Computational Determination of Aqueous pK_a Values of Protonated Benzimidazoles (Part 2)

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Supporting Information

(Figure S1, Tables S1 to S11 and Appendix; Total pages: 19)

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Figure S1:
Plot of the correlation between the experimental pK_a values (at 298.15 K) of the protonated benzimidazoles in water and in 50% water-ethanol solution.

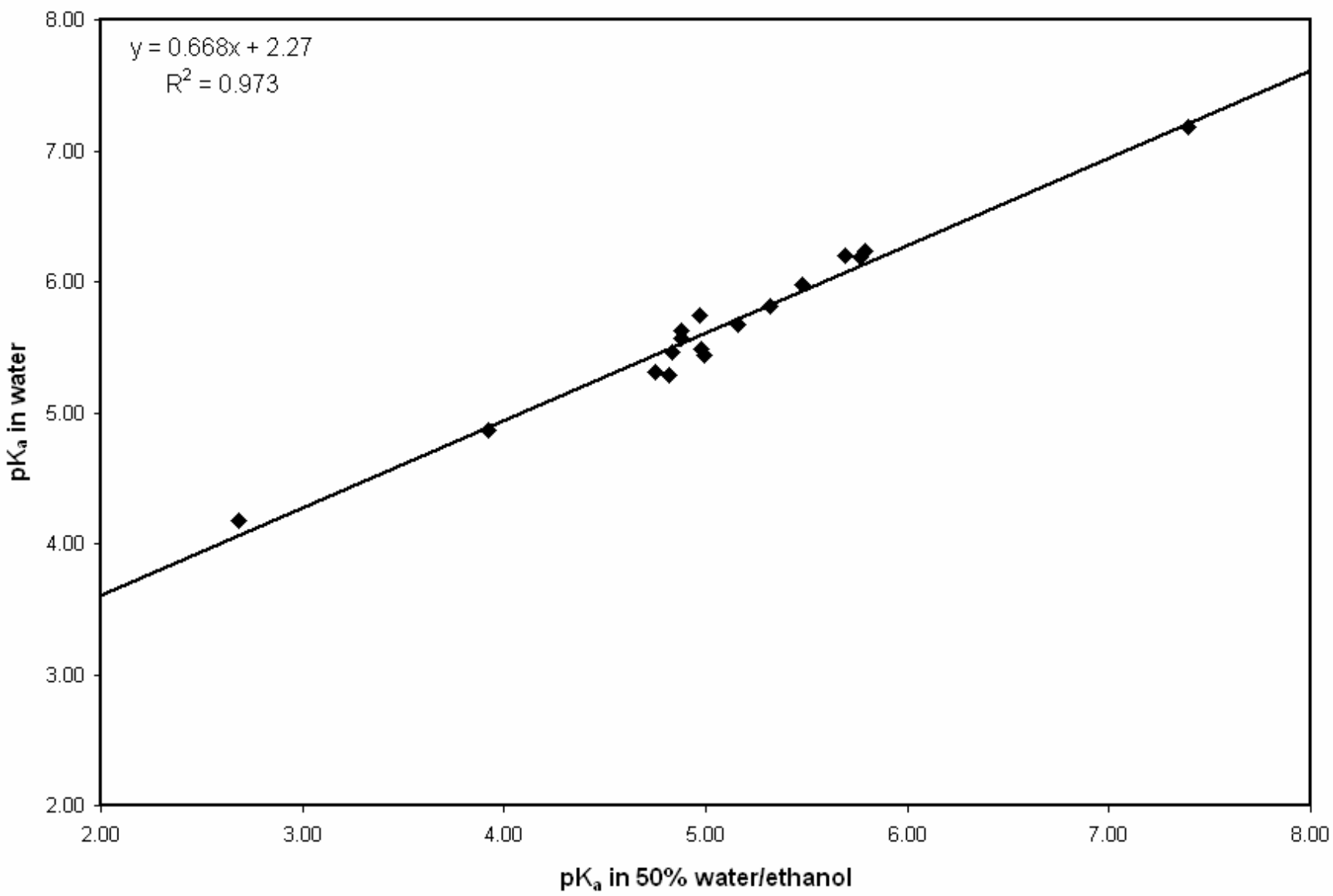

Table S1:
Experimental pK_a values of protonated benzimidazoles in water and in 50% water-ethanol solution at 298.15 K.[a]

Molecule	Aqueous pK_a (H_2O-pK_a)	50% water-ethanol pK_a (50% EtOH-pK_a)
5-nitrobenzimidazole	4.17[b]	2.68
5-chlorobenzimidazole	4.86[d]	3.92
1-(2-hydroxyethyl)-benzimidazole	5.29	4.82
1-n-butylbenzimidazole	5.31	4.75
1-hydroxymethylbenzimidazole	5.44	4.99
benzimidazole	5.48	4.98
1-n-propylbenzimidazole	5.46	4.83
1-methylbenzimidazole	5.57	4.88
1-ethylbenzimidazole	5.62	4.88
4-methylbenzimidazole	5.67	5.16
1-isopropylbenzimidazole	5.74	4.97
5-methylbenzimidazole	5.81	5.32
5,6-dimethylbenzimidazole	5.98	5.48
2-methylbenzimidazole	6.19	5.77
2-ethylbenzimidazole	6.20	5.69
2-isopropylbenzimidazole	6.23	5.79
2-aminobenzimidazole	7.18[c]	7.39
AD[d]	0.586	
Correlation Equation	(H_2O-pK_a) = 0.668 (50% EtOH-pK_a) + 2.27	
R^2	0.973	

[a] From ref 2, unless otherwise indicated. [b] Ref. 3. [c] Ref. 4. [d] Ref. 5.
[d] Mean absolute deviation between aqueous and 50% water-ethanol pK_a values.

Table S2:
Calculated aqueous pK_a values for the protonated benzimidazoles at 298.15 K, using different reaction schemes and equations at the B3LYP/6-31+G(d,p)-PCM(sp) level of theory (Equations and Schemes as indicated in ref. 1).

