Keto-enol tautomerism of curcumin in the preparation of nanobiocomposites with fumed silica

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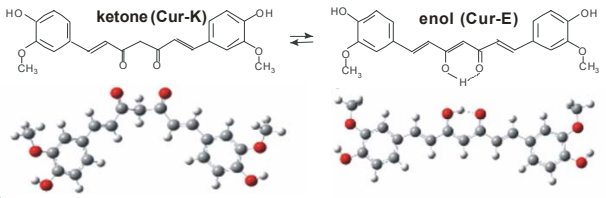
Keto-enol tautomerism of curcumin



The plant polyphenol curcumin (Cur) has anti-inflammatory, antioxidant, neuroprotective, hepatoprotective and other properties. Curcumin confirmed to serve as an adjuvant in the treatment of COVID-19 *(Rattis B.A.C., Ramos S.G., Celes M.R.N. (2021) Curcumin as a Potential Treatment for COVID-19. Front. Pharmacol. 12:675287. doi: 10.3389/fphar.2021.675287).*

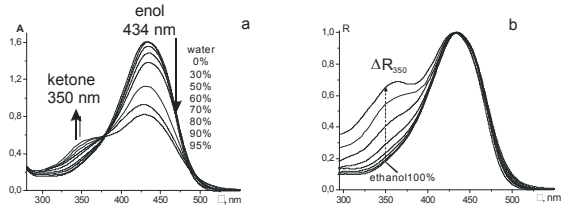
Its pharmacological activity largely depends on the ratio of its ketone (Cur-K) and enol (Cur-E) tautomeric forms, so understanding the dynamics of Cur tautomerization is fundamental in the development of drugs, dietary supplements and for predicting clinical reactions

THE PURPOSE OF THE WORK

complex quantum-chemical, sorption and spectral studies of the curcumin keto-enol tautomerism in the process of preparation of its nanobiocomposites with fumed silica (trademarks "Atoxil", "Polysorb") by the adsorption from water-ethanol solutions used in technology to increase the bioavailability of poorly soluble drugs.

Spectral changes during transition Cur-E ⟶ Cur-K at increase of watercontent in water-ethanol solutions

Fig.1. Absorption spectra (a) and normalized absorption spectra (b) of curcumin at different water content in water-ethanol solutions

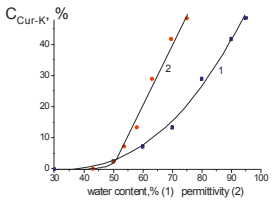


Tautomeric equilibrium shifts towards the formation of Cur-K with an increase in the water content in mixed water-ethanol solutions

Relative intensity at 350 nm ($\Delta R_{350} = R_{350}-R^{0}_{350}$) was found to be proportional to the keto tautomer content and therefore was used to control the degree of its formation in water-ethanol solutions and on the silica surface .

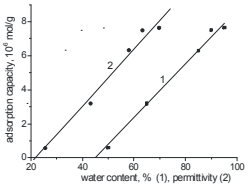
Role of permittivity of water-ethanol solutions

Fig.2. Content of Cur-K (%) depending on water content in water-ethanol solutions (1) and their permittivity (2)



At the water content < 45% curcumin exists only in the enol form. An increase in the water content > 45% promotes formation of Cur-K, and at ε > 50 the relative amount of keto tautomer starts to increase proportionally to the solution permittivtiy.

Fig.3. Curcumin adsorption on silica depending on water content in water- ethanol solutions (1) and their permittivity (2)



Plant polyphenol adsorption from solutions is substantially determined by the solvating properties of the solvent. Curcumin adsorption capacity linearly raises with water addition > 45% to the ethanol solution and corresponding increase in solution permittivtiy.

