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Supporting Information

Acidity Constant (pK_a) Calculation of Large Solvated Dye Molecules: Evaluation of Two Advanced Molecular Dynamics Methods

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S1 Energies

All individual energetic calculations leading up to the pK_a 's from Table 2 are given here for the restrained MD (Table 1) and the insertion/deletion method (Table 2).

Table S1: Free energy difference (ΔF) and corresponding pK_a for each compound, calculated based on restrained MD simulations. Standard deviations are also given

Compound	ΔF (kJ/mol)	pK_a	pK_a (exp)
1 phenol	54.7 ± 4.0	9.7 ± 0.7	10.0
2 2-chlorophenol	42.2 ± 4.9	7.5 ± 0.9	8.5
3 3-chlorophenol	47.9 ± 7.4	8.5 ± 1.3	9.1
4 4-chlorophenol	52.3 ± 4.4	9.3 ± 0.8	9.4
5 2-bromophenol	45.8 ± 3.8	8.2 ± 0.7	8.5
6 2,6-dibromophenol	37.2 ± 2.4	6.6 ± 0.4	6.7
7 2,4-dibromophenol	40.1 ± 4.4	7.1 ± 0.8	7.8
8 2-methylphenol	54.8 ± 6.1	9.8 ± 1.1	10.3
9 3-methylphenol	58.6 ± 6.2	10.4 ± 1.1	10.1
10 4-hydroxybenzoic acid	50.6 ± 5.8	9.0 ± 1.0	9.3

Table S2: Deprotonation free energy for water and all phenol derivatives and pK_a values calculated according to insertion/deletion method with and without ZPE corrections (denoted pK_a and pK_a^*). For the hydronium ion, the results are given for a system consisting out of 64 and 160 water molecules. Standard deviations are also given

Compound	ΔF (eV)	pK_a	pK_a^*	pK_a (exp)
- H_3O^+ (64)	15.52 ± 0.03	-	-	-
- H_3O^+ (160)	15.43 ± 0.04	-	-	-
1 phenol	16.23 ± 0.02	9.0 ± 0.9	9.1 ± 0.9	10.0
2 2-chlorophenol	16.14 ± 0.03	7.3 ± 1.0	8.1 ± 1.0	8.5
3 3-chlorophenol	16.17 ± 0.03	7.9 ± 1.1	8.3 ± 1.1	9.1
4 4-chlorophenol	16.23 ± 0.03	9.0 ± 1.0	9.2 ± 1.0	9.4
5 2-bromophenol	16.16 ± 0.04	7.8 ± 1.1	8.1 ± 1.1	8.5
6 2,6-dibromophenol	16.13 ± 0.03	7.2 ± 1.0	7.6 ± 1.0	6.7
7 2,4-dibromophenol	16.19 ± 0.03	8.2 ± 1.0	8.8 ± 1.0	7.8
8 2-methylphenol	16.26 ± 0.03	9.4 ± 1.1	9.7 ± 1.1	10.3
9 3-methylphenol	16.23 ± 0.03	8.9 ± 1.0	8.9 ± 1.0	10.1
10 4-hydroxybenzoic acid	16.22 ± 0.03	8.8 ± 1.0	9.0 ± 1.0	9.3
11 Bromothymol Blue	16.08 ± 0.03	7.8 ± 1.1	7.8 ± 1.1	7.4

S2 Static approach for calculating the pK_a of Bromothymol Blue

For reference, the pK_a s of Bromothymol Blue and phenol are calculated using a direct thermodynamic cycle.[33] Recommended in the paper by Ho et al. are composite methods (such as G3MP2 or CBS-QB3) for the gas phase energies G_g .[33] The system under study is, however, too large for computationally demanding methods. Therefore, we have opted to calculate the gas phase energies at B3LYP/6-311G(d,p) level of theory. For the free energy of solvation ΔG_s for phenol and derivatives, HF/6-31G(d) has proven to be an accurate method and is therefore also applied here.[21]

The reaction under study is:



and the free energy difference ΔG can be obtained from:

$$\Delta G = G_g(\text{A}^-) + \Delta G_s(\text{A}^-) - G_g(\text{AH}) - \Delta G_s(\text{AH}) + G_{\text{aq}}(\text{H}^+) \quad (\text{S2})$$

in which the free energy of the aqueous proton, $G_{\text{aq}}(\text{H}^+) = -1138.8 \text{ kJ/mol}$, is taken from literature.[33]

The pK_a s of phenol and Bromothymol Blue are calculated to be 15.5 and 11.7, which are far from the experimental values of 10.0 and 7.4 respectively. Since the free energy of solvation ΔG_s for phenol and its anion are comparable to the values found in ref. [33], we can conclude that accurate gas phase energies are indeed required for obtaining good results compared to experiment. The methods applied in this paper use a completely different approach, not relying on these accurate gas phase energies but are based on another thermodynamic cycle.