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**Solvation environment effects on the photoisomerization equilibrium of the
model tannins catechin and epicatechin as natural sunscreens in aquatic
systems**

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Abstract

The photoisomerization equilibrium between the model tannins (-)-catechin and (-)-epicatechin in aqueous solution was investigated at the density functional level of theory in order to gain insights into the action of these compounds as natural sunscreens in aquatic systems. Increasing water temperature, as might be expected on seasonal and diurnal bases, is predicted to shift the equilibrium further in favor of catechin. The isomerization energy between catechin and epicatechin was also considered in a range of polar protic, polar aprotic, apolar protic, and apolar aprotic solvents using the Solvation Model based on Density (SMD) and Integral-Equation-Formalism Polarizable Continuum Model (IEFPCM) solvation models. The IEFPCM model yielded a modest range in isomerization energies depending on solvent polarity/proticity, whereas a substantial variation was observed with the SMD model. The SMD results suggest the solvation environment around catechin and epicatechin will play a major role on the photoisomerization equilibrium between these two compounds. As the freely dissolved monomer in aquatic systems, the catechin-epicatechin photoisomerization equilibrium will be in the range of 11:1 to 14:1. When in the less polar environments of associations with dissolved organic matter or within a larger tannin structural framework, the theoretical modeling efforts indicate that the catechin-epicatechin photoisomerization equilibrium could be as low as 3:1.

Keywords: Catechin; Epicatechin; Photoisomerization equilibrium; Natural sunscreen; Density functional theory

Introduction

Ultraviolet (UV) light comprises less than 5 percent of the total radiation reaching the Earth's surface yet represents the most energetic, and ultimately biologically harmful, wavelengths. As sunlight penetrates into freshwater bodies, the majority of radiation is absorbed by natural dissolved and particulate substances, influenced by the particles suspended in the water and -- of particular importance -- by dissolved organic matter (DOM) ¹⁻⁶. DOM is the residue of decaying organic matter from allochthonous terrestrial soils and vegetation and, to a lesser extent, via autochthonous inputs from plants and microbes within the water body itself ⁷. It is comprised of a complex mixture of large organic polymers derived from humic and fulvic acids. Chromophoric DOM, which absorbs from 300 to 500 nm and thus acts as a natural sunscreen to protect aquatic systems from UV radiation through absorption and subsequent radiative dissipation processes, characterizes the optically active component of DOM ^{5,6,8,9}.

DOM can serve to protect the water column from the direct effects of UV radiation, yet can itself be slowly degraded through photobleaching processes that include the conversion of conjugated unsaturated moieties into less conjugated unsaturated, as well as saturated, functional groups ^{2,3,10}. Photodegradation of DOM can therefore alter the absorption characteristics of the water body, allowing deeper penetration of UV light into the water column ^{2,5,7,11}. Furthermore, as a result of ozone depletion increasing the amount of UV radiation reaching the Earth's surface, and climate change -- which alters the quantity and type of material inputs that contribute to DOM --

freshwater systems are under threat of increased risks from additional UV exposure^{2,12}. This can result in molecular level damage to lipids, proteins, and nucleic acids and a corresponding reduction of productivity, impaired reproduction and development, and increased mutation rates³.

Many aquatic organisms have developed defense mechanisms to deal with UV radiation, including the production of light absorbing compounds to moderate the amount of light that penetrates the cell¹³. Sunscreening compounds include the microsporine-like amino acids found in algae, cyanobacteria, fungi, lichens, corals, and molluscs, scytonemin in cyanobacteria, and the phenylpropanoids in higher plants^{3,8,10,13,14}. Within the phenylpropanoid class, catechin is a simple flavanoid that is not only present in plants as the monomeric species but is also incorporated into, and thereby models, the more complex oligomeric and macromolecular structure of the tannin framework in humic materials. Previous work¹⁵ has shown that catechin - acting both as the monomer and as a model functionality within tannins -- can act as a sunscreen in aquatic systems through a photoisomerization equilibrium with epicatechin. In the current study, we sought to conduct the first modeling of this important reaction using theoretical approaches, and to examine the potential influence of solvation environment on the corresponding equilibrium constant in order to better understand the photochemical behavior of these two compounds in natural surface waters.

