Supplemental Material

On the Accuracy of the Direct Method to Calculate pKa from Electronic Structure Calculations

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Table S1. Experimental pKa values and differences between experimental and calculated values for different levels of theory using SMD solvent model and training set 2: acetic, propanoic, and butanoic acids. HF and DFT calculations used aug-cc-pVDZ basis functions.

Acids	pKa[a] (exp)	G4CEP	AM1	PM6	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	0.24	-0.28	0.18	-0.04	0.08	0.52	-0.20	-0.28	0.50	0.39	-0.15
Propanoic	**4.88**	-0.64	-0.52	0.88	0.23	0.02	-0.36	-0.07	-0.11	-0.45	-0.21	-0.16
Butanoic	**4.82**	0.40	0.80	-1.06	-0.19	-0.10	-0.17	0.28	0.39	-0.06	-0.18	0.30
Pentanoic	**4.82**	-0.19	-0.39	0.25	-0.97	0.47	-0.50	-0.20	-0.18	-0.53	0.00	-0.23
Hexanoic	**4.85**	-1.49	0.89	0.34	-0.99	0.27	-1.05	-1.25	-0.32	0.02	-0.69	-0.43
Chloroacetic	**2.86**	0.92	0.44	-0.25	1.67	2.52	2.34	1.33	1.12	2.29	2.05	1.24
Bromoacetic	**2.90**	0.34	-0.36	-0.28	1.37	2.61	1.82	2.06	1.87	1.61	1.56	1.84
Trichloroacetic	**0.70**	1.17	3.77	2.80	5.22	5.73	6.14	6.32	5.81	5.81	5.69	5.95
2-Chlorobutanoic	**2.83**	0.91	1.42	0.15	1.46	1.84	1.82	2.42	1.86	1.64	1.46	2.44
3-Chlorobutanoic	**3.98**	-0.30	0.24	0.66	0.41	1.19	0.79	1.19	1.02	0.86	0.75	1.06
4-Chlorobutanoic	**4.52**	-0.39	-0.12	0.95	0.43	0.77	0.93	1.24	1.42	1.22	1.71	1.01
3-Butenoic	**4.35**	0.06	0.50	-0.13	0.70	1.14	0.82	1.15	0.11	0.77	-0.08	1.01
2-Methylpropanoic	**4.84**	-0.05	0.16	0.86	-0.26	1.45	1.11	0.09	0.40	0.20	-0.07	0.36
2.2-Dimethylpropanoic	**5.03**	-0.51	0.45	-0.20	-0.32	0.23	0.19	0.52	0.36	0.10	0.29	0.40
3-Methylbutanoic	**4.77**	-1.17	0.34	0.39	-0.19	0.30	-0.06	0.30	0.44	-0.78	0.17	0.18
2-Methylbutanoic	**4.80**	-0.74	0.00	0.15	-0.48	-0.06	0.10	0.35	0.39	-0.12	-0.05	0.38
2-Butynoic	**2.62**	1.30	1.69	-0.14	1.83	2.69	1.86	2.84	2.93	2.20	2.42	1.94
2-Chloropropanoic	**2.83**	0.95	0.06	0.08	1.71	2.14	1.83	2.54	2.34	1.95	1.42	2.23
3-Bromopropanoic	**4.00**	1.14	-0.56	0.35	0.70	2.35	2.36	1.66	1.53	0.99	2.24	1.52
3-Chloropropanoic	**3.98**	0.17	-0.34	-0.37	1.26	2.31	1.50	1.77	1.74	2.28	2.26	1.68
trans-Crotonic	**4.69**	-0.09	-0.50	-0.50	0.25	0.37	0.32	0.67	0.82	0.11	0.46	0.85
Formic	**3.75**	0.76	-2.21	-2.06	1.52	2.32	2.12	2.46	2.37	2.06	1.76	2.21

a. Data from references [64] and [65].

Table S2. Experimental pKa values and differences between experimental and calculated values for different levels of theory using SMD solvent model and training set 3: pentanoic, 2-chlorobutanoic, and 2-metilbutanoic acids. HF and DFT calculations used aug-cc-pVDZ basis functions.

