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Study of the Protonation States of the Curcumin Molecule and Their Visible Absorption Spectra in Aqueous Solution Using M06, SMD, and TDDFT and Compared to Experiment

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Abstract: Curcumin, the primary natural dye from the spice turmeric, has been of recent interest due to its possible health benefits as an antioxidant and possible anti cancer and anti Alzheimer's properties. Limited solubility and instability in water are of primary importance when considering curcumin's possible uses as a pharmaceutical. DFT computations were carried out using B3LYP and MO6 density functionals and the SMD solvent model for water. TDDFT computations were carried out on geometries optimized in water as described by the SMD solvent model. It is found that M06 with the 3-21G* basis set and SMD solvent model gives accurate λ_{max} values though the larger 6-31+G* basis set is needed for accurate description of the trianionic protonation state. The 6-31+G* basis set is also needed for accurate computation of pKa values. The particle-in-a-box model gives unexpectedly good agreement with computational λ_{max} values when delocalization of phenolic lone pair electrons are appropriately considered in the different protonation states and box lengths from optimized geometries are used. This gives a simple model of how the electronic structure of curcumin is influenced by protonation state and is in good agreement with both computation and experiment.

Outline

- Curcumin
- Protonation states, their λ_{max} and pKa
- Computational goals and details
- Results
- Particle-in-a-box application
- Conclusions

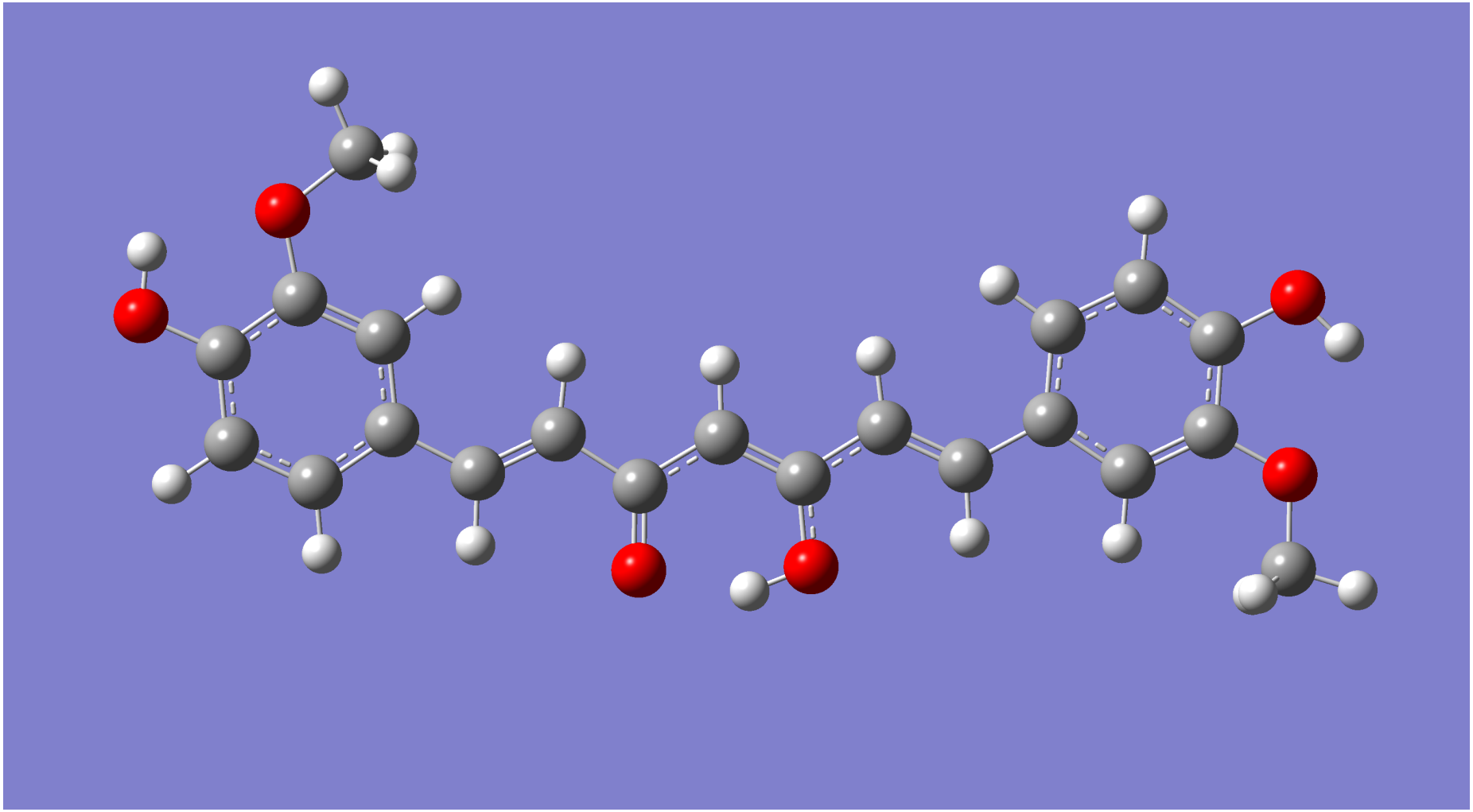
R. Sharma *et al.*, European Journal of Cancer, 41, 2005, 1955-1968

curcumin

- Yellow dye from the spice turmeric
- Beautiful yellow color in curries.
- Keto-enol tautomers
- Five protonation states with different solubility, λ_{max}, and kinetic stability
- Of pharmacological interest [a,b]

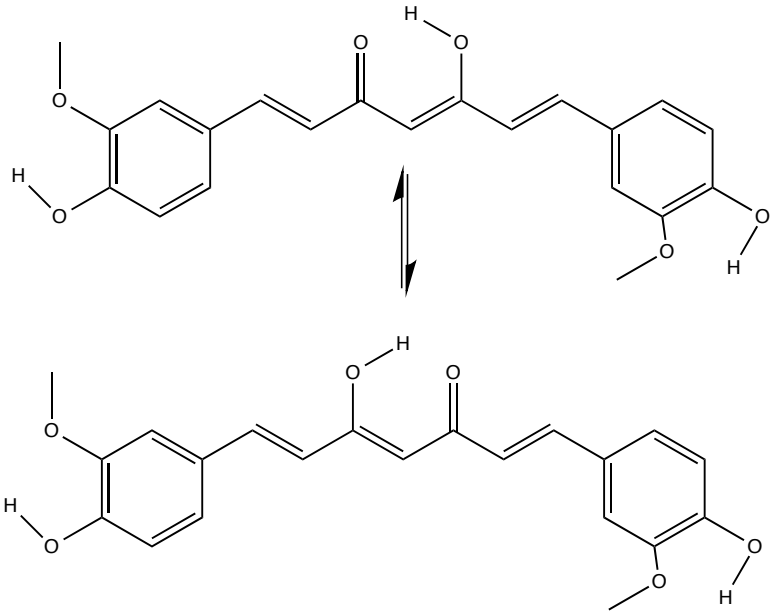
[a] S. Angela et al., Int. J of Clin Pharmacol Ther 2015, 53(1) 54-65.
[b] R. Sharma *et al.*, European Journal of Cancer, 41, 2005, 1955-1968.

