# Supporting Information: Effcient Quantum-Chemical Calculations of Acid Dissociation Constants from Free Energy Relationships

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# 1 Statistical error measures

Statistical measure for a set $x_1, \cdots, x_n$ of data points with references $r_1, \cdots, r_n$ are:

- Average:

$$\overline{x} = \frac{1}{n} \sum_{i}^{n} x_i \tag{1}$$

- Mean deviation (MD):

$$MD = \frac{1}{n} \sum_{i}^{n} (x_i - r_i) \tag{2}$$

- Mean absolute deviation (MAD):

$$MAD = \frac{1}{n} \sum_{i}^{n} |x_i - r_i| \tag{3}$$

- Standard deviation (SD):

$$SD = \sqrt{\frac{\sum_i^n |(x_i - r_i) - MD|^2}{n-1}} \tag{4}$$

- Root-mean-square deviation (RSMD):

$$RMSD = \sqrt{\frac{\sum_i^n |x_i - r_i|^2}{n}} \tag{5}$$

- Bayesian information criterion (BIC):

$$BIC = n \ln(RSS/n) + k \ln(n) \tag{6}$$

# 2 Additional Computational Details

In the manuscript the three steps for computation of dissocation free energies and consequently pKa values were discussed. Some additional technical aspects are given here:

- Ionic starting geometries for the acid and its conjugate base can either be taken from the literature (as was the case e.g. for the SAMPL6 benchmark sets), or generated from the neutral species at GFN2-xTB level with the command `crest inp.xyz --protonate --alpb h2o` (respectively `--deprotonate` for the anion).

- Alternatively, if the acid input geometry is known the pKa at GFN2-xTB level can be calculated in a single-structure approach via `crest inp.xyz --pka <acidic H>`, where `<acidic H>` is the number of the acidic proton in the acid input file. This will automatically generate the base and calculate a pKa value. Note that the charge of the acid should be specified via the `--chrg` command.

- Conformational ensembles for consequitve DFT treatment were generated seperately for the acid and base with `crest`. To reduce computational cost, GFN2-xTB structures were clustered using the `--cluster` command.

- Clustered ensembles were passed to the `censo` program, which interfaces Turbomole and yields ensemble files containing the final free energies at DFT level.

- The respective `censo` ensembles can directly be read by `crest`, which calculates the Boltzmann averaged $\overline{G}^A/\overline{G}^B$ and from this the pKa. The corresponding command is `crest --pka --pkaensemble acid-ensemble.xyz base-ensemble.xyz`. CFER parameters can be read from a plain text file via `--pkaparam <file>`.

# 3 Appenix: Results

## 3.1 Appendix: Adjustment of GFN2-xTB dissociation energies

Table S1: Element specific parameters to calculate an energy correction term $E_{mod}^{\mathrm{TB}}$ for dissociation energies at the GFN2-xTB/ALPB($H_2O$) level.

| element X | $\varepsilon(X)$ | $k_1$ | $k_2$ | $k_3$ | $k_4$ |
|---|---|---|---|---|---|
| C | 0.243240 | 0.006819 | -0.012581 | 0.154801 | 0.143015 |
| N | 0.257074 | 0.037121 | -0.055775 | 0.106734 | 0.023837 |
| O | 0.194618 | 0.024046 | 0.028236 | 0.014825 | 0.149677 |
| F | 0.122274 | -0.147062 | 0.328353 | -0.327531 | 0.234198 |
| Si | 0.212852 | 0.019048 | -0.061229 | 0.026066 | 0.008854 |
| P | 0.274942 | -0.023403 | 0.025728 | -0.013699 | -0.026747 |
| Si | 0.301025 | 0.008263 | -0.080627 | 0.093954 | -0.051587 |
| Cl | 0.278736 | -0.008886 | -0.008372 | 0.014058 | -0.057756 |

Table S2: Energy differences $\Delta E = E_{base} - E_{acid}$ at the r$^2$SCAN-3c/COSMO-RS($H_2O$), GFN2-xTB/ALPB($H_2O$) and GFN2-xTB+$E_{mod}^{\mathrm{TB}}$/ALPB($H_2O$) levels. The element specific parameters of $E_{mod}^{\mathrm{TB}}$ in Tab. S1 were fitted to these energies. All energies are in Eh. The "tag" is a trivial label corresponding to the system as provided in the seperate input structure zip file.

| fit element | tag | $\Delta E_{DFT}$ | $\Delta E_{GFN2}$ | $\Delta E_{GFN2} + E_{mod}^{\mathrm{TB}}$ | $\Delta\Delta E_{DFT/GFN2} + E_{mod}^{\mathrm{TB}}$ |
|---|---|---|---|---|---|
| C | acetaldehyd | 0.518258 | 0.297300 | 0.528032 | -0.009774 |
| C | aceton | 0.479308 | 0.246949 | 0.472988 | 0.006320 |
| C | acetylaceton | 0.446127 | 0.205680 | 0.437789 | 0.008339 |
| C | barbituric | 0.434592 | 0.181474 | 0.420908 | 0.013684 |
| C | benzol | 0.529184 | 0.325102 | 0.527222 | 0.001962 |
| C | butadien | 0.527351 | 0.323373 | 0.525149 | 0.002202 |
| C | bzh+ | 0.375641 | 0.126545 | 0.400290 | -0.024648 |
| C | c4oen | 0.512839 | 0.280436 | 0.522994 | -0.010154 |
| C | cf3h | 0.500405 | 0.217474 | 0.503984 | -0.003579 |
| C | ch2no22 | 0.421813 | 0.147368 | 0.404471 | 0.017342 |
| C | ch3cn | 0.485975 | 0.268872 | 0.493184 | -0.007209 |
| C | ch3nh2 | 0.547339 | 0.328233 | 0.551091 | -0.003752 |
| C | chbr3 | 0.484328 | 0.196193 | 0.485281 | -0.000953 |
| C | chcl3 | 0.489328 | 0.205443 | 0.473581 | 0.015747 |
| C | chexanon | 0.479771 | 0.245278 | 0.474416 | 0.005356 |
| C | chlorethin | 0.475893 | 0.265922 | 0.471883 | 0.004011 |
| C | chme2+ | 0.489907 | 0.241325 | 0.488522 | 0.001385 |
| C | cpdien | 0.458051 | 0.236263 | 0.477236 | -0.019185 |
| C | cyclohexandion | 0.435026 | 0.198086 | 0.432699 | 0.002327 |
| C | cyclononyl | 0.448908 | 0.230845 | 0.471853 | -0.022945 |
| C | dihydrofuran | 0.536414 | 0.306699 | 0.534830 | 0.001583 |
| C | diphenylmethan | 0.503804 | 0.262988 | 0.495229 | 0.008575 |
| C | ethan | 0.547117 | 0.333451 | 0.548228 | -0.001111 |
| C | ethen | 0.526964 | 0.321775 | 0.527700 | -0.000736 |
| C | ethin | 0.470002 | 0.302895 | 0.488944 | -0.018943 |
| C | fluoren | 0.483967 | 0.245019 | 0.482208 | 0.001759 |
| C | lacton5 | 0.487312 | 0.241447 | 0.469354 | 0.017958 |
| C | malonitril | 0.442189 | 0.209823 | 0.449159 | -0.006970 |
| C | pyridin | 0.525787 | 0.314269 | 0.531305 | -0.005518 |
| C | tbutyl+ | 0.403114 | 0.159821 | 0.408595 | -0.005481 |
| C | toluol | 0.515513 | 0.285823 | 0.510551 | 0.004962 |
| N | acetamid | 0.473020 | 0.228146 | 0.468414 | 0.004606 |
| N | anilin | 0.488184 | 0.254263 | 0.490695 | -0.002512 |
| N | ch3cnh+ | 0.395281 | 0.156339 | 0.413997 | -0.018715 |
| N | diphenylamineh+ | 0.422952 | 0.159406 | 0.425642 | -0.002690 |
| N | guanidinium+ | 0.465492 | 0.214756 | 0.457551 | 0.007941 |
| N | hn3 | 0.428340 | 0.203318 | 0.435842 | -0.007501 |
| N | hydrazinium+ | 0.444366 | 0.182031 | 0.442370 | 0.001997 |
| N | imidazol | 0.461993 | 0.221536 | 0.468007 | -0.006014 |
| N | imidazolh+ | 0.447593 | 0.192420 | 0.445405 | 0.002188 |
| N | isocyanic | 0.429788 | 0.199369 | 0.433278 | -0.003489 |
| N | morpholineh+ | 0.450425 | 0.180689 | 0.442596 | 0.007829 |
| N | Naphthyridinium | 0.438535 | 0.181843 | 0.439902 | -0.001367 |
| N | nh3 | 0.508929 | 0.291057 | 0.525937 | -0.017008 |
| N | nh4+ | 0.450836 | 0.200003 | 0.451506 | -0.000669 |
| N | nph3h+ | 0.411569 | 0.147858 | 0.416860 | -0.005291 |
| N | phnh3+ | 0.434460 | 0.174413 | 0.434555 | -0.000095 |
| N | phtalimid | 0.449301 | 0.205287 | 0.452585 | -0.003284 |
| N | pyridinium+ | 0.444893 | 0.182091 | 0.440050 | 0.004843 |
| N | pyrimidinium | 0.433031 | 0.166103 | 0.424219 | 0.008811 |
| N | pyrrol | 0.470363 | 0.240632 | 0.486836 | -0.016472 |
| N | sacharin | 0.428778 | 0.178392 | 0.421435 | 0.007343 |

