Electronic Supplementary Information

(ESI)

Photoabsorption spectra of a natural polyphenol compound for therapeutic applications: the protocatechuic acid in dilute water solution at room temperature

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Computational Setup

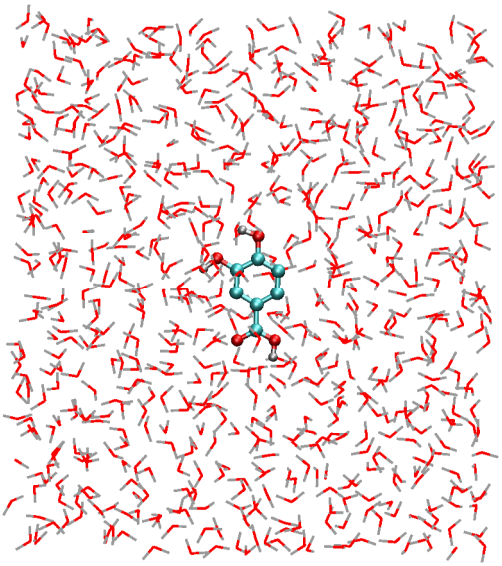
A. Classical Molecular Dynamics Simulations (MD) of PCA in water

We have performed two MD simulations of 10 ns for the protocatechuic acid (the first one considering the optimized structure of the solute at B3LYP/CPCM/6-31G(d,p) level and the second one at VSXC/CPCM/6-31G(d,p)) at 298K in NVT ensemble in water solution. Both simulations were initiated with the PCA molecule at the centre of a rectangular box (see **ESI-Figure 1** reported below) of 21 nm^3 filled with SPC water molecules (H.J.C. Berendsen, J.P.M. Postma, W.F. van Gunsteren, and J. Hermans, *In Intermolecular Forces*, edited by B. Pullman (Reidel, Dordrecht, 1981), p. 331) at its typical liquid density of 997.1 kg/m^3. Furthermore, for PCA solute we used the Gromos96 bond parameters and Lennard-Jones, respectively (van Gunsteren, W. F.; Billeter, S. R.; Eising, A. A.; Hunemberger, P. H.; Kruger, P.; Mark, A. E.; Scott, V. R. P.; Tironi, I. G. Biomolecular simulation: The GROMOS96 manual and user guide. vdf Hochschlverlag AG an der ETH Zurich, Zurich 1996.).

The investigated system (i.e. PCA solute in dilute water solution) was gradually heated from 50 K to 298 K using short (50 ps) MD simulations upon solvent relaxation. Afterwards, the MD trajectories were then

propagated for 10 ns using an integration step of 2.0 fs and the temperature was kept constant by the isokinetic temperature coupling (Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Di Nola, A. J. Chem. Phys. 1994 81, 3684-3690.). Long range electrostatics was computed by the Particle Mesh Ewald (PME) method (Darden, T. A., York, D. M., Pedersen, L. G. (1993) J. Chem. Phys 1993, 98, 10089-10092), with 34 wave vectors in each dimension and a 4th order cubic interpolation. A cut-off of 1.1 nm was used and pair list was updated every 5 integration steps.

All the simulations were carried out using the Gromacs software, version 3.0.3 (E. Lindahl, B. Hess and D. van der Spoel: GROMACS 3.0: A package for molecular simulation and trajectory analysis. J. Mol. Model. 2001, 7, 306-317). Atomic point charges (see data below) were recalculated taking into account relaxed structures, at B3LYP/CPCM/6-31G(d,p) and VSXC/CPCM/6-31G(d,p) level, by mimicking the solvent with a Conductor-like Polarizable Continuum Model (CPCM, V. Barone and M. Cossi, J. Phys. Chem. A 1998, 102, 1995.) by adopting a Merz-Kollman (MK) scheme and ESP fitting procedure (Besler, B. H.; Merz Jr. B. K. M.;, and Kollman, P. A., J. Comp. Chem. 1990, 11, 431.) on different density functionals, namely B3LYP and VSXC with the 6-311++G(d,p) atomic basis set. In this respect, before doing any classical/statistical sampling in dilute solution, CPCM represents a reasonable and well-known computational tool for evaluating the polarization of the surrounding environment on a solute molecule in its own electronic ground state. (see for example, Ludwig, V.; Coutinho, K.; and Canuto, S., Phys. Chem. Chem. Phys. 2007, 9, 4907.)