Acids	pKa[a] (exp)	G4CEP	AM1	PM6	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	0.25	-0.63	0.00	-0.04	-0.67	0.05	-1.06	-0.97	0.18	-0.08	-1.01
Propanoic	**4.88**	-0.63	-0.86	0.70	0.23	-0.73	-0.83	-0.93	-0.80	-0.78	-0.68	-1.02
Butanoic	**4.82**	0.41	0.46	-1.24	-0.19	-0.85	-0.64	-0.58	-0.31	-0.39	-0.65	-0.56
Pentanoic	**4.82**	-0.19	-0.74	0.06	-0.97	-0.28	-0.97	-1.05	-0.87	-0.86	-0.47	-1.09
Hexanoic	**4.85**	-1.48	0.55	0.16	-0.99	-0.48	-1.52	-2.11	-1.01	-0.30	-1.15	-1.30
Chloroacetic	**2.86**	0.92	0.09	-0.43	1.67	1.77	1.86	0.47	0.42	1.97	1.59	0.38
Bromoacetic	**2.90**	0.35	-0.71	-0.46	1.37	1.86	1.35	1.20	1.18	1.28	1.10	0.97
Trichloroacetic	**0.70**	1.18	3.43	2.62	5.22	4.98	5.67	5.46	5.12	5.49	5.23	5.09
2-Chlorobutanoic	**2.83**	0.92	1.08	-0.03	1.46	1.09	1.35	1.56	1.17	1.31	0.99	1.57
3-Chlorobutanoic	**3.98**	-0.29	-0.10	0.48	0.41	0.44	0.32	0.33	0.32	0.53	0.28	0.19
4-Chlorobutanoic	**4.52**	-0.39	-0.46	0.76	0.43	0.02	0.45	0.38	0.72	0.89	1.24	0.15
3-Butenoic	**4.35**	0.07	0.15	-0.32	0.70	0.38	0.35	0.30	-0.58	0.44	-0.55	0.14
2-Methylpropanoic	**4.84**	-0.04	-0.19	0.68	-0.26	0.70	0.63	-0.76	-0.29	-0.12	-0.54	-0.50
2.2-Dimethylpropanoic	**5.03**	-0.50	0.11	-0.38	-0.32	-0.52	-0.28	-0.34	-0.33	-0.23	-0.18	-0.46
3-Methylbutanoic	**4.77**	-1.16	0.00	0.21	-0.19	-0.45	-0.53	-0.56	-0.25	-1.11	-0.30	-0.69
2-Methylbutanoic	**4.80**	-0.73	-0.34	-0.03	-0.48	-0.81	-0.38	-0.51	-0.30	-0.45	-0.52	-0.48
2-Butynoic	**2.62**	1.31	1.35	-0.32	1.83	1.94	1.39	1.98	2.24	1.88	1.96	1.08
2-Chloropropanoic	**2.83**	0.96	-0.29	-0.11	1.71	1.39	1.36	1.68	1.65	1.63	0.95	1.37
3-Bromopropanoic	**4.00**	1.14	-0.91	0.17	0.70	1.60	1.88	0.80	0.84	0.67	1.78	0.65
3-Chloropropanoic	**3.98**	0.18	-0.69	-0.55	1.26	1.56	1.03	0.92	1.05	1.95	1.79	0.82
trans-Crotonic	**4.69**	-0.08	-0.84	-0.69	0.25	-0.38	-0.16	-0.18	0.13	-0.22	0.00	-0.01
Formic	**3.75**	0.77	-2.55	-2.24	1.51	1.57	1.64	1.60	1.68	1.74	1.30	1.35

a. Data from references [64] and [65].

Table S3. Experimental pKa values and differences between experimental and calculated values for HF and different DFT levels with aug-cc-pVTZ basis set, SMD solvent model, and training set 1.