Table S2: Continue previous table...

| fit element | tag | $\Delta E_{DFT}$ | $\Delta E_{GFN2}$ | $\Delta E_{GFN2} + E^{\mathrm{TB}}_{mod}$ | $\Delta\Delta E_{DFT/GFN2} + E^{\mathrm{TB}}_{mod}$ |
|---|---|---|---|---|---|
| O | acetamidh+ | 0.424986 | 0.171974 | 0.424438 | 0.000548 |
| O | acetonh+ | 0.413485 | 0.160852 | 0.419367 | -0.005881 |
| O | ala | 0.437842 | 0.193654 | 0.440525 | -0.002683 |
| O | ccl3cooh | 0.427043 | 0.161688 | 0.417721 | 0.009321 |
| O | cf3cooh | 0.425982 | 0.159606 | 0.417870 | 0.008113 |
| O | ch3cooh2+ | 0.412401 | 0.153267 | 0.410678 | 0.001723 |
| O | ch3cooh | 0.438220 | 0.198504 | 0.444044 | -0.005824 |
| O | dmsoh+ | 0.427113 | 0.172271 | 0.419320 | 0.007793 |
| O | enol | 0.454712 | 0.225257 | 0.463282 | -0.008570 |
| O | h2co3 | 0.431799 | 0.182002 | 0.430707 | 0.001092 |
| O | h2o2 | 0.462396 | 0.220957 | 0.474283 | -0.011887 |
| O | h2o | 0.476512 | 0.257044 | 0.486801 | -0.010289 |
| O | h2po4- | 0.438474 | 0.204968 | 0.444697 | -0.006224 |
| O | h2so4 | 0.407784 | 0.168973 | 0.408284 | -0.000501 |
| O | h3o+ | 0.426699 | 0.165183 | 0.422124 | 0.004575 |
| O | h3po4 | 0.428554 | 0.183783 | 0.428061 | 0.000493 |
| O | hclo3 | 0.408558 | 0.163076 | 0.418918 | -0.010361 |
| O | hclo4 | 0.399627 | 0.134184 | 0.393783 | 0.005844 |
| O | hco3- | 0.452962 | 0.224171 | 0.456057 | -0.003095 |
| O | hcooh | 0.436114 | 0.185716 | 0.436182 | -0.000068 |
| O | hno2 | 0.429749 | 0.179599 | 0.432729 | -0.002980 |
| O | hno3 | 0.415951 | 0.160589 | 0.413361 | 0.002590 |
| O | hocl | 0.451763 | 0.200210 | 0.451526 | 0.000237 |
| O | hso4- | 0.418432 | 0.193737 | 0.432452 | -0.014020 |
| O | meoh2+ | 0.417264 | 0.153797 | 0.418185 | -0.000921 |
| O | meoh | 0.484921 | 0.239711 | 0.477903 | 0.007017 |
| O | mesulfons | 0.412470 | 0.176101 | 0.419065 | -0.006595 |
| O | odiphenol | 0.453611 | 0.217875 | 0.455454 | -0.001843 |
| O | oxal1 | 0.426535 | 0.179940 | 0.433176 | -0.006641 |
| O | oxal2 | 0.430682 | 0.194329 | 0.443352 | -0.012670 |
| O | phboron | 0.456836 | 0.227545 | 0.462502 | -0.005666 |
| O | phcooh | 0.438015 | 0.197940 | 0.443596 | -0.005581 |
| O | phenol | 0.457422 | 0.223836 | 0.463281 | -0.005859 |
| O | pikrin | 0.426762 | 0.166828 | 0.419855 | 0.006907 |
| O | quadratic1 | 0.425330 | 0.175504 | 0.426235 | -0.000905 |
| O | quadratic2 | 0.427702 | 0.197336 | 0.443395 | -0.015693 |
| O | salicylat | 0.435005 | 0.192297 | 0.438312 | -0.003307 |
| O | tbutanol | 0.487440 | 0.254921 | 0.489114 | -0.001674 |
| O | thfh+ | 0.413682 | 0.148052 | 0.414586 | -0.000905 |
| O | trifluorethanol | 0.471973 | 0.216740 | 0.460124 | 0.011849 |
| O | tropolon | 0.446291 | 0.210060 | 0.452503 | -0.006212 |
| O | uracil | 0.450681 | 0.208806 | 0.456783 | -0.006102 |
| O | uronium+ | 0.428774 | 0.178438 | 0.423027 | 0.005746 |
| O | vitcmod | 0.436900 | 0.187780 | 0.435886 | 0.001014 |
| F | etfh+ | 0.357602 | 0.081647 | 0.347701 | 0.009901 |
| F | f2h+ | 0.293090 | 0.029602 | 0.297628 | -0.004539 |
| F | fethenh+ | 0.354159 | 0.123378 | 0.406676 | -0.052517 |
| F | hfdimer | 0.414417 | 0.148024 | 0.398024 | 0.016393 |
| F | lifh+ | 0.423745 | 0.129430 | 0.425556 | -0.001811 |
| F | mefh+ | 0.351819 | 0.079171 | 0.349800 | 0.002020 |
| F | phfh+ | 0.332818 | 0.072970 | 0.337974 | -0.005156 |
| Si | sif2h | 0.475726 | 0.255362 | 0.471139 | 0.004587 |
| Si | sih2cl2 | 0.470784 | 0.252445 | 0.477973 | -0.007188 |
| Si | sih3+ | 0.423495 | 0.214151 | 0.415387 | 0.008109 |
| Si | sih3cn | 0.469097 | 0.279804 | 0.485893 | -0.016796 |
| Si | sihbr3 | 0.448203 | 0.202407 | 0.423487 | 0.024716 |
| Si | sihcl2+ | 0.384558 | 0.177256 | 0.403282 | -0.018724 |
| Si | sihcl3 | 0.457577 | 0.229032 | 0.456155 | 0.001422 |
| Si | sihclch2 | 0.472265 | 0.253635 | 0.503635 | -0.031370 |
| Si | sihcls | 0.439781 | 0.228606 | 0.455766 | -0.015985 |
| Si | sihf-ethene | 0.470471 | 0.274598 | 0.487869 | -0.017398 |
| Si | sihfo | 0.493141 | 0.256100 | 0.506100 | -0.012959 |
| Si | sihme2+ | 0.449635 | 0.229321 | 0.438321 | 0.011315 |