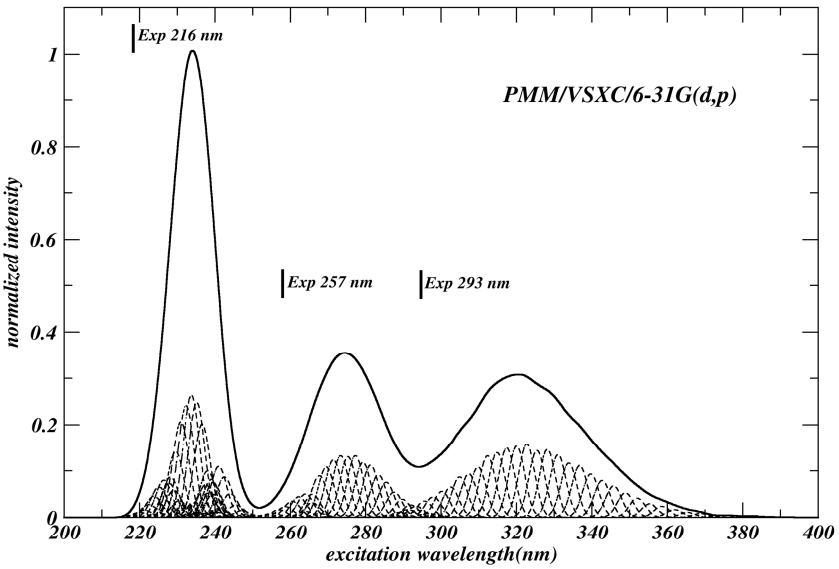


ESI-Figure 1: A pictorial representation of the classical simulation box.

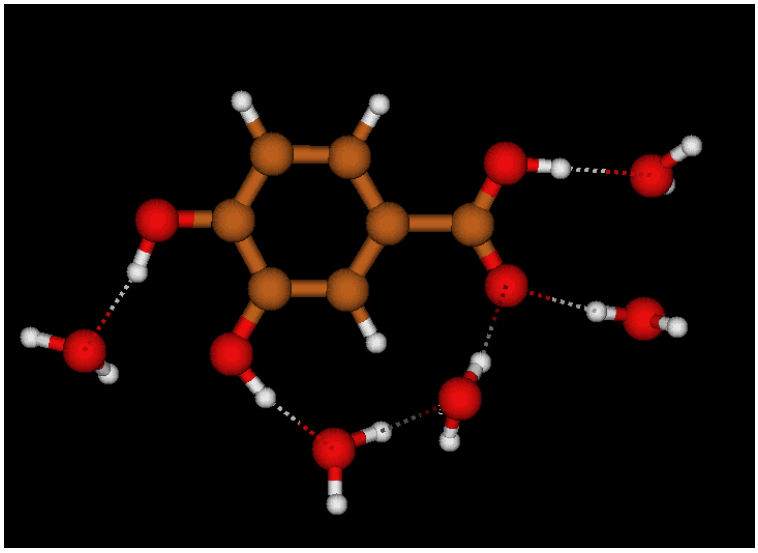
B. Mixed TD/MD calculations

In order to address the electronic properties of the protocatechuic acid (PCA) in dilute water solution we combine Time-Dependent Density functional Theory (TD-DFT) calculations with classical MD sampling in physiological conditions (i.e. PCA molecule in liquid water at 298 K, see Section A). We then selected PCA molecule as quantum centre (QC), with the surrounding SPC solvent molecules acting as an electrostatic perturbation according to standard PMM procedure (see for example, C. Zazza, A. Amadei, N. Sanna and M. Aschi, Chem. Comm. 2008, 29, 3399-3401 and quoted references therein cited). More precisely, by using PMM computational procedure, we modeled the solvent perturbation as an external and homogeneous electric field changing according to the mechanical behavior of the surrounding media and acting on the solute (that is the quantum centre, QC) centre of mass. Moreover, for a comparison with static (i.e. IEF-PCM) calculations reported in literature (E. Andrè, C. Lapouge and J.-P. Cornard, J. Mol. Struct. (Theochem), 2007, 806, 131-140.), we accomplished PMM simulations using exactly the same unperturbed description, e.g. B3LYP/6-31G(d,p) and VSXC/6-31G(d,p) (**see ESI-Figure 2**). Indeed, the molecular structure of the QC was optimized at B3LYP/6-31G(d,p) and VXSC/6-31G(d,p) level of theory in CPCM model, and an unperturbed Hamiltonian matrix of dimension [13x13], was constructed using Time Dependent Density Functional Theory (TD-DFT) calculations in gas-phase conditions (i.e. TD-B3LYP/6-31G(d,p) and TD-VSXC/6-31G(d,p)). It is worth noting that the unperturbed permanent electric dipole moments of the electronic eigenstates considered in our PMM simulation (the ground and the first twelve singlet electronic excited states), as well as, the transition moments above them were also calculated. For this purpose, quantum chemical calculations within Time-Dependent formalism were performed using both linear response theory as currently implemented in the Dalton 2.0 code (DALTON, a molecular electronic structure program, Release 2.0 (2005), see http://www.kjemi.uio.no/software/dalton/dalton.html) and random-phase approximation in Gaussian03 package (Gaussian 03, Revision C.02, Frisch, M. J. et al. Gaussian, Inc., Wallingford CT, 2004.). Finally, the semi-classical theoretical approach was also extended performing PMM simulations at TD-B3LYP/6-311++G(d,p) level of theory and compared with PMM/TD-B3LYP/6-31G(d,p) and CPCM-based calculations also in presence of explicit water molecules surrounding PCA chemical group (see Table 1 into the manuscript). In this respect, CPCM calculations including up to five solvent molecules