Computational Methods

79
80 Molecular mechanics conformational studies to determine the lowest energy conformations of
81 each compound were conducted using the Merck Molecular Force Field 94 (MMFF94) force
82 field and a systematic rotor search within Avogadro v.1.1.1¹⁶. The MMFF94 force field is
83 capable of reproducing experimental bond lengths within 0.014 Å (root mean square [rms]),
84 bond angles within 1.2° rms, and conformational energies within 0.38 kcal/mol/rms. All
85 subsequent calculations were conducted using Gaussian 09 (G09)¹⁷ with the MMFF94
86 optimized geometries as inputs. Full reference details for the density functionals employed
87 within G09 are provided in our previous works^{18,19} and are omitted here for brevity. Dispersion
88 corrections, which can substantially improve the accuracy of isomerization energy calculations
89 for medium to large-sized organic molecules, were applied to selected density functionals using
90 the GD2²⁰, GD3²¹, and GD3BJ (with Becke-Johnson damping)²² versions of Grimme's
91 dispersion approaches, including subsequent comparisons to the performance of each functional
92 without corrections. Solution phase calculations employed the Solvation Model based on Density
93 (SMD)²³ and Integral-Equation-Formalism Polarizable Continuum Model (IEFPCM)^{24,25}
94 continuum solvation models. Under these solvation approaches, the solute is placed in a cavity
95 within the solvent reaction field. Optimized geometries were visualized using the Gabedit 2.4.7
96²⁶ and Avogadro 1.1.1¹⁶ software programs. All final geometries are true minima on the global
97 potential energy surface absent any imaginary frequencies.

98

99 Results and Discussion

100

101 In a prior investigation, the model tannins (-)-catechin (**1**) and (-)-epicatechin (**2**) were observed
102 to undergo a reversible photoisomerization in aqueous solution (Figure 1)¹⁵. Under ultraviolet
103 light irradiation in aqueous solution at 298.15 K, a photostationary state was rapidly reached
104 between the two isomers at a ratio of 93.3:6.7 in favor of (-)-**1** (Figure 2). The reported
105 equilibrium isomeric ratio suggested a Gibbs free energy of isomerization ($\Delta_{\text{isom}}G_{(\text{aq})} = -$
106 $RT\ln K_{\text{isom}}$) for the photoreaction (-)-**2** → (-)-**1** of -1.56 kcal/mol.

107

108 Based on previous experience, the choice of model chemistry employed for thermodynamic
109 studies of isomerization reactions is critical. The vast majority of density functionals display
110 gross systematic errors when applied against isomerization energies²⁷⁻²⁹, necessitating a prior
111 calibration step against experimental data. The $\Delta_{\text{isom}}G_{(\text{aq})}$ of (-)-**2** → (-)-**1** was initially calculated
112 using 39 pure, hybrid, and range-separated hybrid density functionals currently implemented in
113 Gaussian 09 in tandem with the triple- ζ TZVP Ahlrichs-type basis set using both the SMD and
114 IEFPCM solvation models (Table 1). The starting geometries for (-)-**2** and (-)-**1** were obtained
115 using the MMFF94 force field with a systematic rotor search for the lowest energy conformer. In
116 agreement with previous studies^{30,31}, we found that both (-)-**2** and (-)-**1** adopted the
117 pseudoequatorial conformation as the lowest energy state with the pseudoaxial conformer
118 slightly higher (<1 kcal/mol) in energy. The $\Delta_{\text{isom}}G_{(\text{aq})}$ obtained with the SMD solvation model
119 ranged from -1.01 (M11L) to +0.35 (M06L) kcal/mol, with the corresponding range for the
120 IEFPCM solvation model from -1.07 (BMK) to -0.09 (M06L) kcal/mol.

121

122 None of the density functionals used in this initial step included dispersion correction terms, and
123 they all yielded unsatisfactory theoretical results for the reaction under consideration with
124 minimum/maximum errors against the experimental data of 0.49 and 1.91 kcal/mol, respectively.
125 Although errors on the order of ~ 0.5 to 2 kcal/mol are generally considered at or near effective
126 thermochemical accuracy for theoretical methods, when modeling equilibria such as that for (-)-
127 **2** $\rightarrow$ (-)-**1** with $\Delta_{\text{isom}}G_{\text{(aq)}}$ within a few kcal/mol of isoenergonicity a greater standard of maximal
128 error is required. For example, even a $\Delta_{\text{isom}}G_{\text{(aq)}}$ of -1.07 kcal/mol -- which is very close in
129 absolute terms to the experimental value of -1.56 kcal/mol -- leads to a corresponding $K_{\text{isom}} \approx 6.1$,
130 far from the experimental K_{isom} of 13.9 (a 0.36 $\log_{10}$ unit deviation).