Molecular structure of curcumin

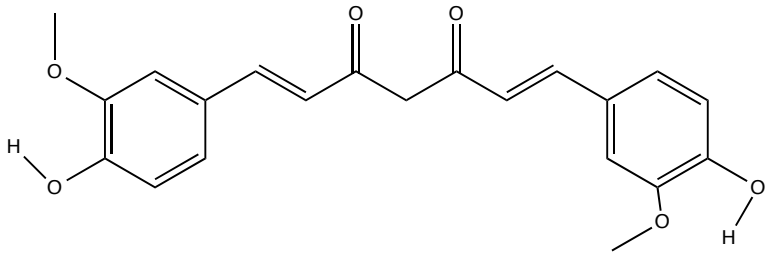


Enol-keto tautomers favored according to NMR

enol - keto tautomers



diketone



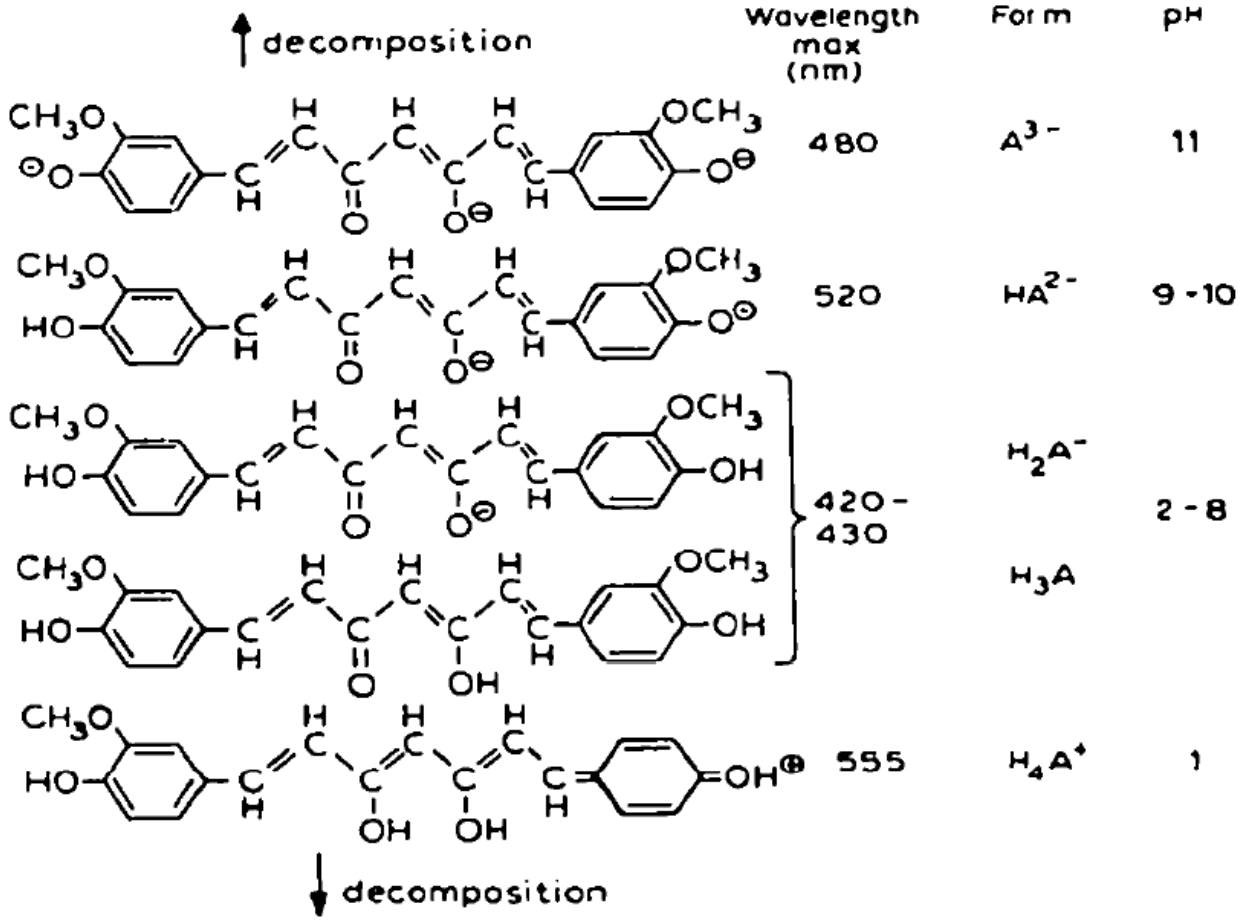
- Enol-keto favored in $DCCl_3$ and DMSO-d_6, CD_3OD, D_2O, H_2O buffered mixtures from pH 3-9 (^{13}C and ^{1}H NMR techniques.[a])
- Enol-keto tautomers favored in solid state.[b]
- Enol-keto tautomers favored in gas phase and methanol medium[c] (B3LYP/6-311G**)

[a] Payton *et al.*, *Journal of Natural Products*, 2007, 70(2), 143-146.

[b] Parimita *et al., Acta Cryst. 2007, E63, 860-862.*

[c] R. Benassi et al., Journal of Molecular Structure 892, 2008 168-176.

Protonation states in solution of given pH



D. Dyrssen, Y. Novikov, L. Uppstrom, *Anal. Chim. Acta*, 60, 1972, 145

Experimental aqueous pKa

species	pKa			
	UV-vis	UV-vis	Potentiometric titratoin	HCl titration
H_3Curr	8.38[a]	8.55[b]	8.54[b]	8.38[b]
H_2Curr^{1-}	9.88[a]	——	9.30[b]	9.88[b]
$HCurr^{2-}$	10.51[a]	10.41[b]	10.69[b]	10.51[b]

[a]M. Bernabe-Pineda et al., Spectrochimica Acta Part A 60 (2004) 1091-1097

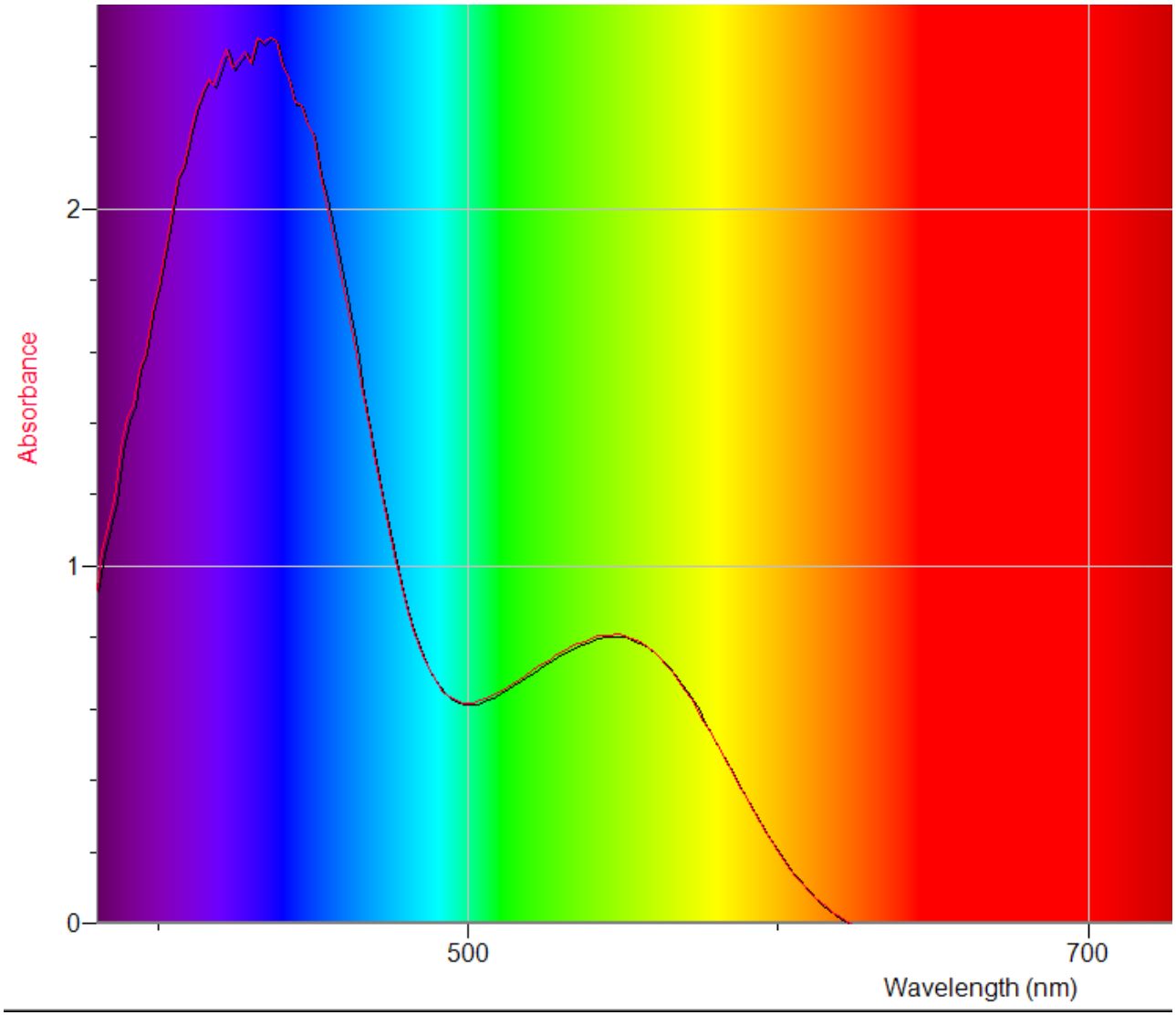
[b]M. Lestari, G Indrayanto, *Profiles of Drug Substances, Excipients, and Related Methodology*, Volume 39, Chapter 3, 2014, Elsevier, page 115

UV-vis Experimental λ_{max}

species	λ_{max} (nm)		
	Dyrrsen 1972	Bernabe-Pineda 2007	Goemann and Roettgen 2014
H_4Curr^{1+}	555	---------	555
H_3Curr	420 -430	422	420 - 430
H_2Curr^{1-}	420 - 430	---------	-------
$HCurr^{2-}$	520	463	450
$Curr^{3-}$	480	----------	470

[a]D. Dyrssen, Y. Novikov, L. Uppstrom, Anal. Chim. Acta, 60, 1972, 145
[b]M. Bernabe-Pineda et al, Spectrochimica Acta Part A 60, 2004, 1091-1097
[c]H. Goemann, T. Roettgen, CURF funded summer research at UMM, 2014