Molecule	Literature Value	Sch. 1 Eqn. 9[(a)]	Sch. 2 Eqn. 5[(b)]	Sch. 2 Eqn. 9[(b)]	Sch. 2 Eqn. 9[(a)]	Sch. 3 Eqn. 5[(b)]	Sch. 3 Eqn. 9[(b)]	Sch. 4 Eqn. 5[(b)]	Sch. 4 Eqn. 9[(b)]	Sch. 4 Eqn. 9[(a)]
5-nitrobenzimidazole	4.17	-0.25	2.89	2.45	1.13	1.01	1.03	-2.17	-2.38	1.11
5-floro-6-chlorobenzimidazole	4.33	1.89	4.92	4.60	3.28	3.04	3.18	-0.14	-0.24	3.26
2-chlorobenzimidazole	4.68	-1.01	2.18	1.70	0.38	0.30	0.28	-2.89	-3.14	0.35
5-chlorobenzimidazole	4.86	2.75	5.86	5.45	4.13	3.98	4.04	0.80	0.62	4.11
benzimidazole	5.48	4.12	7.29	6.83	5.51	5.48[(c)]	5.48[(c)]	2.22	1.99	5.48
1-methylbenzimidazole	5.57	4.76	7.94	7.46	6.14	6.06	6.05	2.87	2.63	6.12
1-ethylbenzimidazole	5.62	4.99	8.15	7.70	6.38	6.27	6.28	3.08	2.86	6.35
4-methylbenzimidazole	5.67	4.37	7.49	7.07	5.75	5.61	5.66	2.42	2.24	5.73
5-methylbenzimidazole	5.81	4.59	7.75	7.29	5.97	5.87	5.88	2.69	2.46	5.95
5,6-dimethylbenzimidazole	5.98	5.24	8.40	7.94	6.63	6.52	6.53	3.33	3.11	6.60
5-aminobenzimidazole	6.11	7.59	13.35	10.30	8.98	11.47	8.88	8.28	5.46	8.96
2-methylbenzimidazole	6.19	5.76	8.96	8.46	7.14	7.08	7.04	3.90	3.63	7.12
2-ethylbenzimidazole	6.20	5.08	8.07	7.79	6.47	6.19	6.37	3.01	2.95	6.45
2-isopropylbenzimidazole	6.23	5.14	8.37	7.85	6.53	6.49	6.43	3.30	3.01	6.51
2-aminobenzimidazole	7.18	8.64	11.78	11.34	10.02	9.90	9.92	6.71	6.51	10.00
5-chloro-1-methylbenzimidazole	-	3.52	6.56	6.22	4.91	4.68	4.81	1.49	1.39	4.88
5,6-dichlorobenzimidazole	-	1.72	4.74	4.42	3.10	2.86	3.01	-0.32	-0.41	3.08
5-methoxy-2-methylbenzimidazole	-	6.13	9.33	8.84	7.52	7.45	7.42	4.26	4.00	7.50
2-methoxybenzimidazole	-	3.67	6.94	6.38	5.06	5.06	4.96	1.88	1.54	5.04
MD[(d)]		-1.361	1.954	1.342	0.024	0.094	-0.064	-3.112	-3.491	0.002
AD[(e)]		1.753	2.458	1.970	**1.240**	1.747	1.566	3.401	3.491	**1.229**
A[(f)]		0.288	0.240	0.288	0.288	0.240	0.288	0.240	0.288	0.288
B[(f)]		4.384	3.789	3.606	3.985	4.246	4.020	5.006	4.997	3.992
R^2		**0.834**	0.734	**0.834**	**0.834**	0.734	**0.835**	0.734	**0.834**	**0.834**
LAD[(g)]		0.265	0.332	0.265	0.265	0.410	0.356	0.332	0.265	0.265

[(a)] Values of G_{gas} and ΔG_{solv} for OH^-, H_2O, H_3O^+ and H^+ are taken from the literature.[23]
[(b)] pK_a values calculated using only *ab initio* data.

[c] Experimental pK_a value. All other pK_a values are calculated relative to this value, which was not included in the calculation of deviations.
[d] Mean deviation of the calculated pK_a values from the literature values.
[e] Mean absolute deviation of the calculated pK_a values from the literature values.
[f] Coefficients of the linear correlation equation of the form $pK_{a\ (experimental)} = A\ pK_{a\ (calculated)} + B$, and the correlation factor R^2.
[g] Mean absolute deviation of calculated values from experimental aqueous pK_a values after application of the linear correction.

Table S3:
Raw data (energies in atomic units and G_{solv} in kcal/mol) for the aqueous pK_a calculations (at 298.15 K) of the protonated benzimidazoles under study at the B3LYP/6-31+G(d,p)-PCM(sp) level of theory. The data provided corresponds to the neutral, the tautomer (taut., when applicable), the protonated benzimidazole (cat.), water and the hydroxide and hydronium ions.

Species	$f_{1,2}$ (Eqn. 5)	$f_{1,2}$ (Eqn. 9)	E^{Total}_{gas}	E^{Total}_{aq}	TCG_{gas}	ZPC	G_{solv}	q
hydroxide	-	-	-75.80343	-75.96619	-0.00771	0.00855	-100.87	3.02E+07
water	-	-	-76.43405	-76.44624	0.00364	0.02129	-6.94	1.31E+08
hydronium	-	-	-76.70777	-76.87848	0.01621	0.03432	-107.28	2.14E+08
5-nit	0.668	0.656	-584.40386	-584.42745	0.08623	0.12065	-12.16	6.80E+15
5-nit taut	0.332	0.344	-584.40414	-584.42686	0.08631	0.12069	-11.65	6.51E+15
5-nit cat	-	-	-584.76039	-584.87115	0.09980	0.13431	-67.13	7.44E+15
5f-6cl	0.479	0.480	-938.72099	-938.73958	0.06670	0.10030	-9.22	2.84E+15
5f-6cl taut	0.521	0.520	-938.72111	-938.73972	0.06676	0.10034	-9.23	2.81E+15
5f-6cl cat	-	-	-939.08587	-939.18835	0.08061	0.11419	-62.28	2.81E+15
2-chl	0.500	0.500	-839.48516	-839.49987	0.07610	0.10850	-6.99	8.02E+14
2-chl taut	0.500	0.500	-839.48516	-839.49987	0.07610	0.10850	-6.99	8.02E+14
2-chl cat	-	-	-839.85222	-839.94246	0.08984	0.12227	-54.59	8.28E+14
5-chl	0.461	0.390	-839.48670	-839.50466	0.07620	0.10859	-9.17	7.88E+14
5-chl taut	0.539	0.610	-839.48689	-839.50481	0.07620	0.10859	-9.32	7.91E+14
5-chl cat	-	-	-839.85659	-839.95547	0.09006	0.12247	-60.35	8.03E+14
benz	0.500	0.500	-379.89326	-379.91020	0.08801	0.11820	-9.39	7.68E+13
benz taut	0.500	0.500	-379.89326	-379.91020	0.08801	0.11820	-9.39	7.68E+13
benz cat	-	-	-380.26975	-380.36417	0.10202	0.13224	-58.24	7.97E+13
1-met	1.000	1.000	-419.20682	-419.22052	0.11360	0.14609	-6.98	8.83E+14
1-met taut	0.000	0.000	-419.20682	-419.22052	0.11360	0.14609	-6.98	8.83E+14
1-met cat	-	-	-419.58951	-419.67525	0.12761	0.15997	-52.40	7.67E+14
1-et	1.000	1.000	-458.52644	-458.54049	0.14007	0.17457	-6.52	7.44E+15
1-et taut	0.000	0.000	-458.52644	-458.54049	0.14007	0.17457	-6.52	7.44E+15
1-et cat	-	-	-458.91115	-458.99554	0.15395	0.18836	-50.91	6.77E+15
4-met	0.536	0.482	-419.21568	-419.23141	0.11311	0.14569	-8.13	9.65E+14
4-met taut	0.464	0.518	-419.21480	-419.23151	0.11334	0.14569	-8.87	7.55E+14
4-met cat	-	-	-419.59443	-419.68584	0.12721	0.15970	-55.98	8.80E+14
5-met	0.439	0.433	-419.21333	-419.23024	0.11251	0.14545	-9.10	1.42E+15
5-met taut	0.561	0.567	-419.21359	-419.23051	0.11254	0.14547	-9.12	1.40E+15
5-met cat	-	-	-419.59379	-419.68557	0.12673	0.15952	-56.32	1.20E+15
5,6-dm	0.500	0.500	-458.53282	-458.54987	0.13933	0.17332	-8.99	4.32E+15
5,6-dm taut	0.500	0.500	-458.53282	-458.54987	0.13933	0.17332	-8.99	4.32E+15
5,6-dm cat	-	-	-458.91649	-459.00618	0.15327	0.18731	-54.82	4.58E+15
2-met	0.500	0.500	-419.22050	-419.23683	0.11280	0.14550	-8.67	1.10E+15
2-met taut	0.500	0.500	-419.22050	-419.23683	0.11280	0.14550	-8.67	1.10E+15
2-met cat	-	-	-419.60428	-419.69394	0.12631	0.15954	-54.87	1.92E+15
5-am	0.279	0.274	-435.25296	-435.27564	0.10264	0.13454	-12.90	4.72E+14
5-am taut	0.721	0.726	-435.25388	-435.27664	0.10275	0.13460	-12.97	4.49E+14
5-am cat	-	-	-435.63970	-435.74192	0.11523	0.14792	-59.53	1.08E+15
2-et	0.500	0.500	-458.53712	-458.55368	0.13868	0.17423	-8.55	2.25E+16
2-et taut	0.500	0.500	-458.53712	-458.55368	0.13868	0.17423	-8.55	2.25E+16
2-et cat	-	-	-458.92317	-459.00989	0.15323	0.18828	-53.05	1.33E+16
2-is	0.500	0.500	-497.85440	-497.87093	0.16478	0.20221	-7.97	1.63E+17
2-is taut	0.500	0.500	-497.85440	-497.87093	0.16478	0.20221	-7.97	1.63E+17
2-is cat	-	-	-498.24200	-498.32803	0.17958	0.21645	-51.74	9.06E+16
2-am	0.500	0.500	-435.26303	-435.28697	0.10304	0.13489	-13.89	4.44E+14
2-am taut	0.500	0.500	-435.26303	-435.28697	0.10304	0.13489	-13.89	4.44E+14
2-am cat	-	-	-435.64709	-435.74897	0.11531	0.14771	-63.06	7.96E+14
5cl-1mt	1.000	1.000	-878.80044	-878.81499	0.10176	0.13644	-6.63	8.93E+15
5cl-1mt taut	0.000	0.000	-878.80044	-878.81499	0.10176	0.13644	-6.63	8.93E+15

