Cyclodextrins as Protective Hosts for Chemical UV Filters

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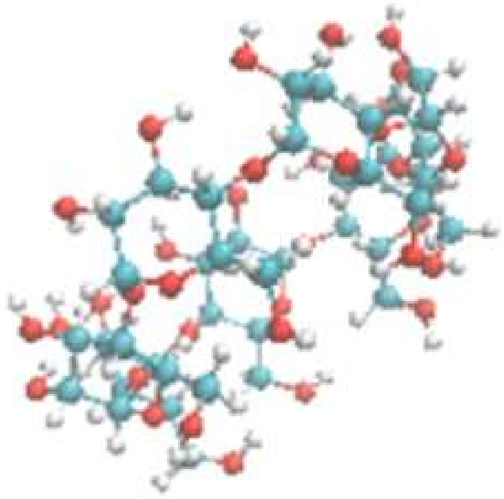
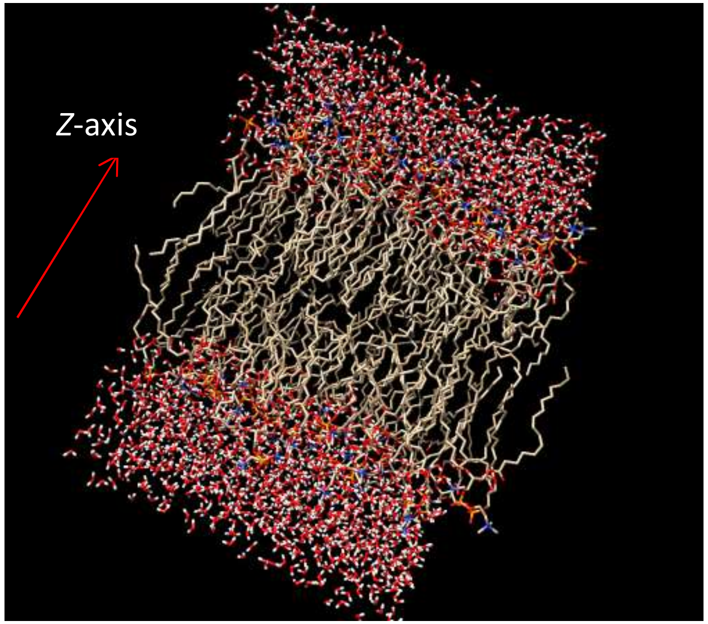
Physics-Based Modeling of Chemical UV Filters

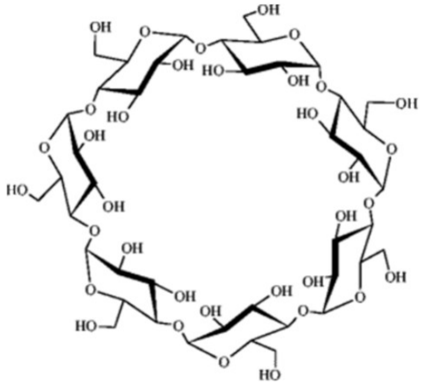
- Molecular simulations of chemical UV filters at the atomistic level of description in an aqueous environment.
- Investigation of chemical UV filters in more complex environments (e.g. cyclodextrins and fully hydrated lipid bilayers). Such environments contain hydrophilic and hydrophobic regions and provide further insight into the investigation of the molecules under consideration.
- The *in silico* approach described herein shall be applied to the best candidates (5-10) obtained from the machine learning modeling. Detailed comparison of the properties with those concerning chemical UV filters used in commercial sunscreen products.

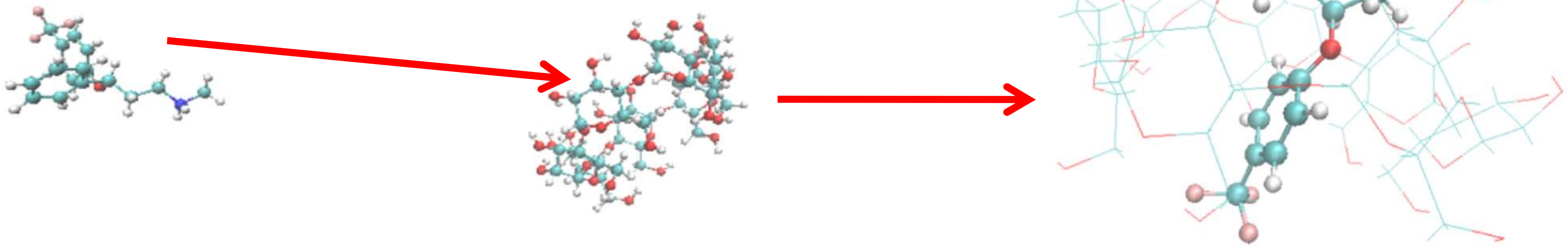




Cyclodextrins (I)

- Cyclodextrins consist of an outer hydrophilic surface and a hydrophobic interior cavity. [1]
- Cyclodextrins can host small lipophilic or hydrophobic molecules in their interior cavity, thereby forming stable noncovalent complexes that have found applications in diverse fields, such as cosmetics, pharmaceuticals, food science and the environment.[1]
- Specifically, regarding the topic under examination, cyclodextrins can act as a shield protecting UV filters and antioxidants, which also offer UV protection by neutralizing free radicals and reactive oxygen species induced by UV radiation.[1]
- In general, cyclodextrins enhance the low aqueous solubility, provide protection to substances susceptible to undesirable reactions and degradation, improve bioavailability, mask unpleasant characteristics and offer other beneficial properties.





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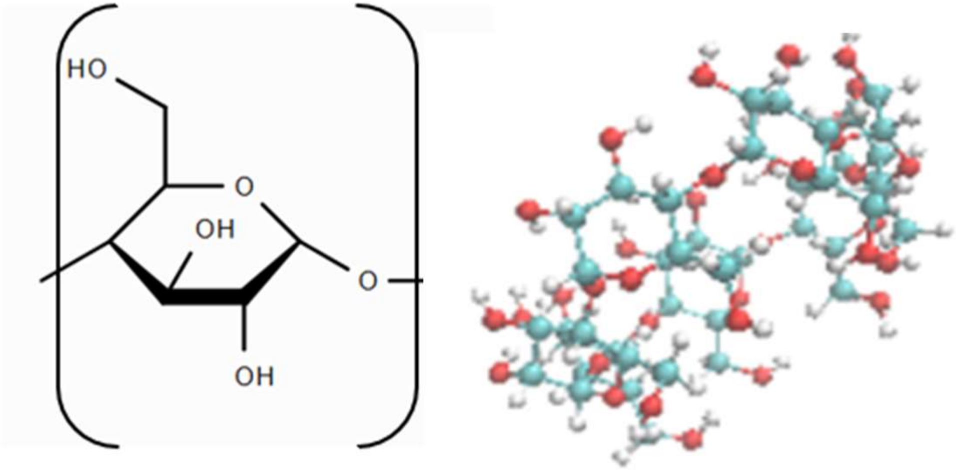
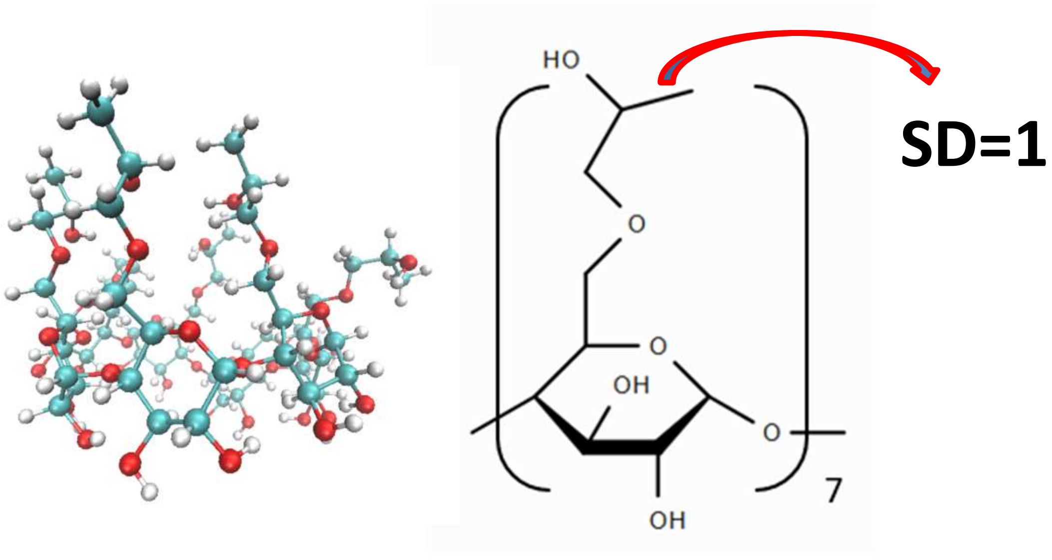
Cyclodextrins (II)

