Electronic Supplementary Information

The unique catalytic role of water in aromatic C–H activation at neutral pH: a combined NMR and DFT study of polyphenolic compounds

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†Electronic supplementary information (ESI) available: pK_a values, NBO charges, H/D exchange of catechin and resorcinol, isomers of resorcinol, DFT structures of the ground and transition states of resorcinol and phloroglucinol, computed $\Delta H^{\ddagger}$, $T\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ values

Table S1 pK_a values of the molecules investigated in the present work

Compound	pKa_1	pKa_2	pKa_2
Catechin[45]	8.68±0.23	9.70±0.24	11.55±0.20
Resorcinol[46]	9.20	10.9	
Phloroglucinol[47]	8.0	9.2	14

Table S2 Activation enthalpy ($\Delta H^{\ddagger}$), activation entropy ($\Delta S^{\ddagger}$), and Gibbs free energies ($\Delta G^{\ddagger}$) of catechin (**a**), resorcinol (**b**), and phloroglucinol (**c**): (i) in vaccuo, (ii) IEF-PCM (H_2O), (iii) with one explicit H_2O molecule, and (iv) with two explicit H_2O molecules

Complex	**Position**	**B3LYP/6-31+G(d)**			**PBE1PBE/6-31+G(d)**		
		$\Delta H^{\ddagger}$ **kcal mol^{-1}**	$-T\Delta S^{\ddagger}$ **kcal mol^{-1}**	$\Delta G^{\ddagger}$ **kcal mol^{-1}**	$\Delta H^{\ddagger}$ **kcal mol^{-1}**	$-T\Delta S^{\ddagger}$ **kcal mol^{-1}**	$\Delta G^{\ddagger}$ **kcal mol^{-1}**
Resorcinol + H_2O Vacumm)	TS_at 2_position	62.05	0.37	62.42	50.64	0.28	50.92
	2_enone	51.19	0.65	51.8	49.27	1.00	50.28
	TS_at 4_position	61.16	0.39	61.55	49.76	0.30	50.06
	4_enone	51.27	0.93	52.20	49.68	0.98	50.67
Resorcinol (Water Cont. Med)	TS_at 2_position	61.67	0.31	61.98	61.09	0.30	61.39
	2_enone	52.39	0.85	53.25	50.69	0.91	51.60
	TS_at 4_position	61.02	0.35	61.37	60.47	0.34	60.81
	4_enone	53.14	0.81	53.14	51.47	0.86	52.33
Resorcinol + 1H_2O (Vacumm)	TS_at 2_position	34.08	4.14	38.21	32.04	4.04	36.08
	2_enone	23.04	4.01	27.06	20.11	3.93	24.04
	TS_at 4_position	33.45	4.14	37.59	31.45	4.04	35.49
	4_enone	33.46	5.63	39.09	21.29	3.82	25.11
Resorcinol + 1H_2O (Water Cont. Med)	TS_at 2_position	35.31	3.34	38.65	33.31	3.17	36.48
	2_enone	25.17	5.63	30.80	21.60	4.50	26.10
	TS_at 4_position	34.93	3.38	38.32	33.23	3.19	36.42
	4_enone	26.43	4.32	30.75	22.92	4.22	27.14
Resorcinol + 2H_2O (Vacumm)	TS_at 2_position	26.73	3.96	30.69	24.40	3.52	27.92
	2_enone	15.93	4.08	20.01	12.57	4.00	16.57
	TS_at 4_position	26.08	3.71	29.79	24.12	3.44	27.56
	4_enone	17.27	4.30	21.57	13.8	4.16	18.02
Resorcinol + 2H_2O (Water Cont. Med)	TS_at 2_position	24.77	3.67	28.44	22.86	3.25	26.11
	2_enone	16.00	5.96	21.96	12.47	4.21	16.68
	TS_at 4_position	26.04	5.03	31.07	23.84	4.61	28.45
	4_enone	17.46	5.89	23.35	13.90	4.65	18.55
Phloroglucinol (Vacumm)	TS_at 2_position	58.27	0.49	58.75	57.30	0.46	57.76
	2_enone	51.57	0.86	52.43	49.98	0.89	50.87
Phloroglucinol (Water Cont. Med)	TS_at 2_position	57.76	0.45	58.21	57.00	0.43	57.43
	2_enone	52.41	0.75	54.16	51.75	0.80	52.54
Phloroglucinol + 1H_2O (Vacumm)	TS_at 2_position	30.21	4.19	34.40	28.08	4.14	32.22
	2_enone	23.99	4.10	28.09	21.20	4.66	25.86
Phloroglucinol + 1H_2O (Water Cont. Med)	TS_at 2_position	31.88	3.55	35.43	29.76	3.32	33.08
	2_enone	26.89	3.99	30.88	23.56	4.66	28.22
Phloroglucinol + 2H_2O (Vacumm)	TS_at 2_position	23.38	4.17	27.55	20.97	3.78	24.75