Acids	pKa[a] (exp)	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	-0.13	0.12	-0.35	-0.64	-0.12	-0.88	-0.79	-0.30
Propanoic	**4.88**	-0.90	-0.23	-1.24	-1.11	-1.39	-1.72	-1.06	-1.41
Butanoic	**4.82**	-1.17	-0.04	-1.03	-1.58	-1.23	-1.53	-0.85	-0.88
Pentanoic	**4.82**	-1.35	-0.09	-1.37	-1.50	-1.11	-1.28	-1.17	-1.11
Hexanoic	**4.85**	-2.04	0.21	-1.96	-1.25	-1.79	-1.38	-1.09	-1.70
Chloroacetic	**2.86**	1.72	-0.26	-0.53	2.08	1.19	0.54	1.29	1.21
Bromoacetic	**2.90**	0.79	-0.18	0.52	0.72	0.43	0.23	0.56	0.34
Trichloroacetic	**0.70**	4.37	-1.12	5.04	4.42	4.30	4.33	3.85	4.50
2-Chlorobutanoic	**2.83**	1.04	-0.29	0.84	1.04	1.00	0.43	0.33	1.27
3-Chlorobutanoic	**3.98**	-0.09	-0.13	-0.12	-0.28	-0.25	-0.24	-0.03	-0.18
4-Chlorobutanoic	**4.52**	-0.78	0.22	0.04	-0.64	0.09	0.08	-0.14	-0.17
3-Butenoic	**4.35**	-0.62	-0.36	0.19	-0.63	-1.12	-0.62	-0.63	0.12
2-Methylpropanoic	**4.84**	-0.85	0.42	-1.06	0.21	-0.81	-0.52	-0.39	-0.87
2.2-Dimethylpropanoic	**5.03**	-1.09	0.26	-0.73	-1.04	-0.96	-0.98	-0.87	-0.91
3-Methylbutanoic	**4.77**	-1.69	0.21	-0.95	-1.39	-0.84	-0.79	-0.29	-1.00
2-Methylbutanoic	**4.80**	-0.73	1.43	-1.55	-0.61	-1.58	-1.49	-0.94	-1.28
2-Butynoic	**2.62**	1.79	-0.56	0.62	0.96	1.98	1.68	0.76	0.19
2-Chloropropanoic	**2.83**	0.74	-0.76	0.86	0.60	0.82	0.91	0.72	0.89
3-Bromopropanoic	**4.00**	0.77	0.58	1.55	0.63	0.25	1.55	0.49	0.24
3-Chloropropanoic	**3.98**	0.03	-0.28	0.61	0.12	0.50	1.11	0.35	0.47
trans-Crotonic	**4.69**	-0.68	0.45	-0.53	-1.07	-0.42	-0.38	-0.72	-0.37
Formic	**3.75**	0.86	0.41	1.15	0.97	1.08	0.93	0.63	0.96

a. Data from references [64] and [65].

Table S4. Experimental pKa values and differences between experimental and calculated values for HF and different DFT levels with aug-cc-pVTZ basis set, SMD solvent model, and training set 2.

Acids	pKa[a] (exp)	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	0.61	0.17	0.53	0.47	0.79	0.50	0.11	0.56
Propanoic	**4.88**	-0.17	-0.18	-0.37	0.00	-0.48	-0.34	-0.16	-0.55
Butanoic	**4.82**	-0.44	0.01	-0.16	-0.47	-0.32	-0.16	0.05	-0.02
Pentanoic	**4.82**	-0.62	-0.03	-0.49	-0.39	-0.19	0.10	-0.27	-0.24
Hexanoic	**4.85**	-1.30	0.26	-1.09	-0.15	-0.87	-0.01	-0.19	-0.83
Chloroacetic	**2.86**	2.46	-0.21	0.34	3.19	2.11	1.91	2.19	2.08
Bromoacetic	**2.90**	1.53	-0.13	1.39	1.83	1.35	1.60	1.46	1.21
Trichloroacetic	**0.70**	5.10	-1.07	5.91	5.53	5.21	5.71	4.76	5.36
2-Chlorobutanoic	**2.83**	1.77	-0.24	1.71	2.15	1.92	1.81	1.23	2.14
3-Chlorobutanoic	**3.98**	0.64	-0.08	0.75	0.83	0.66	1.14	0.87	0.69
4-Chlorobutanoic	**4.52**	-0.05	0.27	0.91	0.46	1.01	1.45	0.76	0.70
3-Butenoic	**4.35**	0.11	-0.31	1.06	0.48	-0.20	0.76	0.27	0.99
2-Methylpropanoic	**4.84**	-0.12	0.47	-0.19	1.32	0.10	0.85	0.51	0.00
2.2-Dimethylpropanoic	**5.03**	-0.35	0.31	0.14	0.07	-0.04	0.40	0.03	-0.04
3-Methylbutanoic	**4.77**	-0.96	0.26	-0.08	-0.28	0.08	0.59	0.61	-0.13
2-Methylbutanoic	**4.80**	0.00	1.48	-0.68	0.50	-0.67	-0.12	-0.04	-0.42
2-Butynoic	**2.62**	2.53	-0.51	1.50	2.07	2.89	3.05	1.67	1.05
2-Chloropropanoic	**2.83**	1.47	-0.71	1.73	1.71	1.73	2.29	1.62	1.76
3-Bromopropanoic	**4.00**	1.50	0.63	2.42	1.74	1.16	2.92	1.40	1.11
3-Chloropropanoic	**3.98**	0.76	-0.23	1.48	1.23	1.41	2.49	1.25	1.33
trans-Crotonic	**4.69**	0.05	0.50	0.35	0.04	0.49	1.00	0.18	0.49
Formic	**3.75**	1.59	0.46	2.03	2.08	1.99	2.31	1.53	1.82

a. Data from references [64] and [65].

Table S5. Experimental pKa values and differences between experimental and calculated values for HF and different DFT levels with aug-cc-pVTZ basis set, SMD solvent model, and training set 3.