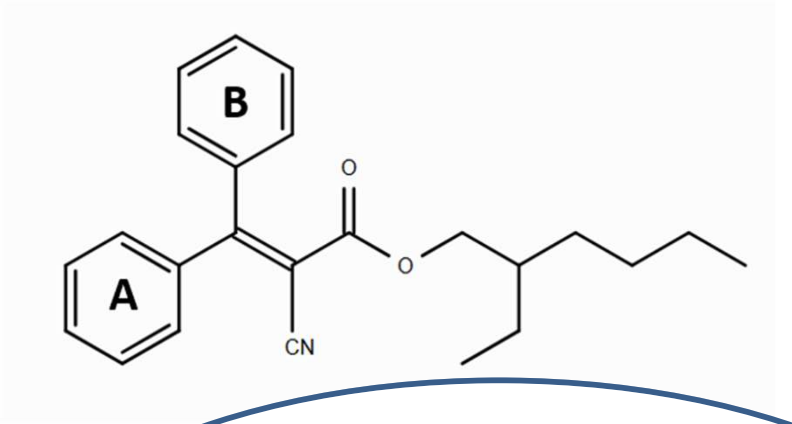




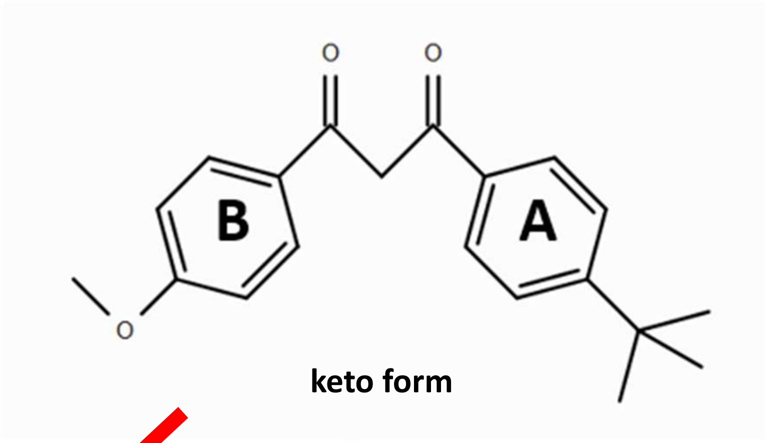
- The cyclodextrins taken into account herein are β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), both consisting of seven repeat units. Both β-CD and HP-β-CD are generally considered safe for use in skin formulations, provided they are used within recommended concentrations and formulations.
- In general, HP-β-CDs exhibit superior solubility and a more favorable safety profile than β-CD.
- The HP-β-CD depicted in this slide has also been used in many studies concerning small organic molecules (e.g., drugs).

Chemical UV Filter Used in this Study

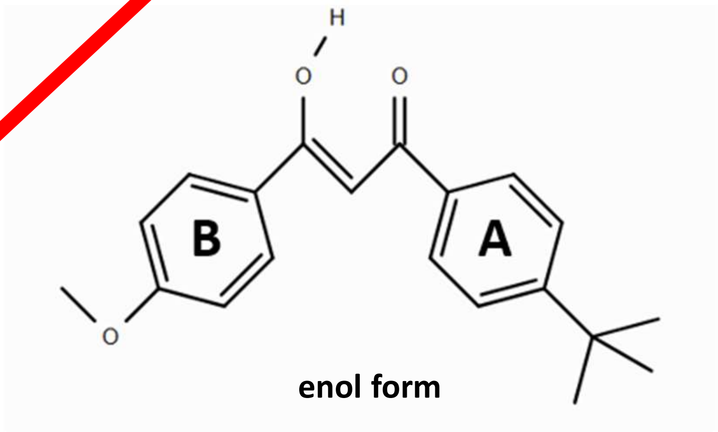
Octocrylene



Avobenzone



keto form



enol form

Avobenzone contains a β-diketone group. Both its keto and enol forms are considered to account for the tautomeric equilibrium between these two forms.

Cyclodextrins and Chemical UV Filters

- In general, cyclodextrins have been assessed for protecting UV filters against photodegradation and oxidation, as well as for their ability to restrict UV filter permeation into deep skin layers (some UV filters have been detected in blood plasma following topical application).
- Concerning enol avobenzone, the chelated and nonchelated forms are further investigated due to their role in photoprotection and photodegradation.
- Effective photoprotective hosts for avobenzone must preserve this intramolecular hydrogen bond, since photodegradation typically initiates through the chelated-to-nonchelated transition when avobenzone is found in the enol form.
- Reduced diffusivity upon complexation suggests that photodegradation fragments may more readily recombine into the original avobenzone structure via cage reactions.

Simulated Chemical UV Filter - Cyclodextrin Complexes in an Aqueous Environement

(1) avobenzone (keto form) – β-CD

(2) avobenzone (enol form) – β-CD

(3) octocrylene – β-CD

(4) avobenzone (keto form) – HP-β-CD

(5) avobenzone (enol form) – HP-β-CD

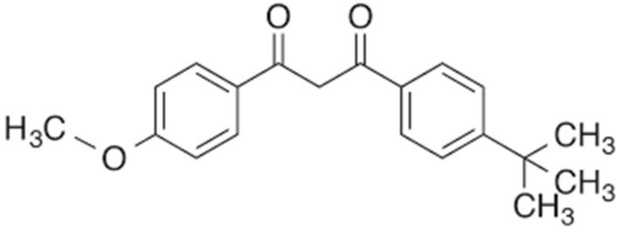
(6) octocrylene – HP-β-CD

Molecular Dynamics Simulations of Chemical UV Filters in Water Solutions Containing Cyclodextrins