Phloroglucinol + $2H_2O$ (Water Cont. Med)	2_enone	17.47	4.30	21.77	14.20	4.13	18.33
	TS_at 2_position	26.76	2.10	28.86	19.98	3.68	23.66
Catechin (Vacumm)	2_enone	18.77	5.30	27.07	15.32	4.49	19.81
	TS_at 6_position	56.59	1.13	57.72	57.89	0.49	58.38
	TS_at 8_position	56.57	1.12	57.69	58.69	0.19	58.88
Catechin (Water Cont. Med.)	TS_at 6_position	57.26	0.36	57.62	57.89	0.49	58.38
	TS_at 8_position	57.27	0.60	57.87	57.75	0.45	58.20
Catechin + $1H_2O$ (Vacumm)	TS_at 6_position	28.39	4.61	33.00	25.98	4.62	30.60
	TS_at 8_position	28.43	5.01	33.44	26.17	4.92	31.09
Catechin + $1H_2O$ (Water Cont. Med.)	TS_at 6_position	30.74	3.50	34.14	29.04	3.52	32.56
	TS_at 8_position	29.26	4.71	33.97	27.07	4.96	32.06
Catechin + $2H_2O$ (Vacumm)	TS_at 6_position	20.55	5.17	25.72	21.59	3.81	25.40
	6_enone	16.00	4.43	20.43	12.82	4.46	17.28
	TS_at 8_position	25.00	2.39	27.39	22.99	2.75	25.74
	8_enone	16.67	4.38	21.05	13.70	4.28	17.98
Catechin + $2H_2O$ (Water Cont. Med.)	TS_at 6_position	23.48	4.34	27.82	20.77	4.15	24.92
	6_enone	18.30	4.78	23.08	14.62	4.19	18.81
	TS_at 8_position	23.05	2.39	25.44	20.98	1.98	22.97
	8_enone	19.00	5.95	24.95	15.27	4.59	19.85

Table S3 Computed activation enthalpy ($\Delta H^{\ddagger}$), activation entropy ($-T\Delta S^{\ddagger}$) and Gibbs activation energies ($\Delta G^{\ddagger}$), for resorcinol, phloroglucinol, and catechin for various molecular solvation species.

Functional	Complex	Group	$\Delta H^{\ddagger}$ kcal mol^{-1}	$-T\Delta S^{\ddagger}$ kcal mol^{-1}	$\Delta G^{\ddagger}$ kcal mol^{-1}
PBE1PBE/6-31+G(d) (IEF-PCM water)	Resorcinol (in-out conformer)	C(2)-H	61.09	0.30	61.39
		C(4,6)-H	60.47	0.34	60.81
PBE1PBE/6-31+G(d) (IEF-PCM water)	Resorcinol+2H_2O (in-out conformer)	C(2)-H	22.86	3.25	26.11
		C(4,6)-H	23.84	4.61	28.45
PBE1PBE-GD3BJ/6-31+G(d) (IEF-PCM water)	Resorcinol+2H_2O (in-out conformer)	C(2)-H	22.78	2.88	25.66
		C(4,6)-H	20.30	5.08	25.38
PBE1PBE /6-31+G(d) (IEF-PCM water)	Resorcinol+4H_2O (in-out conformer)	C(2)-H	22.98	5.49	28.47
		C(4,6)-H	27.05	2.07	29.12
PBE1PBE-GD3BJ/6-31+G(d) (IEF-PCM water)	Resorcinol+4H_2O (in-out conformer)	C(2)-H	29.23	0.82	30.06
		C(4,6)-H	26.63	1.21	27.84
PBE1PBE/6-31+G(d) (IEF-PCM water)	Resorcinol+4H_2O (in-in conformer)	C(2)-H	23.69	2.58	26.27
		C(4,6)-H	-	-	-
PBE1PBE-GD3BJ/6-31+G(d) (IEF-PCM water)	Resorcinol+4H_2O (in-in conformer)	C(2)-H	23.01	2.57	25.58
		C(4,6)-H	-	-	-
PBE1PBE/6-31+G(d) (IEF-PCM water)	Phloroglucinol +2H_2O	C(2,4,6)-H	19.98	3.68	23.66
PBE1PBE-GD3BJ/6-31+G(d) (IEF-PCM water)	Phloroglucinol +2H_2O	C(2,4,6)-H	19.35	3.81	23.16
PBE1PBE/6-31+G(d) (IEF-PCM water)	Catechin+2H_2O	C(6)-H	20.77	4.15	24.92
		C(8)-H	20.98	1.99	22.97

