5 Supplemental Material

Table S1 Glossary of abbreviations

DFT	Density functional theory
NBB	non-Boltzmann Bennett
QM	Quantum Mechanics
SAMPL	Statistical Assessment of the Modeling of Proteins and Ligands
SMD	Solvation Model Density

Fig. S1 Chemical structures of the analog molecules used to compute pK_a values for selected molecules in the SAMPL5 distribution challenge.

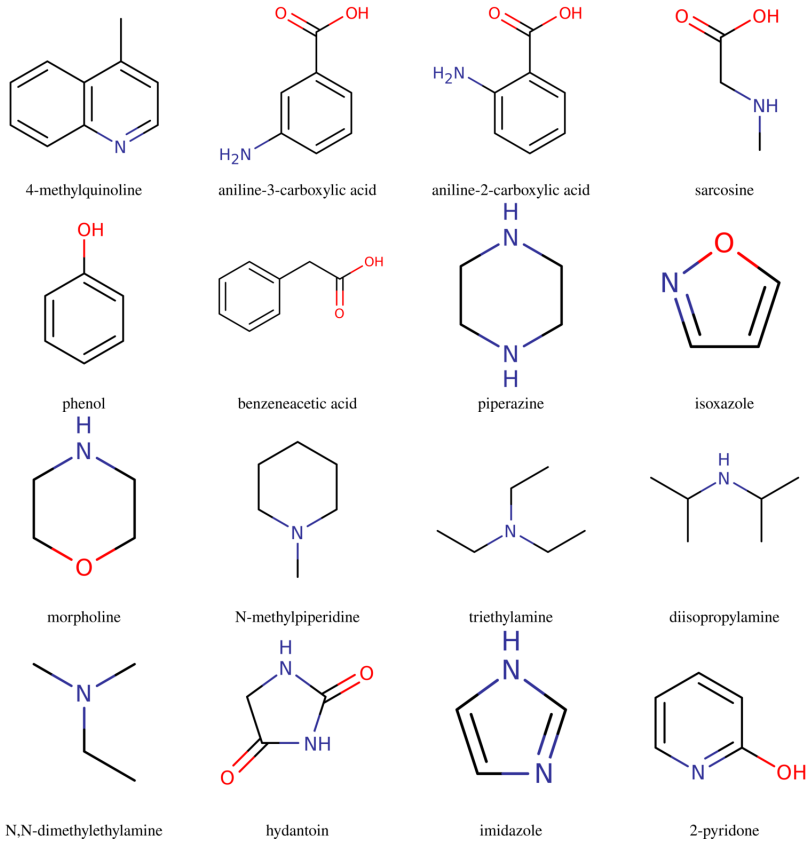

Table S2 Predicted values for partition coefficients of various QM schemes. The predictions from the vertical solvation scheme appear in the leftmost column with the predictions from the adiabatic scheme in the adjacent column. These predictions are the same as in Table 1, however predictions for 83 are not present. The next three columns are predictions resulting from the adiabatic scheme, but with either the frequency corrections removed (− Freq), the triple-ζ basis set SPC corrections removed (− SPC), or both removed. The partition coefficient predictions are relatively insensitive to these two corrections, especially given the relatively large magnitude of other sources of error, such as protonation and aggregation.