5cl-1mt cat	-	-	-879.17660	-879.26658	0.11563	0.15016	-54.37	7.64E+15
5,6-dicl	0.500	0.500	-1299.07462	-1299.09281	0.06450	0.09892	-8.48	6.84E+15
5,6-dicl taut	0.500	0.500	-1299.07462	-1299.09281	0.06450	0.09892	-8.48	6.84E+15
5,6-dicl cat	-	-	-1299.43969	-1299.54098	0.07823	0.11266	-61.05	6.81E+15
5-mx	0.392	0.328	-533.74764	-533.76629	0.14146	0.17779	-9.79	5.16E+16
5-mx taut	0.608	0.672	-533.74746	-533.76695	0.14170	0.17784	-10.48	4.19E+16
5-mx cat	-	-	-534.13578	-534.22480	0.15534	0.19187	-54.25	6.37E+16
2-mx	0.500	0.500	-494.42148	-494.44228	0.11580	0.15018	-11.37	6.52E+15
2-mx taut	0.500	0.500	-494.42148	-494.44228	0.11580	0.15018	-11.37	6.52E+15
2-mx cat	-	-	-494.80783	-494.89584	0.13013	0.16423	-53.63	4.80E+15

E^{total}_{gas}: total gas-phase energy; E^{total}_{aq}: total aqueous-phase energy; ZPC: zero-point energy correction; TCG_{gas}: thermal correction to the Gibbs energy; q: total molecular partition function; G_{solv}: Gibbs free energy of solvation (286.15 K). E^{total}_{gas}, ZPC, TCG_{gas} and q were taken from the gas-phase geometry optimization and frequency calculation at the B3LYP/6-31+G(d,p) level of theory (see Table S4 of ref. 1). E^{total}_{aq} and G_{solv} were taken from the aqueous-phase single-point calculation at the B3LYP/6-31+G(d,p)-PCM level of theory.
The value of f_1 is the relative population of tautomer 1 which is the named tautomer; $f_2 = 1 - f_1$.

Table S4:
Descriptors of all species at the B3LYP/6-31+G(d,p)-PCM(opt) level of theory.