Table S2: Continue previous table...

| fit element | tag | $\Delta E_{DFT}$ | $\Delta E_{GFN2}$ | $\Delta E_{GFN2} + E^{\mathrm{TB}}_{mod}$ | $\Delta\Delta E_{DFT/GFN2} + E^{\mathrm{TB}}_{mod}$ |
|---|---|---|---|---|---|
| P | p2me2h+ | 0.386058 | 0.159947 | 0.404984 | -0.018926 |
| P | p2meh | 0.452386 | 0.223084 | 0.484567 | -0.032180 |
| P | p4o6h+ | 0.388565 | 0.139646 | 0.389646 | -0.001082 |
| P | p-betaine | 0.433219 | 0.201049 | 0.451049 | -0.017830 |
| P | pbr3h+ | 0.371490 | 0.046515 | 0.300179 | 0.071312 |
| P | pcl3h+ | 0.375187 | 0.123525 | 0.379625 | -0.004438 |
| P | ph3 | 0.461970 | 0.199120 | 0.460304 | 0.001666 |
| P | ph3ph+ | 0.431622 | 0.177402 | 0.435493 | -0.003871 |
| P | ph4+ | 0.418091 | 0.158223 | 0.424313 | -0.006223 |
| P | phcl2 | 0.478012 | 0.191442 | 0.474129 | 0.003883 |
| P | pme3h+ | 0.447142 | 0.190459 | 0.448621 | -0.001479 |
| P | poh3h+ | 0.431011 | 0.167001 | 0.429280 | 0.001731 |
| P | pphh3+ | 0.422571 | 0.162900 | 0.425931 | -0.003360 |
| P | p-sbetaine | 0.437980 | 0.198606 | 0.448606 | -0.010626 |
| P | verkadeh+ | 0.472521 | 0.238576 | 0.488576 | -0.016055 |
| S | allylthiol | 0.443474 | 0.211998 | 0.449145 | -0.005671 |
| S | diphenylsh+ | 0.390624 | 0.140349 | 0.394892 | -0.004268 |
| S | etsh2+ | 0.400411 | 0.146905 | 0.395044 | 0.005367 |
| S | etsh | 0.444463 | 0.214382 | 0.449585 | -0.005121 |
| S | h2s2 | 0.436570 | 0.184950 | 0.424855 | 0.011715 |
| S | h2s | 0.429694 | 0.206467 | 0.443384 | -0.013690 |
| S | hsoh | 0.437938 | 0.202132 | 0.439223 | -0.001285 |
| S | isopentylthiol | 0.447607 | 0.220069 | 0.456043 | -0.008436 |
| S | mesh | 0.443412 | 0.211144 | 0.446565 | -0.003152 |
| S | nh2sh | 0.443779 | 0.207725 | 0.443774 | 0.000004 |
| S | nitrophenol | 0.433827 | 0.179988 | 0.435886 | -0.002059 |
| S | o-nh2thiopenol | 0.437640 | 0.204633 | 0.448381 | -0.010741 |
| S | phsh2+ | 0.389787 | 0.139083 | 0.391911 | -0.002124 |
| S | phsh | 0.438371 | 0.202816 | 0.444290 | -0.005919 |
| S | s8h+ | 0.360310 | 0.115683 | 0.369747 | -0.009438 |
| S | scl2h+ | 0.359797 | 0.128463 | 0.374592 | -0.014795 |
| S | senol | 0.436870 | 0.203782 | 0.443672 | -0.006801 |
| S | shpyridone | 0.436175 | 0.201701 | 0.445757 | -0.009582 |
| S | sthfh+ | 0.409844 | 0.154024 | 0.402663 | 0.007180 |
| S | tbutylsh | 0.447163 | 0.220320 | 0.456369 | -0.009205 |
| S | thioac | 0.438270 | 0.196116 | 0.445785 | -0.007515 |
| S | thioacetamidh+ | 0.417425 | 0.164474 | 0.412065 | 0.005360 |
| S | thioacetonh+ | 0.408605 | 0.155542 | 0.407414 | 0.001192 |
| S | thioessig | 0.429063 | 0.174817 | 0.423240 | 0.005824 |
| S | thionapthol | 0.440106 | 0.201315 | 0.446364 | -0.006258 |
| S | thiuronium | 0.419348 | 0.170448 | 0.413593 | 0.005755 |
| Cl | br2clh | 0.381402 | 0.158967 | 0.387806 | -0.006403 |
| Cl | brclh+ | 0.324728 | 0.067346 | 0.305718 | 0.019009 |
| Cl | cl2h+ | 0.321884 | 0.097324 | 0.333836 | -0.011951 |
| Cl | clethenh+ | 0.342988 | 0.111484 | 0.353297 | -0.010309 |
| Cl | clh2+ | 0.346346 | 0.111824 | 0.348884 | -0.002537 |
| Cl | etclh+ | 0.356187 | 0.116316 | 0.357475 | -0.001289 |
| Cl | hclhf | 0.393733 | 0.158526 | 0.395230 | -0.001497 |
| Cl | meclh+ | 0.353979 | 0.116803 | 0.357406 | -0.003427 |
| Cl | phclh+ | 0.340075 | 0.108151 | 0.350073 | -0.009998 |

## 3.2 Appendix: Free energy relationships

Table S3: Statistical measures of different orders of FER, determined for r$^2$SCAN-3c/COSMO-RS on the PKA74 set.

| | FER orders | | | | | |
|---|---|---|---|---|---|---|
| | LFER | QFER | CFER | (4)FER | (5)FER | (6)FER |
| MAD | 2.061 | 1.939 | 1.856 | 1.675 | 1.603 | 1.603 |
| RMSD | 2.668 | 2.584 | 2.416 | 2.315 | 2.250 | 2.250 |
| SD | 2.685 | 2.600 | 2.431 | 2.330 | 2.263 | 2.263 |
| $R^2$ | 0.956 | 0.959 | 0.964 | 0.967 | 0.969 | 0.969 |
| BIC | 531.108 | 530.256 | 523.663 | 521.067 | 520.758 | 525.164 |

Table S4: CFER parameters for GFN2-xTB/ALPB with and without the energy correction $E_{mod}^{\mathrm{TB}}$ on the PKA74 set.

| | | FER parameters | | | | statistics [p$K_a$] | |
|---|---|---|---|---|---|---|---|
| | method | $c_0$ | $c_1$ | $c_2$ | $c_3$ | MAD | RMSD |
| CFER | GFN2-xTB | -95.392771 | 2.318512 | -0.018978 | 0.000068 | 3.13 | 4.30 |
| CFER | GFN2-xTB+$E_{mod}^{\mathrm{TB}}$ | -1855.025277 | 26.075982 | -0.12496355 | 0.00020571 | 2.79 | 3.68 |

Table S5: CFER parameters determined for GFN2-xTB+$E_{mod}^{\mathrm{TB}}$/ALPB, r$^2$SCAN-3c, B97-3c, B97-D/TZ, PBE0-D3/TZ, PW6B95-D3/TZ, and $\omega$B97X-V/TZ levels of theory using data from the PKA74 set. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation. TZ is an abbreviation for the def2-TZVPP basis set.