131

132 Upon examination of a range of functionals using the GD2, GD3, and GD3BJ dispersion
133 corrections with the TZVP basis set (Table 2), only the B97D3 functional with the SMD
134 solvation model and a GD3BJ dispersion correction yielded a $\Delta_{\text{isom}}G_{\text{(aq)}}$ (-1.39 kcal/mol) in good
135 agreement ($< 11\%$ deviation) with the experimental data. The IEFPCM solvation model gave a
136 $\Delta_{\text{isom}}G_{\text{(aq)}}$ of -1.07 kcal/mol (31% deviation from experimental) at the B97D3-GD3BJ/TZVP
137 level. Overall, dispersion corrections had a mixed impact, both in terms of magnitude and
138 direction on $\Delta_{\text{isom}}G_{\text{(aq)}}$, depending on the functional and solvation model employed, but no
139 combination performed adequately with the exception of the SMD-B97D3-GD3BJ/TZVP
140 method. The APF (SMD=-0.61 kcal/mol; IEFPCM=-0.67 kcal/mol) and APF-D (SMD=+1.06
141 kcal/mol; IEFPCM=-0.01 kcal/mol) functionals without and with dispersion correction,

respectively, were also examined, but neither gave satisfactory $\Delta_{\text{isom}}G_{(\text{aq})}$ results.

Different types (Pople, Dunning, and Ahlrichs) and levels of basis sets were also considered using the B97D3-GD3BJ dispersion corrected functional with the SMD and IEFPCM solvation models (Table 3). Increasing basis set size tends to decrease $\Delta_{\text{isom}}G_{(\text{aq})}$ with the exception of the cc-pVDZ (-1.69 kcal/mol) and cc-pVTZ (-1.19 kcal/mol) basis sets with the IEFPCM solvation model, whereby the move from a double- ζ to triple- ζ basis set increased $\Delta_{\text{isom}}G_{(\text{aq})}$. The cc-pVDZ result is only a 8.3% deviation from the experimental $\Delta_{\text{isom}}G_{(\text{aq})}$ data, but the cc-pVTZ data increases to a 24% discrepancy. Overall, the Ahlrichs suite of basis sets with the SMD solvation model provided the most coherent trend towards the closest agreement with experiment data. For this reason, the SMD-B97D3-GD3BJ/TZVP was viewed as the most reliable out of all approaches examined, and thereafter applied to investigate temperature and solvent effects on the catechin/epicatechin equilibrium.

Warming of surface waters takes place on seasonal and diurnal bases, and this is anticipated to have a substantial impact on the nature and extent of natural suncreening materials in aquatic systems. Aqueous phase calculations at the B97D3-GD3BJ/TZVP level using the SMD and IEFPCM solvation models suggest that increasing the water temperature from 0°C to 30°C will shift the photoisomerization equilibrium more exergonic in favor of catechin. With the SMD solvation model the catechin-epicatechin photoisomerization equilibrium would increase from 9:1 to 11:1, whereas the IEFPCM solvation model indicates this shift would be from 5.5:1 to

6.2:1.

The $\Delta_{\text{isom}}G_{(\text{aq})}$ was subsequently calculated at the B97D3-GD3BJ/TZVP level using both the SMD and IEFPCM solvation models with a range of polar protic (water, ethanol, and formic acid), polar aprotic (dimethylsulfoxide [DMSO], dichloromethane, and acetone), apolar protic (acetic acid and n-octanol), and apolar aprotic (benzene, cyclohexane, aniline, diethyl ether, tetrahydrofuran, heptane, and argon matrix) solvents (Table 4). These efforts were undertaken in order to approximate how changes in the microsolvation environment of the two compounds in natural aquatic systems can influence the corresponding photoisomerization equilibrium. Only a modest -- but still significant -- range in $\Delta_{\text{isom}}G_{(\text{aq})}$ (0.33 kcal/mol; from -1.25 kcal/mol in argon matrix up to -0.92 kcal/mol in dichloromethane and n-octanol) was observed with the IEFPCM solvation model among all solvents. The SMD model provided a much greater level of variability (1.05 kcal/mol; from -1.74 kcal/mol in argon matrix up to -0.68 kcal/mol in acetic acid).

If the SMD results more accurately represent differential solvation influences on $\Delta_{\text{isom}}G_{(\text{aq})}$, then the solvation environment around catechin and epicatechin would have a substantial impact on their photoisomerization equilibrium. In natural aquatic systems, these compounds are often associated with dissolved organic matter or are components within a larger natural macromolecule. This behavior leads to the catechin and epicatechin moieties residing, while still dissolved in the water column, within near-proximity environments whose impacts on reaction

energetics can be approximated by considering the effects on moving from the free dissolved pure aqueous phase to a range of other solvents and matrices with varying polarities and abilities to hydrogen bond and π -stack with the compounds of interest. Consequently, the theoretical results suggest that as the freely dissolved monomer in aquatic systems, the catechin-epicatechin photoisomerization equilibrium would reside at ~11-14:1. However, in less polar environments -- such as associations with other dissolved organic matter or being a moiety within a larger tannin macromolecule -- the catechin-epicatechin photoisomerization equilibrium is expected to be as low as 3:1. While these findings await experimental testing, their implications are significant for our understanding of how tannins behave under solar irradiation in natural aquatic systems, as well as the mechanistic details and efficacy of their role as sunscreens for aquatic biota.