Table S4 Computed activation enthalpy ($\Delta H^{\ddagger}$), activation entropy ($-T\Delta S^{\ddagger}$) and Gibbs activation energies ($\Delta G^{\ddagger}$), for resorcinol + H_2O.

Functional	Compound	Group	$\Delta H^{\ddagger}$ kcal mol^{-1}	$-T\Delta S^{\ddagger}$ kcal mol^{-1}	$\Delta G^{\ddagger}$ kcal mol^{-1}
M0-62X/6-31+G(d) (IEF-PCM water)	Resorcinol+2H_2O (in-out conformer)	C(2)-H	24.47	3.37	27.84
		C(4,6)-H	25.41	3.63	29.03
ωB97XD/6-31+G(d) (IEF-PCM water)	Resorcinol+2H_2O (in-out conformer)	C(2)-H	24.46	4.56	29.03
		C(4,6)-H	24.56	4.89	29.45

Table S5 Computational values of the different contributions to the total activation entropy $\Delta S^{\ddagger}$: translational entropy ΔS_{Trans}, rotational entropy ΔS_{Rot}, and vibration entropy ΔS_{Vib} (kcal mol^{-1}) at the B3LYP/6-31+G(d) and PBE1PBE/6-31+G(d) level

Solvation species	Position	B3LYP/6-31+G(d)			PBE1PBE/6-31+d		
		$-T\Delta S_{Trans}$ kcal mol^{-1}	$-T\Delta S_{Rot}$ kcal mol^{-1}	$-T\Delta S_{Vib}$ kcal mol^{-1}	$-T\Delta S_{Trans}$ kcal mol^{-1}	$-T\Delta S_{Rot}$ kcal mol^{-1}	$-T\Delta S_{Vib}$ kcal mol^{-1}
Resorcinol (Vacumm)	TS_at 2_position	0	0.02	0.29	0	0.01	0.27
	TS_at 4_position	0	0.02	0.37	0	0.02	-0.02
Resorcinol (Water Cont. Med)	TS_at 2_position	0	0.02	0.29	0	0.05	0.27
	TS_at 4_position	0	0.02	0.32	0	0.02	0.32
Resorcinol + 1H_2O (Vacumm)	TS_at 2_position	0	0.16	3.98	0	0.16	3.89
	TS_at 4_position	0	0.12	4.02	0	0.11	3.92
Resorcinol + 1H_2O (Water Cont. Med)	TS_at 2_position	0	0.15	3.19	0	0.14	3.03
	TS_at 4_position	0	0.11	3.28	0	-0.00	-0.01
Resorcinol + 2H_2O (Vacumm)	TS_at 2_position	0	0.09	3.57	0	0.06	3.42
	TS_at 4_position	0	0.09	3.57	0	0.09	3.60
Resorcinol + 2H_2O (Water Cont. Med)	TS_at 2_position	0	0.06	3.57	0	0.06	3.16
	TS_at 4_position	0	0.18	4.77	0	0.17	4.41
Phloroglucinol (Vacumm)	TS_at 2_position	0	0.02	0.29	0	0.02	0.29
Phloroglucinol (Water Cont. Med)	TS_at 2_position	0	0.02	0.29	0	0.02	0.29
Phloroglucinol + 1H_2O (Vacumm)	TS_at 2_position	0	0.13	4.06	0	0.13	4.01
Phloroglucinol + 1H_2O (Water Cont. Med)	TS_at 2_position	0	0.12	3.42	0	0.12	3.20
Phloroglucinol + 2H_2O (Vacumm)	TS_at 2_position	0	0.06	3.87	0	0.06	3.60
Phloroglucinol + 2H_2O (Water Cont. Med)	TS_at 2_position	0	0.17	4.77	0	0.06	3.60
Catechin (Vacumm)	TS_at 6_position	0	0.01	1.11	0	0.01	0.48
	TS_at 8_position	0	0.01	1.11	0	0.01	0.48
Catechin (Water Cont. Med)	TS_at 6_position	0	0.01	0.35	0	0.01	0.48
	TS_at 8_position	0	0.01	0.59	0	0.01	0.45
Catechin + 1H_2O (Vacumm)	TS_at 6_position	0	-0.00	-0.02	0	-0.00	-0.02
	TS_at 8_position	0	-0.00	-0.02	0	-0.00	-0.02
Catechin + 1H_2O (Water Cont. Med)	TS_at 6_position	0	-0.00	-0.01	0	-0.00	-0.01
	TS_at 8_position	0	-0.00	-0.02	0	-0.00	-0.2
Catechin + 2H_2O (Vacumm)	TS_at 6_position	0	0.02	5.06	0	0.04	3.57
	TS_at 8_position	0	0.05	2.68	0	0.06	2.68
Catechin + 2H_2O (Water Cont. Med)	TS_at 6_position	0	0.08	4.47	0	0.03	3.87
	TS_at 8_position	0	0.06	2.38	0	0.07	1.78