Species	$f_{1,2}$	ε_{HOMO-2}	ε_{HOMO-1}	ε_{HOMO}	ε_{LUMO}	ε_{LUMO+1}	ε_{LUMO+2}	Q_{N1}	Q_{N3}	Q_{H1}	Q_{H3}	V_{sc}
water	-	-0.52374	-0.39037	-0.31556	0.04186	0.12734	0.14264	-	-	-	-	34.321
hydronium	-	-0.60911	-0.60911	-0.45813	0.00347	0.10590	0.10590	-	-	-	-	24.921
5-nit	0.644	-0.30644	-0.26504	-0.25710	-0.10835	-0.04490	0.00467	-0.57473	-0.53260	0.50709	-	201.719
5-nit taut	0.356	-0.30527	-0.26338	-0.25817	-0.11064	-0.04045	-0.00027	-0.57278	-0.54245	0.50792	-	201.602
5-nit cat	-	-0.32430	-0.29958	-0.29238	-0.12442	-0.07706	-0.03076	-0.52477	-0.52017	0.53744	0.53734	205.728
5f-6cl	0.524	-0.30183	-0.24850	-0.24291	-0.04598	-0.00716	-0.00168	-0.57875	-0.54950	0.50341	-	199.756
5f-6cl taut	0.476	-0.30191	-0.24784	-0.24337	-0.04424	-0.00680	-0.00485	-0.58083	-0.54498	0.50334	-	199.766
5f-6cl cat	-	-0.34065	-0.28090	-0.27253	-0.07823	-0.03060	-0.02487	-0.52586	-0.52276	0.53405	0.53373	201.031
2-chl	0.500	-0.30830	-0.24459	-0.24051	-0.03476	-0.00232	-0.00072	-0.58961	-0.54143	0.50655	-	199.040
2-chl taut	0.500	-0.30830	-0.24459	-0.24051	-0.03476	-0.00232	-0.00072	-0.58961	-0.54143	0.50655	-	199.040
2-chl cat	-	-0.36725	-0.27529	-0.27419	-0.07440	-0.02497	-0.02351	-0.53219	-0.53224	0.53503	0.53484	202.772
5-chl	0.434	-0.29867	-0.24576	-0.23985	-0.03999	-0.00557	0.00483	-0.58066	-0.55205	0.50115	-	196.383
5-chl taut	0.566	-0.29810	-0.24837	-0.23752	-0.03938	-0.00457	0.00459	-0.58175	-0.55006	0.50113	-	193.656
5-chl cat	-	-0.33365	-0.28137	-0.26811	-0.07431	-0.03064	-0.02194	-0.52462	-0.52594	0.53189	0.53166	197.649
benz	0.500	-0.29332	-0.24037	-0.23672	-0.03145	0.00494	0.00999	-0.58474	-0.55711	0.49762	-	167.840
benz taut	0.500	-0.29332	-0.24037	-0.23672	-0.03145	0.00494	0.00999	-0.58474	-0.55711	0.49762	-	167.840
benz cat	-	-0.37491	-0.27491	-0.27136	-0.06814	-0.02114	-0.01559	-0.52752	-0.52748	0.52895	0.52859	171.712
1-met	1.000	-0.29221	-0.23928	-0.23433	-0.03245	0.00358	0.00833	-0.40195	-0.55692	-	-	193.333
1-met taut	0.000	-0.29221	-0.23928	-0.23433	-0.03245	0.00358	0.00833	-0.40195	-0.55692	-	-	193.333
1-met cat	-	-0.35279	-0.27441	-0.26994	-0.06829	-0.02224	-0.01361	-0.34516	-0.52886	-	0.52757	197.218
1-et	1.000	-0.29143	-0.23854	-0.23374	-0.03218	0.00183	0.00843	-0.40321	-0.55627	-	-	219.279
1-et taut	0.000	-0.29143	-0.23854	-0.23374	-0.03218	0.00183	0.00843	-0.40321	-0.55627	-	-	219.279
1-et cat	-	-0.34937	-0.27389	-0.26929	-0.06800	-0.02171	-0.01478	-0.34837	-0.52832	-	0.52729	223.018
4-met	0.494	-0.29000	-0.23775	-0.22899	-0.02824	0.00695	0.00744	-0.58476	-0.55406	0.49647	-	195.717
4-met taut	0.506	-0.29247	-0.23818	-0.23085	-0.02826	0.00430	0.00570	-0.58541	-0.55728	0.49562	-	193.195
4-met cat	-	-0.36534	-0.27317	-0.26194	-0.06624	-0.02004	-0.01118	-0.52650	-0.52861	0.52822	0.52484	197.119
5-met	0.413	-0.29173	-0.23506	-0.23112	-0.02902	0.00520	0.00852	-0.58470	-0.56073	0.49685	-	193.290
5-met taut	0.587	-0.29184	-0.23739	-0.22924	-0.02773	0.00359	0.00774	-0.58555	-0.55820	0.49645	-	193.231
5-met cat	-	-0.36693	-0.27029	-0.26221	-0.06496	-0.02048	-0.01337	-0.52653	-0.52836	0.52788	0.52711	197.089
5,6-dm	0.500	-0.29039	-0.23034	-0.22635	-0.02614	0.00758	0.01061	-0.58625	-0.56134	0.49559	-	216.704
5,6-dm taut	0.500	-0.29039	-0.23034	-0.22635	-0.02614	0.00758	0.01061	-0.58625	-0.56134	0.49559	-	216.704
5,6-dm cat	-	-0.36044	-0.26249	-0.25751	-0.06257	-0.01434	-0.01195	-0.52791	-0.52786	0.52634	0.52611	220.486
2-met	0.500	-0.28948	-0.23614	-0.23196	-0.02683	0.00614	0.00701	-0.58651	-0.55842	0.49229	-	194.268
2-met taut	0.500	-0.28948	-0.23614	-0.23196	-0.02683	0.00614	0.00701	-0.58651	-0.55842	0.49229	-	194.268
2-met cat	-	-0.37033	-0.26850	-0.26787	-0.06125	-0.01855	-0.01247	-0.53040	-0.53019	0.52200	0.52180	198.234
5-am	0.286	-0.28949	-0.23369	-0.20141	-0.02801	0.00624	0.01513	-0.58521	-0.57078	0.49547	-	183.200
5-am taut	0.714	-0.28984	-0.23610	-0.20081	-0.02464	0.00530	0.01396	-0.59217	-0.55717	0.49392	-	183.271
5-am cat	-	-0.32566	-0.26848	-0.22248	-0.06097	-0.01233	-0.00371	-0.52344	-0.53675	0.52563	0.52307	187.199

2-et	0.500	-0.28876	-0.23598	-0.23176	-0.02783	0.00520	0.00759	-0.58492	-0.55549	0.49131	-	217.313
2-et taut	0.500	-0.28876	-0.23598	-0.23176	-0.02783	0.00520	0.00759	-0.58492	-0.55549	0.49131	-	217.313
2-et cat	-	-0.36657	-0.26818	-0.26744	-0.06193	-0.01826	-0.01324	-0.52994	-0.52877	0.52155	0.52177	221.696
2-am	0.500	-0.28928	-0.23283	-0.21044	-0.01567	0.00146	0.00948	-0.61219	-0.62247	0.49112	-	179.271
2-am taut	0.500	-0.28928	-0.23283	-0.21044	-0.01567	0.00146	0.00948	-0.61219	-0.62247	0.49112	-	179.271
2-am cat	-	-0.33002	-0.26178	-0.24294	-0.03796	-0.01265	-0.00588	-0.57929	-0.57919	0.51496	0.51488	183.392
5cl-1mt	1.000	-0.29750	-0.24438	-0.23780	-0.04080	-0.00662	0.00431	-0.39799	-0.55112	-	-	221.936
5cl-1mt taut	0.000	-0.29750	-0.24438	-0.23780	-0.04080	-0.00662	0.00431	-0.39799	-0.55112	-	-	221.936
5cl-1mt cat	-	-0.33363	-0.28005	-0.26761	-0.07440	-0.03157	-0.02001	-0.34238	-0.52734	-	0.53060	223.147
5,6-dicl	0.500	-0.30256	-0.24723	-0.24366	-0.04705	-0.01744	-0.01214	-0.57884	-0.54555	0.50394	-	223.943
5,6-dicl taut	0.500	-0.30256	-0.24723	-0.24366	-0.04705	-0.01744	-0.01214	-0.57884	-0.54555	0.50394	-	223.943
5,6-dicl cat	-	-0.32849	-0.27785	-0.27130	-0.08001	-0.03790	-0.02689	-0.52391	-0.52381	0.53432	0.53423	225.095
5-mx	0.412	-0.28895	-0.23432	-0.21464	-0.02626	0.00511	0.01547	-0.58389	-0.56736	0.49187	-	229.827
5-mx taut	0.588	-0.28872	-0.23785	-0.21287	-0.02234	0.00440	0.01010	-0.58809	-0.55518	0.49093	-	227.026
5-mx cat	-	-0.33186	-0.26931	-0.24059	-0.05708	-0.01492	-0.00584	-0.52414	-0.53514	0.52139	0.51967	231.325
2-mx	0.500	-0.29821	-0.23898	-0.22389	-0.02140	0.00334	0.00566	-0.62250	-0.59446	0.49431	-	206.067
2-mx taut	0.500	-0.29821	-0.23898	-0.22389	-0.02140	0.00334	0.00566	-0.62250	-0.59446	0.49431	-	206.067
2-mx cat	-	-0.35290	-0.26869	-0.25986	-0.04905	-0.01857	-0.00484	-0.56341	-0.58021	0.52050	0.52409	210.707

Orbital energies (ε_{HOMO-2} to ε_{LUMO-2}) and NBO atomic charges (Q_i) in atomic units; volume of the solvent cavity (V_{sc}) in $Å^3$; f_1 and f_2 are the relative populations of the tautomers.