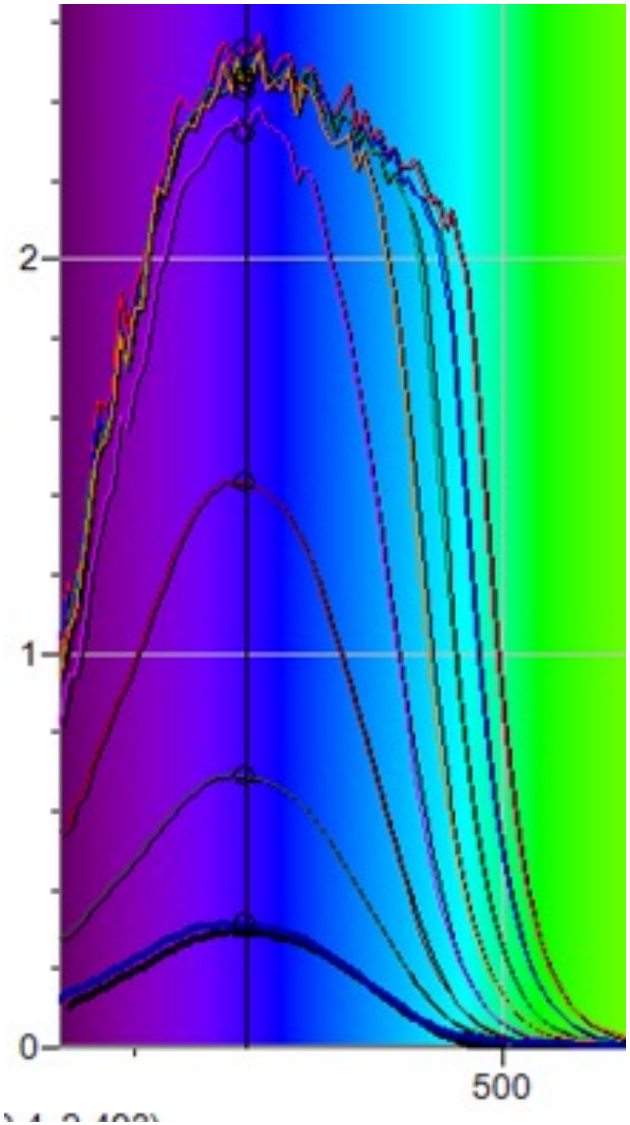
Absorbance at pH < 1



Roughly 10^{-5} M curcumin in an acetic acid – sulfuric acid mix

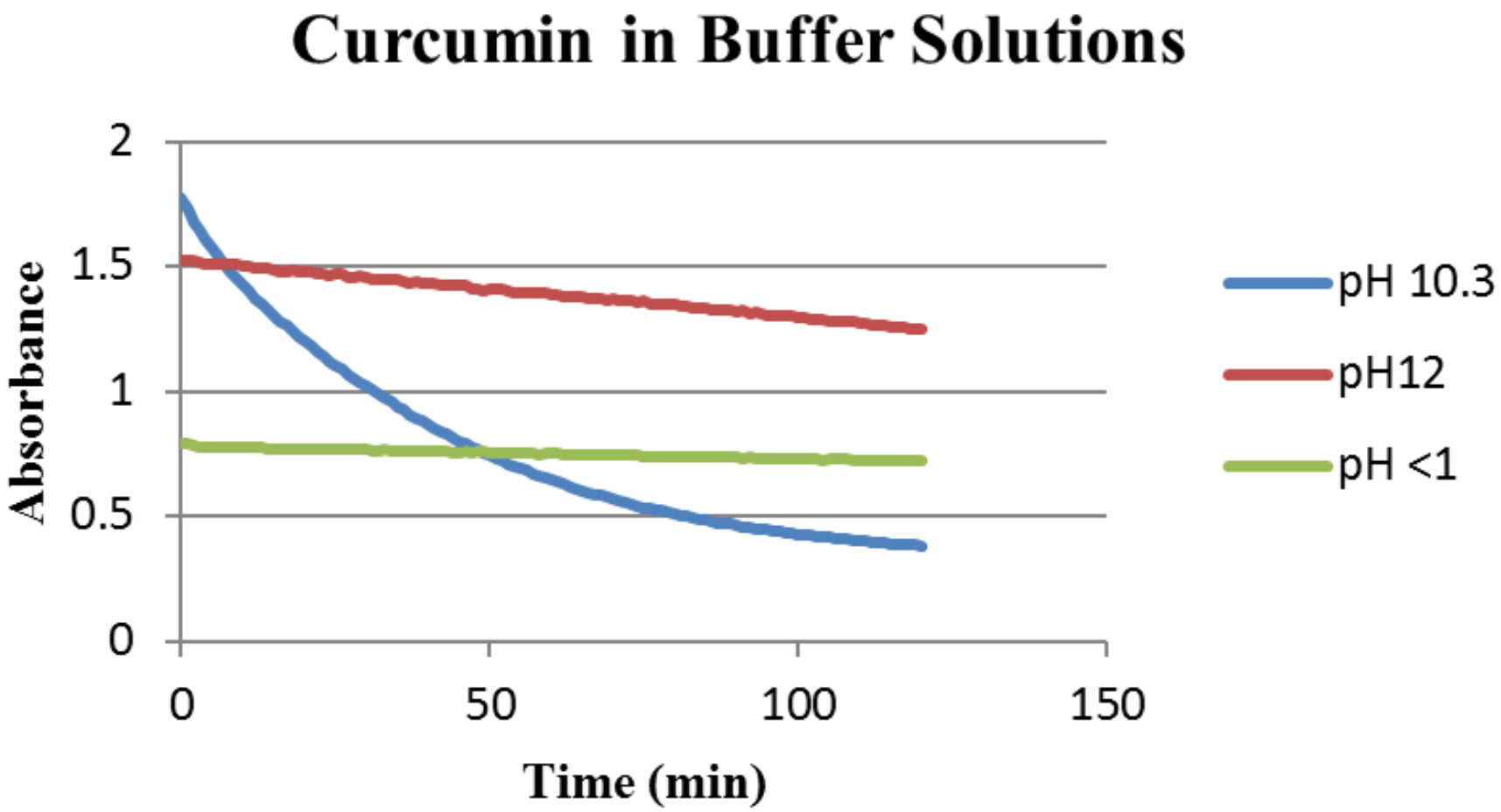
λ_{max} for the smaller peak is 555 nm.

Curcumin absorbance at neutral pH

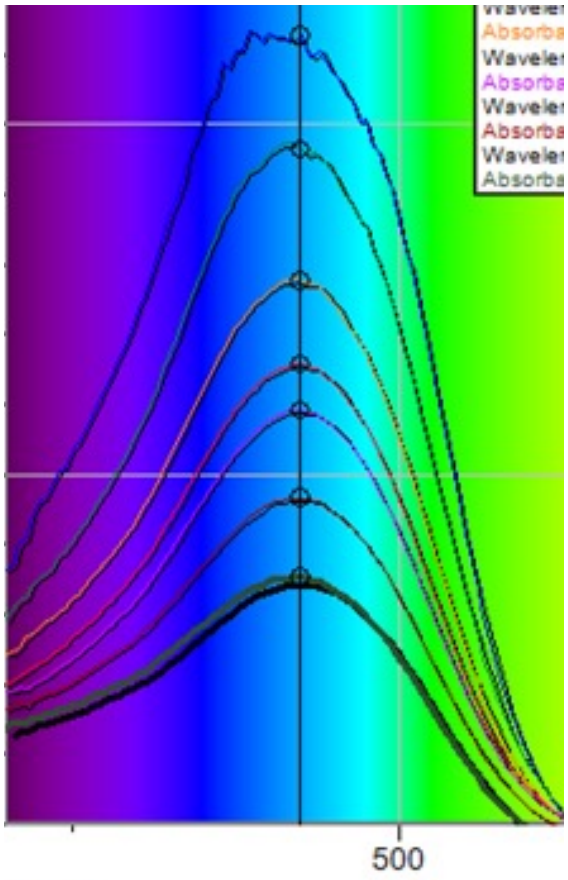


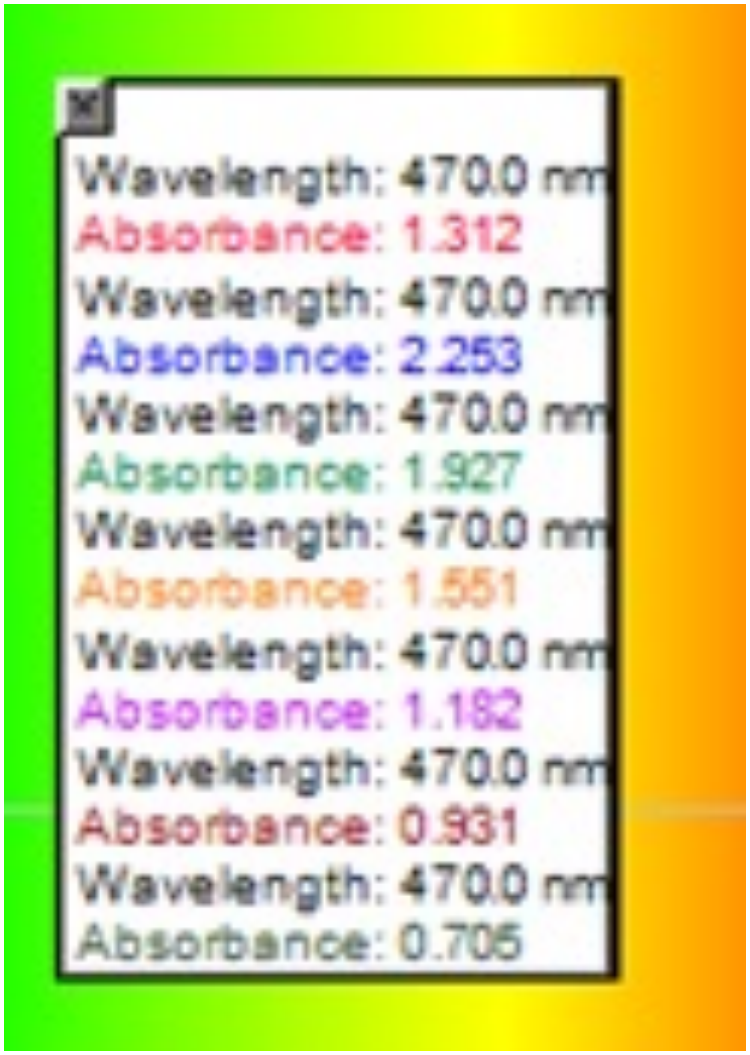
Roughly 10^{-5} M curcumin in roughly 1 % ethanol aqueous solution

Measurements at pH 10 are problematic



Absorbance at pH greater than 12





Roughly 10^{-5} M curcumin in roughly 0.05 M NaOH (aq)

Computational Goals

Use HF, B3LYP[a], and M06 family[b,c] methods with small basis sets and the SMD[d] solvent model to

- predict relative stability of enol – keto tautomers vs the diketone
- compute pKa values for curcumin protonation states in aqueous solution.
- compute accurate λ_{max} for curcumin protonation states in aqueous solution.
- Interpret results in terms of molecular structure and electron delocalization
- Clarify experimental results if possible

[a] A. Becke, *J. Chem. Phys*. 1996, 104, 1040-1046

[b] D. Jacquemin et al. *J. Chem Theory Comput*. 2010, 6, 2071-2085.

[c] Y. Zhao, D. Truhlar, *Theor. Chem. Acc*. 2008, 120, 215

[d] Marenich et al., *J. Phys. Chem. B*, 113, 18, 2009, 6378 – 6396.