Acids	pKa[a] (exp)	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	0.22	-0.23	0.35	-0.28	0.44	-0.10	-0.19	0.07
Propanoic	**4.88**	-0.55	-0.58	-0.55	-0.76	-0.83	-0.94	-0.47	-1.04
Butanoic	**4.82**	-0.83	-0.39	-0.34	-1.22	-0.67	-0.75	-0.26	-0.51
Pentanoic	**4.82**	-1.00	-0.44	-0.67	-1.14	-0.55	-0.50	-0.58	-0.73
Hexanoic	**4.85**	-1.69	-0.14	-1.27	-0.90	-1.22	-0.60	-0.49	-1.32
Chloroacetic	**2.86**	2.07	-0.61	0.16	2.43	1.76	1.32	1.88	1.58
Bromoacetic	**2.90**	1.14	-0.53	1.21	1.07	0.99	1.00	1.15	0.71
Trichloroacetic	**0.70**	4.71	-1.47	5.73	4.77	4.86	5.11	4.45	4.87
2-Chlorobutanoic	**2.83**	1.39	-0.64	1.53	1.39	1.56	1.21	0.92	1.65
3-Chlorobutanoic	**3.98**	0.25	-0.48	0.57	0.08	0.31	0.54	0.57	0.19
4-Chlorobutanoic	**4.52**	-0.43	-0.13	0.73	-0.29	0.65	0.86	0.45	0.21
3-Butenoic	**4.35**	-0.27	-0.71	0.88	-0.28	-0.55	0.16	-0.04	0.50
2-Methylpropanoic	**4.84**	-0.50	0.07	-0.37	0.56	-0.25	0.26	0.21	-0.50
2.2-Dimethylpropanoic	**5.03**	-0.74	-0.09	-0.04	-0.68	-0.40	-0.20	-0.28	-0.53
3-Methylbutanoic	**4.77**	-1.34	-0.14	-0.26	-1.04	-0.27	-0.01	0.31	-0.63
2-Methylbutanoic	**4.80**	-0.38	1.07	-0.86	-0.25	-1.02	-0.71	-0.34	-0.91
2-Butynoic	**2.62**	2.14	-0.91	1.32	1.32	2.54	2.46	1.36	0.56
2-Chloropropanoic	**2.83**	1.08	-1.11	1.55	0.96	1.38	1.69	1.31	1.27
3-Bromopropanoic	**4.00**	1.12	0.22	2.24	0.98	0.81	2.33	1.09	0.61
3-Chloropropanoic	**3.98**	0.37	-0.63	1.30	0.47	1.06	1.89	0.94	0.84
trans-Crotonic	**4.69**	-0.33	0.10	0.17	-0.72	0.14	0.40	-0.12	0.00
Formic	**3.75**	1.20	0.06	1.85	1.33	1.64	1.71	1.22	1.33

a. Data from references [64] and [65].

Table S6. Experimental pKa values and differences between experimental and calculated values for different levels of theory using SMD solvent model, one explicit water molecule, and training set 1. HF and DFT calculations used aug-cc-pVDZ basis functions.