Curcumin adsorption on the silica surface as a function of concentration

Fig.3. Isotherms of curcumin adsorption on silica from water-ethanol solutions with water content 70%, calculated: (1) by formula a = (C - [C]) · V / m
(2) by absorbance of curcumin adsorbed on silica (ε^{s}_{434}= 3.44*10⁵ g · mol⁻¹ cm⁻¹)

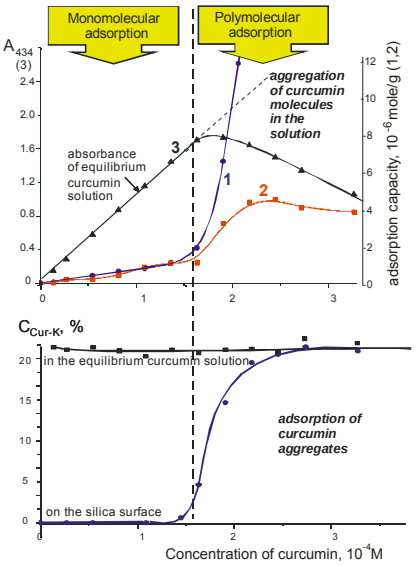
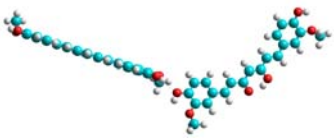


Fig.4. Content of curcumin keto-tautomer (%) on the silica surface and in the corresponding equilibrium solution depending on the initial curcumin concentration.

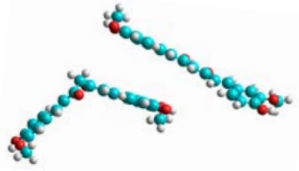
Quantum-chemical modeling of mono- and polymolecular adsorption

Curcumin dimers

Keto dimer Cur-K – Cur-K with parallel orientation of phenyl rings



Enol dimer Cur-E – Cur-E with intermolecular H-bond



Keto-Enol dimer Cur-K – Cur-E

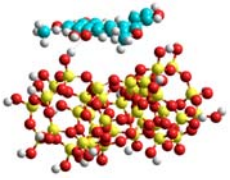
Keto dimer Cur-K - Cur-K with antiparallel orientation of phenyl rings

Table. Calculated values of Gibbs free energy $G_{(liq)}$ of system and energies of solvation ΔG_s and adsorption ΔG_{ads} for different dimers of curcumin in water (SM5.42/6-31G(d)//6-31G(d,p) for G (liq) and ΔG_s and SM5.42/6-31G(d)//PM7 for G_{ads})

Dimer	-G(liq) (Hartree)	$-\Delta G_s$, kJ/mol (per 1 molecule)	$-\Delta G_{ads}$, kJ/mol (per 1 molecule)
Antiparallel Keto-Keto	2512.002785794	83.2	6.6
Parallel Keto-Keto	2511.996334552	78.5	7.1
Keto-Enol	2511.996194217	79.3	3.4
Enol-Enol	2511.992922831	74.4	5.7

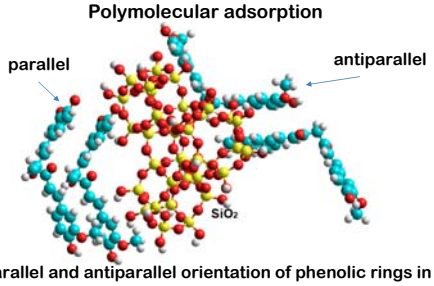
Curcumin adsorption on fumed silica

Monomolecular adsorption



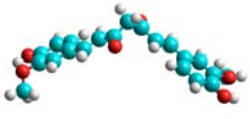
Silica cluster with adsorbed enol monomer (ΔGads = -19.3 kJ/mol)

Polymolecular adsorption



Parallel and antiparallel orientation of phenolic rings in curcumin keto-tautomer aggregates on the silica surface

Optimized Cur-K molecule



Torsion angle 72 ° in solution and 73 ° on the surface

Conclusions

At low curcumin concentrations in solution (<1.5•10⁻⁴ M), exclusively enol tautomer is adsorbed forming a monolayer on the silica surface. The keto tautomer is adsorbed only as part of molecular assemblies, which are formed in curcumin solutions at a concentration of > 1.5 × 10⁻⁴ M.

According to quantum-chemical calculations, the monomolecular adsorption of curcumin on silica surface takes place due to the formation of H-bond between Cur-E monomers and SiO_2 cluster. At polymolecular adsorption Cur-K aggregates with both parallel and antiparallel orientation of phenyl rings are adsorbed on the surface. In the case of dimers the adsorption energy is maximum for Cur-K – Cur-K with parallel orientation of the phenyl rings.