Computational details

- Computations were carried out using G09[a] iMac
- Geometries optimized for each protonation state and tautomer using HF, B3LYP[b], M062x[c], M06HF[c], and M06[c], the SMD[d] (water) solvent model and 3-21Gd basis set.
- Geometries re-optimized when larger basis sets, 6-31Gd and 6-31+Gd, were tried.
- Frequency calculations verified local minima and provided thermochemical data.
- TD calculations performed on optimized geometries for each respective method and optimization of the transition with greatest oscillator strength to predict visible λ_{max}

[a] Revision B .01, Gaussian Inc. 2010

[b] A. Becke, *J. Chem. Phys*. 1996, 104, 1040-1046

[c] D. Jacquemin et al. *J. Chem Theory Comput*. 2010, 6, 2071-2085.

[d] Y. Zhao, D. Truhlar, *Theor. Chem. Acc*. 2008, 120, 215

[e] Marenich et al., *J. Phys. Chem. B*, 113, 18, 2009, 6378 – 6396.

Method for computing pKa

$$pKa = \frac{\Delta G^o}{(\ln 10) RT}, \qquad \Delta G^o = G^o_{(H^+(aq))} + G^o_{(A^-(aq))} - G^o_{(HA(aq))}$$

$G^o_{(A^-(aq))}$ and $G^o_{(HA(aq)}$ include contributions from HF or DFT electronic energy, solvation (SMD-water), thermal vibrational energy at 298 K and ZPE.

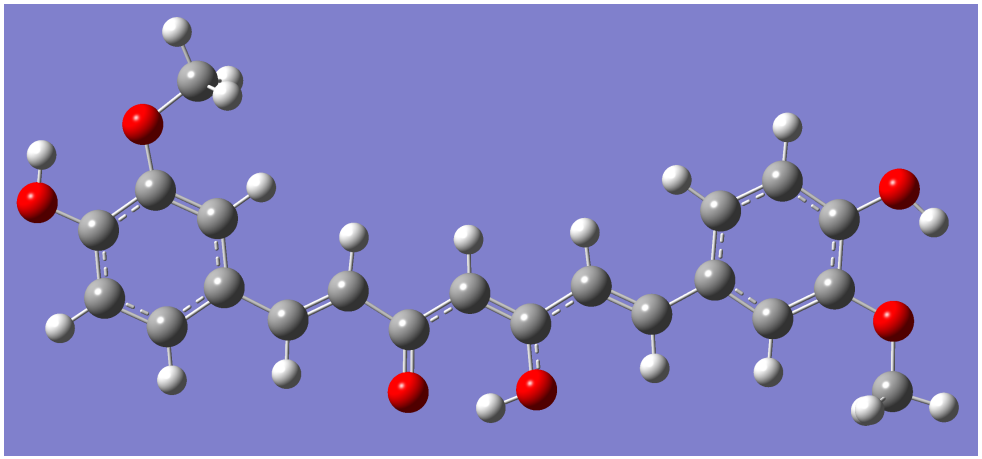
$$\Delta G^o_{(H^+(aq))} = G^o_{(H^+(g))} + \Delta_{solv} G^o_{(H^+(g \rightarrow aq))} + RT \ln(24.46)$$

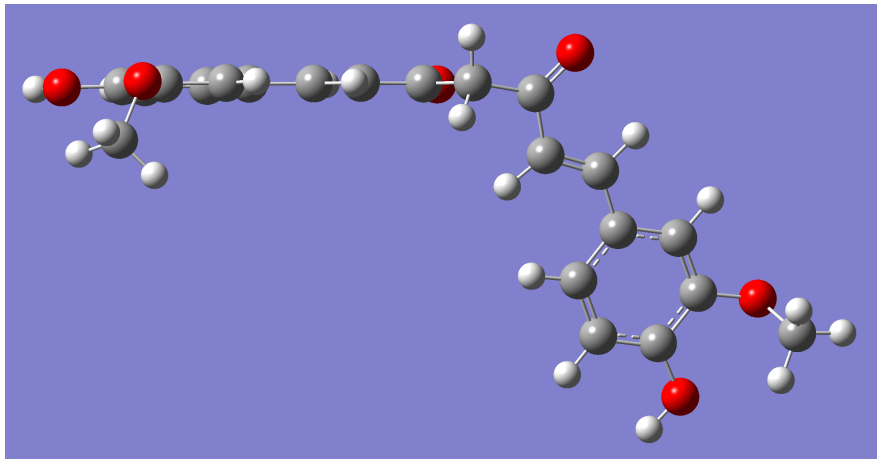
$$G^o_{(H^+(aq))} = -6.28 \frac{kcal}{mol} + -264.61 \frac{kcal}{mol} + 1.89 \frac{kcal}{mol} = -269.00 \frac{kcal}{mol}$$

G. Shields, S. Alongi. *Annual Reports in Computational Chemistry*, Volume 6, Chapter 8, Elsevier 2010.

Relative stability of tautomers

$$enol \rightarrow keto$$





$$\Delta_{taut} G^{o} = G^{o}_{keto} - G^{o}_{enol}$$

$G^{o}_{(keto\ (aq))}$ and $G^{o}_{(enol\ (aq)}$ include contributions from HF or DFT electronic energy, solvation (SMD-water), thermal vibrational energy at 298 K and ZPE.

Computational Results

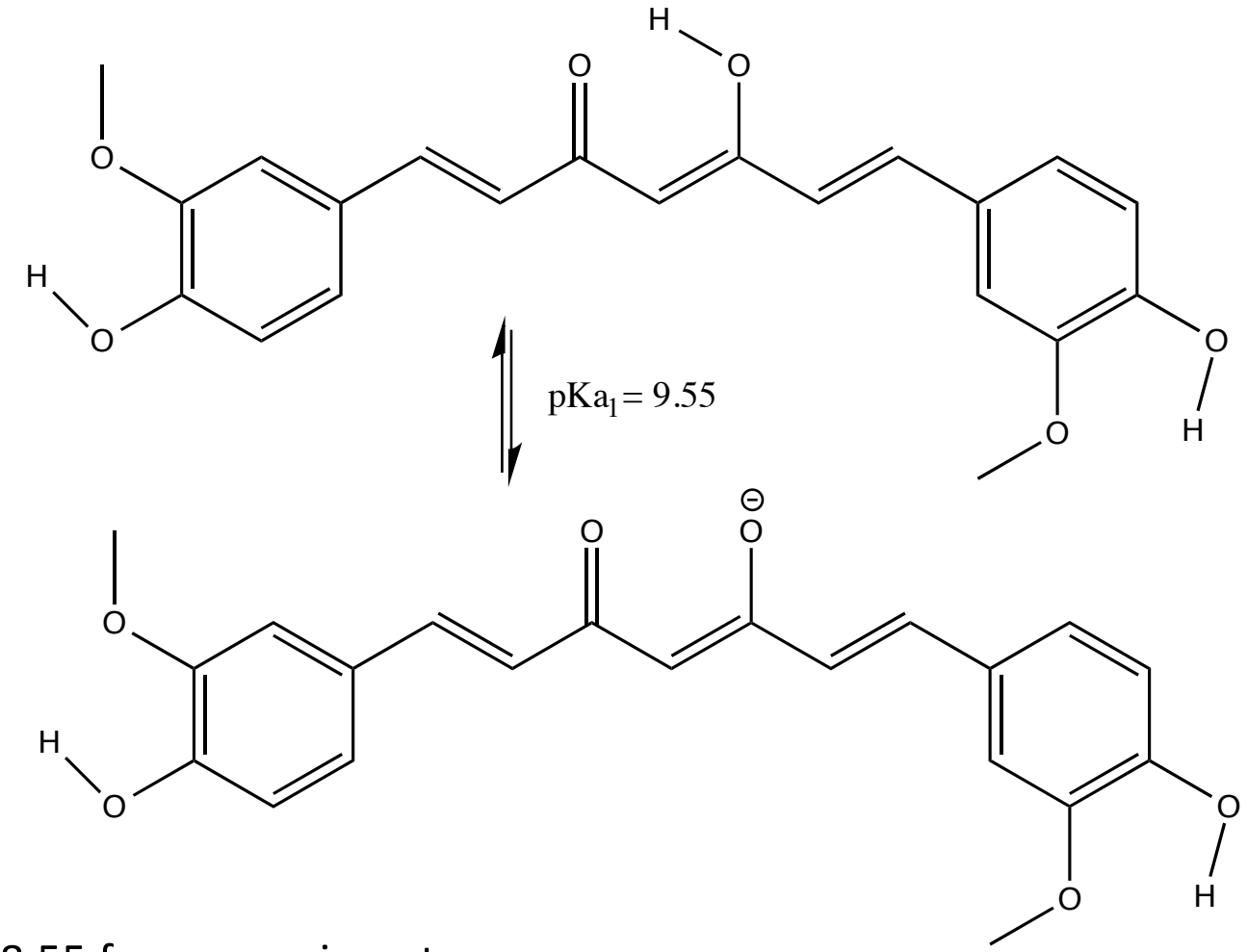
Relative stability of enol vs diketo

Method (including SMD H_2O)	$\Delta_{taut}G^o$ (kJ/mol)	Favored at 298 K
HF/3-12Gd	-29.4	diketo
HF/6-31Gd	-42.3	diketo
B3LYP/6-31Gd	-38.7	diketo
M062x/6-31Gd	13.7	enol
M06HF/6-31Gd	17.9	enol
M06/3-21Gd	50.9	enol
M06/6-31Gd	12.6	enol
M06/6-31+Gd	29.2	enol

HF and B3LYP with SMD favor the keto tautomer
M06 family with SMD favor the enol tautomer or neither.