Table S6 NBO charges of the aromatic carbons involved in H/D exchange of the compounds investigated in the present work using PBE1PBE/B3LYP level of theory

Compound	Carbon No	NBO Charges		
		Ground State	(transition state)	Keto Product
Catechin	C(6)-H	-0.400	-0.633	-0.632
	C(8)-H	-0.376	-0.626	-0.627
Resorcinol	C(2)-H	-0.380	-0.639	-0.647
	C(4,6)-H	-0.368	-0.621	-0.633
Phloroglucinol	C(2,4,6)-H	-0.413	-0.643	-0.638

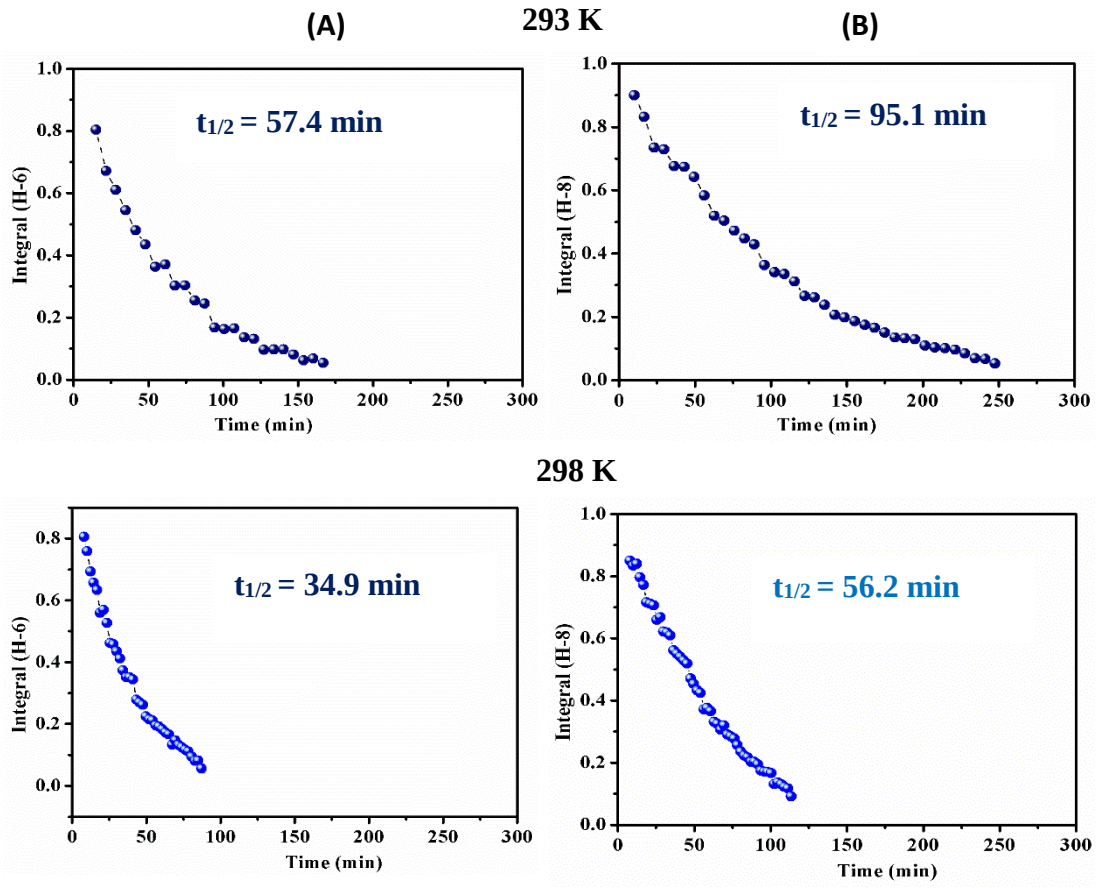