Table S5:
Descriptors and of all species at the B3LYP/6-31+G(d,p)-PCM(sp) level of theory.

Species	$f_{1,2}$	ε_{HOMO-2}	ε_{HOMO-1}	ε_{HOMO}	ε_{LUMO}	ε_{LUMO+1}	ε_{LUMO+2}	Q_{N1}	Q_{N3}	Q_{H1}	Q_{H3}	V_{sc}
hydroxide	-	-0.34647	-0.22367	-0.22367	0.07782	0.15373	0.16825	-	-	-	-	15.538
water	-	-0.52901	-0.38960	-0.31630	0.04278	0.12722	0.14276	-	-	-	-	34.321
hydronium	-	-0.64351	-0.64351	-0.45540	0.01034	0.10884	0.10884	-	-	-	-	24.921
5-nit	0.656	-0.29866	-0.27267	-0.26466	-0.09813	-0.05413	-0.02383	-0.57532	-0.53056	0.50075	-	201.677
5-nit taut	0.344	-0.30608	-0.26326	-0.25780	-0.10913	-0.03991	-0.00073	-0.57425	-0.53905	0.50122	-	201.559
5-nit cat	-	-0.32977	-0.29989	-0.29195	-0.12163	-0.07753	-0.03153	-0.52060	-0.51658	0.52927	0.52923	205.632
5f-6cl	0.480	-0.30254	-0.24802	-0.24297	-0.04568	-0.00573	-0.00174	-0.57978	-0.54545	0.49757	-	199.640
5f-6cl taut	0.520	-0.30259	-0.24777	-0.24318	-0.04376	-0.00522	-0.00520	-0.58175	-0.54087	0.49752	-	199.662
5f-6cl cat	-	-0.34140	-0.28024	-0.27122	-0.07856	-0.03119	-0.02519	-0.52194	-0.51873	0.52626	0.52607	200.892
2-chl	0.500	-0.30923	-0.24444	-0.24127	-0.03476	-0.00242	-0.00092	-0.58863	-0.53829	0.49998	-	198.996
2-chl taut	0.500	-0.30923	-0.24444	-0.24127	-0.03476	-0.00242	-0.00092	-0.58863	-0.53829	0.49998	-	198.996
2-chl cat	-	-0.36815	-0.27605	-0.27502	-0.07562	-0.02567	-0.02377	-0.52786	-0.52794	0.52643	0.52630	202.879
5-chl	0.390	-0.29949	-0.24667	-0.23922	-0.03966	-0.00583	0.00620	-0.58155	-0.54765	0.49556	-	196.246
5-chl taut	0.610	-0.29899	-0.24784	-0.23811	-0.03912	-0.00468	0.00535	-0.58246	-0.54567	0.49551	-	193.559
5-chl cat	-	-0.33463	-0.28180	-0.26748	-0.07491	-0.03153	-0.02272	-0.52051	-0.52199	0.52453	0.52435	197.584
benz	0.500	-0.29433	-0.24005	-0.23756	-0.03120	0.00484	0.01012	-0.58555	-0.55229	0.49231	-	167.772
benz taut	0.500	-0.29433	-0.24005	-0.23756	-0.03120	0.00484	0.01012	-0.58555	-0.55229	0.49231	-	167.772
benz cat	-	-0.37449	-0.27559	-0.27226	-0.06906	-0.02178	-0.01651	-0.52333	-0.52334	0.52202	0.52185	171.802
1-met	1.000	-0.29320	-0.23902	-0.23467	-0.03214	0.00362	0.00834	-0.40456	-0.55232	-	-	193.203
1-met taut	0.000	-0.29320	-0.23902	-0.23467	-0.03214	0.00362	0.00834	-0.40456	-0.55232	-	-	193.203
1-met cat	-	-0.35283	-0.27484	-0.27053	-0.06871	-0.02262	-0.01425	-0.34447	-0.52564	-	0.52076	197.303
1-et	1.000	-0.29239	-0.23839	-0.23403	-0.03190	0.00180	0.00850	-0.40545	-0.55172	-	-	219.154
1-et taut	0.000	-0.29239	-0.23839	-0.23403	-0.03190	0.00180	0.00850	-0.40545	-0.55172	-	-	219.154
1-et cat	-	-0.34982	-0.27426	-0.26988	-0.06838	-0.02200	-0.01534	-0.34745	-0.52525	-	0.52040	223.125
4-met	0.482	-0.29081	-0.23761	-0.22954	-0.02808	0.00709	0.00755	-0.58543	-0.54960	0.49116	-	195.589
4-met taut	0.518	-0.28071	-0.23557	-0.22902	-0.02644	-0.01479	0.00785	-0.58605	-0.55244	0.49051	-	193.143
4-met cat	-	-0.36574	-0.27373	-0.26298	-0.06730	-0.02049	-0.01223	-0.52250	-0.52417	0.52140	0.51811	197.274
5-met	0.433	-0.29277	-0.23603	-0.23069	-0.02886	0.00521	0.00863	-0.58559	-0.55575	0.49162	-	193.185
5-met taut	0.567	-0.29287	-0.23702	-0.23004	-0.02745	0.00351	0.00786	-0.58635	-0.55321	0.49128	-	193.134
5-met cat	-	-0.36760	-0.27113	-0.26270	-0.06585	-0.02128	-0.01418	-0.52232	-0.52423	0.52097	0.52036	197.216
5,6-dm	0.500	-0.29145	-0.23060	-0.22657	-0.02592	0.00766	0.01045	-0.58713	-0.55621	0.49050	-	216.588
5,6-dm taut	0.500	-0.29145	-0.23060	-0.22657	-0.02592	0.00766	0.01045	-0.58713	-0.55621	0.49050	-	216.588
5,6-dm cat	-	-0.36109	-0.26326	-0.25780	-0.06351	-0.01522	-0.01263	-0.52372	-0.52372	0.51959	0.51944	220.577
2-met	0.500	-0.29039	-0.23597	-0.23277	-0.02661	0.00601	0.00711	-0.58705	-0.55441	0.48754	-	194.204
2-met taut	0.500	-0.29039	-0.23597	-0.23277	-0.02661	0.00601	0.00711	-0.58705	-0.55441	0.48754	-	194.204
2-met cat	-	-0.36954	-0.26942	-0.26892	-0.06219	-0.01919	-0.01336	-0.52667	-0.52644	0.51525	0.51512	198.360
5-am	0.274	-0.29064	-0.23468	-0.20090	-0.02782	0.00639	0.01551	-0.58634	-0.56545	0.49032	-	183.069
5-am taut	0.726	-0.29082	-0.23576	-0.20121	-0.02425	0.00543	0.01391	-0.59275	-0.55198	0.48895	-	183.146