$\mathrm{ChemUV}_{(aq)} + \mathrm{CD}_{(aq)}$ $\mathrm{CD\text{-}ChemUV}_{(aq)}$

Avobenzone

β-CD



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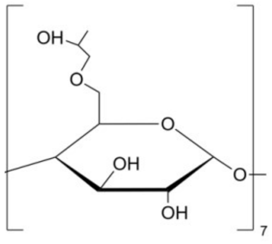
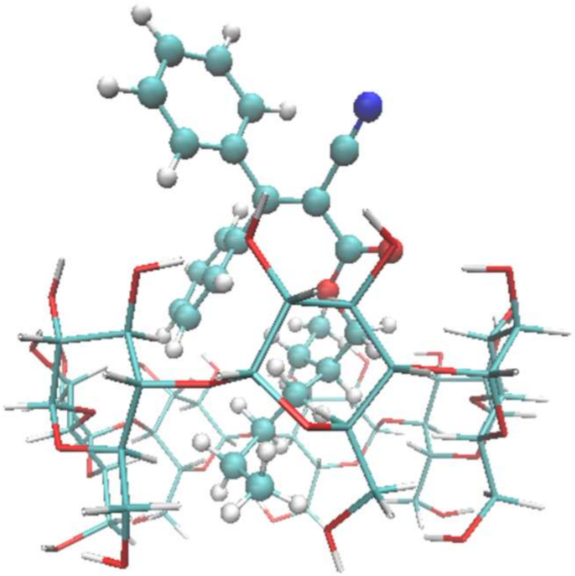
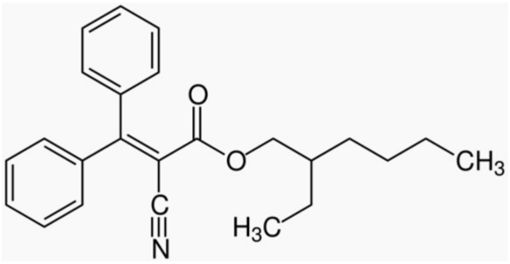




Octocrylene

HP-β-CD



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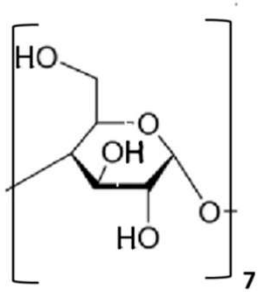
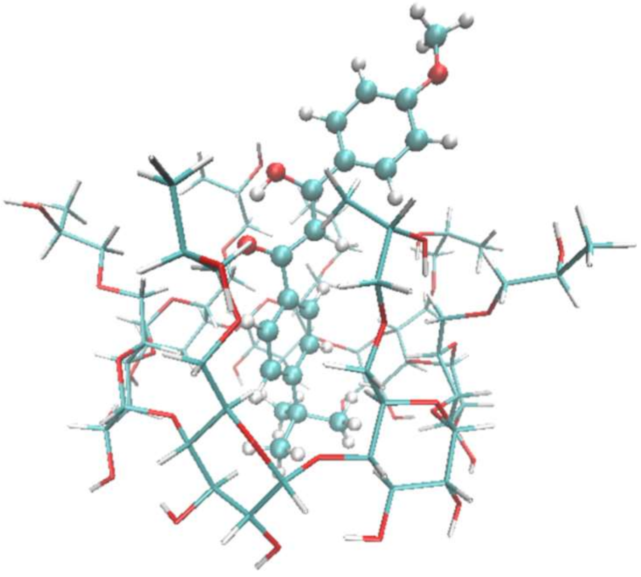
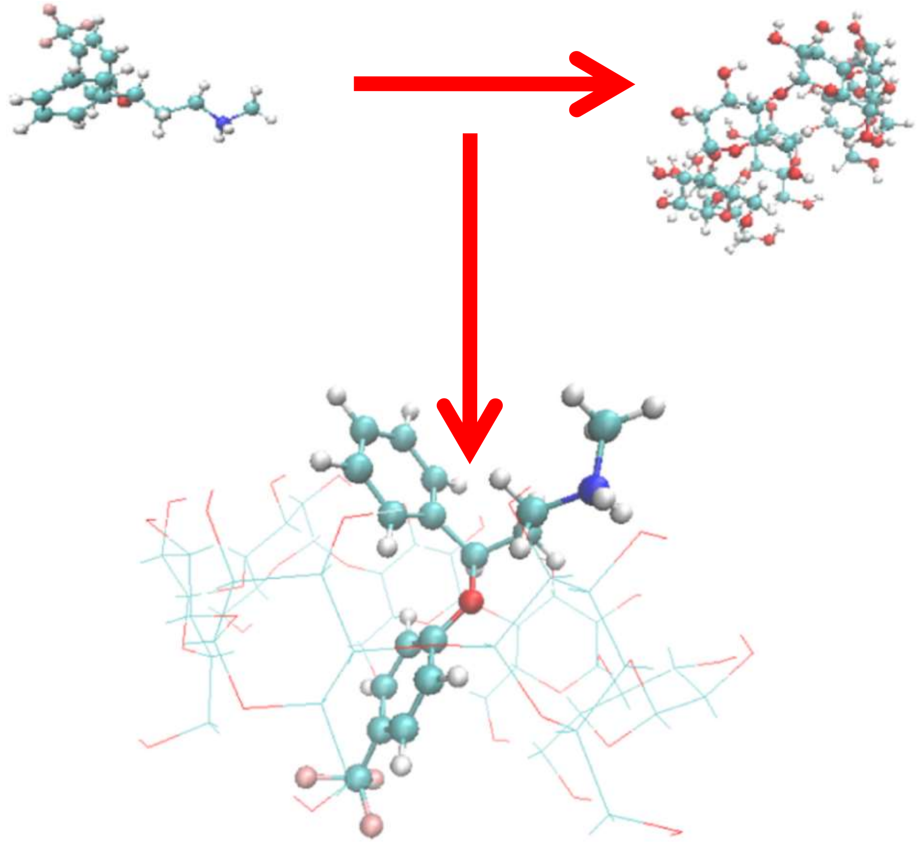