Conclusions

Density functional theory calculations were used to investigate the photoisomerization equilibrium between the model tannins (-)-catechin and (-)-epicatechin in aquatic systems. Using the B97D3 functional with the SMD solvation model and a GD3BJ dispersion correction coupled to the triple- ζ TZVP Ahlrichs-type basis set produced good agreement (<11% [0.17 kcal/mol] deviation) against room temperature (298.15 K) experimental data ($K_{\text{isom}}[\text{catechin:epicatechin}]=13.9$). Subsequent computational modeling revealed that higher water temperatures are expected to shift the equilibrium more exergonic in favor of catechin.

205 In natural surface waters, catechin and epicatechin are not only present as the respective
206 monomers, but also as structural components within larger dissolved organic macromolecules.
207 For both cases, the actual microsolvation environment around much of the catechin and
208 epicatechin residing in natural aquatic systems may not be pure water, but rather an environment
209 that may include various other organic compounds acting as effective co-solvents. These other
210 naturally occurring compounds that help solubilize catechin and epicatechin monomers, as well
211 as the larger organic macromolecules of which catechin and epicatechin are structural members,
212 will contain a range of functional groups in proximity to the catechin and epicatechin moieties.
213 As a result, to best understand the actual in situ isomerization energy of this system, modeling
214 needs to be conducted both in pure water and a range of organic solvents that act as proxies for
215 the potential microsolvation environments around catechin and epicatechin. Corresponding
216 calculations in a range of polar protic, polar aprotic, apolar protic, and apolar aprotic solvents
217 using the SMD and IEFPCM solvation models indicated a significant solvation environment
218 effect on the photoisomerization equilibrium. The SMD results suggested that substantial
219 reductions in the polarity of the microsolvation environment around catechin and epicatechin
220 may reduce the photoisomerization equilibrium by as much as an order of magnitude to a near
221 isoenergetic state.
222
223 The theoretical results offer guidance and benchmarks for future experimental studies regarding
224 the influence of temperature and microsolvation environment on the photoisomerization
225 equilibrium between catechin and epicatechin, as well as insights into the importance of these

factors in better understanding how this important suncreening system operates in natural surface waters.

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Table 1. Aqueous phase standard state (298.15 K; 1 M) Gibbs free energies of isomerization ($\Delta_{\text{isom}}G^\circ_{(\text{aq})}$) for the photoisomerization of (-)-epicatechin (**2**) to (-)-catechin (**1**) at the x/TZVP level of theory (where x is the model chemistry employed) using the SMD and IEFPCM solvation models. Values are in kcal/mol.

Model chemistry	SMD	IEFPCM	Model chemistry	SMD	IEFPCM
APF	-0.61	-0.67	M062X	0.12	-0.45
B1B95	-0.28	-0.93	M06HF	-0.05	-0.62
B1LYP	-0.04	-0.82	M06L	0.35	-0.09
B3LYP	0.04	-0.83	M11L	-1.01	-0.92
B3P86	-0.43	-0.64	MN12L	0.33	-0.12
B3PW91	-0.67	-0.75	MN12SX	0.23	-0.60
B98	-0.08	-0.80	mPW1LYP	0.05	-0.80
BHandH	-0.30	-0.54	mPW1PBE	-0.59	-0.65
BHandHLYP	-0.32	-0.77	mPW3PBE	-0.65	-0.67
BLYP	-0.61	-0.88	OPBE	0.20	-0.76
BMK	0.03	-1.07	OTPSS	-0.07	-0.75
CAM-B3LYP	-0.45	-0.66	PBE0	-0.57	-0.63
HCTH/147	-0.38	-0.68	SOGGA11X	-0.73	-0.56
HCTH/407	-0.07	-0.70	tHCTH	0.29	-0.73
HISSbPBE	-0.66	-0.73	tHCTHhyb	-0.44	-0.78
HSE06	-0.57	-0.63	TPSSh	-0.34	-0.75
LC-wPBE	-0.56	-0.44	wB97	-0.64	-0.60
M05	0.04	-0.42	wB97X	-0.61	-0.62
M052X	-0.79	-0.60	X3LYP	0.03	-0.80
M06	-0.28	-0.31			

Table 2. Aqueous phase standard state (298.15 K; 1 M) Gibbs free energies of isomerization ($\Delta_{\text{isom}}G^\circ_{\text{(aq)}}$) for the photoisomerization of (-)-epicatechin (**2**) to (-)-catechin (**1**) at the x/TZVP level of theory (where x is the model chemistry employed) using the SMD and IEFPCM solvation models with the GD2, GD3, and GD3BJ dispersion corrections. Values are in kcal/mol.