Acids	pKa[a] (exp)	G4CEP	AM1	PM6	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	0.37	0.09	0.62	-0.82	-0.35	-2.12	-0.18	-0.13	-1.15	-0.62	-0.33
Propanoic	**4.88**	0.83	0.90	-0.47	-2.19	-0.41	-1.35	-0.73	-1.58	-0.58	-0.25	-0.67
Butanoic	**4.82**	0.82	0.37	0.00	-1.01	-0.52	-0.36	-1.01	-0.72	-0.81	-1.59	-0.63
Pentanoic	**4.82**	0.24	-0.42	0.87	-2.05	-0.91	-1.85	-2.14	-1.80	-2.00	-0.51	-2.14
Hexanoic	**4.85**	0.25	-0.45	0.97	-1.63	-0.46	-1.05	-1.27	-1.02	-1.14	-0.54	-1.34
Chloroacetic	**2.86**	0.35	0.38	0.23	1.39	0.73	0.84	0.25	0.43	0.84	0.68	0.43
Bromoacetic	**2.90**	-0.70	-0.52	-0.92	0.35	0.62	0.73	0.17	0.28	0.24	-0.06	0.13
Trichloroacetic	**0.70**	0.61	3.25	1.99	4.25	1.51	2.14	2.69	2.20	2.77	2.84	2.67
2-Chlorobutanoic	**2.83**	0.21	0.18	-0.92	0.77	0.53	0.04	0.45	0.80	0.03	0.08	0.93
3-Chlorobutanoic	**3.98**	-0.79	-0.94	1.06	1.03	-0.01	0.45	0.69	0.12	-0.30	0.07	0.42
4-Chlorobutanoic	**4.52**	-0.40	-0.73	0.63	-0.92	-0.26	0.62	-0.10	-0.04	0.07	-0.79	-0.16
3-Butenoic	**4.35**	0.24	-0.55	-0.14	-0.61	0.59	-0.41	-0.70	-0.75	-0.63	-0.57	-1.11
2-Methylpropanoic	**4.84**	0.55	-0.95	-0.23	-0.39	-0.14	-0.15	-0.43	-0.04	-0.11	-0.20	0.24
2.2-Dimethylpropanoic	**5.03**	-0.32	0.01	-1.20	-1.14	-0.41	-1.04	-0.66	-1.04	-0.64	-0.45	-0.64
3-Methylbutanoic	**4.77**	0.37	-0.40	2.09	0.24	-0.53	-0.62	-0.80	-0.49	-0.15	-0.30	-0.47
2-Methylbutanoic	**4.80**	-0.70	0.46	0.24	-0.75	-0.45	-0.20	-0.60	-0.56	-0.12	-0.32	-0.59
2-Butynoic	**2.62**	-1.33	1.43	-2.25	0.46	-0.03	0.38	0.75	0.96	0.72	0.61	1.05
2-Chloropropanoic	**2.83**	-0.30	0.27	0.30	1.50	0.07	0.88	0.76	0.32	0.42	-0.01	0.44
3-Bromopropanoic	**4.00**	0.49	0.62	-0.15	-0.16	-0.61	1.46	1.07	1.05	0.50	0.65	0.90
3-Chloropropanoic	**3.98**	0.13	-0.19	0.61	0.77	0.32	1.58	1.23	1.25	1.63	1.11	0.39
trans-Crotonic	**4.69**	-0.81	-0.44	0.12	-0.66	-0.35	-0.86	-0.61	-0.46	-0.83	-0.33	-0.46
Formic	**3.75**	-0.12	-2.36	-3.46	1.57	1.07	0.90	1.16	1.23	1.28	0.50	0.92

a. Data from references [64] and [65].

Table S7. Experimental pKa values and differences between experimental and calculated values for different levels of theory using SMD solvent model, one explicit water molecule, and training set 2. HF and DFT calculations used aug-cc-pVDZ basis functions.

Acids	pKa[a] (exp)	G4CEP	AM1	PM6	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	-0.31	-0.37	0.57	0.52	0.08	-0.84	0.46	0.68	-0.30	0.20	0.21
Propanoic	**4.88**	0.16	0.45	-0.52	-0.85	0.02	-0.08	-0.09	-0.77	0.27	0.57	-0.13
Butanoic	**4.82**	0.14	-0.08	-0.05	0.33	-0.10	0.92	-0.37	0.09	0.04	-0.77	-0.09
Pentanoic	**4.82**	-0.43	-0.88	0.83	-0.72	-0.48	-0.57	-1.50	-0.99	-1.15	0.31	-1.60
Hexanoic	**4.85**	-0.42	-0.91	0.92	-0.29	-0.03	0.22	-0.62	-0.21	-0.29	0.28	-0.79
Chloroacetic	**2.86**	-0.33	-0.07	0.18	2.73	1.15	2.11	0.89	1.24	1.69	1.50	0.97
Bromoacetic	**2.90**	-1.37	-0.97	-0.97	1.69	1.05	2.01	0.82	1.09	1.09	0.76	0.67
Trichloroacetic	**0.70**	-0.06	2.80	1.94	5.59	1.94	3.42	3.33	3.01	3.62	3.66	3.22
2-Chlorobutanoic	**2.83**	-0.47	-0.27	-0.97	2.10	0.95	1.32	1.10	1.61	0.87	0.90	1.47
3-Chlorobutanoic	**3.98**	-1.46	-1.40	1.02	2.37	0.42	1.72	1.33	0.93	0.55	0.89	0.96
4-Chlorobutanoic	**4.52**	-1.08	-1.18	0.58	0.42	0.17	1.90	0.54	0.77	0.92	0.02	0.39
3-Butenoic	**4.35**	-0.43	-1.00	-0.19	0.73	1.02	0.86	-0.06	0.07	0.22	0.25	-0.57
2-Methylpropanoic	**4.84**	-0.12	-1.41	-0.28	0.95	0.29	1.12	0.21	0.77	0.73	0.62	0.79
2.2-Dimethylpropanoic	**5.03**	-0.99	-0.45	-1.25	0.20	0.02	0.23	-0.02	-0.23	0.21	0.37	-0.09
3-Methylbutanoic	**4.77**	-0.30	-0.85	2.05	1.58	-0.10	0.66	-0.16	0.32	0.70	0.51	0.08
2-Methylbutanoic	**4.80**	-1.37	0.01	0.20	0.59	-0.03	1.08	0.04	0.25	0.73	0.50	-0.05
2-Butynoic	**2.62**	-2.00	0.98	-2.30	1.80	0.40	1.66	1.39	1.78	1.57	1.43	1.60
2-Chloropropanoic	**2.83**	-0.97	-0.19	0.26	2.84	0.50	2.16	1.41	1.14	1.27	0.81	0.98
3-Bromopropanoic	**4.00**	-0.18	0.17	-0.20	1.18	-0.18	2.74	1.72	1.86	1.35	1.46	1.45
3-Chloropropanoic	**3.98**	-0.54	-0.65	0.56	2.11	0.74	2.86	1.87	2.06	2.48	1.93	0.94
trans-Crotonic	**4.69**	-1.48	-0.89	0.07	0.68	0.08	0.41	0.03	0.35	0.02	0.49	0.09
Formic	**3.75**	-0.79	-2.82	-3.51	2.91	1.49	2.18	1.80	2.04	2.13	1.31	1.46