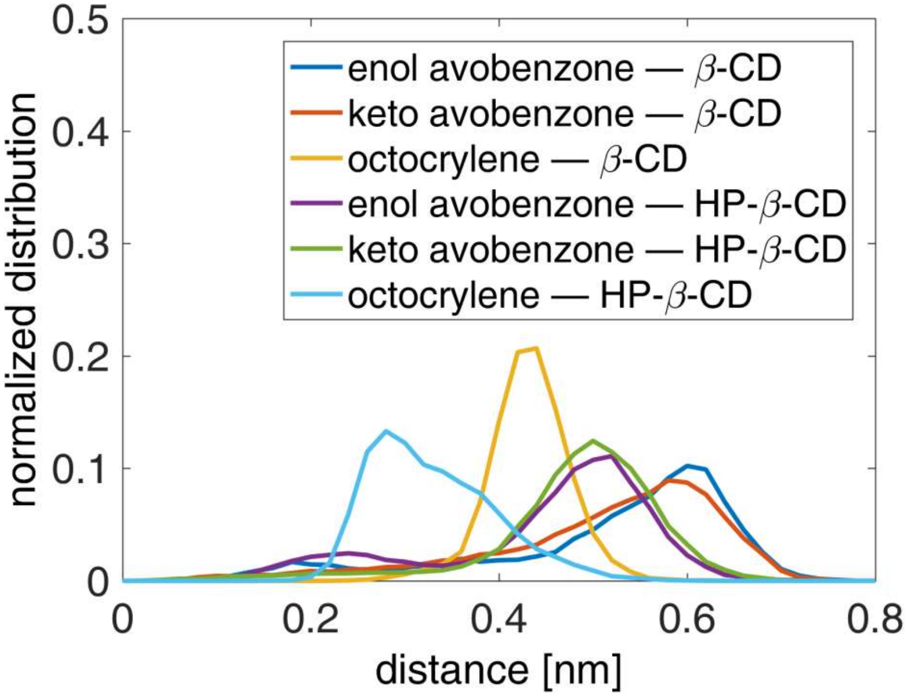


Details of the Atomistic Molecular Dynamics Simulations

- All simulations are conducted with GROMACS 5.1.3 in the isothermal-isobaric ensemble at the temperature of 305 K and at the pressure of 1 bar by employing the Nose´-Hoover thermostat (τ_T = 1.0 ps) and the Parrinello-Rahman barostat (τ_p = 1.0 ps).
- The time step for the numerical integration of the equations of motion is set to 2 fs, with all covalent bonds involving hydrogen atoms being constrained to their equilibrium length by using the LINCS algorithm.
- The nonbonded (Lennard-Jones) interactions are computed by employing a r_c = 1.2 nm cutoff radius. It is pointed out that the forces due to the nonbonded interactions are smoothly switched to zero between a distance of $r_{\text{vdw-switch}}$ = 1.0 nm and the cutoff radius, r_c, by applying the force-switch option of GROMACS. In addition, pressure and energy correction terms are applied due to the abovementioned truncation of the potentials.
- The long-range electrostatics is treated with the Particle Mesh Ewald (PME) method.
- Use of GLYCAM, TIP3P and GAFF force fields.

Spontaneous Complexation (I)

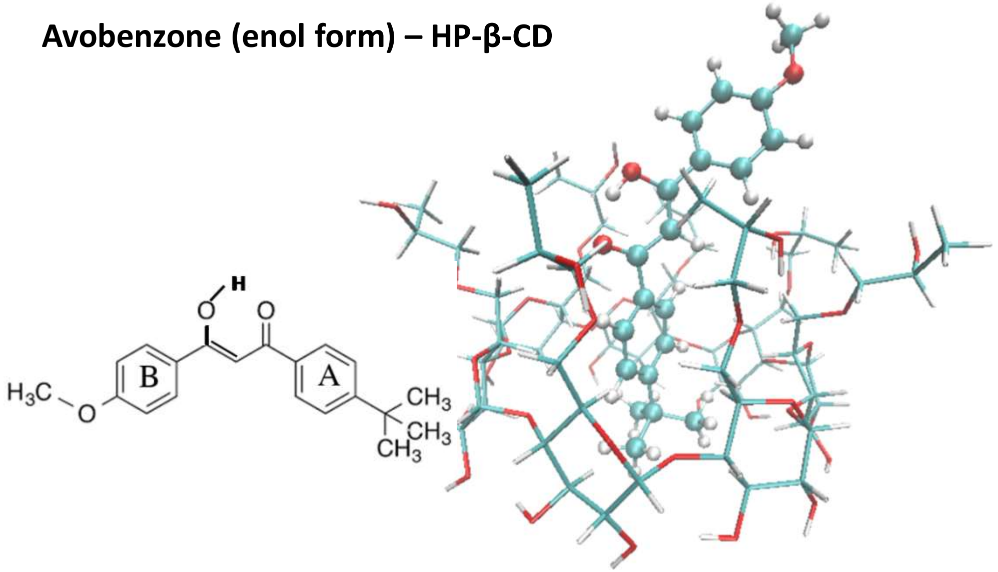




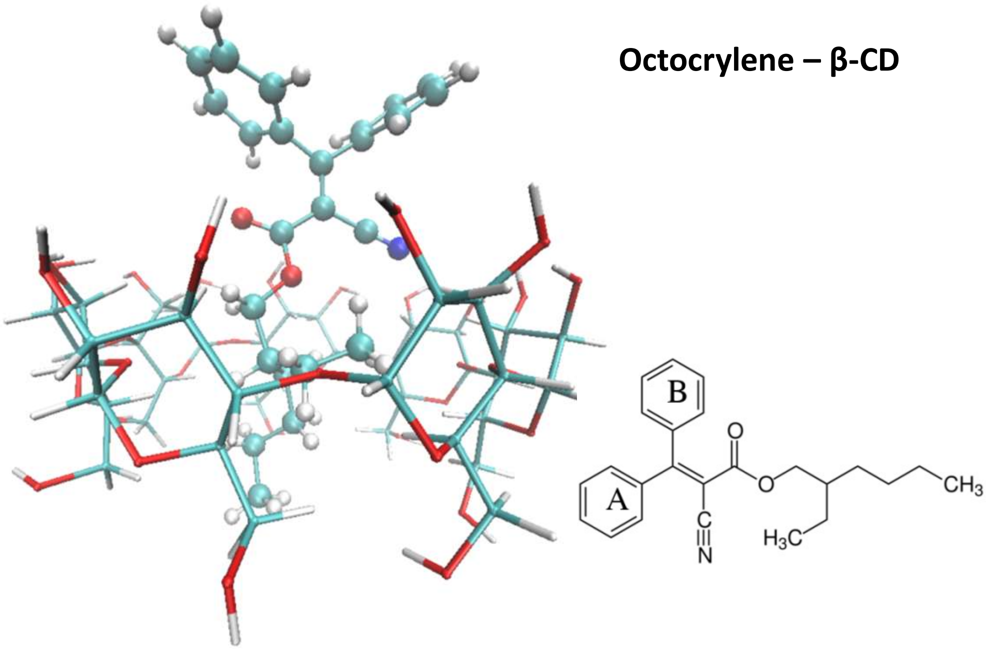
- Stable spontaneous complexation occurs on timescales ranging from tens to a few hundred nanoseconds (up to 140 ns) and the formed noncovalent complexes remain in the bound state for the rest of the simulations.
- No binding on the exterior surfaces of cyclodextrins.
- In all complexes, the hydrophobic parts of the UV filters have penetrated deeper into the cavity of cyclodextrins, whereas their more hydrophilic parts interact favorably with the hydrophilic rims of cyclodextrins, as well as the surrounding water molecules.

Spontaneous Complexation (II)