| | CFER parameters | | | |
|---|---|---|---|---|
| | $c_0$ | $c_1$ | $c_2$ | $c_3$ |
| GFN2-xTB | -1855.0252772 | 26.0759822 | -0.1249636 | 0.0002057 |
| r$^2$SCAN-3c | -1511.8899792 | 21.1100681 | -0.1011999 | 0.0001683 |
| B97-3c | -1835.3033945 | 25.4169227 | -0.1201689 | 0.0001956 |
| B97-D/TZ | -1852.5125079 | 25.7839522 | -0.1226496 | 0.0002009 |
| PBE0-D3/TZ | -1441.4834019 | 20.0872293 | -0.0961330 | 0.0001597 |
| PW6B95-D3/TZ | -1580.6043989 | 22.2170835 | -0.1069510 | 0.0001777 |
| $\omega$B97X-V/TZ | -1796.5154741 | 25.4641832 | -0.1231099 | 0.0002043 |

Table S6: CFER parameters determined for GFN2-xTB+$E_{mod}^{\mathrm{TB}}$/ALPB, r$^2$SCAN-3c, B97-3c, B97-D/TZ, PBE0-D3/TZ, PW6B95-D3/TZ, and $\omega$B97X-V/TZ levels of theory using data from the TR224 set. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation. TZ is an abbreviation for the def2-TZVPP basis set.

| | CFER parameters | | | |
|---|---|---|---|---|
| | $c_0$ | $c_1$ | $c_2$ | $c_3$ |
| GFN2-xTB | 6702.3111485 | -100.4483504 | 0.4988740 | -0.0008201 |
| r$^2$SCAN-3c | 5014.2837220 | -75.7090708 | 0.3781462 | -0.0006239 |
| B97-3c | 3032.1086142 | -45.1533848 | 0.2212100 | -0.0003555 |
| B97-D/TZ | 7250.3854583 | -106.5703614 | 0.5191041 | -0.0008370 |
| PBE0-D3/TZ | 5655.4664440 | -84.3407514 | 0.4163611 | -0.0006795 |
| PW6B95-D3/TZ | 5013.0940026 | -74.7015098 | 0.3682453 | -0.0005996 |
| $\omega$B97X-V/TZ | -1852.6895447 | 25.5589506 | -0.1193445 | 0.0001901 |

## 3.3 Appendix: The PKA74 set

Table S7: Dissociation free energy for the PKA74 set for all levels of theory discussed in the manuscript. All DFT methods employ COSMO-RS.

| | exp. $pK_a$ | GFN2-xTB | $r^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| aceton | 20.00 | 212.20352 | 214.76880 | 217.32276 | 217.95139 | 214.99135 | 217.17341 | 217.87325 |
| acetylaceton | 9.00 | 195.88290 | 199.74523 | 202.21462 | 203.55419 | 199.80033 | 202.03999 | 203.99023 |
| barbituric | 4.00 | 189.09334 | 195.19923 | 198.15227 | 199.14465 | 195.39072 | 197.18324 | 198.74507 |
| benzol | 43.00 | 234.50254 | 235.82799 | 238.19299 | 238.40700 | 236.18575 | 238.10884 | 236.73326 |
| bzh+ | -24.00 | 181.47535 | 169.24948 | 172.97912 | 173.40195 | 169.34709 | 169.44482 | 169.62491 |
| ch3cn | 25.00 | 219.67854 | 216.56670 | 219.67577 | 219.83199 | 216.84529 | 219.70658 | 220.61503 |
| chcl3 | 25.00 | 212.26211 | 217.91378 | 221.46449 | 222.48056 | 219.49572 | 223.62573 | 225.12038 |
| cpdien | 16.00 | 214.32850 | 204.20298 | 208.03149 | 208.59722 | 204.80820 | 206.52780 | 207.04647 |
| cyclohexandion | 5.00 | 193.87012 | 195.03204 | 197.36135 | 199.21603 | 194.91731 | 197.76590 | 199.63630 |
| diphenylmethan | 33.50 | 221.42982 | 224.64024 | 227.72958 | 228.23777 | 225.26239 | 228.18801 | 231.60312 |
| ethan | 50.00 | 242.81419 | 241.56928 | 244.05712 | 243.63445 | 243.07631 | 243.92646 | 243.24671 |
| ethen | 44.00 | 233.89682 | 232.51591 | 234.67055 | 234.61881 | 234.15880 | 234.72940 | 233.66125 |
| ethin | 25.00 | 218.48936 | 209.29619 | 211.57882 | 211.96208 | 210.08057 | 211.76499 | 210.47333 |
| fluoren | 23.00 | 215.58056 | 215.83960 | 219.36070 | 220.14240 | 216.38988 | 219.12034 | 221.31874 |
| malonitril | 11.20 | 200.92355 | 197.81855 | 200.69295 | 201.41488 | 197.71336 | 201.08317 | 203.20410 |
| tbutyl+ | -12.00 | 183.79697 | 182.60914 | 185.09901 | 185.39320 | 182.38892 | 182.35252 | 182.96778 |
| toluol | 41.00 | 228.03701 | 229.77670 | 233.32908 | 233.40761 | 230.50261 | 233.37531 | 234.56750 |
| acetamid | 15.00 | 212.77864 | 212.09974 | 214.39543 | 215.45646 | 212.41026 | 214.57754 | 214.08831 |
| anilin | 27.00 | 219.66524 | 218.21182 | 221.06173 | 221.71120 | 218.48169 | 221.45857 | 221.30201 |
| ch3cnh+ | -10.00 | 186.62335 | 178.26390 | 180.78428 | 181.53533 | 178.00898 | 179.66644 | 179.05868 |
| diphenylamineh+ | 0.80 | 189.93869 | 189.10111 | 193.41511 | 193.24644 | 188.96276 | 190.55723 | 191.92577 |
| guanidinium+ | 13.40 | 204.81388 | 208.42280 | 211.30658 | 211.91802 | 208.34904 | 210.76512 | 210.32000 |
| hn3 | 4.70 | 196.93040 | 195.02320 | 197.48753 | 198.77380 | 193.16997 | 198.09892 | 198.44004 |
| hydrazinium+ | 8.10 | 198.60457 | 199.85492 | 203.60415 | 203.32436 | 199.23569 | 201.53644 | 201.43695 |
| imidazol | 14.50 | 198.93214 | 200.10742 | 202.73512 | 203.39539 | 200.24171 | 201.82940 | 201.54800 |
| imidazolh+ | 7.00 | 209.76073 | 206.51012 | 209.32085 | 210.35081 | 206.69316 | 209.08698 | 208.36953 |
| isocyanic | 3.90 | 195.43616 | 194.42710 | 197.04591 | 198.24342 | 193.82645 | 196.07387 | 195.19715 |
| morpholineh+ | 8.50 | 197.55272 | 201.49350 | 204.95763 | 205.11424 | 201.21260 | 202.66967 | 202.65111 |
| Naphthyridinium | 3.40 | 197.03335 | 195.99162 | 198.77070 | 199.79041 | 196.13148 | 197.72451 | 197.28197 |
| nh3 | 36.00 | 234.76382 | 226.74442 | 230.48856 | 229.71389 | 227.12123 | 229.86449 | 229.19075 |
| nh4+ | 9.40 | 201.63088 | 201.90391 | 205.82940 | 204.82143 | 201.92648 | 203.34136 | 203.28099 |
| nph3h+ | -5.00 | 185.77282 | 184.05552 | 187.99155 | 188.64328 | 183.85070 | 185.33975 | 186.75997 |
| phnh3+ | 4.60 | 194.66299 | 194.43714 | 198.88709 | 198.21552 | 194.62543 | 196.31647 | 196.60919 |
| phtalimid | 9.60 | 202.67650 | 200.98894 | 203.58549 | 205.45821 | 201.15931 | 203.67594 | 203.08803 |
| pyridinium+ | 5.20 | 196.73601 | 198.81479 | 201.43017 | 202.06016 | 198.96258 | 200.13778 | 199.86478 |
| pyrimidinium | 1.30 | 190.10311 | 193.96579 | 196.46963 | 197.29926 | 193.85476 | 195.32419 | 195.19211 |
| pyrrol | 15.00 | 217.72524 | 209.83845 | 212.44663 | 213.59191 | 210.14841 | 212.51300 | 211.75736 |
| sacharin | 1.60 | 188.97227 | 192.44899 | 195.73433 | 197.59603 | 192.34721 | 194.61154 | 194.07873 |
| acetamidh+ | 0.00 | 189.78396 | 189.89838 | 191.84264 | 192.86571 | 189.96835 | 191.34970 | 191.13705 |
| acetonh+ | -7.00 | 188.58811 | 185.56096 | 187.29736 | 188.23528 | 185.45734 | 186.17292 | 185.93249 |
| ala | 2.40 | 197.42156 | 195.96900 | 197.08868 | 199.37158 | 196.33711 | 198.21193 | 197.75204 |