5-am cat	-	-0.32139	-0.26388	-0.21225	-0.05493	-0.00663	0.00360	-0.52110	-0.53706	0.52331	0.52119	165.671
2-et	0.500	-0.28952	-0.23578	-0.23236	-0.02758	0.00543	0.00753	-0.58480	-0.55222	0.48733	-	217.425
2-et taut	0.500	-0.28952	-0.23578	-0.23236	-0.02758	0.00543	0.00753	-0.58480	-0.55222	0.48733	-	217.425
2-et cat	-	-0.36351	-0.26943	-0.26775	-0.06090	-0.01883	-0.01244	-0.52513	-0.52823	0.50895	0.51414	220.392
2-is	0.500	-0.28912	-0.23578	-0.23250	-0.02697	0.00306	0.00623	-0.58542	-0.54791	0.48502	-	242.353
2-is taut	0.500	-0.28912	-0.23578	-0.23250	-0.02697	0.00306	0.00623	-0.58542	-0.54791	0.48502	-	242.353
2-is cat	-	-0.35980	-0.26922	-0.26847	-0.06227	-0.01914	-0.01321	-0.52306	-0.52739	0.51486	0.51046	247.365
2-am	0.500	-0.29162	-0.23437	-0.21487	-0.01705	0.00173	0.00764	-0.61221	-0.60915	0.48690	-	179.287
2-am taut	0.500	-0.29162	-0.23437	-0.21487	-0.01705	0.00173	0.00764	-0.61221	-0.60915	0.48690	-	179.287
2-am cat	-	-0.33004	-0.26347	-0.24537	-0.03906	-0.01358	-0.00549	-0.57501	-0.57494	0.50974	0.50971	183.540
5cl-1mt	1.000	-0.29833	-0.24506	-0.23700	-0.04039	-0.00673	0.00529	-0.40075	-0.54692	-	-	221.731
5cl-1mt taut	0.000	-0.29833	-0.24506	-0.23700	-0.04039	-0.00673	0.00529	-0.40075	-0.54692	-	-	221.731
5cl-1mt cat	-	-0.33453	-0.28006	-0.26693	-0.07456	-0.03220	-0.02044	-0.34190	-0.52420	-	0.52326	223.083
5,6-dicl	0.500	-0.30332	-0.24704	-0.24382	-0.04679	-0.01558	-0.01250	-0.57977	-0.54144	0.49814	-	223.848
5,6-dicl taut	0.500	-0.30332	-0.24704	-0.24382	-0.04679	-0.01558	-0.01250	-0.57977	-0.54144	0.49814	-	223.848
5,6-dicl cat	-	-0.32972	-0.27755	-0.27013	-0.08055	-0.03909	-0.02760	-0.51985	-0.51983	0.52663	0.52647	224.975
5-mx	0.328	-0.28991	-0.23535	-0.21438	-0.02613	0.00523	0.01531	-0.58456	-0.56332	0.48711	-	229.727
5-mx taut	0.672	-0.28955	-0.23780	-0.21341	-0.02194	0.00449	0.00962	-0.58858	-0.55110	0.48644	-	226.892
5-mx cat	-	-0.33389	-0.26993	-0.23953	-0.05736	-0.01517	-0.00592	-0.51997	-0.53189	0.51435	0.51278	231.586
2-mx	0.500	-0.30012	-0.23906	-0.22548	-0.02155	0.00347	0.00520	-0.62227	-0.58688	0.48869	-	205.737
2-mx taut	0.500	-0.30012	-0.23906	-0.22548	-0.02155	0.00347	0.00520	-0.62227	-0.58688	0.48869	-	205.737
2-mx cat	-	-0.35379	-0.26972	-0.26119	-0.04948	-0.01940	-0.00556	-0.57673	-0.56118	0.51293	0.51711	211.140

Orbital energies (ε_{HOMO-2} to ε_{LUMO-2}) and NBO atomic charges (Q_i) in atomic units; volume of the solvent cavity (V_{sc}) in $Å^3$; f_1 and f_2 are the relative populations of the tautomers.

Table S6:
Correlation of the reduced set of B3LYP/6-31+G(d,p)-PCM(sp) descriptors to the experimental aqueous pK_a values of benzimidazoles at 298.15 K. [(a)]

Molecule	$\varepsilon^{acid}_{HOMO}$	$\varepsilon^{acid}_{LUMO}$	$\varepsilon^{base}_{HOMO-2}$	$\varepsilon^{base}_{HOMO-1}$	$\varepsilon^{base}_{HOMO}$	$\varepsilon^{base}_{LUMO}$	Q^{acid}_{H}	Q^{base}_{N}	ΔG_{aq}	ΔV_{sc}
5-nitrobenzimidazole	-0.2920	-0.1216	-0.3012	-0.2694	-0.2623	-0.1019	0.5292	-0.5335	140	-3.996
5-floro-6-chlorobenzimidazole	-0.2712	-0.0786	-0.3026	-0.2479	-0.2431	-0.0447	0.5262	-0.5431	12531	-1.241
2-chlorobenzimidazole	-0.2750	-0.0756	-0.3092	-0.2444	-0.2413	-0.0348	0.5264	-0.5383	-4037	-3.883
5-chlorobenzimidazole	-0.2675	-0.0749	-0.2992	-0.2474	-0.2385	-0.0393	0.5245	-0.5464	17349	-2.977
benzimidazole	-0.2723	-0.0691	-0.2943	-0.2401	-0.2376	-0.0312	0.5219	-0.5523	25247	-4.030
1-methylbenzimidazole	-0.2705	-0.0687	-0.2932	-0.2390	-0.2347	-0.0321	0.5208	-0.5523	27166	-4.100
1-ethylbenzimidazole	-0.2699	-0.0684	-0.2924	-0.2384	-0.2340	-0.0319	0.5204	-0.5517	28494	-3.971
4-methylbenzimidazole	-0.2630	-0.0673	-0.2856	-0.2366	-0.2293	-0.0272	0.5198	-0.5511	26651	-2.953
5-methylbenzimidazole	-0.2627	-0.0659	-0.2928	-0.2366	-0.2303	-0.0281	0.5207	-0.5543	27890	-4.060
5,6-dimethylbenzimidazole	-0.2578	-0.0635	-0.2915	-0.2306	-0.2266	-0.0259	0.5195	-0.5562	31627	-3.989
2-methylbenzimidazole	-0.2689	-0.0622	-0.2904	-0.2360	-0.2328	-0.0266	0.5152	-0.5544	34574	-4.156
5-aminobenzimidazole	-0.2123	-0.0549	-0.2908	-0.2355	-0.2011	-0.0252	0.5227	-0.5557	44806	17.454
2-ethylbenzimidazole	-0.2678	-0.0609	-0.2895	-0.2358	-0.2324	-0.0276	0.5115	-0.5522	30732	-2.967
2-isopropylbenzimidazole	-0.2685	-0.0623	-0.2891	-0.2358	-0.2325	-0.0270	0.5127	-0.5479	31074	-5.012
2-aminobenzimidazole	-0.2454	-0.0391	-0.2916	-0.2344	-0.2149	-0.0171	0.5097	-0.6092	51016	-4.253
5-chloro-1-methylbenzimidazole	-0.2669	-0.0746	-0.2983	-0.2451	-0.2370	-0.0404	0.5233	-0.5469	20097	-1.352
5,6-dichlorobenzimidazole	-0.2701	-0.0806	-0.3033	-0.2470	-0.2438	-0.0468	0.5266	-0.5414	11520	-1.127
5-methoxy-2-methylbenzimidazole	-0.2395	-0.0574	-0.2897	-0.2370	-0.2137	-0.0233	0.5138	-0.5551	36583	-3.764
2-methoxybenzimidazole	-0.2612	-0.0495	-0.3001	-0.2391	-0.2255	-0.0216	0.5150	-0.5869	22684	-5.403
R^2	0.333	**0.734**	0.598	0.650	0.592	0.542	**0.815**	0.605	**0.842**	0.009
A [(b)]	26.80	39.75	100.63	69.78	46.56	30.21	-128.47	-37.41	5.08E-05	0.01
B [(b)]	12.69	8.34	35.21	22.39	16.44	6.65	72.42	-15.09	4.30	5.64