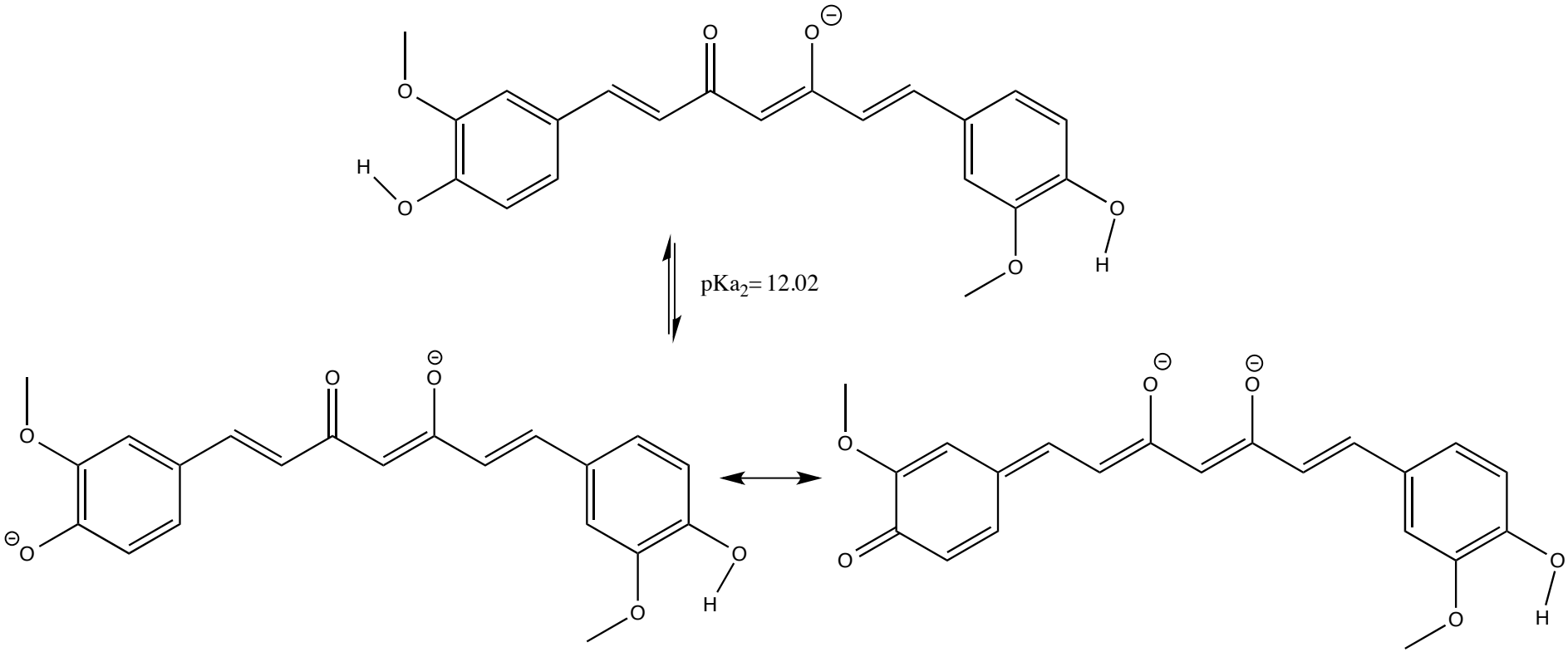
Experimental results indicate that the enol is favored at room temp.

pKa_1 = 9.55 (M06/6-31+Gd SMD)



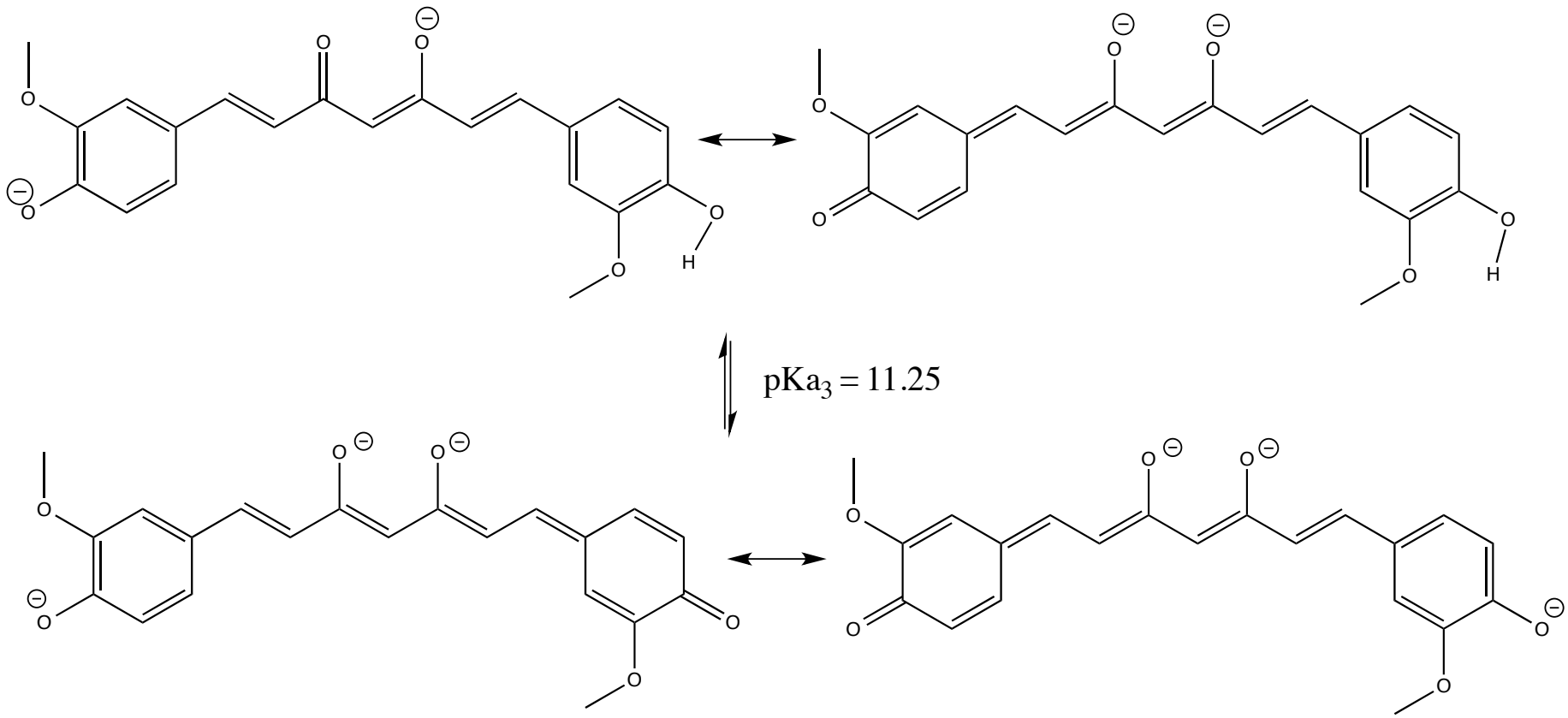
8.38 or 8.55 from experiment

pKa_2 = 12.02 (M06/6-31+Gd)



9.88 or 9.30 from experiment

pKa_3 = 11.25 (M06/6-31+Gd SMD)



10.41, 10.51, 10.69 from experiment

UV-vis λ_{max} based on TD computations

SMD (water)	6-31Gd					3-21Gd		6-31+Gd	Exp
λ_{max} (nm)	HF	M06HF	M062x	M06	B3LYP	B3LYP	M06	M06	Ours/Lit
H_4A^+	----	-------	------	529	-----	------	528	537	555[a]/555[b]
H_3A (enol)	300	327	375	438	450	436	434	452	430[a]/ 420-430[b,c]
H_3A (keto)	268	274	306	356	362	328	352	368	----------
H_2A^-	288	326	356	401	419	381	392	417	?/420-430[a]
HA^{2-}	-----	------	------	457	------	------	459	471	450[a]/ 430 & 520[b]/ 463[c]
A^{3-}	-----	------	------	455	-----	-----	443	482	470[a]/480[b]

[a]H. Goemann, T. Roettgen, CURF funded summer research at UMM

[b]D. Dyrssen, Y. Novikov, L. Uppstrom, Anal. Chim. Acta, 60, 1972, 145

[c]M. Bernabe-Pineda et al, Spectrochimica Acta Part A 60, 2004, 1091-1097

Effect of SMD (water) solvation on λ_{max} according to TD computations

λ_{max} (nm)	SMD	H_4A^+	H_3A (enol)	H_3A (keto)	H_2A^-	HA^{2-}	A^{3-}
M06/3-21Gd	water	527.59	434.43	332.29	392.02	461.56	
M06/3-21Gd		549.29	403.64	313.82	500.79	801.73	
M06/6-31+Gd	water		451.89		416.63		881.53
M06/6-31+Gd			415.75		533.64		1332.7

Computed transitions are different for gas phase than for solvated species described by the SMD (water) model.

Gas phase results for anions should be viewed with more doubt than the others. Oscillator strengths are small or zero. Transition orbitals for the gas phase anions have positive energy.

Interpretation based on the particle-in-a-box-model

Delocalization of phenolic electrons changes the box length

Balasubramian used MO theory Pariser-Parr-Pople (PPP) Hamiltonian.

Theoretical n -> π^* transitions match experiment the best. Delocalization including the phenolic C-O group explains red-shift for the anion.

$$n \rightarrow \pi^* \quad 430\,nm\,(neutral)$$

$$n \rightarrow \pi^* \quad 483\,nm\,(anion)$$

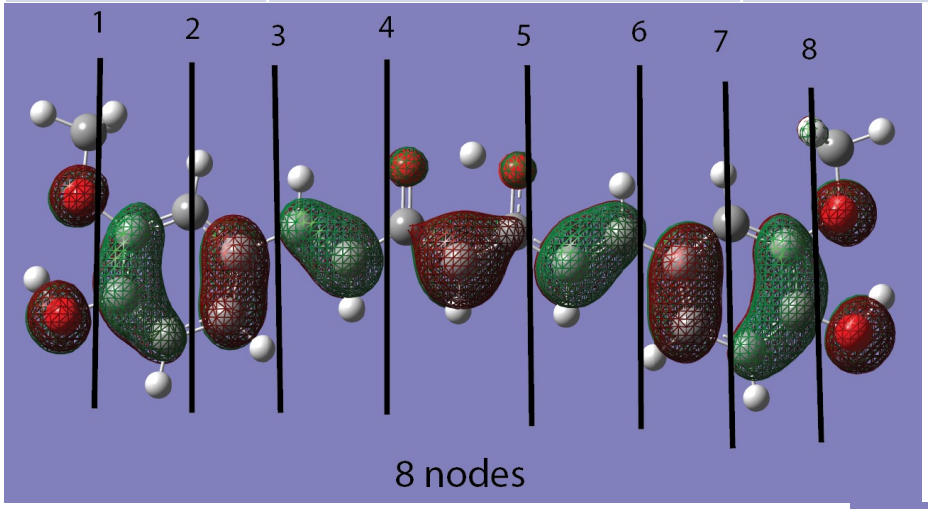
K. Balasubramanian, *Indian Journal of Chemistry*, Volume 30 A, 1991, 61-65.
K. Balasubramanian, Int. J. Quant. Chem. 37, 1990. 449-463.