Table S7: Continue previous table...

| | exp. $pK_a$ | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| ccl3cooh | 0.65 | 187.66397 | 190.46348 | 192.35554 | 194.29844 | 191.41585 | 193.12826 | 192.98196 |
| cf3cooh | 0.00 | 186.75904 | 189.66818 | 191.27395 | 193.51122 | 190.42088 | 191.83530 | 191.64673 |
| ch3cooh | 4.80 | 184.54494 | 185.12829 | 187.01868 | 188.08384 | 185.02627 | 186.29746 | 186.15939 |
| ch3cooh2+ | -6.00 | 199.55347 | 196.06586 | 197.18986 | 199.47730 | 196.26689 | 198.31271 | 197.90082 |
| dmsoh+ | -1.50 | 188.61974 | 191.49020 | 194.08632 | 193.40534 | 192.11592 | 192.06835 | 192.04927 |
| enol | 10.50 | 207.00412 | 202.66913 | 203.80724 | 205.53057 | 203.07367 | 205.18904 | 205.01668 |
| h2co3 | 3.60 | 192.76472 | 193.55052 | 194.93697 | 197.07089 | 193.56484 | 195.78770 | 195.39406 |
| h2o | 15.70 | 213.47525 | 208.53482 | 209.50865 | 211.88403 | 208.30854 | 211.12815 | 210.86365 |
| h2o2 | 11.60 | 219.20978 | 214.85623 | 216.59402 | 217.72147 | 214.78288 | 217.42654 | 216.77278 |
| h2po4- | 7.20 | 199.97158 | 198.08996 | 199.29085 | 201.56372 | 197.11522 | 200.56114 | 200.02687 |
| h2so4 | -3.00 | 183.72398 | 183.41473 | 186.04267 | 187.21730 | 183.54725 | 184.69039 | 184.23503 |
| h3o+ | -1.74 | 189.34861 | 192.07450 | 195.05873 | 194.83849 | 191.66506 | 193.43670 | 193.38388 |
| h3po4 | 2.20 | 192.14726 | 191.80256 | 193.69456 | 195.28014 | 192.62767 | 193.82087 | 193.39499 |
| hclo3 | -2.70 | 188.77803 | 185.54831 | 189.32549 | 189.67510 | 183.53572 | 184.82092 | 183.47234 |
| hclo4 | -10.00 | 178.47795 | 181.48394 | 185.12952 | 185.49504 | 179.81486 | 181.05272 | 180.13684 |
| hco3- | 10.30 | 205.70287 | 203.44705 | 203.46371 | 207.85270 | 203.50794 | 206.97226 | 206.25532 |
| hcooh | 3.80 | 195.06533 | 193.04378 | 194.11707 | 196.37165 | 194.72352 | 195.25132 | 195.06118 |
| hno2 | 3.30 | 194.43467 | 193.44207 | 195.31018 | 197.79133 | 192.75863 | 196.12839 | 195.88125 |
| hno3 | -1.40 | 186.34188 | 187.38380 | 189.31676 | 191.75670 | 186.72517 | 188.78617 | 188.35846 |
| hocl | 7.50 | 203.83681 | 202.86709 | 205.87096 | 206.76133 | 203.94697 | 205.65656 | 205.49720 |
| hso4- | 1.90 | 195.93799 | 189.44101 | 191.36947 | 193.61575 | 188.38498 | 191.31376 | 190.70213 |
| meoh | 15.50 | 187.40273 | 187.74261 | 190.30081 | 190.76659 | 186.89417 | 188.90374 | 188.89700 |
| meoh2+ | -2.00 | 213.70884 | 215.02545 | 216.02343 | 217.21571 | 216.45186 | 217.12785 | 216.87814 |
| mesulfons | -2.60 | 189.06169 | 185.58173 | 188.19856 | 189.13506 | 185.56030 | 186.59931 | 186.05905 |
| odiphenol | 9.50 | 204.13115 | 203.09149 | 204.41329 | 206.31205 | 203.28127 | 205.63722 | 205.49574 |
| oxal1 | 1.20 | 194.36952 | 191.16753 | 192.65389 | 194.90959 | 191.12668 | 193.26832 | 192.88966 |
| oxal2 | 4.20 | 199.62809 | 193.25085 | 194.26556 | 197.41446 | 193.20140 | 196.09355 | 195.61609 |
| phboron | 8.80 | 206.58483 | 203.44663 | 204.88763 | 206.40646 | 204.32205 | 205.81007 | 205.32084 |
| phcooh | 4.20 | 199.02042 | 196.08712 | 197.68422 | 199.79158 | 196.14091 | 198.31370 | 197.67026 |
| phenol | 10.00 | 207.89355 | 204.57893 | 205.91167 | 208.08181 | 204.86121 | 207.45840 | 207.17486 |
| pikrin | 0.25 | 187.79133 | 191.28660 | 193.56643 | 195.57454 | 190.93559 | 193.98405 | 194.70205 |
| quadratic1 | 1.50 | 191.01450 | 190.33864 | 191.95712 | 194.09027 | 190.55319 | 192.80673 | 192.74606 |
| quadratic2 | 3.40 | 199.90976 | 192.16528 | 193.33408 | 196.23422 | 191.78332 | 195.15793 | 194.98446 |
| salicylat | 2.75 | 196.21715 | 194.67003 | 196.31027 | 198.24702 | 194.68809 | 196.94799 | 196.20726 |
| tbutanol | 20.00 | 219.54687 | 217.87329 | 217.80392 | 220.27849 | 218.28955 | 219.77573 | 219.53119 |
| thfh+ | -2.10 | 184.67089 | 186.01943 | 188.49426 | 189.57540 | 184.68914 | 186.94628 | 186.86012 |
| trifluorethanol | 12.50 | 205.68129 | 210.18702 | 211.33660 | 213.50609 | 211.10963 | 212.76205 | 212.58870 |
| tropolon | 6.50 | 202.93731 | 199.48237 | 201.23362 | 203.41057 | 199.76824 | 202.44953 | 202.23078 |
| uracil | 9.40 | 204.22204 | 200.73761 | 203.29906 | 205.26579 | 201.41371 | 203.41862 | 202.90427 |
| uronium+ | 0.10 | 189.02196 | 191.73113 | 193.87550 | 195.06031 | 191.99404 | 193.49317 | 193.10196 |
| vitcmod | 4.50 | 195.59710 | 195.91690 | 197.56262 | 199.67952 | 195.98809 | 198.52243 | 198.29509 |