[(a)] The symbols ε and Q indicate orbital energies and atomic charges, respectively (both in au), ΔG_{aq} is the change in Gibbs free energy (in J, using eq 1 and Scheme 1), and ΔV_{sc} is the change in the volume of the solvent cavity going from the protonated to the neutral species (in $Å^3$).
[(b)] Coefficients of the correlation equation $pK_{a\,exp} = A \cdot \text{Descriptor} + B$.

Table S7:
Inter-variable correlations (R^2 values) of the B3LYP/6-31+G(d,p)-PCM(sp) descriptors for the set of benzimidazoles under study.

	$\varepsilon^{acid}_{HOMO}$	$\varepsilon^{acid}_{LUMO}$	$\varepsilon^{base}_{HOMO\ -2}$	$\varepsilon^{base}_{HOMO\ -1}$	$\varepsilon^{base}_{HOMO}$	$\varepsilon^{base}_{LUMO}$	Q^{acid}_{H}	Q^{base}_{N}	ΔG_{aq}	ΔV_{sc}
$\varepsilon^{acid}_{HOMO}$	-	0.456	0.167	0.321	0.903	0.316	0.074	0.250	0.520	0.658
$\varepsilon^{acid}_{LUMO}$	0.456	-	0.307	0.847	0.731	0.910	0.561	0.526	0.680	0.037
$\varepsilon^{base}_{HOMO\ -2}$	0.167	0.307	-	0.422	0.320	0.256	0.497	0.166	0.660	0.012
$\varepsilon^{base}_{HOMO\ -1}$	0.321	**0.847**	0.422	-	0.603	0.922	0.482	0.253	0.566	0.013
$\varepsilon^{base}_{HOMO}$	**0.903**	**0.731**	0.320	0.603	-	0.584	0.253	0.388	0.711	0.387
$\varepsilon^{base}_{LUMO}$	0.316	**0.910**	0.256	**0.922**	0.584	-	0.415	0.278	0.470	0.013
Q^{acid}_{H}	0.074	0.561	0.497	0.482	0.253	0.415	-	0.456	0.574	0.034
Q^{base}_{N}	0.250	0.526	0.166	0.253	0.388	0.278	0.456	-	0.573	0.000
ΔG_{aq}	0.520	0.680	0.660	0.566	**0.711**	0.470	0.574	0.573	-	0.099
ΔV_{sc}	0.658	0.037	0.012	0.013	0.387	0.013	0.034	0.000	0.099	-
SIVC[(a)]	4.666	6.055	3.807	5.430	5.880	5.164	4.345	3.890	5.853	2.253

[(a)] Sum of the inter-variable correlations.

Table S8:

Correlations between the experimental aqueous pK_a values (at 298.15 K) of the protonated benzimidazoles and the calculated values from the multiple linear regressions with the selected descriptors at the B3LYP/6-31+G(d,p)-PCM(sp) level of theory.

Molecules	pK_a	ΔG_{aq}- Q_H^{acid}	ΔG_{aq}- $\varepsilon_{LUMO}^{acid}$	Q_H^{acid} - $\varepsilon_{LUMO}^{acid}$	ΔG_{aq}- Q_H^{acid} - $\varepsilon_{LUMO}^{acid}$	ΔG_{aq}- Q_H^{acid} - $\varepsilon_{HOMO}^{base}$
5-nitrobenzimidazole	4.17	4.19	3.91	3.82	4.02	4.02
5-floro-6-chlorobenzimidazole	4.33	4.78	4.98	4.90	4.82	4.75
2-chlorobenzimidazole	4.68	4.27	4.42	4.94	4.40	4.52
5-chlorobenzimidazole	4.86	5.05	5.21	5.12	5.07	5.03
benzimidazole	5.48	5.46	5.59	5.44	5.48	5.37
1-methylbenzimidazole	5.57	5.60	5.66	5.55	5.60	5.54
1-ethylbenzimidazole	5.62	5.67	5.72	5.59	5.66	5.60
4-methylbenzimidazole	5.67	5.65	5.66	5.66	5.66	5.69
5-methylbenzimidazole	5.81	5.63	5.73	5.61	5.64	5.62
5,6-dimethylbenzimidazole	5.98	5.82	5.90	5.75	5.83	5.83
5-aminobenzimidazole	6.11	6.00	6.51	5.64	6.02	6.16
2-methylbenzimidazole	6.19	6.21	6.03	6.15	6.19	6.13
2-ethylbenzimidazole	6.20	6.35	5.91	6.48	6.33	6.38
2-isopropylbenzimidazole	6.23	6.28	5.90	6.36	6.26	6.29
2-aminobenzimidazole	7.18	7.09	6.96	7.05	7.11	7.10
R^2		0.943	0.873	0.891	0.949	0.959
AD[(a)]		0.101	0.183	0.168	0.089	0.096

[(a)] Mean absolute deviation of the predicted values from experimental pK_a values.

Table S9:
Best four results of the "Best Subsets" regression analysis of the MINTAB program for two-, three- and four-variable correlation equations

B3LYP/6-31+G(d,p)-PCM(sp)

# Variables	R^2	$\varepsilon^{acid}_{HOMO}$	$\varepsilon^{acid}_{LUMO}$	$\varepsilon^{base}_{HOMO-2}$	$\varepsilon^{base}_{HOMO-1}$	$\varepsilon^{base}_{HOMO}$	$\varepsilon^{base}_{LUMO}$	Q^{acid}_{H}	Q^{base}_{N}	ΔG_{aq}	ΔV_{sc}
2	0.949					X		X			
2	0.943							X		X	
2	0.935	X						X			
2	0.891		X					X			
3	0.959					X		X		X	
3	0.955					X		X			X
3	0.954					X		X	X		
3	0.954			X		X		X			
4	0.981	X				X	X	X			
4	0.975		X			X		X			X
4	0.971					X	X	X			X
4	0.969	X	X			X		X			

Table S10:
Correlation equations of selected multivariable linear regressions using non-normalized descriptors.
The R^2 value is the multivariable correlation coefficient as calculated by Minitab.