a. Data from references [64] and [65].

Table S8. Experimental pKa values and differences between experimental and calculated values for different levels of theory using SMD solvent model, one explicit water molecule, and training set 3. HF and DFT calculations used aug-cc-pVDZ basis functions.

Acids	pKa[a] (exp)	G4CEP	AM1	PM6	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	0.45	0.01	0.55	-0.14	-0.07	-1.45	0.59	0.39	-0.45	-0.37	0.27
Propanoic	**4.88**	0.92	0.83	-0.54	-1.51	-0.13	-0.68	0.03	-1.06	0.12	0.00	-0.07
Butanoic	**4.82**	0.90	0.30	-0.07	-0.33	-0.24	0.31	-0.25	-0.20	-0.11	-1.34	-0.03
Pentanoic	**4.82**	0.33	-0.50	0.81	-1.37	-0.63	-1.18	-1.38	-1.28	-1.30	-0.26	-1.54
Hexanoic	**4.85**	0.33	-0.53	0.90	-0.95	-0.18	-0.39	-0.50	-0.50	-0.44	-0.29	-0.73
Chloroacetic	**2.86**	0.43	0.31	0.16	2.08	1.00	1.51	1.01	0.95	1.54	0.93	1.03
Bromoacetic	**2.90**	-0.61	-0.59	-0.99	1.03	0.90	1.40	0.94	0.80	0.94	0.19	0.73
Trichloroacetic	**0.70**	0.70	3.18	1.92	4.93	1.79	2.81	3.45	2.72	3.47	3.09	3.27
2-Chlorobutanoic	**2.83**	0.29	0.11	-0.98	1.45	0.81	0.71	1.22	1.32	0.72	0.33	1.53
3-Chlorobutanoic	**3.98**	-0.71	-1.01	1.00	1.71	0.27	1.11	1.45	0.64	0.40	0.32	1.02
4-Chlorobutanoic	**4.52**	-0.32	-0.80	0.57	-0.24	0.02	1.29	0.67	0.48	0.77	-0.55	0.44
3-Butenoic	**4.35**	0.33	-0.62	-0.21	0.07	0.87	0.25	0.06	-0.22	0.07	-0.32	-0.51
2-Methylpropanoic	**4.84**	0.64	-1.03	-0.30	0.30	0.14	0.51	0.33	0.48	0.59	0.05	0.85
2.2-Dimethylpropanoic	**5.03**	-0.23	-0.07	-1.26	-0.46	-0.13	-0.38	0.10	-0.52	0.06	-0.20	-0.04
3-Methylbutanoic	**4.77**	0.45	-0.47	2.03	0.92	-0.25	0.05	-0.03	0.03	0.55	-0.06	0.14
2-Methylbutanoic	**4.80**	-0.62	0.39	0.18	-0.07	-0.17	0.47	0.16	-0.04	0.58	-0.07	0.01
2-Butynoic	**2.62**	-1.25	1.36	-2.32	1.14	0.25	1.05	1.51	1.49	1.42	0.86	1.65
2-Chloropropanoic	**2.83**	-0.22	0.19	0.24	2.18	0.35	1.55	1.53	0.85	1.12	0.24	1.04
3-Bromopropanoic	**4.00**	0.58	0.55	-0.22	0.52	-0.33	2.13	1.84	1.57	1.20	0.89	1.51
3-Chloropropanoic	**3.98**	0.22	-0.27	0.55	1.45	0.60	2.25	2.00	1.77	2.33	1.36	0.99
trans-Crotonic	**4.69**	-0.72	-0.51	0.05	0.02	-0.07	-0.19	0.16	0.06	-0.13	-0.08	0.14
Formic	**3.75**	-0.04	-2.43	-3.53	2.25	1.35	1.57	1.92	1.75	1.98	0.74	1.52

a. Data from references [64] and [65].