## 3.4 Appendix: The TR224 set

Table S8: Acid dissociation free energies calculated for the Ar-N subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.10 | 190.115867 | 193.977038 | 196.483659 | 197.310060 | 195.599813 | 195.344158 | 195.212046 |
| 2 | 2.10 | 197.240853 | 195.015125 | 197.881165 | 198.583421 | 196.986500 | 196.692696 | 196.395971 |
| 3 | 2.84 | 195.249593 | 195.635663 | 198.370557 | 199.176163 | 197.424035 | 197.202207 | 196.943663 |
| 4 | 3.28 | 194.838811 | 196.365336 | 199.269024 | 200.128078 | 198.146915 | 197.853330 | 197.549057 |
| 5 | 3.39 | 198.441879 | 196.523354 | 199.497979 | 200.291161 | 198.473750 | 198.203529 | 197.571257 |
| 6 | 4.85 | 197.184139 | 198.165439 | 201.048686 | 201.854425 | 199.824570 | 199.679565 | 199.120046 |
| 7 | 4.86 | 196.859786 | 198.826531 | 201.529807 | 202.255870 | 200.273334 | 199.982081 | 199.434848 |
| 8 | 4.88 | 196.321834 | 198.297739 | 201.044074 | 201.783543 | 199.766898 | 199.493749 | 198.952970 |
| 9 | 5.05 | 197.541736 | 198.187766 | 201.148605 | 201.989145 | 199.837582 | 199.697936 | 199.050610 |
| 10 | 5.17 | 196.721605 | 198.776474 | 201.389449 | 202.018938 | 200.291350 | 200.095951 | 199.822849 |
| 11 | 5.60 | 198.673928 | 198.618401 | 201.642914 | 202.688140 | 200.524452 | 200.426506 | 199.873110 |
| 12 | 5.70 | 197.056020 | 199.012875 | 201.666119 | 202.366093 | 200.573698 | 200.405929 | 199.942684 |
| 13 | 5.82 | 197.433857 | 199.149922 | 201.919099 | 202.576136 | 200.763649 | 200.526754 | 200.072279 |
| 14 | 5.87 | 200.020069 | 200.894281 | 204.739112 | 204.935278 | 203.178968 | 202.838327 | 202.302087 |
| 15 | 5.97 | 198.757867 | 199.336643 | 202.092071 | 202.842371 | 200.984329 | 200.754089 | 200.265330 |
| 16 | 5.99 | 197.631772 | 199.581448 | 202.237806 | 202.958036 | 201.150456 | 200.906799 | 200.503295 |
| 17 | 6.00 | 198.646376 | 198.175052 | 201.108307 | 201.846684 | 200.175755 | 200.125761 | 199.693576 |
| 18 | 6.02 | 197.543085 | 199.715160 | 202.301734 | 203.003398 | 201.279155 | 201.094776 | 200.691385 |
| 19 | 6.45 | 198.693371 | 198.790957 | 201.644842 | 202.553870 | 200.998628 | 200.788467 | 200.433444 |
| 20 | 6.62 | 199.321102 | 200.454591 | 203.028456 | 203.776849 | 201.947559 | 201.724978 | 201.374327 |
| 21 | 7.05 | 199.899897 | 199.565994 | 202.067651 | 202.817369 | 201.246355 | 201.182517 | 200.786681 |
| 22 | 7.75 | 202.422789 | 201.220654 | 203.940811 | 204.660141 | 203.136484 | 203.018673 | 202.567536 |

Table S9: Acid dissociation free energies calculated for the R-OH subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. $pK_a$ | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 23 | 11.60 | 209.037950 | 212.153040 | 212.827748 | 215.350180 | 214.700359 | 214.272191 | 214.132604 |
| 24 | 12.02 | 203.360314 | 209.041596 | 210.596351 | 212.344186 | 212.344332 | 212.290220 | 212.446469 |
| 25 | 12.43 | 205.591053 | 210.084215 | 211.232873 | 213.415284 | 212.838167 | 212.649483 | 212.477988 |
| 26 | 13.55 | 213.958350 | 210.499430 | 211.715152 | 213.443423 | 212.844100 | 213.060691 | 212.711728 |
| 27 | 14.80 | 212.755883 | 213.819875 | 213.857787 | 216.375618 | 216.161466 | 216.214021 | 215.977647 |
| 28 | 14.90 | 206.779384 | 210.887787 | 212.107666 | 213.578032 | 212.839351 | 213.880197 | 213.329939 |
| 29 | 15.10 | 207.896957 | 210.749159 | 211.682885 | 213.226716 | 212.567223 | 213.378013 | 212.944860 |
| 30 | 15.40 | 213.753676 | 213.389716 | 214.388939 | 216.399404 | 215.775155 | 215.873375 | 215.720534 |
| 31 | 15.52 | 214.508838 | 213.791948 | 214.627761 | 216.764668 | 216.185507 | 216.340681 | 216.112463 |
| 32 | 15.54 | 213.739857 | 215.114006 | 216.115700 | 217.298355 | 217.059246 | 217.216412 | 216.959534 |
| 33 | 15.90 | 214.702139 | 215.426546 | 215.627909 | 217.537746 | 217.365908 | 217.460453 | 217.239901 |
| 34 | 16.10 | 214.632956 | 215.172641 | 215.331292 | 217.516034 | 217.238437 | 217.338072 | 217.048762 |
| 35 | 16.84 | 216.691498 | 216.185789 | 216.064294 | 218.679743 | 218.370962 | 218.326296 | 217.985604 |
| 36 | 17.00 | 219.416616 | 217.732738 | 217.666263 | 220.146252 | 219.760677 | 219.638594 | 219.403941 |
| 37 | 17.10 | 217.044434 | 216.417537 | 216.357809 | 218.637530 | 218.352796 | 218.357526 | 218.125359 |

Table S10: Acid dissociation free energies calculated for the R-SH subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 38 | 7.86 | 201.513422 | 197.204107 | 200.535311 | 203.149968 | 200.376856 | 201.282013 | 200.487229 |
| 39 | 7.95 | 200.744478 | 197.560197 | 201.032557 | 203.610363 | 200.981917 | 201.772230 | 201.146538 |
| 40 | 8.62 | 197.982347 | 199.789849 | 202.831003 | 205.398865 | 202.862854 | 203.910627 | 203.192934 |
| 41 | 9.38 | 199.795227 | 199.388646 | 202.641670 | 205.149047 | 202.546244 | 203.468691 | 202.636618 |
| 42 | 9.72 | 200.321726 | 199.403833 | 202.474235 | 205.071624 | 202.498721 | 203.288284 | 202.776414 |
| 43 | 9.85 | 203.505379 | 200.171414 | 203.137848 | 205.511524 | 202.784151 | 203.496539 | 203.073069 |
| 44 | 9.96 | 202.798602 | 199.514601 | 202.934889 | 205.440851 | 202.889813 | 203.859737 | 203.115982 |
| 45 | 10.27[a] | 192.480106 | 195.384472 | 196.712235 | 198.982670 | 197.909141 | 197.695733 | 197.232550 |
| 46 | 10.33 | 202.177916 | 199.844077 | 203.075787 | 205.626446 | 203.226642 | 204.230034 | 203.539655 |
| 47 | 10.61 | 202.863657 | 200.188027 | 203.365549 | 205.854229 | 203.360012 | 204.306277 | 203.581392 |
| 48 | 10.67 | 202.560474 | 200.169139 | 203.484169 | 205.886284 | 203.351077 | 204.340194 | 203.448571 |
| 49 | 10.86 | 204.749428 | 200.931692 | 204.121264 | 206.458184 | 203.893087 | 204.787613 | 203.987366 |
| 50 | 11.05 | 206.692815 | 201.742469 | 205.029854 | 207.149297 | 204.527850 | 205.318580 | 204.514290 |
| 51 | 11.22 | 206.144958 | 202.106424 | 205.457969 | 207.503475 | 204.912029 | 205.715085 | 204.842760 |