B3LYP/6-31+G(d,p)-PCM(opt)	**R^2**
$pK_a = -0.12992 \times \Delta V_{sc} + -94.696 \times Q_H^{acid} + 31.265 \times \varepsilon_{LUMO+2}^{acid} + 55.536$	0.990
$pK_a = -0.00000622 \times \Delta G_{aq} + -112.45 \times Q_H^{acid} + 34.82 \times \varepsilon_{LUMO+2}^{acid} + 65.59$	0.977
$pK_a = -101.77 \times Q_H^{acid} + 31.7 \times \varepsilon_{LUMO+2}^{acid} + 59.739$	0.976
$pK_a = 0.0000055 \times \Delta G_{aq} + -115.17 \times Q_H^{acid} + 3.344 \times \varepsilon_{LUMO}^{acid} + 66.39$	0.958
B3LYP/6-31+G(d,p)-PCM(sp)	
$pK_a = 0.00001491 \times \Delta G_{aq} + -81.24 \times Q_H^{acid} + 15.417 \times \varepsilon_{HOMO}^{base} + 51.06$	0.959
$pK_a = 0.00002555 \times \Delta G_{aq} + -63.74 \times Q_H^{acid} + 6.544 \times \varepsilon_{LUMO}^{acid} + 38.551$	0.949

Table S11:
Selected equations of the multivariable linear regressions obtained using normalized descriptors.

B3LYP/6-31+G(d,p)-PCM(sp)
$pK_a = -0.2202 \times \Delta G_{aq} - 0.4592 \times Q_H^{acid} + 0.2044 \times \varepsilon_{HOMO}^{base} + 5.6054$
$pK_a = 0.3746 \times \Delta G_{aq} - 0.3610 \times Q_H^{acid} + 0.1121 \times \varepsilon_{LUMO}^{acid} + 5.6053$

Appendix

1. Additional comments that show how the descriptors considered provide an example of how electrostatic and orbitalic factors help explain the acidity (basicity) order of the protonated benzimidazoles (neutral benzimidazoles). Refer to the Tables 3 and S6.

The orbital energies considered show positive correlations (since they become less negative as the pK_a increases) with the experimental data. The PCM(opt) orbital energies of the of the two species (independently) show greater slopes the stronger the correlation to the experimental pK_a values. The smaller the frontier orbital energy difference between the interacting molecules (solute-solvent in our case), the more stabilizing the orbitalic interaction.[22] Most likely the frontier orbitals of the solvent molecule (water) are lower in energy than the frontier orbitals of the neutral benzimidazole, because of its much reduced size.

The energy of the occupied molecular orbitals of the base ($\varepsilon^{base}_{HOMO-2}$, $\varepsilon^{base}_{HOMO-1}$, $\varepsilon^{base}_{HOMO}$) can be related to the strength of its basicity. The stronger the base (neutral benzimidazole) the higher (less negative) the energy of its occupied (and virtual) orbitals, specially the one that contains primarily non-bonding electrons. This situation can be related to the ease with which the LUMO of a solvent molecule interacts with a benzimidazole. A basic molecule with higher occupied molecular orbital energies will interact more strongly with the LUMO of a solvent molecule (since the energy difference between these two orbitals would be smaller) making the molecule more basic as it can accept a proton more readily.

Once the neutral benzimidazole (the base) becomes protonated, its occupied molecular orbitals increase in energy, while its virtual orbitals decrease in energy. The stronger the acid the lower its LUMO energy, and closer in value to the HOMO energy of the solvent molecule, making the proton transfer process to the solvent easier.

2. Additional comments on the B3LYP/6-31+G(d,p)-PCM(sp) calculations reported in this section.

Table S2

The correlation of the PCM(sp) calculated values with the experimental ones are slightly better (R^2 = 0.859) than when single points applying the COSMO model are performed (R^2 = 0.817-0.828),[1] when the values are calculated using the Gibbs free energy equation and the same group of thirteen benzimidazoles is considered. Unlike the COSMO(sp) results, the pK_a values calculated using the

equation which employs molecular partition functions and zero-point energies have a lower correlation to the experimental values (R^2 = 0.734). As observed in our previous paper, the strength of the correlation to experimental pK_a is independent of the reaction scheme applied. When the two additional benzimidazoles are added, the R^2 value when employing eq 1 becomes 0.834 and remains unaltered when applying the other equation.

Table S6

The primary differences with the PCM(opt) results are that the ΔG_{aq} is the descriptor with the highest correlation, and the energy of the LUMO of the protonated benzimidazoles has the highest correlation of the orbitalic descriptors rather than that of LUMO+2. The changes in the correlation between the experimental pK_a values and the molecular orbital energies should be an artifact of the level of theory. We are unable to detect differences in the ordering or the shapes of the benzimidazole orbitals at the two levels of theory. Only the orbital energies are slightly different and it seems that this is enough to change their correlation with the experimental pK_a values.

From the correlations it appears that the LUMO of the acids and HOMO-1 of the bases are more involved in the equilibrium under study at this level of theory.

Table S8

The multiple linear regressions using B3LYP/6-31+G(d,p)-PCM(sp) descriptors have R^2 values (0.873-0.959) that are higher than those of the individual variables correlated to the pK_a values. In all three cases, when both the ΔG and Q_H^{acid} descriptors are included, the correlation to experimental values is approximately $R^2 \sim 0.95$ and the mean absolute deviation from experimental values is AD ~ 0.1.

Table S9

At the B3LYP/6-31+G(d,p)-PCM(sp) level of theory the best two-variable correlation includes Q_H^{acid} and $\varepsilon_{HOMO}^{base}$, the best three-variable correlation includes these two plus ΔG_{aq}, and the best four-variable correlation includes $\varepsilon_{HOMO}^{acid}$, $\varepsilon_{HOMO}^{base}$, $\varepsilon_{LUMO}^{base}$, and Q_H^{acid}. Including ΔG_{aq} in the three-variable correlation increases the R^2 value a small but significant amount. As noted previously the $\varepsilon_{HOMO}^{acid}$ and $\varepsilon_{HOMO}^{base}$ descriptors have very strong inter-variable correlations, so the best three-variable correlation equation is used to calculate pK_a values, and these results are shown in Table S8.

Table S11

At the B3LYP/6-31+G(d,p)-PCM(sp) level of theory the contributions of ΔG_{aq} and Q_H^{acid} are equal, and larger than the contribution of $\varepsilon_{LUMO}^{acid}$. In the second correlation the weight of Q_H^{acid} increases, and the contributions of ΔG_{aq} and $\varepsilon_{HOMO}^{base}$ decrease and are approximately equal.