(**see ESI-Figure 3**) interacting with the solute were accomplished using, as starting coordinates, the most sampled local conformations (at the solute-solvent interface) spanned by means of classical MD sampling at 298K. As a conclusive remark, PMM/TD-VSXC/6-311++G(d,p) simulations were not carried out since CPCM/VSXC/6-311++G(d,p) and CPCM($3H_2O$)/VSXC/6-311++G(d,p) calculations are found to systematically overestimate the available experimental data (see Table 1 into the manuscript).



ESI-Figure 2: Calculated (solid line), at PMM/VSXC/6-31G(d,p) level of theory from 10 ns of MD simulation in water solution, UV spectrum of the PCA acid, generated by convoluting the PMM calculated spectra (20.000 configurations, excluding quantum vibrational effects) with a gaussian broadening function having a standard deviation of 3 nm; the experimental absorptions were detected at 293 nm, 257 nm, and 216 nm (see E. Andrè, C. Lapouge and J.-P. Cornard, J. Mol. Struct. (Theochem), 2007, 806, 131-140.), respectively.



ESI-Figure 3: Optimized geometry, at CPCM/B3LYP/6-311++G(d,p) level of computation, of the **1:5** hydrated complex of the PCA compound with explicit water molecules.

C. Optimized geometries

Molecular geometry of PCA at CPCM/B3LYP/6-311++G(d,p) level of theory

C	0.634801	-1.418128	0.000000
C	-0.727130	-1.781620	0.000000
C	-1.705783	-0.789150	0.000000
C	-1.347388	0.554285	0.000000
C	0.004783	0.919644	0.000000
C	0.991697	-0.079594	0.000000
O	-1.116113	-3.081027	0.000000
H	-2.750974	-1.087965	0.000000
H	-2.119984	1.314804	0.000000
C	0.436154	2.334525	0.000000
H	2.044161	0.194020	0.000000
O	1.524698	-2.452054	0.000000
H	2.453869	-2.125584	0.000000
H	-0.348247	-3.687801	0.000000
O	1.599859	2.704285	0.000000
O	-0.588141	3.207034	0.000000
H	-0.216294	4.125942	0.000000

Molecular geometry of PCA at CPCM/VSXC/6-311++G(d,p) level of theory

C	0.635621	-1.420168	0.000000
C	-0.730104	-1.780010	0.000000
C	-1.717796	-0.789449	0.000000
C	-1.357296	0.559464	0.000000
C	0.003474	0.917359	0.000000
C	1.000665	-0.079888	0.000000

O	-1.113118	-3.084779	0.000000
H	-2.759892	-1.104401	0.000000
H	-2.122419	1.330884	0.000000
C	0.436477	2.327759	0.000000
H	2.055598	0.199796	0.000000
O	1.515954	-2.466288	0.000000
H	2.441993	-2.135436	0.000000
H	-0.335575	-3.676902	0.000000
O	1.605551	2.700199	0.000000
O	-0.599592	3.198818	0.000000
H	-0.220973	4.112352	0.000000

Molecular geometry of the hydrated cluster (1:3) of PCA at CPCM/B3LYP(3H_2O)/6-311++G(d,p) level of theory