[a] Alternative value found in the literature: 4.34

Table S11: Acid dissociation free energies calculated for the R-$NH_2$ subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 52 | 5.30 | 194.662725 | 195.110667 | 199.203321 | 198.511168 | 196.958901 | 196.647033 | 196.658606 |
| 53 | 9.34 | 200.736907 | 201.698589 | 205.778403 | 205.255248 | 203.562330 | 203.209171 | 203.054539 |
| 54 | 9.68 | 200.812020 | 201.875349 | 205.857766 | 205.373319 | 203.877945 | 203.545827 | 203.442054 |
| 55 | 9.80 | 202.076768 | 203.193613 | 207.069401 | 206.629577 | 204.941020 | 204.492905 | 204.287754 |
| 56 | 10.59 | 200.899498 | 203.124429 | 206.910425 | 206.458417 | 204.915422 | 204.536721 | 204.381489 |
| 57 | 10.60 | 200.942397 | 203.270006 | 207.041604 | 206.566662 | 205.049204 | 204.672601 | 204.540834 |
| 58 | 10.63 | 200.950249 | 203.857769 | 207.535744 | 206.913660 | 205.538895 | 205.199720 | 205.158102 |
| 59 | 10.68 | 202.832649 | 203.215633 | 207.199354 | 206.760641 | 205.015583 | 204.493889 | 204.248799 |
| 60 | 10.70 | 201.024693 | 203.361598 | 207.090920 | 206.576482 | 205.093298 | 204.717720 | 204.587262 |
| 61 | 11.23 | 201.674387 | 202.720452 | 206.812209 | 206.422595 | 204.656995 | 204.212218 | 203.901430 |

Table S12: Acid dissociation free energies calculated for the R2-NH subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 62 | 8.55 | 201.849709 | 202.414582 | 206.003067 | 205.920654 | 203.974036 | 203.623884 | 203.580596 |
| 63 | 10.54 | 201.227946 | 204.194754 | 207.610055 | 207.502593 | 205.651774 | 205.363595 | 205.331964 |
| 64 | 10.78 | 200.799674 | 204.185214 | 207.516458 | 207.324669 | 205.644248 | 205.396289 | 205.475774 |
| 65 | 11.00 | 200.836799 | 203.794234 | 207.348991 | 207.405619 | 205.280868 | 204.960347 | 204.751460 |
| 66 | 11.02 | 201.179214 | 203.867257 | 207.354168 | 207.319584 | 205.261270 | 204.981375 | 204.821812 |
| 67 | 11.22 | 200.934314 | 204.231320 | 207.783461 | 207.782240 | 205.819870 | 205.442119 | 205.359229 |
| 68 | 11.23 | 200.904716 | 203.697764 | 207.372827 | 207.507393 | 205.251683 | 204.971884 | 204.616073 |
| 69 | 11.27 | 200.789471 | 204.787758 | 208.244691 | 208.245968 | 206.310707 | 206.043943 | 205.956774 |

Table S13: Acid dissociation free energies calculated for the R3-N subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 70 | 9.69 | 202.133797 | 202.541872 | 205.824312 | 206.353399 | 203.694107 | 203.436760 | 203.403418 |
| 71 | 9.69 | 202.174824 | 202.607752 | 205.889439 | 206.400243 | 203.734311 | 203.472000 | 203.443435 |
| 72 | 9.80 | 201.855754 | 203.584649 | 206.441310 | 206.708106 | 204.692030 | 204.513669 | 204.784778 |
| 73 | 10.16 | 202.046195 | 203.667295 | 206.533912 | 206.921077 | 204.747218 | 204.512621 | 204.692042 |
| 74 | 10.75 | 202.087589 | 204.171933 | 207.322477 | 207.683954 | 205.212442 | 205.023919 | 204.942692 |

Table S14: Acid dissociation free energies calculated for the R-COOH subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 75 | -0.26 | 186.596023 | 189.584151 | 191.190858 | 193.438633 | 192.165648 | 191.749687 | 191.540387 |
| 76 | 0.65 | 187.217078 | 190.335127 | 192.228814 | 194.172398 | 193.221878 | 192.979023 | 192.817915 |
| 77 | 1.24 | 190.952639 | 191.503693 | 192.985112 | 195.283318 | 194.107245 | 193.765296 | 193.555324 |
| 78 | 1.30 | 190.268271 | 191.976924 | 193.714282 | 195.778907 | 194.686207 | 194.450449 | 194.185869 |
| 79 | 2.44 | 192.963036 | 193.677885 | 194.995400 | 196.791395 | 195.997114 | 195.827334 | 195.563628 |
| 80 | 2.66 | 195.186535 | 193.077929 | 194.341239 | 196.614303 | 195.739689 | 195.460850 | 195.159831 |
| 81 | 2.80 | 194.262459 | 193.903271 | 195.312008 | 197.435154 | 196.416501 | 196.224959 | 195.876856 |
| 82 | 2.81 | 194.102665 | 193.373608 | 194.826289 | 197.006985 | 196.254577 | 196.055042 | 195.924226 |
| 83 | 2.86 | 197.564805 | 194.943041 | 196.150567 | 198.250764 | 197.456045 | 197.350669 | 196.991985 |
| 84 | 2.86 | 192.344778 | 193.244529 | 194.886621 | 196.894354 | 195.988088 | 195.813211 | 195.688340 |
| 85 | 3.07 | 193.690388 | 194.165437 | 195.636043 | 197.808207 | 196.685958 | 196.357132 | 196.056207 |
| 86 | 3.53 | 194.041093 | 195.264270 | 196.336941 | 198.326374 | 197.743830 | 197.543932 | 197.420947 |
| 87 | 3.54 | 196.759069 | 193.806672 | 195.010781 | 197.457182 | 196.447698 | 196.257871 | 195.905411 |
| 88 | 3.75 | 195.042475 | 193.364806 | 194.416025 | 196.526145 | 195.620690 | 195.457764 | 195.309873 |
| 89 | 3.83 | 195.756453 | 194.341207 | 195.508787 | 197.436785 | 196.531545 | 196.279217 | 196.069921 |
| 90 | 3.87 | 196.412473 | 194.721480 | 195.883504 | 197.849754 | 196.746653 | 196.433137 | 196.264253 |
| 91 | 4.10 | 196.551424 | 195.598476 | 196.950613 | 199.115460 | 198.146830 | 197.897942 | 197.580953 |
| 92 | 4.26 | 198.818863 | 195.592421 | 196.923091 | 199.206608 | 198.028008 | 197.858047 | 197.351410 |
| 93 | 4.31 | 197.653624 | 196.159828 | 197.574794 | 199.764081 | 198.813777 | 198.639094 | 198.200909 |
| 94 | 4.35 | 197.805492 | 195.693588 | 197.072664 | 199.315251 | 198.299100 | 198.126832 | 197.741088 |
| 95 | 4.52 | 197.440755 | 196.064702 | 197.388578 | 199.621380 | 198.604710 | 198.403365 | 197.955825 |
| 96 | 4.76 | 198.994457 | 196.037076 | 197.172787 | 199.461770 | 198.478741 | 198.302242 | 197.890309 |
| 97 | 4.82 | 198.769803 | 196.466089 | 197.530190 | 199.815678 | 198.892160 | 198.714255 | 198.219475 |
| 98 | 4.87 | 199.450318 | 196.481917 | 197.638155 | 199.917711 | 198.963637 | 198.761792 | 198.321672 |
| 99 | 4.90 | 199.103301 | 196.892194 | 197.947430 | 200.239982 | 199.213837 | 198.983822 | 198.478865 |
| 100 | 5.05 | 199.595908 | 197.125912 | 198.416052 | 200.511514 | 199.514616 | 199.247195 | 198.814270 |