Avobenzone (enol form) – HP-β-CD



Octocrylene – β-CD

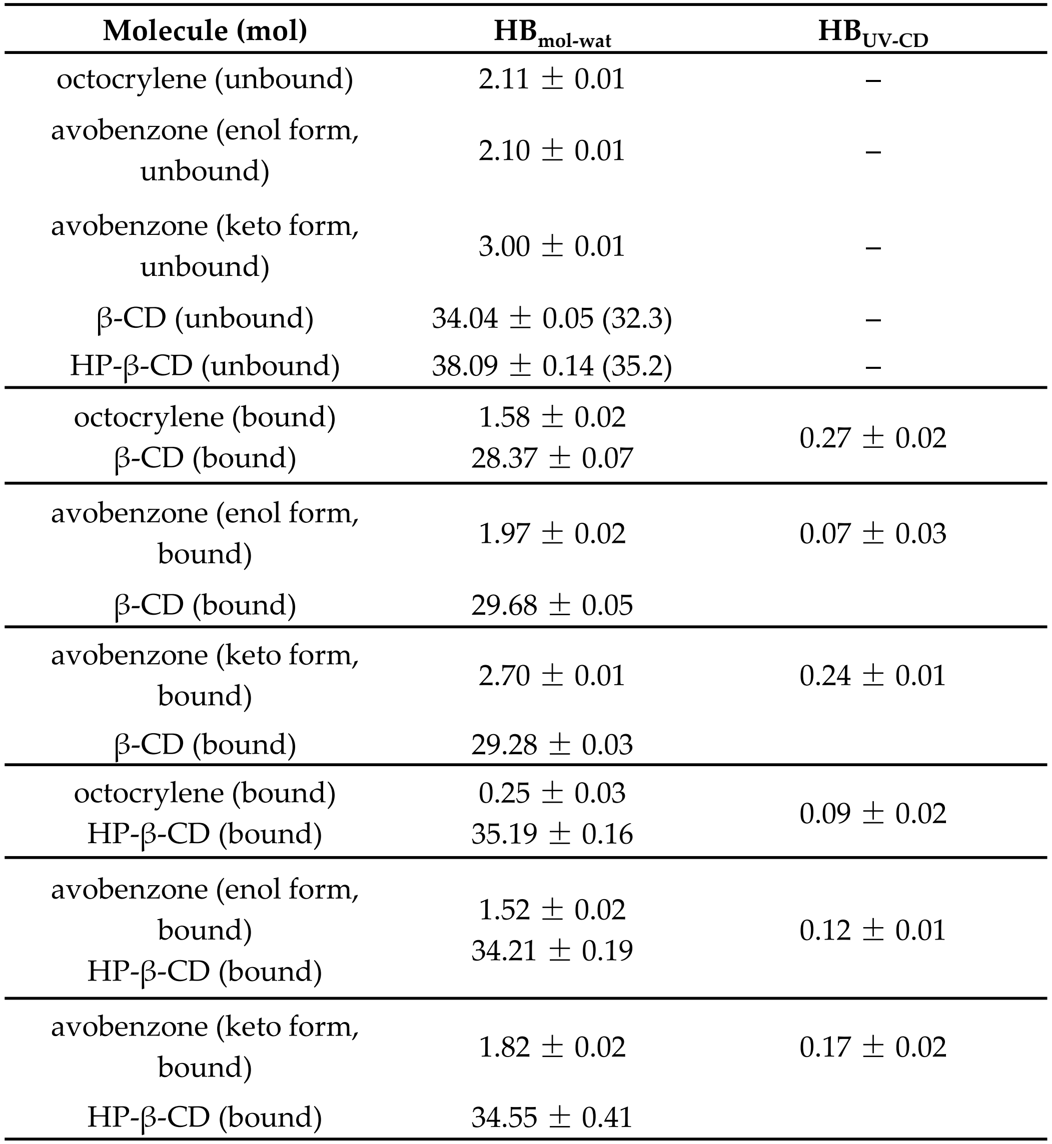


- The aromatic ring A of avobenzone is mainly inserted into the cavity of the cyclodextrins due to its greater hydrophobicity, an observation that is fully supported by the related literature. The aromatic ring B is primarily in direct contact with the surrounding aqueous phase and the methoxy group itself participates in hydrogen bonding with water molecules.
- As for octocrylene, its long alkyl chain is positioned in the hydrophobic interior of cyclodextrins, while the aromatic rings A and B reside mainly at the cyclodextrin-water interface region; this geometry agrees with other published articles on β-CD – octocrylene complexes.

Hydrogen Bonding

- In their unbound state, both UV filters form a hydrogen-bond network with water molecules. Upon complexation, this network remains present but is somewhat attenuated. The reductions are 6.2% (enol avobenzone), 10.0% (keto avobenzone) and 24.7% (octocrylene) for β-CD, and 27.6%, 39.3% and 88.2% for the same compounds, respectively, with HP-β-CD.
- In the case of enol avobenzone, an intramolecular hydrogen bond between the hydroxyl and carbonyl group is also observed for both cyclodextrin-based complexes. The average value of 0.8 intramolecular hydrogen bonds per molecule suggests that the chelated form of avobenzone predominates over the nonchelated one.
- An effective photoprotective host for avobenzone must preserve this intramolecular hydrogen bond, since photodegradation typically initiates through the chelated-to-nonchelated transition when avobenzone is found in the enol form.

Average numbers of hydrogen bonds formed in the systems under consideration

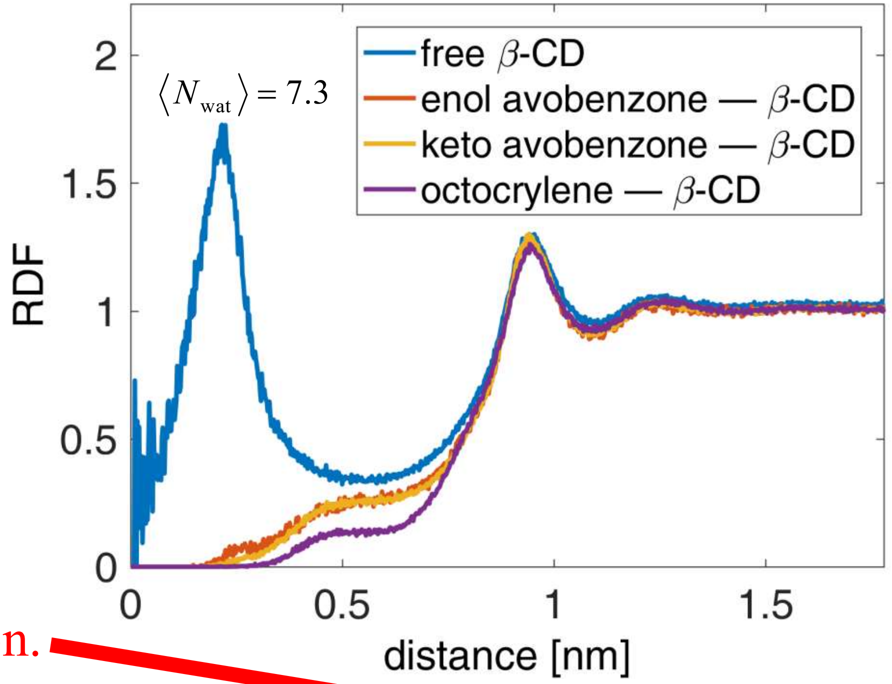


Molecule (mol)	$HB_{mol\text{-}wat}$	$HB_{UV\text{-}CD}$
octocrylene (unbound)	2.11 ± 0.01	–
avobenzone (enol form, unbound)	2.10 ± 0.01	–
avobenzone (keto form, unbound)	3.00 ± 0.01	–
β-CD (unbound)	34.04 ± 0.05 (32.3)	–
HP-β-CD (unbound)	38.09 ± 0.14 (35.2)	–
octocrylene (bound)	1.58 ± 0.02	0.27 ± 0.02
β-CD (bound)	28.37 ± 0.07	
avobenzone (enol form, bound)	1.97 ± 0.02	0.07 ± 0.03
β-CD (bound)	29.68 ± 0.05	
avobenzone (keto form, bound)	2.70 ± 0.01	0.24 ± 0.01
β-CD (bound)	29.28 ± 0.03	
octocrylene (bound)	0.25 ± 0.03	0.09 ± 0.02
HP-β-CD (bound)	35.19 ± 0.16	
avobenzone (enol form, bound)	1.52 ± 0.02	0.12 ± 0.01
HP-β-CD (bound)	34.21 ± 0.19	
avobenzone (keto form, bound)	1.82 ± 0.02	0.17 ± 0.02
HP-β-CD (bound)	34.55 ± 0.41	