C	-1.594694	-1.279820	-0.041711
C	-1.302394	0.102081	0.001182
C	0.020373	0.522744	0.003440
C	1.071329	-0.408473	-0.037875
C	0.776230	-1.776663	-0.082366
C	-0.547622	-2.201982	-0.083983
O	-2.370002	0.944832	0.037949
C	2.463291	0.097576	-0.029724
O	2.758457	1.285243	0.012712
O	-2.865241	-1.740624	-0.044197
O	3.391553	-0.865199	-0.073142
O	-1.699527	3.564021	0.109669
O	-5.168015	-0.293750	0.052957
O	5.941866	-0.015070	-0.077847
H	-2.090417	1.890805	0.062636
H	-3.547151	-1.029876	0.002773
H	4.303332	-0.466870	-0.059547
H	6.124880	0.885514	0.249416
H	6.561346	-0.593512	0.405366
H	-5.867633	-0.756068	0.549510
H	-5.154160	0.610081	0.414258
H	-1.937824	4.092829	-0.674657
H	-2.032717	4.072418	0.872552
H	0.244263	1.582405	0.037738
H	1.576111	-2.507709	-0.114856
H	-0.791972	-3.260779	-0.117354

Molecular geometry of the hydrated cluster (1:3) of PCA at CPCM/VSXC($3H_2O$)/6-311++G(d,p) level of theory

C	-1.679727	-1.307144	-0.043423
C	-1.334503	0.064795	-0.041122
C	0.003701	0.442673	-0.025284
C	1.011406	-0.544773	-0.012739
C	0.668752	-1.909743	-0.019335
C	-0.676324	-2.282968	-0.035712
O	-2.386221	0.939916	-0.056895
C	2.414850	-0.092025	0.011186
O	2.764908	1.086648	0.011710
O	-2.977200	-1.704395	-0.056288
O	3.307482	-1.109304	0.037152
O	-1.219400	3.500036	-0.105495
O	-5.105786	0.164119	0.133165
O	5.609315	0.498010	0.013004
H	-2.043559	1.855054	-0.042324
H	-3.589514	-0.943740	-0.015930
H	4.201905	-0.707365	0.052011
H	5.246404	1.344181	0.320860
H	6.515830	0.464692	0.358971
H	-5.968129	-0.040851	0.528798
H	-4.836982	1.004698	0.535596
H	-1.685074	4.201974	-0.590750
H	-0.982755	3.908582	0.744378
H	0.278652	1.495253	-0.027292
H	1.449635	-2.665650	-0.010797
H	-0.979783	-3.328561	-0.040278

Molecular geometry of the hydrated cluster (1:5) of PCA at CPCM/B3LYP($5H_2O$)/6-311++G(d,p) level of theory

C	1.576620	-2.427395	0.139058
C	2.427741	-1.337851	0.071334
C	1.935208	-0.037347	0.013032
C	0.560453	0.167943	0.023207
C	-0.318970	-0.907496	0.090642
C	0.206065	-2.192442	0.147672
O	3.772796	-1.538924	0.061390
O	2.782129	1.022534	-0.053132
C	-1.830931	-0.672637	0.101373
O	-2.560548	-1.688654	0.163570
O	-2.282261	0.490889	0.049372
O	1.147624	2.980168	-0.498061
O	5.368666	0.624166	-0.472216
O	-5.156523	-1.098986	-0.227971
H	2.277500	1.880944	-0.088932
H	4.250905	-0.658667	0.009805
H	-3.528088	-1.460493	0.166506
H	-5.437862	-0.895553	-1.155313
H	-5.912584	-1.542403	0.266349
H	6.264327	0.260374	-0.747618
H	4.945106	1.098280	-1.250878
H	1.237348	3.957915	-0.318448
H	0.239574	2.795051	-0.885717
H	0.174213	1.185126	-0.022378
H	-0.461197	-3.051417	0.201009
H	1.985449	-3.435747	0.183860
H	-1.571197	1.767096	1.232624
O	-1.081580	2.335645	1.847383
H	-0.815681	3.082825	1.288887

H	-3.864045	1.195044	-0.683110
O	-4.724534	1.448924	-1.051895
H	-5.247055	1.658868	-0.262089

D. Atomic point charges

Atomic point charges at CPCM/B3LYP/6-31G(d,p)