Fig. S1 H/D exchange of catechin (a). C(6)-H (A) and C(8)-H (B) H/D exchange kinetic curves of 2.5 mM catechin (**a**) in D_2O, phosphate buffer solution (25 mM), pD = 8.88 at 298K and 293K.

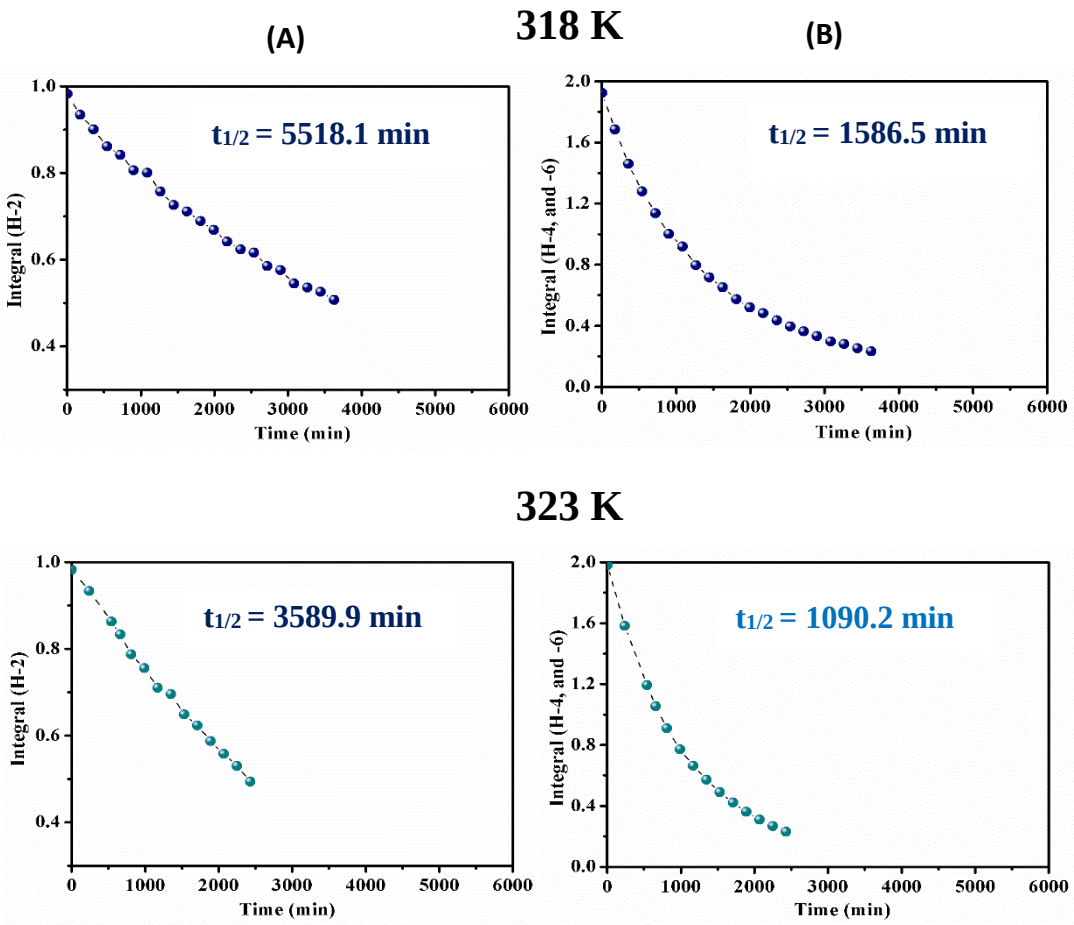


Fig. S2 H/D exchange of resorcinol (b). C(2)-H and C(4,6)-H H/D exchange kinetic curves of 2.5 mM resorcinol (**b**) in D_2O, phosphate buffer solution (25 mM), pD = 9.91 at 318 K and 323 K.