Our particle-in-a-box approach.

1. Look at orbitals involved in the optimized transition based on TDDFT
2. Count nodes in the transition orbitals to calculate quantum number n and the number, N, of delocalized electrons in the box.
3. Compare N with resonance structures for the protonation state of interest to see if it makes sense.
4. Calculate L based on λ_{max} from the computation.
5. Measure L based on the optimized geometry and the resonance structures.
6. Compare L based on λ_{max} and L based on geometry.

Particle-in-a-box (enol)

species	# of nodes/HOMO	n/HOMO	λ_{max}	L (Angstroms)
enol	8	9 (N = 18 e^-)	434.43 nm	15.8

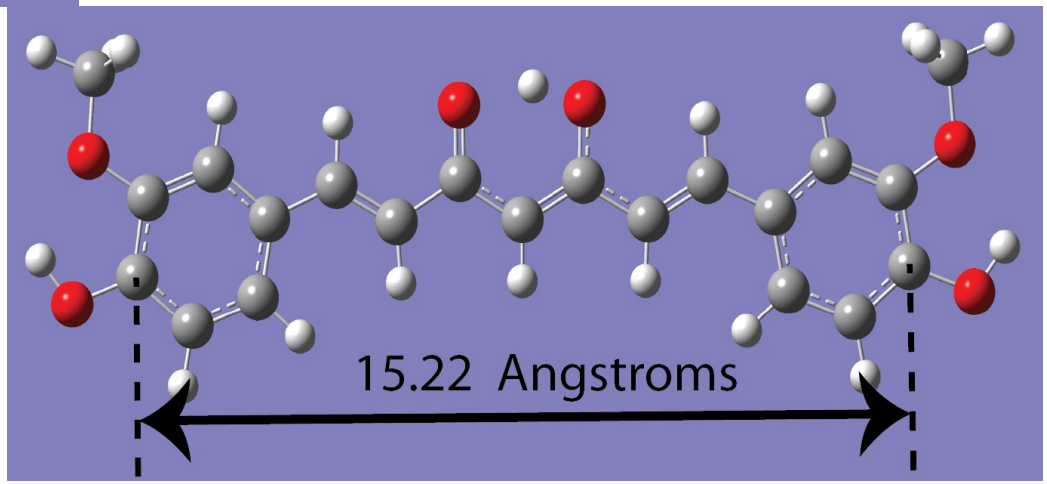


$$L_\lambda = \left(\frac{(n_{LUMO}^2 - n_{HOMO}^2) h\lambda}{8\, m_e\, c} \right)^{1/2}$$

$$= 15.5\ Angstroms$$

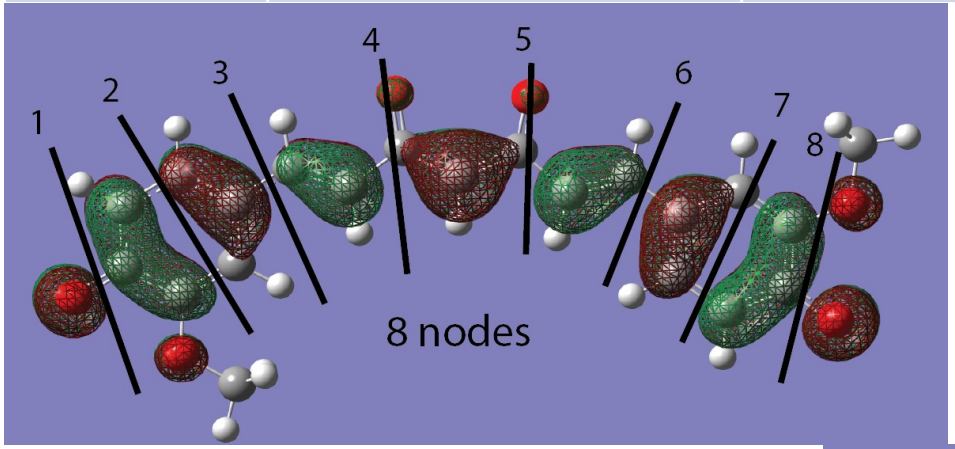
$$\pi_{HOMO} \rightarrow \pi^*_{LUMO}$$

Comfirmed by TD DFT



Particle-in-a-box (trianion)

species	# of nodes/HOMO	n/HOMO	λ_{max}	L (Angstroms)
trianion	8	9 (N = 18 e^-)	481.53 nm	16.7

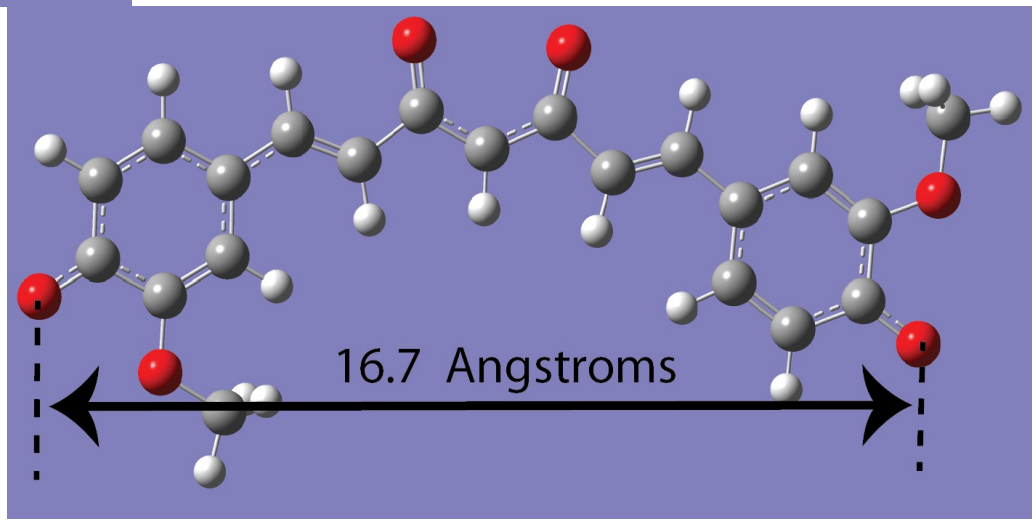


$$L_\lambda = \left(\frac{(n_{LUMO}^2 - n_{HOMO}^2) h\lambda}{8\, m_e\, c} \right)^{1/2}$$

$$= 16.7\ Angstroms$$

$$\pi_{HOMO} \rightarrow \pi^*_{LUMO}$$

Comfirmed by TD DFT



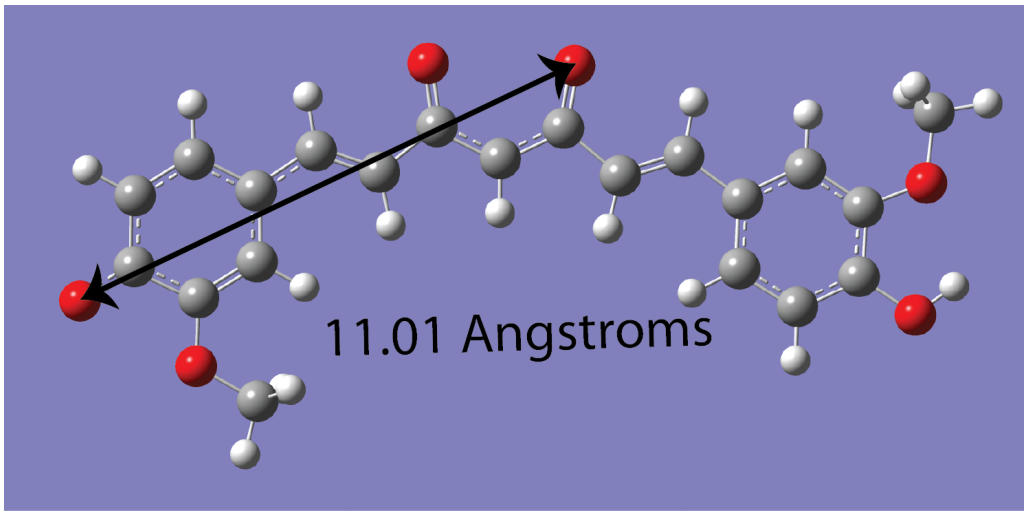
Particle-in-a-box (dianion)