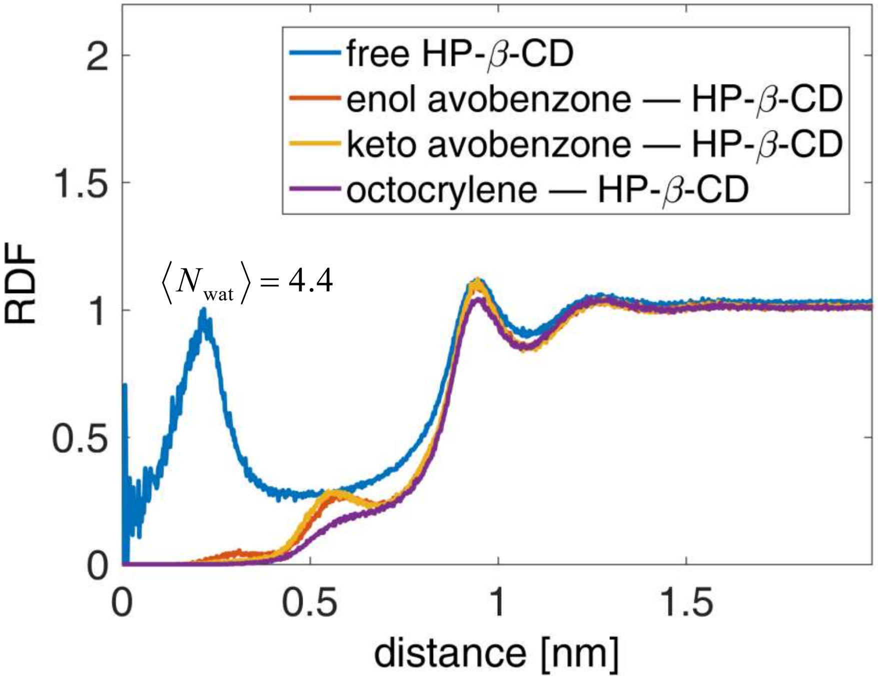
Trapped Water Molecules in the Cavity of the Cyclodextrins

$$\langle N_{\text{wat}} \rangle = \rho_{\infty}^{\text{wat}} \int_{0}^{R_{\text{eq}}} 4\pi r^{2} g(r)\,dr,$$

$g(r)$ is the radial distribution function (RDF) between the water molecules surrounding the cyclodextrin and its center of mass.



- Expulsion of water molecules upon complexation.



System	$\langle N_{\text{wat}} \rangle$
avobenzone (keto form) – β-CD	0.6
avobenzone (enol form) – β-CD	0.8
octocrylene – β-CD	0.2
avobenzone (keto form) – HP-β-CD	1.0
avobenzone (enol form) – HP-β-CD	0.3

Linear Interaction Energy (LIE) Method

- The thermodynamic analysis is based on **Gibbs energy**, as all molecular dynamics simulations are carried out in the *NPT* ensemble.
- **Calculation of (standard) binding Gibbs energies:** Use of the linear interaction energy (LIE) method,[1] which has been utilized successfully for the prediction of binding affinities in host-guest systems including β-cyclodextrin as a host molecule[2].

$$\mathrm{ChemUV}_{(\mathrm{aq})} + \mathrm{CD}_{(\mathrm{aq})} \rightleftharpoons \mathrm{CD\text{-}ChemUV}_{(\mathrm{aq})}$$

Noncovalent complex

$$\Delta G^{\circ}_{\mathrm{bind}} = a\Delta\left\langle V_{\mathrm{vdw}}\right\rangle + \beta\Delta\left\langle V_{\mathrm{el}}\right\rangle + \Delta E_{\mathrm{strain}},\ (\alpha{=}0.43,\ \beta{=}0.20)^{2}$$

$$\Delta G^{\circ}_{\mathrm{bind}} = -RT\ln K^{\circ}_{\mathrm{eq}}$$

- The last term represents the strain energy of the cyclodextrin upon complexation.
- Two simulations are needed for each system: one with the UV filter free in an aqueous environment, and another with the UV filter – cyclodextrin complex in the same environment.
- The LIE method has a low computational cost compared to other *in silico* methods, such as umbrella sampling and metadynamics.
- **Using HPC resources, it can be used to screen tens of substances complexed with cyclodextrins in water.**

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1. J. Åqvist, C. Medina, J.-E. Samuelsson, A new method for predicting binding affinity in computer-aided drug design, Protein Eng. Des. Sel. 7 (1994) 385–391.
2. J.J. Montalvo-Acosta, P. Pacak, D.E.B. Gomes, M. Cecchini, A Linear Interaction Energy Model for Cavitand Host–Guest Binding Affinities, J. Phys. Chem. B. 122 (2018) 6810–6814.

Binding Gibbs Energies

Calculation of standard binding Gibbs energies using the LIE method

Standard binding Gibbs energies of all the UV filter – cyclodextrin complexes

System	**ΔG_{bind} [kJ/mol]**
avobenzone (keto form) – β-CD	–19.9 ± 0.2
avobenzone (enol form) – β-CD	–14.5 ± 0.3
octocrylene – β-CD	–23.8 ± 0.5
avobenzone (keto form) – HP-β-CD	-17.7± 0.6
avobenzone (enol form) – HP-β-CD	-18.9± 0.6
octocrylene – HP-β-CD	-17.8± 0.5

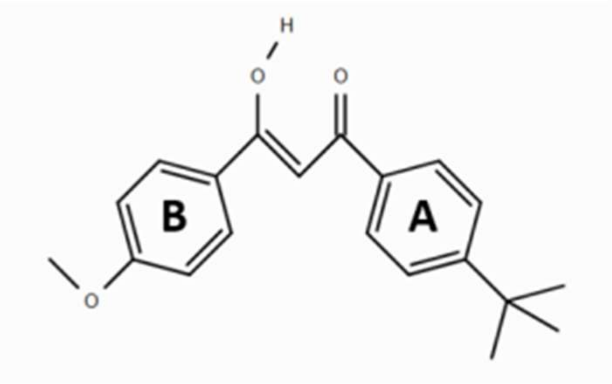
Experimental studies report binding constants which are converted to binding Gibbs energies

Experimental values of standard binding Gibbs Energies of the avobenzone – cyclodextrin complexes

System	ΔG_{bind} [kJ/mol]
avobenzone – HP-β-CD	–18.4 –19.2
avobenzone – β-CD	–22.5 –18.1

The optimal free energy interval for cyclodextrin–drug inclusion complexes is between -8 and -30 kJ/mol.

Chelated-to-Nonchelated Transition (Enol Avobenzone)