6	0.638703	-1.421310	0.000000	1	C	0.270078
6	-0.724492	-1.789748	0.000000	2	C	0.315319
6	-1.709508	-0.798965	0.000000	3	C	-0.296722
6	-1.354625	0.548856	0.000000	4	C	-0.184092
6	0.000000	0.918731	0.000000	5	C	-0.062973
6	0.993160	-0.078789	0.000000	6	C	-0.335349
8	-1.110104	-3.092763	0.000000	7	O	-0.589788
1	-2.755295	-1.101722	0.000000	8	H	0.200431
1	-2.130856	1.308372	0.000000	9	H	0.175271
6	0.425177	2.335626	0.000000	10	C	0.702512
1	2.045945	0.199814	0.000000	11	H	0.181653
8	1.533186	-2.454414	0.000000	12	O	-0.639884
1	2.464503	-2.125295	0.000000	13	H	0.513984
1	-0.340051	-3.701669	0.000000	14	H	0.488755
8	1.594149	2.713956	0.000000	15	O	-0.603386
8	-0.600545	3.208664	0.000000	16	O	-0.616540
1	-0.228223	4.130553	0.000000	17	H	0.480732

Atomic point charges at CPCM/VSXC/6-31G(d,p)

6	0.638232	-1.418834	0.000000	1	C	0.262891
6	-0.731538	-1.778858	0.000000	2	C	0.294641
6	-1.721567	-0.788002	0.000000	3	C	-0.290806
6	-1.361464	0.562680	0.000000	4	C	-0.198611
6	0.000000	0.919111	0.000000	5	C	-0.051125
6	1.000548	-0.076791	0.000000	6	C	-0.347016
8	-1.104945	-3.084419	0.000000	7	O	-0.558856
1	-2.762808	-1.107316	0.000000	8	H	0.202889
1	-2.122582	1.339745	0.000000	9	H	0.179206
6	0.437457	2.328772	0.000000	10	C	0.663626
1	2.052006	0.217688	0.000000	11	H	0.180934
8	1.510521	-2.469940	0.000000	12	O	-0.615005
1	2.435782	-2.134916	0.000000	13	H	0.508910
1	-0.309948	-3.654044	0.000000	14	H	0.476952
8	1.610696	2.696404	0.000000	15	O	-0.583853
8	-0.598900	3.200867	0.000000	16	O	-0.594007
1	-0.201427	4.107068	0.000000	17	H	0.469230

Atomic point charges at CPCM/B3LYP/6-311++G(d,p)

6	0.634801	-1.418128	0.000000	1	C	0.333236
6	-0.727130	-1.781620	0.000000	2	C	0.392612
6	-1.705783	-0.789150	0.000000	3	C	-0.347617
6	-1.347388	0.554285	0.000000	4	C	-0.210742
6	0.004783	0.919644	0.000000	5	C	-0.107751
6	0.991697	-0.079594	0.000000	6	C	-0.373308
8	-1.116113	-3.081027	0.000000	7	O	-0.663525
1	-2.750974	-1.087965	0.000000	8	H	0.231872
1	-2.119984	1.314804	0.000000	9	H	0.204108
6	0.436154	2.334525	0.000000	10	C	0.869368
1	2.044161	0.194020	0.000000	11	H	0.217170

8	1.524698	-2.452054	0.000000	12	O	-0.711906
1	2.453869	-2.125584	0.000000	13	H	0.535134
1	-0.348247	-3.687801	0.000000	14	H	0.514337
8	1.599859	2.704285	0.000000	15	O	-0.694142
8	-0.588141	3.207034	0.000000	16	O	-0.691490
1	-0.216294	4.125942	0.000000	17	H	0.502645

Atomic point charges at CPCM/VSXC/6-311++G(d,p)

6	0.635621	-1.420168	0.000000	1	C	0.327081
6	-0.730104	-1.780010	0.000000	2	C	0.352152
6	-1.717796	-0.789449	0.000000	3	C	-0.313097
6	-1.357296	0.559464	0.000000	4	C	-0.223404
6	0.003474	0.917359	0.000000	5	C	-0.095768
6	1.000665	-0.079888	0.000000	6	C	-0.368492
8	-1.113118	-3.084779	0.000000	7	O	-0.631189
1	-2.759892	-1.104401	0.000000	8	H	0.223909
1	-2.122419	1.330884	0.000000	9	H	0.202366
6	0.436477	2.327759	0.000000	10	C	0.820886
1	2.055598	0.199796	0.000000	11	H	0.205612
8	1.515954	-2.466288	0.000000	12	O	-0.686692
1	2.441993	-2.135436	0.000000	13	H	0.528700
1	-0.335575	-3.676902	0.000000	14	H	0.505760
8	1.605551	2.700199	0.000000	15	O	-0.672192
8	-0.599592	3.198818	0.000000	16	O	-0.667520
1	-0.220973	4.112352	0.000000	17	H	0.491889