Molecule	Vertical	Adiabatic + Freq + SPC	Adiabatic − Freq + SPC	Adiabatic + Freq − SPC	Adiabatic − Freq − SPC	Expt.
02	−0.34	−1.25	−0.91	−1.18	−0.83	1.40
03	1.80	1.19	1.13	1.26	1.19	1.90
04	2.70	1.91	2.43	2.08	2.59	2.20
05	−0.20	−0.29	−0.64	−0.27	−0.62	−0.86
06	−2.69	−2.47	−2.57	−2.82	−2.92	−1.02
07	1.37	0.92	1.45	0.57	1.09	1.40
10	−3.75	−3.87	−4.34	−3.97	−4.44	−1.70
11	2.13	0.53	2.00	0.49	1.96	−2.96
13	2.00	0.56	1.15	0.38	0.97	−1.50
15	−3.92	−2.59	−3.18	−3.63	−4.22	−2.20
17	3.68	2.83	3.30	2.84	3.31	2.50
19	4.92	4.42	4.75	4.51	4.84	1.20
20	1.15	0.83	0.55	0.97	0.68	1.60
21	0.24	0.08	−0.17	0.23	−0.03	1.20
24	2.35	0.83	0.73	0.85	0.75	1.00
26	−1.25	−1.49	−1.59	−1.47	−1.56	−2.60
27	0.70	−0.28	0.14	−0.30	0.12	−1.87
33	3.85	3.52	3.59	3.67	3.75	1.80
37	−5.81	−6.58	−7.20	−6.18	−6.80	−1.50
42	−0.30	−0.92	−1.20	−1.02	−1.29	−1.10
44	−0.34	−1.37	−0.65	−1.41	−0.68	1.00
45	−2.31	−2.80	−3.02	−2.84	−3.06	−2.10
46	0.21	−0.43	−0.47	−0.34	−0.39	0.20
47	−0.12	−0.90	−0.36	−0.85	−0.31	−0.40
48	0.21	0.25	−0.22	0.28	−0.19	0.90
49	1.31	0.53	1.17	0.53	1.17	1.30
50	−1.72	−2.55	−2.01	−2.57	−2.02	−3.20
55	−3.66	−3.78	−3.81	−3.93	−3.96	−1.50
56	−2.42	−2.76	−2.64	−2.79	−2.67	−2.50
58	1.34	0.05	0.60	0.02	0.57	0.80
59	−1.13	−1.65	−1.26	−1.71	−1.32	−1.30
60	−2.66	−3.47	−2.79	−3.67	−3.00	−3.90
61	−3.66	−3.51	−3.07	−3.54	−3.09	−1.45
63	−6.86	−6.94	−7.67	−7.19	−7.92	−3.00
65	−4.90	−5.43	−6.43	−5.00	−6.00	0.70
67	1.14	1.06	0.92	1.05	0.91	−1.30
68	0.55	−0.13	0.09	−0.06	0.17	1.40
69	−2.09	−3.36	−2.42	−3.47	−2.53	−1.30
70	3.62	3.79	2.45	4.15	2.81	1.60
71	−2.38	−3.87	−3.56	−3.75	−3.44	−0.10
72	1.93	2.63	1.58	2.80	1.74	0.60
74	−7.05	−9.26	−8.97	−9.29	−8.99	−1.90
75	−1.54	−0.27	−0.37	−0.06	−0.17	−2.80
80	−0.26	−0.92	−0.66	−0.96	−0.70	−2.20
81	−4.51	−4.36	−4.66	−4.57	−4.87	−2.20
82	4.80	5.20	4.18	5.44	4.42	2.50
84	0.89	0.45	0.15	0.52	0.22	−0.00
85	−0.25	−0.93	−1.06	−1.07	−1.21	−2.20
86	2.47	2.05	1.64	2.16	1.75	0.70
88	−2.33	−3.78	−3.64	−3.75	−3.61	−1.90
90	0.33	−0.43	−0.25	−0.33	−0.14	0.80
92	−3.49	−4.07	−5.00	−3.85	−4.78	−0.40
RMSD	2.16	2.32	2.44	2.32	2.43	
τ	0.39	0.36	0.36	0.37	0.36	
R	0.64	0.62	0.58	0.64	0.61	

Table S3 Enumeration of protomer state labels. The number preceding the slash indicates the molecule. The first number following the slash encodes the net charge of the state, with a leading underscore indicating an anion. After the underscore, the remaining digits indicate the presence (h) or absence (0) of a proton at a given site. The leading digit in this scheme is listed as '1' in Figure S2, and so on. These states were only considered in the aqueous phase. Additional calculations after the D3R meeting considered additional states **83** that are not enumerated here.

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['04/0_0', '04/1_h']
['10/0_h00', '10/0_00h', '10/0_0h0', '10/1_h0h', '10/1_hh0', '10/_1_000']
['11/0_h00', '11/0_00h', '11/0_0h0', '11/_1_000', '11/1_h0h', '11/1_hh0']
['15/0_h00', '15/_1_000', '15/0_0h0', '15/0_00h', '15/1_h0h', '15/1_hh0']
['17/0_h00', '17/0_00h', '17/0_0h0', '17/1_hh0', '17/_1_000']
['26/0_h', '26/_1_0']
['27/0_000', '27/1_00h', '27/1_0h0', '27/1_h00']
['37/0_0', '37/1_h']
['47/0_h0', '47/0_0h', '47/1_hh', '47/_1_00']
['48/0_h0', '48/0_0h', '48/1_hh', '48/_1_00']
['49/0_h0', '49/0_0h', '49/1_hh', '49/_1_00']
['50/0_h000', '50/0_000h', '50/0_00h0', '50/0_0h00', '50/_1_0000']
['56/0_h0', '56/0_0h', '56/_1_00']
['60/0_h0', '60/0_0h', '60/_1_00', '60/1_hh']
['61/0_0', '61/1_h']
['63/0_00', '63/1_0h', '63/1_h0', '63/2_hh']
['65/0_0', '65/1_h']
['67/0_0', '67/1_h']
['69/0_0hh', '69/0_h0h', '69/0_hh0', '69/1_hhh']
['70/0_0', '70/1_h']
['71/0_0', '71/1_h']
['72/0_0', '72/1_h']
['75/0_0', '75/1_h']
['81/0_0', '81/1_h']
['82/0_0', '82/1_h']
['84/0_0', '84/1_h']
['85/0_hh', '85/_1_h0', '85/_1_0h']
['86/0_0', '86/1_h']
['92/0_00', '92/1_h0']
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Fig. S2 Scheme used to map protomer state labels (Table S3) to their proper structures.