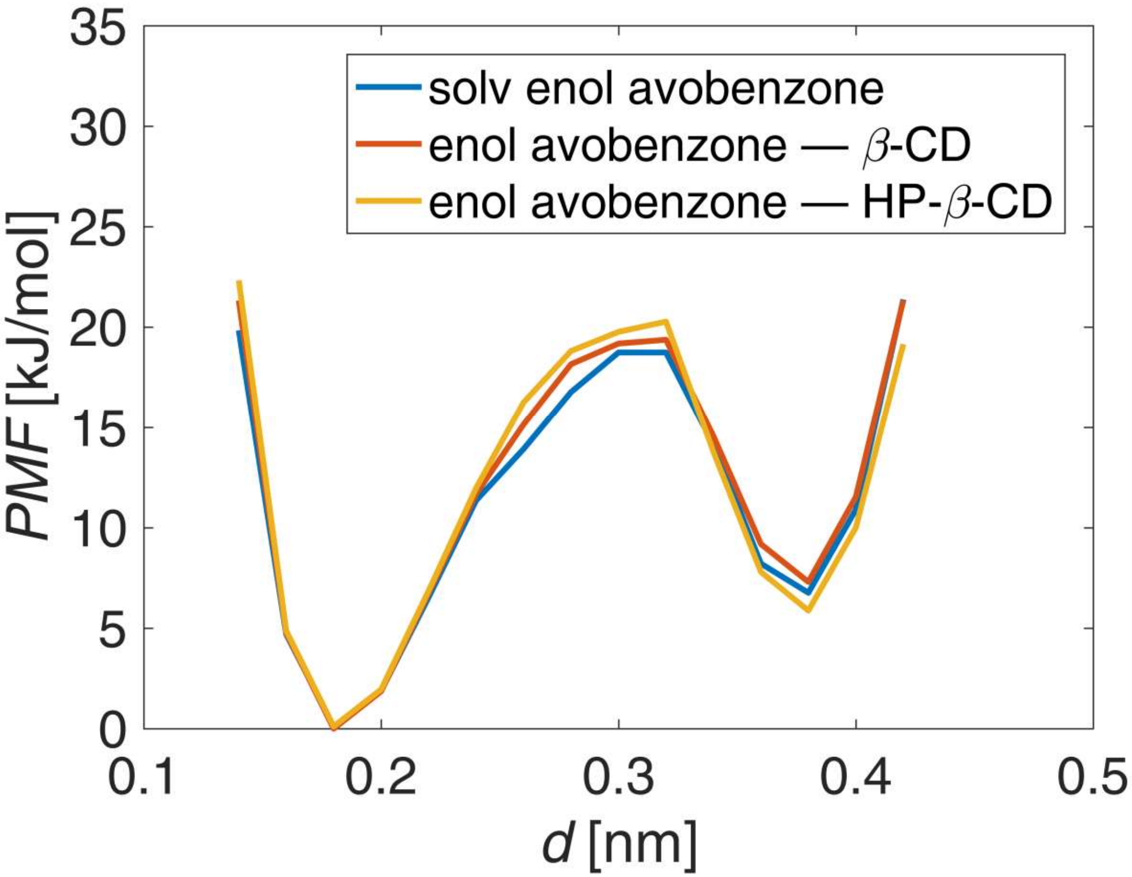


- Thermodynamic analysis based on the calculation of a properly defined potential of mean force (PMF).

$$PMF(d) = -RT \ln \rho(d) + C$$

$\rho(d)$ represents the normalized distribution of the distance, d, between the ketonic oxygen and hydroxylic hydrogen.

- Two minima with the global minimum corresponding to the chelated form.
- The chelated form is more negative than the nonchelated form by 7.3±0.4 kJ/mol (complexed with β-CD), 5.8±0.4 kJ/mol (complexed with HP-β-CD) and 6.5±0.4 kJ/mol (in the unbound state).



One-dimensional PMF as a function of the distance between the ketonic oxygen and hydroxylic hydrogen of enol avobenzone: (a) free enol avobenzone in water (blue), (b) enol avobenzone – β-CD (red) and (c) enol avobenzone – HP-β-CD (yellow).

Self-Diffusion Coefficients (I)

$$D_{cc} = \lim_{t\to\infty} \frac{\left\langle \left(r_c(t+t_0) - r_c(t_0) \right)^2 \right\rangle}{2t}, \{c=x, y, z\}$$

$$D = \frac{D_{xx} + D_{yy} + D_{zz}}{3}$$

$$D_{\mathrm{corr}} = D + \delta D = D + \frac{\xi k_B T}{6\pi\eta L}$$

The correction term, δD, is incorporated to calculate the self-diffusion coefficient in the thermodynamic limit.

System	**D_{corr} [10^{-5} cm^2/s]**
β-CD free in water	0.52 ± 0.01
HP-β-CD free in water	0.55 ± 0.01
octocrylenefree in water	0.74 ± 0.01
avobenzone (keto form) free in water	0.92 ± 0.01
octocrylene – β-CD	0.52 ± 0.01
octocrylene – HP-β-CD	0.52 ± 0.01
avobenzone (keto form) – HP-β-CD	0.51 ± 0.01
avobenzone (keto form) – β-CD	0.52 ± 0.01

- Self-diffusion coefficients of β-CD from other computational studies: $[0.35 - 1.10]\times10^{-5}$ cm^2/s). Experimentally estimated mean diffusion coefficients are $(0.423 - 0.430)\times10^{-5}$ cm^2/s for β-CD and $(0.406 - 0.408)\times10^{-5}$ cm^2/s for HP-β-CD in aqueous solutions.
- The self-diffusion coefficients of both sunscreens free in water are larger than those of the cyclodextrins, with avobenzone exhibiting the highest value.

Self-Diffusion Coefficients (II)

- Upon complexation, the self-diffusion coefficient of each complex, as a unified chemical entity, is very close to the self-diffusion coefficients of both cyclodextrins when they are free in water.
- This implies that both octocrylene and avobenzone exhibit lower mobility when they are found in the bound state, suggesting that their free motion in an aqueous environment is noticeably hindered upon complexation.
- The aforementioned finding is also observed in published studies on avobenzone – cyclodextrin complexes.[1,2] For avobenzone, the reduced diffusivity upon complexation suggests that photodegradation fragments may more readily recombine into the original avobenzone structure via cage reactions .[1,2]

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Solvent-Accessible Surface Area (SASA) Analysis

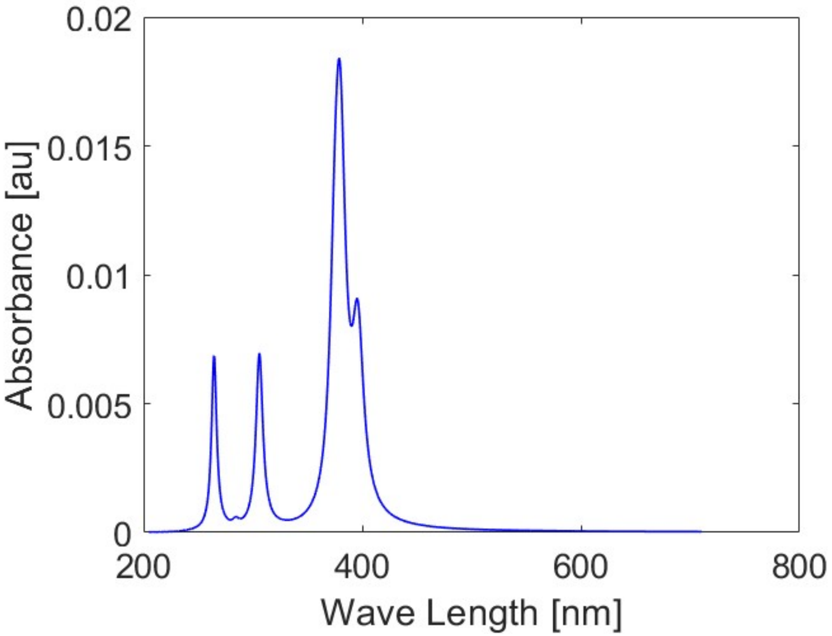
$$\Delta SASA = SASA_{complex} - (SASA_{UV} + SASA_{cyclo})$$

- ΔSASA may be considered as an indicator of the extent to which the surface area of the UV filter is buried in the cyclodextrin cavity upon complexation.
- ΔSASA values also indicate that the chemical UV filters form inclusion complexes rather than associating on the cyclodextrin exterior surfaces.
- Moreover, ΔSASA indicates that the hydrophobic effect participates in the complexation under investigation and is, more specifically, one of the driving forces, facilitated by the displacement of trapped water molecules from the cyclodextrin cavity.
- The drop in $SASA_{UV}$ upon complexation indicates an enhancement in UV filter solubility since the hydrophobic portions are shielded from water, whereas the hydrophilic exterior of cyclodextrins dominates the interactions of the complex with the surrounding aqueous environment.