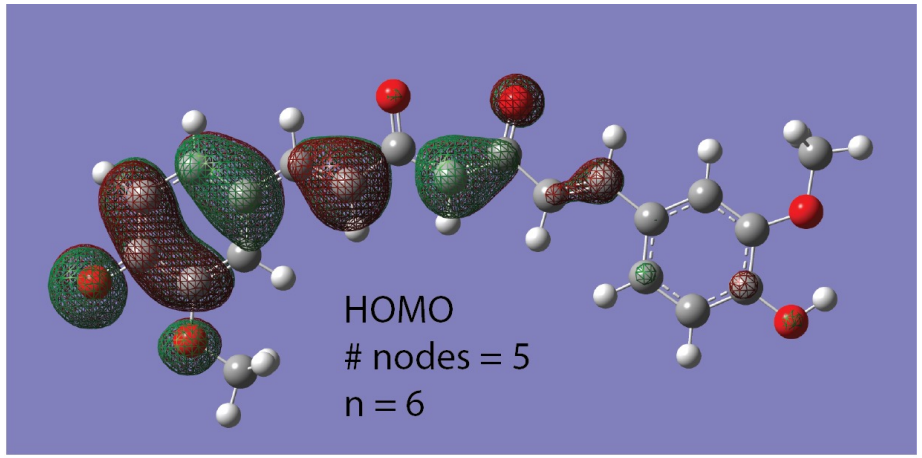
species	n/HOMO	n/LUMO	λ_{max}	L (Angstroms)
trianion	6 (N = 12e$^-$)	10 (N = 18 e$^-$)	461.53 nm	11.01

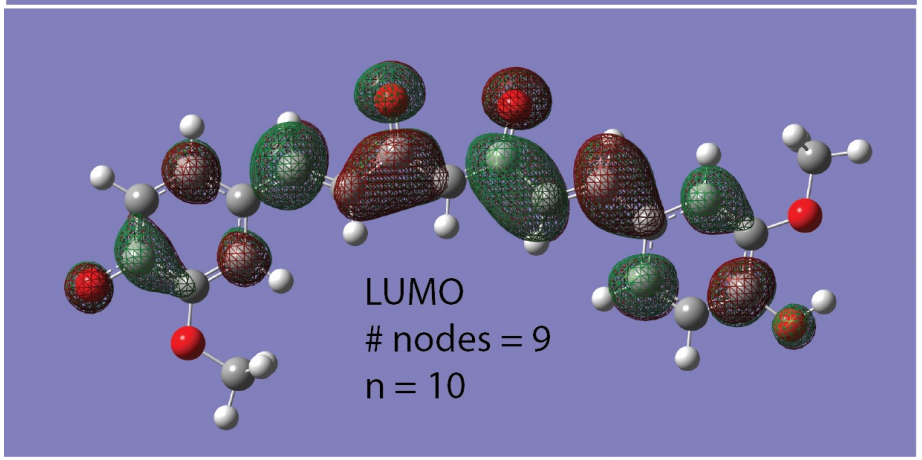
$$\Delta E = E_{final} - E_{initial} = \frac{hc}{\lambda_{\max}}$$

$$\frac{10^2 h^2}{8\, m_e (15.8\times10^{-10}\, m)^2} - \frac{6^2 h^2}{8 m_e L^2} = \frac{hc}{4.61\times10^{-9}\, m}$$

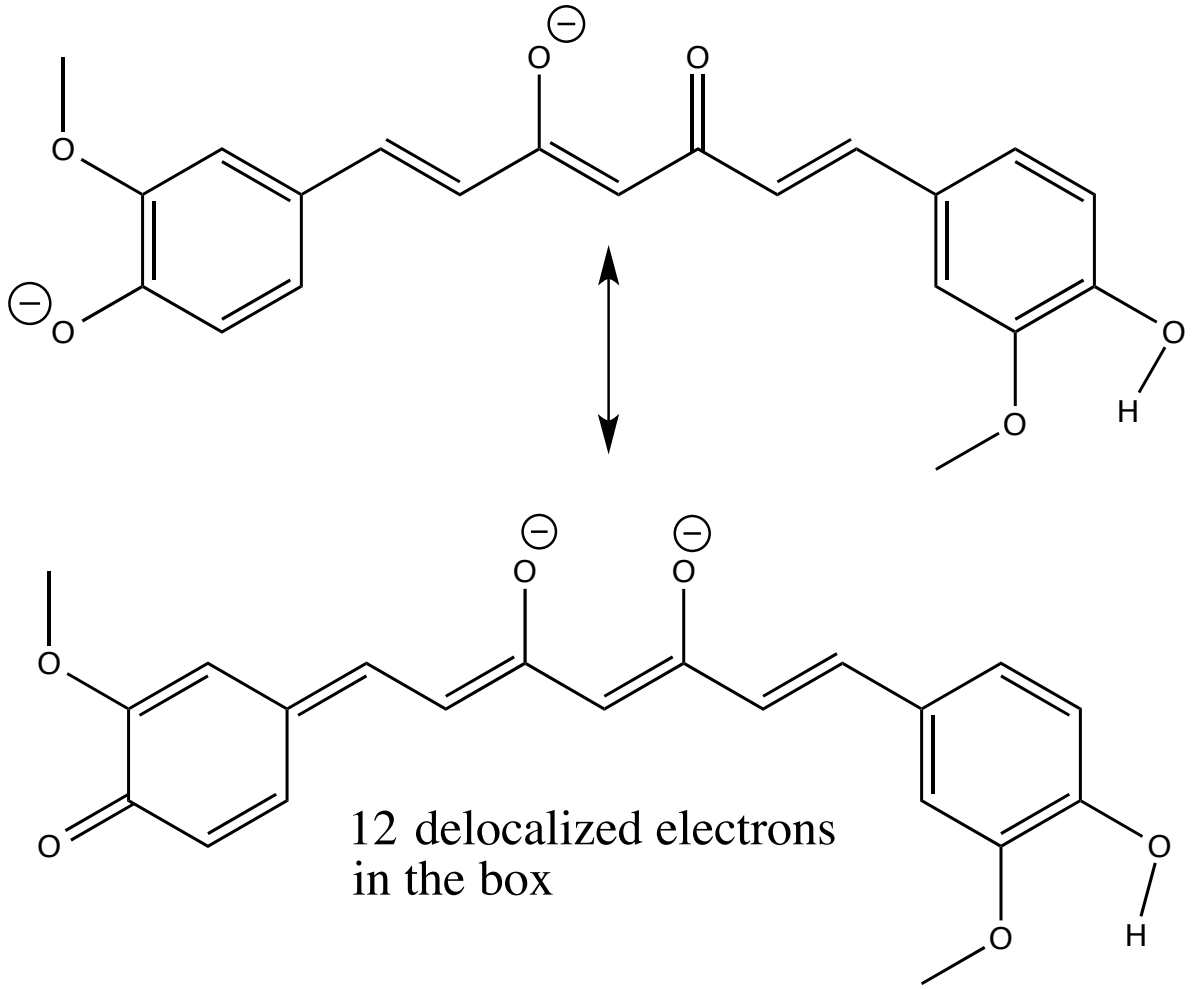
Solve for $L = 11.01$ *Angstroms*







Dianion resonance structures



particle-in-a-box results

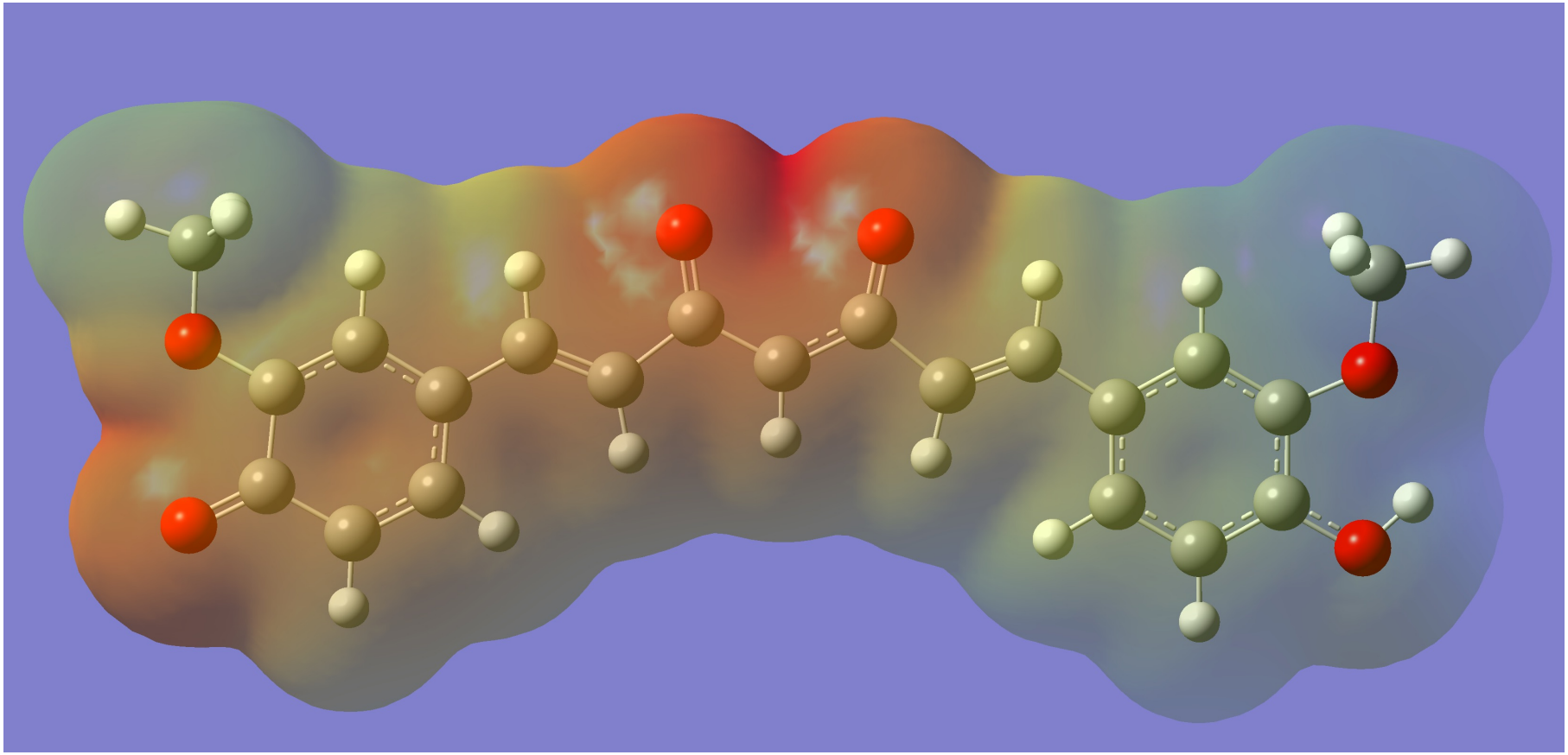
species	Nodes in HOMO	n	λ (nm)	L (PIAB) (Å)	L (DFT) (Å)
Protonated	8	9	527	17.44	17.35
enol	8	9	434	15.8	15.2
keto	4	5	332	12.48 (LUMO)	13.24 (LUMO)
enolate	8	9	417	15.50	14.52
dianion	5	6	461	11.01	11.01
trianion	8	9	482	16.70	16.71

Hypothesis

- Our computed pKa_2 is too high.
- Dyrrsen et al's 520 nm peak for HA^{2-} seems to indicate a different molecular structure.