Model chemistry	SMD				IEFPCM			
	None	GD2	GD3	GD3BJ	None	GD2	GD3	GD3BJ
B3LYP	0.04	0.05	-0.53	-0.63	-0.83	-0.62	-0.67	-0.59
BLYP	-0.61	0.04	-0.55	-0.76	-0.88	-0.80	-0.79	-1.00
PBE0	-0.57	n/d ^a	0.06	-0.03	-0.63	n/d	-0.51	-0.50
BMK	0.03	n/d	0.20	0.37	-1.07	n/d	-0.27	-1.08
B3PW91	-0.67	n/d	0.05	0.04	-0.75	n/d	-0.50	-0.46
CAM-B3LYP	-0.45	n/d	-0.35	-0.81	-0.66	n/d	-0.52	-0.52
LC-wPBE	-0.56	n/d	0.14	-0.11	-0.44	n/d	-0.40	-0.35
M05	0.04	n/d	n/d	0.17	-0.42	n/d	n/d	-0.40
M052X	-0.79	n/d	n/d	-0.72	-0.60	n/d	n/d	-0.53
M06	-0.28	n/d	n/d	-0.22	-0.31	n/d	n/d	-0.23
M06L	0.35	n/d	n/d	0.36	-0.09	n/d	n/d	-0.05
M06HF	-0.05	n/d	n/d	-0.01	-0.62	n/d	n/d	-0.62
M062X	0.12	n/d	n/d	0.13	-0.45	n/d	n/d	-0.44
wB97X	-0.61	-0.70	n/d	n/d	-0.62	-0.45	n/d	n/d
B97	--	-0.07	-0.97	-1.39	--	-0.79	-0.64	-1.07

^a Dispersion correction parameters not defined for this functional.

Table 3. Aqueous phase standard state (298.15 K; 1 M) Gibbs free energies of isomerization ($\Delta_{\text{isom}}G^\circ_{(\text{aq})}$) for the photoisomerization of (-)-epicatechin (**2**) to (-)-catechin (**1**) at the B97-GD3BJ/y level of theory (where y is the basis set employed) using the SMD and IEFPCM solvation models. Values are in kcal/mol.

Basis set	SMD	IEFPCM
6-31G(d)	0.05	-1.07
6-311+G(d)	-1.20	i ^a
cc-pVDZ	-0.65	-1.69
cc-pVTZ	-1.06	-1.19
SV	-0.21	-0.65
SVP	0.36	-0.71
TZV	0.02	i
TZVP	-1.39	-1.07

^a Unable to obtain a converged geometry for either the reactant or product absent any imaginary frequencies.

Table 4. Solvent phase standard state (298.15 K; 1 M) Gibbs free energies of isomerization ($\Delta_{\text{isom}}G^\circ_{(\text{aq})}$) for the photoisomerization of (-)-epicatechin (**2**) to (-)-catechin (**1**) at the B97-GD3BJ/TZVP level of theory using the SMD and IEFPCM solvation models with a range of solvents. Values are in kcal/mol.

Solvent	SMD	IEFPCM
Acetic acid	-0.68	-0.94
Acetone	-0.73	-0.99
Aniline	-1.00	-0.93
Argon	-1.74	-1.25
Benzene	-1.00	-1.13
Cyclohexane	-1.10	-1.17
Dichloromethane	-0.87	-0.92
Diethyl ether	-0.89	-0.98
DMSO	-1.27	-1.04
Ethanol	-1.05	-1.00
Formic acid	-1.12	-1.05
Heptane	-1.17	-1.18
n-Octanol	-0.90	-0.92
Tetrahydrofuran	-1.18	-0.93
Water	-1.39	-1.07

Figure Captions

Figure 1. Photoisomerization reaction between (-)-catechin (**1**) and (-)-epicatechin (**2**).

Figure 2. Photochemical conversion of (-)-epicatechin (**2**) to (-)-catechin (**1**) under 254 nm irradiation in aqueous acetonitrile (1:1, v/v) at various irradiation times. Adapted from ref. ¹⁵.

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Figure 1.

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334 Figure 2.
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