System	SASA [nm^2]	Nonpolar SASA [nm^2]	Polar SASA [nm^2]
avobenzone (keto form) – β-CD	13.20 ± 0.01	6.45 ± 0.01	6.75 ± 0.01
avobenzone (enol form) – β-CD	13.03 ± 0.02	6.35 ± 0.04	6.68 ± 0.03
octocrylene – β-CD	13.17 ± 0.02	7.13 ± 0.02	6.04 ± 0.01
avobenzone (keto form) – HP-β-CD	17.11 ± 0.14	10.60 ± 0.15	6.51 ± 0.05
avobenzone (enol form) – HP-β-CD	16.57 ± 0.06	9.89 ± 0.07	6.68 ± 0.03
octocrylene – HP-β-CD	16.77 ± 0.07	10.58 ± 0.07	6.46 ± 0.02
free octocrylene	6.44 ± 0.01	5.62 ± 0.01	0.82 ± 0.01
free avobenzone (keto form)	5.97 ± 0.01	5.18 ± 0.01	0.79 ± 0.01
free avobenzone (enol form)	6.01 ± 0.01	5.21 ± 0.01	0.81 ± 0.01
free HP-β-CD	15.71 ± 0.28	8.89 ± 0.28	6.82 ± 0.03
free β-CD	12.10 ± 0.01	4.94 ± 0.01	7.16 ± 0.01

Fine Graining

- A significant trend in multiscale modelling is fine-graining, i.e., the process of moving from a coarser level of description to a more detailed one, revealing underlying structures and phenomena that are not visible at the higher level.
- Fine-graining from the atomistic to the quantum level will be implemented for cyclodextrin–UV-filter systems in aqueous environments.
- Representative configurations obtained from a clustering analysis of the trajectories of the MD simulations are employed as input for TD-DFT simulations with the NWCHEM package.
- The water environment is represented using the conductor-like screening model (COSMO).



UV-Vis spectrum of avobenzone in water using COSMO (without cyclodextrins)

Concluding Remarks

- In all *in silico* experiments, the complexes are spontaneously formed within time scales of a few hundred nanoseconds and remain in the bound state for the rest of the simulations.

- The chemical UV filters displace the trapped water molecules when entering the hydrophobic cavity.

- Negative binding Gibbs energies whose values are in good agreement with published articles.

- In the case of enol avobenzone, the chelated form is more stable than the nonchelated form (the chelated form of avobenzone predominates over the nonchelated one). Photodegradation typically initiates through the chelated-to-nonchelated transition when avobenzone is found in the enol form.

- Both chemical UV filters form a hydrogen-bond network with water molecules. Upon complexation, this network remains present but is attenuated.

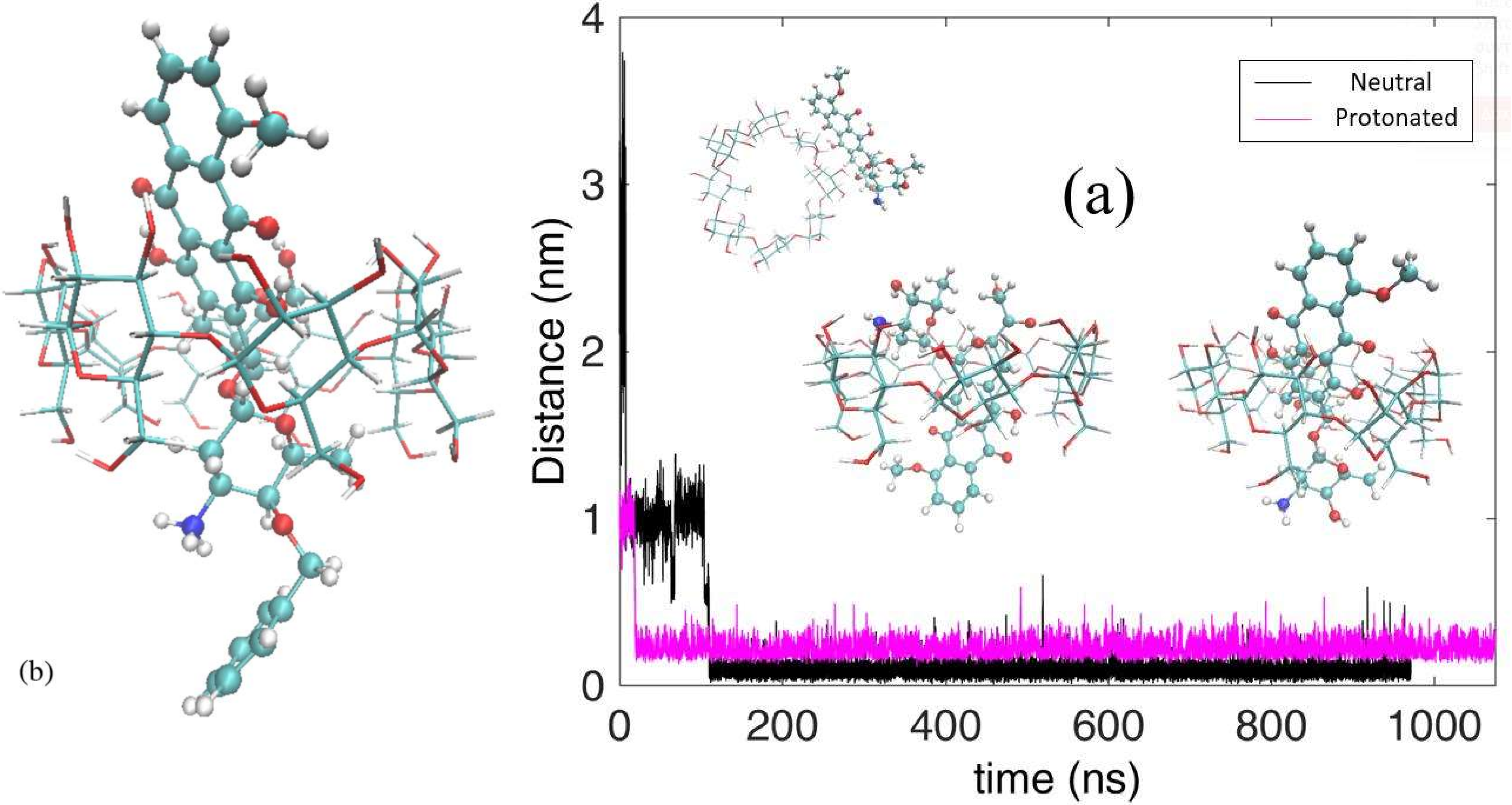
- Both octocrylene and avobenzone exhibit lower mobility when they are found in the bound state, suggesting that their free motion in an aqueous environment is noticeably hindered upon complexation. The observed drop in diffusivity has potentially advantageous effects, such as prolonged use and slowing of degradation processes.

- SASA calculations show that the complexation process improves the behavior of avobenzone and octocrylene in a water environment.

- We have established a robust in silico protocol that will be applied to the best candidates obtained from machine learning modeling, as complexes with cyclodextrins in water.

THANK YOU FOR YOUR ATTENTION!!!

Backup Slides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(a)
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