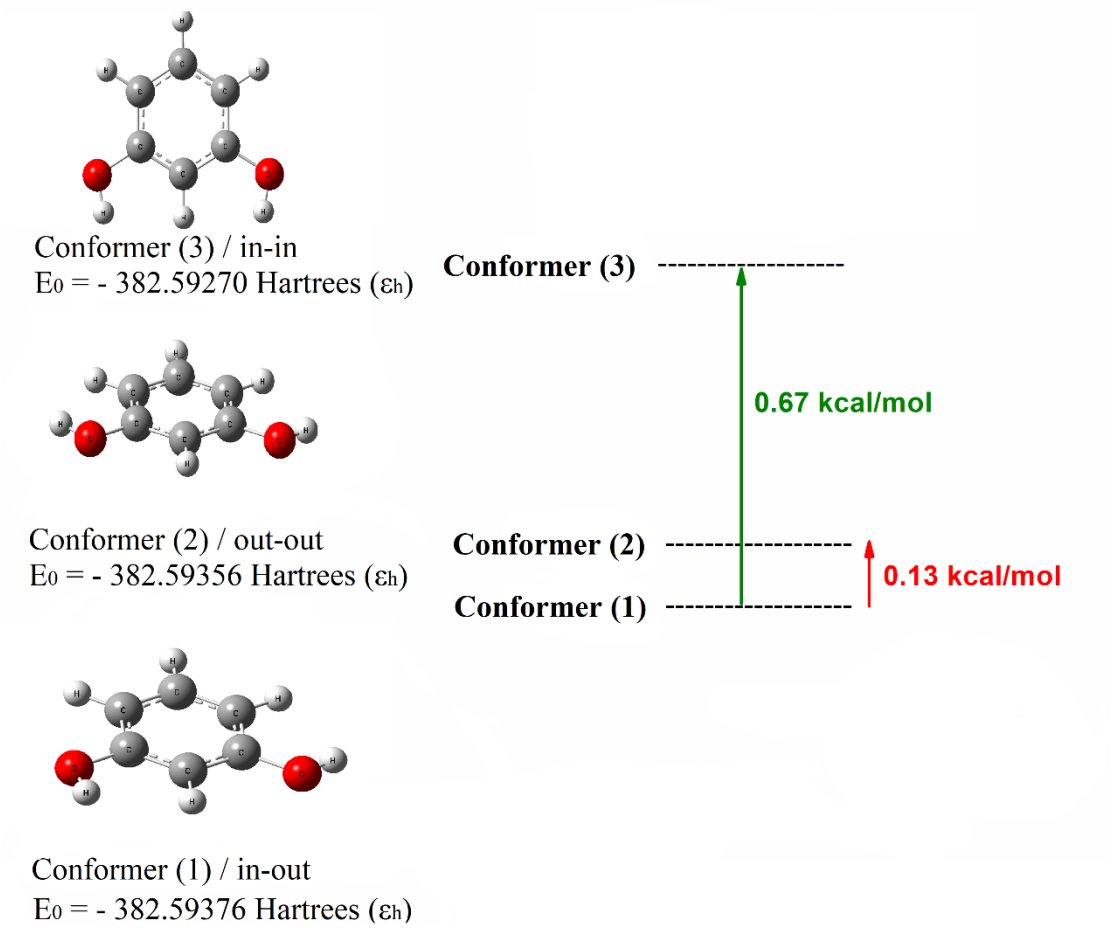
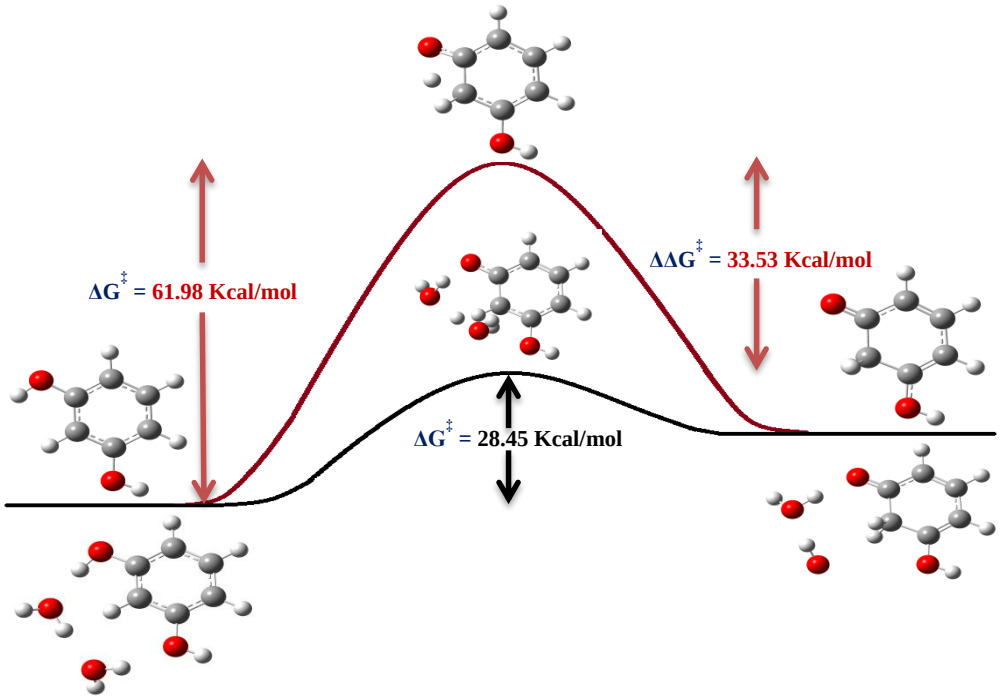