Table S9. Experimental pKa values and differences between experimental and calculated values for HF and different DFT levels with aug-cc-pVTZ basis set, SMD solvent model, one explicit water molecule, and training set 1.

Acids	pKa[a] (exp)	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	-0.09	-1.07	-0.07	-0.26	-1.23	-0.72	-0.88	-0.09
Propanoic	**4.88**	-2.02	-0.52	-1.11	-1.60	-1.44	-0.95	-0.87	-0.44
Butanoic	**4.82**	-0.99	-0.56	0.07	-0.15	-0.63	-0.63	-0.87	-0.34
Pentanoic	**4.82**	-1.96	-0.97	-1.91	-1.15	-1.05	-1.80	-0.87	-1.89
Hexanoic	**4.85**	-1.98	0.19	-1.12	-1.41	-1.19	-0.83	-0.81	-0.58
Chloroacetic	**2.86**	1.22	0.72	0.64	1.16	0.96	0.92	0.61	0.42
Bromoacetic	**2.90**	0.78	0.37	-0.28	0.66	0.73	-0.20	0.62	0.21
Trichloroacetic	**0.70**	3.18	1.16	1.91	2.15	1.95	2.71	2.20	2.63
2-Chlorobutanoic	**2.83**	-0.84	0.65	0.04	0.67	0.50	0.01	0.71	0.73
3-Chlorobutanoic	**3.98**	0.16	-0.04	0.02	-0.44	-0.21	-0.47	0.08	-0.20
4-Chlorobutanoic	**4.52**	0.42	-0.25	0.45	0.59	0.57	0.13	0.94	0.18
3-Butenoic	**4.35**	-0.54	-0.59	-0.42	-0.44	-0.38	-0.50	-0.29	-0.69
2-Methylpropanoic	**4.84**	0.29	-0.25	-0.59	-0.25	-0.15	-0.03	-0.13	-0.13
2.2-Dimethylpropanoic	**5.03**	-1.07	-0.14	-0.52	-0.82	-0.01	-0.12	-0.76	-0.55
3-Methylbutanoic	**4.77**	-0.78	-0.18	0.20	-1.27	-1.08	-0.51	-0.19	-0.68
2-Methylbutanoic	**4.80**	-0.45	-0.10	-0.25	-0.02	-0.39	0.28	-1.12	-1.39
2-Butynoic	**2.62**	1.93	0.30	0.30	0.22	1.10	0.68	0.44	0.41
2-Chloropropanoic	**2.83**	-0.38	-0.12	0.61	0.38	-0.10	0.58	0.11	0.57
3-Bromopropanoic	**4.00**	0.98	0.73	1.42	0.35	0.49	-0.05	-0.07	0.98
3-Chloropropanoic	**3.98**	0.22	0.18	0.63	0.57	0.93	1.69	0.39	0.18
trans-Crotonic	**4.69**	-0.03	-0.40	-0.91	0.11	-0.15	-1.15	0.29	-0.52
Formic	**3.75**	1.94	0.89	0.89	0.95	0.79	0.96	0.48	1.18

a. Data from references [64] and [65].

Table S10. Experimental pKa values and differences between experimental and calculated values for HF and different DFT levels with aug-cc-pVTZ basis set, SMD solvent model, one explicit water molecule, and training set 2.