<u>Hypothesis:</u> Perhaps a more stable structure for the HA^{2-} protonation state is the diphenolate.

Instability of enolate-phenolate dianion

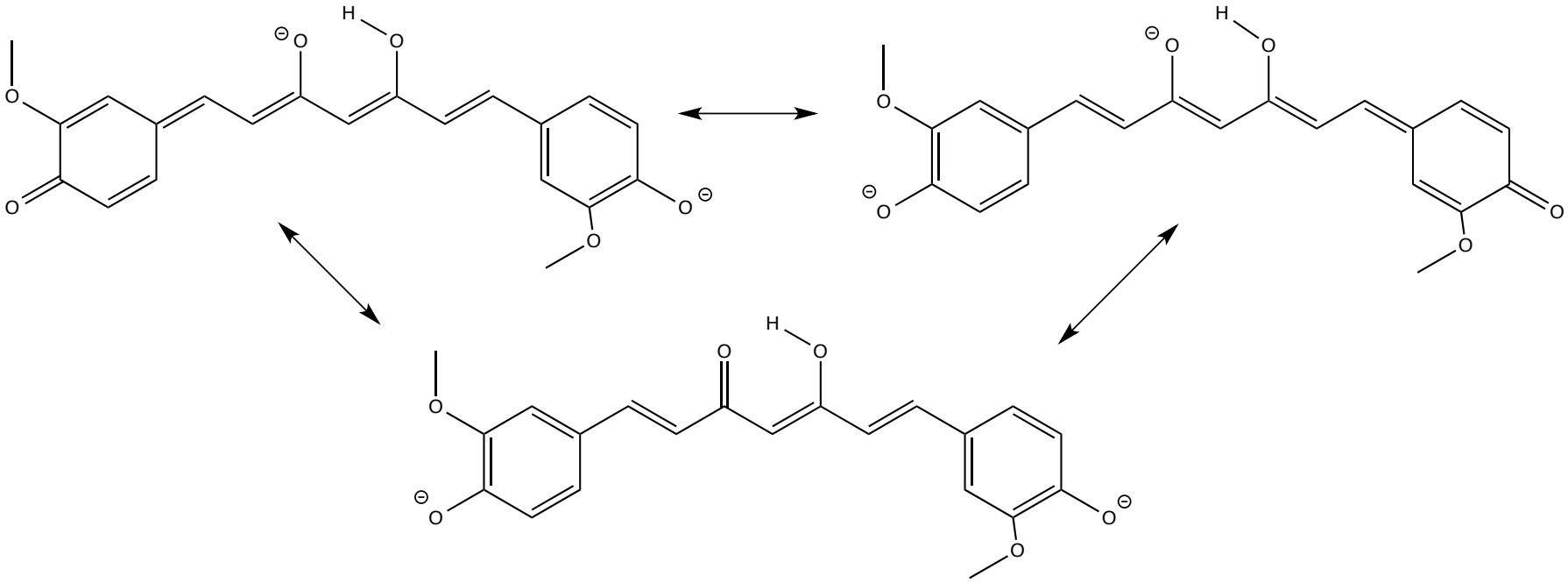


Electrostatic potential mapped onto total electron density (GaussView 5.1)

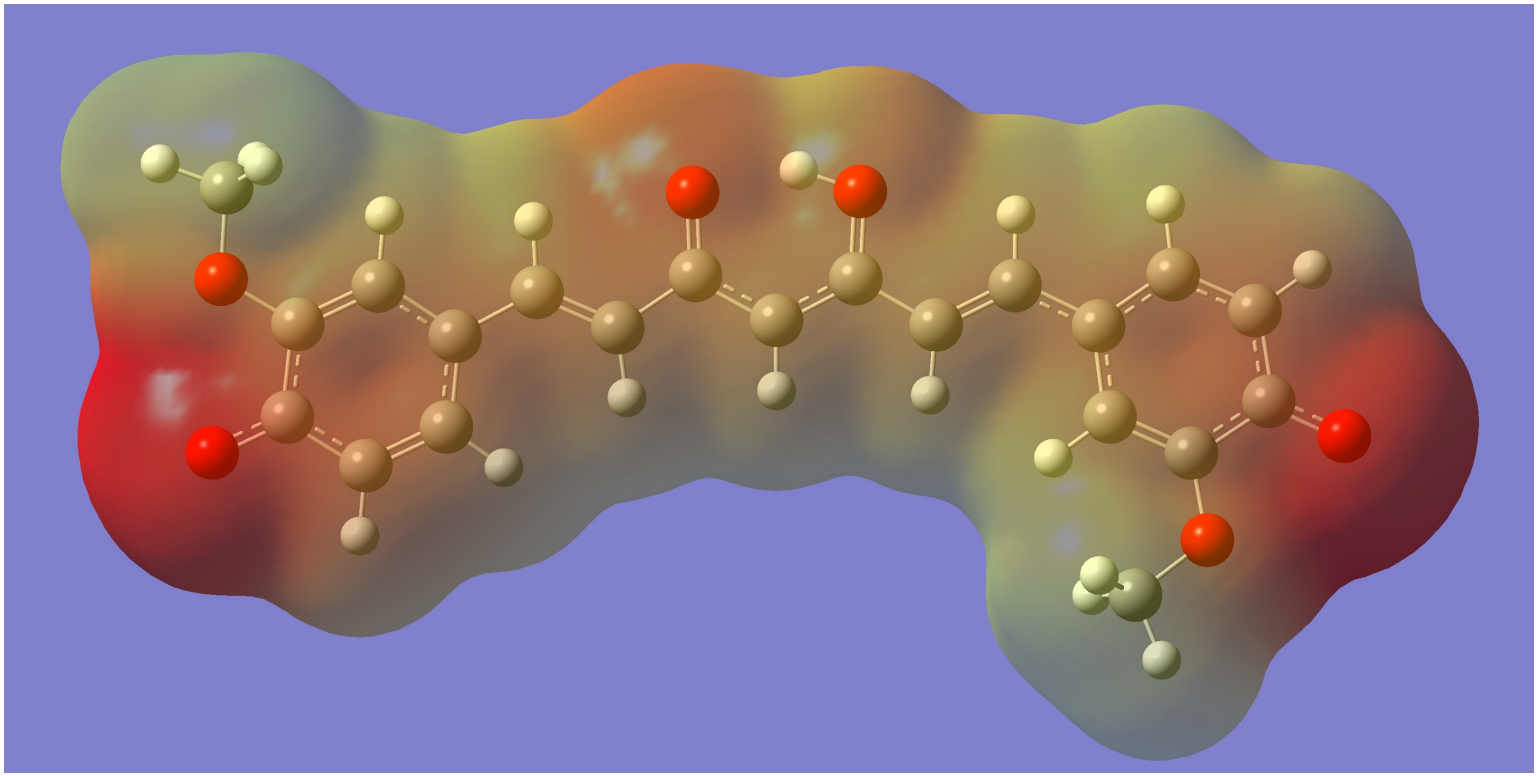
1. Repulsion between carbonyl groups
2. π-electron delocalization does not extend through the entire molecule.

Proposed diphenolate

diphenolate resonance structures



Diphenolate M06/6-31+Gd results



$pKa_2 = 9.88$, $pKa_3 = 13.38$, $\lambda_{max} = 543$ nm

experimental and computed pKa

species	Experimental pKa			M06/6-31+Gd pKa			
	UV-vis	Potentiometric titratoin	HCl titration	Dianion 1	Dianion 2	Averaged dianion 1&2	Averaged dianion 1&2*
H_3Curr	8.38[a]	8.54[b]	8.38[b]	9.55	9.55	9.55	8.60
H_2Curr^{1-}	9.88[a]	9.30[b]	9.88[b]	12.02	9.88	10.95	10.00
$HCurr^{2-}$	10.51[a]	10.69[b]	10.51[b]	11.25	13.38	12.33	11.38

$\Delta_s G(H^+(aq))$ = -265.9 kcal/mol used instead of $\Delta_s G(H^+(aq))$ = -264. kcal/mol
Lowers all of our computed pKa values by 0.95 pKa units.

M. Tissandier *et al.*, *J. Phys. Chem. A*, 1998, 102, 7787.
Kelly *et al.*, *J. Phys. Chem. B*, 2006, 110, 16066.

[a]M. Bernabe-Pineda et al., *Spectrochimica Acta Part* A 60 (2004) 1091-1097
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Conclusions

1. M06 methods with SMD confirm the enol–keto tautomer is more stable than the diketone.
2. M06 and B3LYP both SMD give reasonable λ_{max} but best results varied with 3-21Gd, 6-31Gd, and 6-31+Gd basis sets.
3. M06/6-31+Gd SMD gave pKa values in good agreement with experiment. $\Delta_s G(H^+(aq))$ = -265.9 kcal/mol should be used.
4. The-particle-in-a-box model gives remarkable agreement with computed geometry and λ_{max}
5. Best agreement of our results with experimental pKa and λ_{max} seems to imply a mixture of dianion protonation states.

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