Fig. S3 Three possible conformers of resorcinol (**b**): (1) in-out, (2) out-out, and (3) in-in, on the basis of placement of OH groups and their respective electronic energies in Hatree.

(A)



(B)

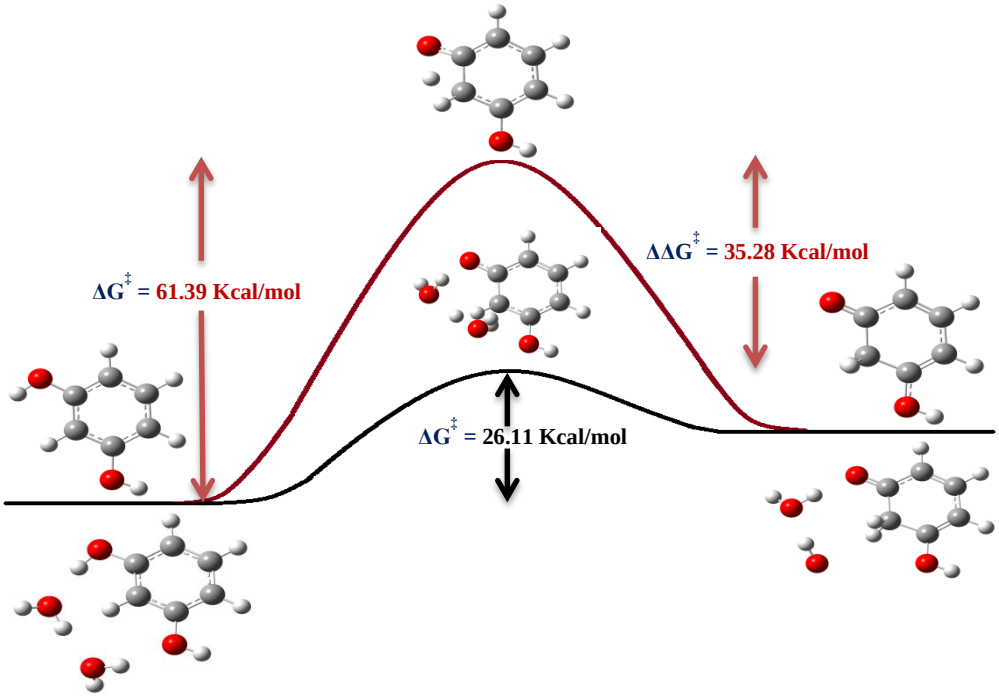


Fig. S4 DFT structure of the ground state of C(2)–H proton of resorcinol (**b**) with respect to its transition state and keto product, without and with two discrete water molecules at the DFT/B3LYP/6-31+G(d) (IEF-PCM, Water) (A), and DFT/PBE1PBE/6-31+G(d) (IEF-PCM Water) (B) level.