Acids	pKa[a] (exp)	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	0.94	-0.35	0.30	0.41	-0.13	0.05	-0.01	0.20
Propanoic	**4.88**	-0.99	0.19	-0.74	-0.93	-0.34	-0.18	0.00	-0.15
Butanoic	**4.82**	0.05	0.16	0.44	0.52	0.47	0.14	0.01	-0.05
Pentanoic	**4.82**	-0.92	-0.26	-1.54	-0.48	0.05	-1.04	0.01	-1.60
Hexanoic	**4.85**	-0.95	0.91	-0.75	-0.75	-0.09	-0.07	0.06	-0.29
Chloroacetic	**2.86**	2.25	1.43	1.01	1.83	2.06	1.68	1.49	0.71
Bromoacetic	**2.90**	1.82	1.09	0.09	1.32	1.83	0.57	1.49	0.50
Trichloroacetic	**0.70**	4.22	1.88	2.27	2.81	3.05	3.48	3.08	2.92
2-Chlorobutanoic	**2.83**	0.19	1.36	0.41	1.34	1.60	0.78	1.58	1.02
3-Chlorobutanoic	**3.98**	1.20	0.68	0.38	0.23	0.89	0.29	0.96	0.09
4-Chlorobutanoic	**4.52**	1.45	0.47	0.82	1.26	1.67	0.90	1.82	0.47
3-Butenoic	**4.35**	0.50	0.13	-0.05	0.23	0.72	0.27	0.58	-0.40
2-Methylpropanoic	**4.84**	1.32	0.47	-0.22	0.41	0.95	0.73	0.75	0.16
2.2-Dimethylpropanoic	**5.03**	-0.04	0.58	-0.15	-0.15	1.09	0.65	0.11	-0.26
3-Methylbutanoic	**4.77**	0.26	0.54	0.57	-0.60	0.02	0.25	0.68	-0.40
2-Methylbutanoic	**4.80**	0.59	0.62	0.12	0.65	0.71	1.05	-0.25	-1.10
2-Butynoic	**2.62**	2.96	1.02	0.67	0.88	2.20	1.44	1.31	0.70
2-Chloropropanoic	**2.83**	0.66	0.59	0.98	1.04	1.00	1.34	0.99	0.85
3-Bromopropanoic	**4.00**	2.01	1.45	1.79	1.02	1.59	0.72	0.81	1.27
3-Chloropropanoic	**3.98**	1.25	0.89	1.00	1.24	2.03	2.45	1.26	0.47
trans-Crotonic	**4.69**	1.00	0.32	-0.55	0.78	0.95	-0.38	1.17	-0.23
Formic	**3.75**	2.97	1.61	1.26	1.62	1.89	1.73	1.35	1.47

a. Data from references [64] and [65].

Table S11. Experimental pKa values and differences between experimental and calculated values for HF and different DFT levels with aug-cc-pVTZ basis set, SMD solvent model, one explicit water molecule, and training set 3.

Acids	pKa[a] (exp)	HF	LSDA	PBE	B3LYP	CAM B3LYP	WB97XD	M062X	B2PLYP
Acetic	**4.76**	0.99	-0.93	0.64	-0.09	-0.92	-0.22	-0.45	0.76
Propanoic	**4.88**	-0.94	-0.38	-0.40	-1.43	-1.13	-0.44	-0.44	0.41
Butanoic	**4.82**	0.09	-0.41	0.78	0.02	-0.32	-0.12	-0.44	0.51
Pentanoic	**4.82**	-0.88	-0.83	-1.20	-0.98	-0.74	-1.30	-0.44	-1.04
Hexanoic	**4.85**	-0.90	0.33	-0.41	-1.25	-0.88	-0.33	-0.38	0.27
Chloroacetic	**2.86**	2.30	0.86	1.35	1.33	1.27	1.42	1.04	1.27
Bromoacetic	**2.90**	1.86	0.51	0.43	0.82	1.04	0.30	1.04	1.06
Trichloroacetic	**0.70**	4.27	1.31	2.61	2.31	2.27	3.22	2.63	3.48
2-Chlorobutanoic	**2.83**	0.24	0.79	0.74	0.84	0.81	0.52	1.14	1.58
3-Chlorobutanoic	**3.98**	1.24	0.11	0.72	-0.27	0.10	0.03	0.51	0.65
4-Chlorobutanoic	**4.52**	1.50	-0.10	1.16	0.76	0.88	0.64	1.37	1.03
3-Butenoic	**4.35**	0.55	-0.44	0.28	-0.27	-0.07	0.00	0.14	0.16
2-Methylpropanoic	**4.84**	1.37	-0.10	0.12	-0.09	0.16	0.47	0.30	0.72
2.2-Dimethylpropanoic	**5.03**	0.01	0.01	0.18	-0.65	0.30	0.38	-0.34	0.30
3-Methylbutanoic	**4.77**	0.30	-0.03	0.91	-1.10	-0.77	-0.01	0.23	0.16
2-Methylbutanoic	**4.80**	0.63	0.04	0.46	0.15	-0.08	0.78	-0.70	-0.54
2-Butynoic	**2.62**	3.01	0.45	1.01	0.38	1.41	1.18	0.87	1.26
2-Chloropropanoic	**2.83**	0.71	0.02	1.32	0.54	0.22	1.08	0.54	1.41
3-Bromopropanoic	**4.00**	2.06	0.88	2.13	0.52	0.80	0.46	0.36	1.83
3-Chloropropanoic	**3.98**	1.30	0.32	1.34	0.73	1.24	2.19	0.82	1.03
trans-Crotonic	**4.69**	1.05	-0.26	-0.21	0.28	0.17	-0.64	0.72	0.33
Formic	**3.75**	3.02	1.03	1.60	1.12	1.11	1.47	0.91	2.03

a. Data from references [64] and [65].