders. These data give valuable information about the binding mode of curcumin and their derivative on the surface of the TiO_2 anatase nanoparticles. McNamara, *et al*. (2008)

reported that four different modes are possible to anchor an acetylacetonate group (acac) on the TiO_2 anatase surface. These models include acac anchor to TiO_2 surface by bridging two Ti^{4+}, bidentate chelating a single Ti^{4+}, monodentate binding to a Ti^{4+} ion, and bidentate chelating a single Ti^{4+} center at an oxygen vacancy. Among them, only "the monodentate binding to a center" mode can enhance the electron density in the C=O bond. Also, this anchoring mode was reported as energetically favorable binding between acac and TiO_2 (101) surface. So, this mode reduces the π electron extension and can enhance the twisted structure of these molecules on the surface of the TiO_2 nanoparticles. Although monodentate binding of the acac anchors is energetically favorable on the TiO_2 (101) surface, the bidentate chelating to a single Ti^{4+} is energetically favorable on the oxygen vacancy defects of TiO_2. The concentration of these sites (defects) are low compared with the available sites for the monodentate binding. Thus, the peak with low intensity next to the 1665 cm^{-1} could be assigned to this binding mode.

Conclusion

Two derivative of the curcumin were synthesized, and the structure and properties of them were investigated and compared with the extracted curcumin. The UV–Vis absorption results indicated that the addition of the electron donor functional groups to the aryl rings induces a red redshift in their spectra. Also, the extension of the π electron cloud has the same effect on the UV–Vis spectra of them. The UV–Vis and ^{1}HNMR spectra show that two or three isomers of curcumin exist in different solutions. Consequently, three isomers including Enol-Cis, Keto- Keto, and Twisted could exist in different solutions. These results show that these molecules have tendency to make strong hydrogen bonding and intermolecular interaction.

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