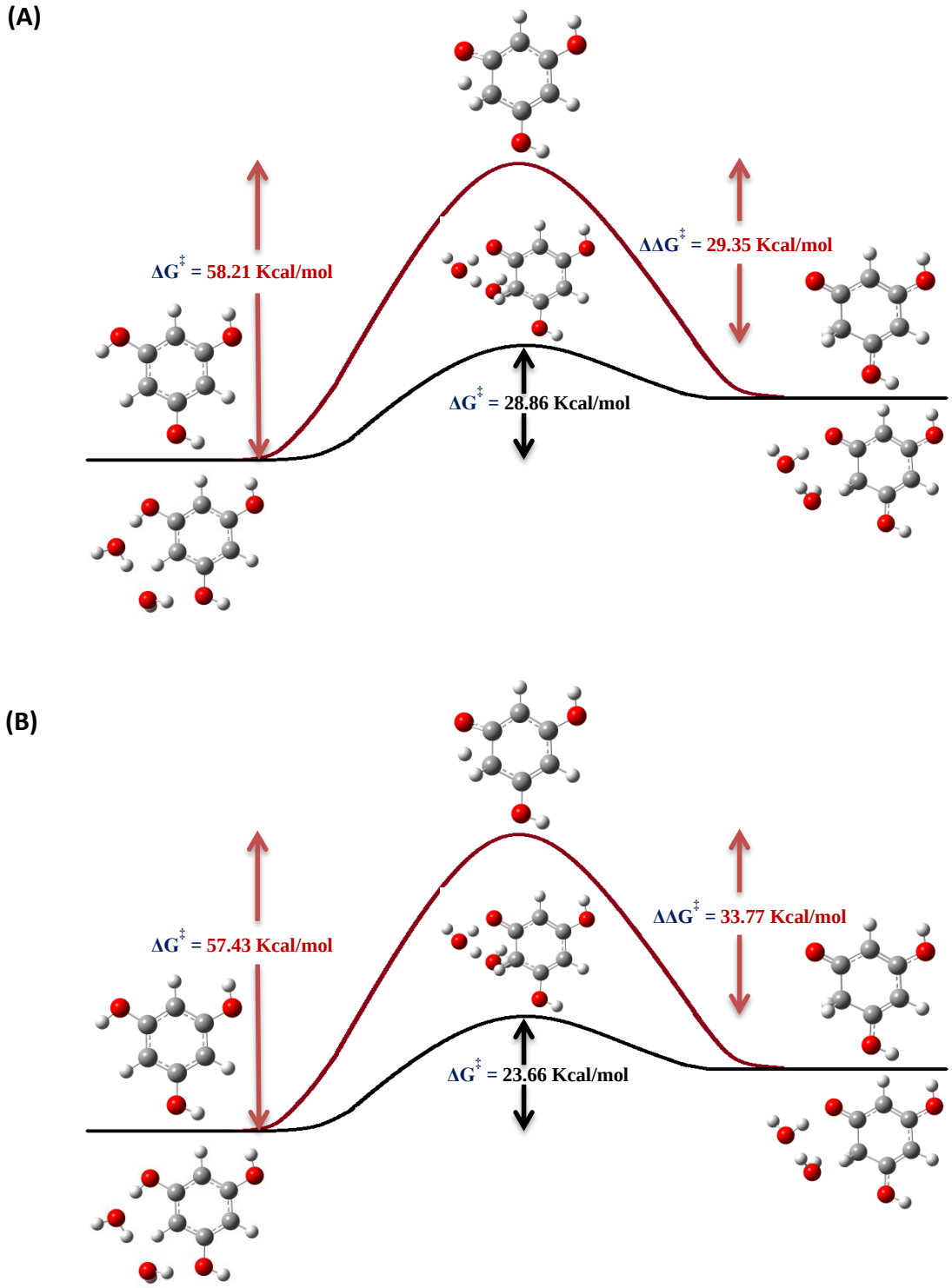


Fig. S5 DFT structure of the ground state of C(2,4,6)–H proton phloroglucinol (**c**) with respect to its transition state and keto product without and with two discrete water molecules at the DFT/B3LYP/6-31+G(d) (IEF-PCM, Water) (A), and DFT/PBE1PBE/6-31+G(d) (IEF-PCM Water) (B) level.