Table S15: Acid dissociation free energies calculated for the Ph-SH subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 101 | 4.72 | 197.033546 | 195.059912 | 198.265454 | 200.734142 | 198.561857 | 199.215724 | 199.156030 |
| 102 | 5.24 | 199.249799 | 195.553563 | 198.980015 | 201.498759 | 198.747066 | 199.508298 | 198.801346 |
| 103 | 5.30 | 197.301170 | 194.619619 | 198.036210 | 200.627683 | 197.829910 | 198.563839 | 197.791704 |
| 104 | 5.33 | 199.401909 | 195.891518 | 199.266352 | 201.755253 | 199.193037 | 199.955242 | 199.373430 |
| 105 | 5.78 | 198.849278 | 196.596119 | 200.028000 | 202.597159 | 199.855303 | 200.665167 | 199.809384 |
| 106 | 6.02 | 197.229989 | 196.910394 | 200.321703 | 202.841144 | 200.090615 | 200.926758 | 200.040078 |
| 107 | 6.14 | 199.716082 | 196.891931 | 200.293470 | 202.860053 | 200.084718 | 200.903387 | 200.023331 |
| 108 | 6.39 | 200.415895 | 197.056654 | 200.511001 | 203.122202 | 200.257067 | 201.114626 | 200.183583 |
| 109 | 6.61 | 200.970487 | 197.213209 | 200.621832 | 203.153199 | 200.347686 | 201.247112 | 200.342006 |
| 110 | 6.64 | 201.960016 | 198.309556 | 201.698159 | 204.247113 | 201.338604 | 202.174312 | 201.297490 |
| 111 | 6.66 | 201.461880 | 197.484687 | 200.949991 | 203.505544 | 200.661265 | 201.573652 | 200.636302 |
| 112 | 6.78 | 201.145213 | 197.339990 | 200.758663 | 203.336409 | 200.500669 | 201.383909 | 200.474405 |
| 113 | 6.82 | 201.361864 | 197.420360 | 200.848347 | 203.399052 | 200.567312 | 201.479556 | 200.550574 |

Table S16: Acid dissociation free energies calculated for the Ph-OH subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 114 | 6.79 | 200.909051 | 202.429487 | 204.152676 | 206.168918 | 205.486801 | 205.163560 | 205.060773 |
| 115 | 7.14 | 198.053483 | 198.836150 | 200.078007 | 201.997337 | 201.836901 | 201.733325 | 202.784103 |
| 116 | 7.23 | 198.102956 | 200.309466 | 202.169679 | 204.303421 | 203.573265 | 203.033084 | 203.460629 |
| 117 | 7.66 | 201.225078 | 200.399777 | 201.745554 | 203.623295 | 203.210437 | 203.289895 | 203.570396 |
| 118 | 7.95 | 202.430834 | 201.222793 | 202.643440 | 204.472998 | 203.854117 | 203.996638 | 204.025344 |
| 119 | 8.00 | 202.439794 | 203.354571 | 204.590906 | 206.544792 | 206.030941 | 206.147983 | 206.185827 |
| 120 | 8.35 | 200.314357 | 202.481770 | 203.742129 | 205.730118 | 205.162275 | 205.171284 | 205.291321 |
| 121 | 8.41 | 202.800699 | 201.983561 | 203.378937 | 205.364359 | 204.634294 | 204.716246 | 204.776999 |
| 122 | 8.47 | 202.901739 | 201.940665 | 203.326745 | 205.273611 | 204.614219 | 204.708433 | 204.755345 |
| 123 | 8.47 | 202.914083 | 202.054610 | 203.466496 | 205.454791 | 204.720244 | 204.809159 | 204.835410 |
| 124 | 8.48 | 200.732351 | 203.174012 | 204.787002 | 206.754617 | 205.918513 | 206.102403 | 205.846497 |
| 125 | 8.50 | 202.850103 | 202.178594 | 203.572808 | 205.563417 | 204.848121 | 204.905926 | 204.969904 |
| 126 | 8.61 | 201.455197 | 202.791743 | 204.152594 | 206.025486 | 205.419147 | 205.551595 | 205.495102 |
| 127 | 8.81 | 201.597007 | 203.270042 | 204.673838 | 206.866072 | 206.067836 | 206.172665 | 205.952450 |
| 128 | 9.02 | 203.784992 | 203.677294 | 205.053729 | 207.110087 | 206.394365 | 206.542248 | 206.326912 |
| 129 | 9.28 | 203.992254 | 204.014599 | 205.405886 | 207.384488 | 206.592663 | 206.734899 | 206.417153 |
| 130 | 9.38 | 203.913365 | 204.453703 | 205.760269 | 207.796545 | 207.020272 | 207.181536 | 206.896255 |
| 131 | 9.39 | 202.892311 | 201.999086 | 203.391296 | 205.338959 | 204.753884 | 204.816511 | 204.846531 |
| 132 | 9.44 | 206.139898 | 204.530905 | 205.981492 | 208.104759 | 207.115323 | 207.355594 | 206.901685 |
| 133 | 9.48 | 203.951068 | 203.067744 | 204.317215 | 206.174159 | 205.347011 | 205.492717 | 205.414120 |
| 134 | 9.51 | 207.136961 | 204.675435 | 206.060637 | 208.128706 | 207.258563 | 207.435002 | 207.397142 |
| 135 | 9.59 | 206.458170 | 204.815467 | 206.259067 | 208.454417 | 207.547574 | 207.786430 | 207.311187 |
| 136 | 9.65 | 206.185014 | 204.195202 | 205.671254 | 207.826849 | 206.829987 | 207.063988 | 206.615375 |
| 137 | 9.82 | 206.908367 | 204.360411 | 205.623428 | 207.736508 | 207.049218 | 207.288901 | 207.084507 |
| 138 | 9.83 | 206.280805 | 204.400741 | 205.741758 | 207.914112 | 207.225448 | 207.493145 | 207.101374 |
| 139 | 9.90 | 206.994444 | 204.624572 | 206.064881 | 208.257478 | 207.347454 | 207.676699 | 207.214600 |
| 140 | 9.92 | 203.335681 | 203.763221 | 205.126796 | 206.917016 | 205.854349 | 206.200276 | 205.905730 |
| 141 | 9.93 | 206.873409 | 205.405143 | 207.062397 | 208.951355 | 207.994706 | 208.222821 | 208.043097 |
| 142 | 9.93 | 207.177091 | 203.981825 | 205.403351 | 207.770903 | 206.908727 | 207.165891 | 206.855512 |
| 143 | 9.94 | 203.319712 | 203.950759 | 205.250647 | 207.300027 | 206.560739 | 206.654343 | 206.543176 |
| 144 | 9.95 | 204.033210 | 205.189412 | 206.363167 | 208.491469 | 207.793910 | 207.920622 | 207.707362 |
| 145 | 9.96 | 205.767361 | 205.888688 | 207.114265 | 209.308363 | 208.587830 | 208.815202 | 208.491318 |
| 146 | 9.98 | 207.871925 | 204.563042 | 205.912840 | 208.064297 | 207.175833 | 207.467089 | 207.168639 |
| 147 | 10.00 | 208.321447 | 205.102586 | 206.434088 | 208.649647 | 207.750016 | 208.030858 | 207.731961 |
| 148 | 10.08 | 208.157009 | 204.742900 | 206.194117 | 208.366908 | 207.418359 | 207.718866 | 207.327010 |
| 149 | 10.19 | 207.458478 | 205.455379 | 206.760528 | 208.965126 | 208.096394 | 208.378681 | 208.085396 |
| 150 | 10.20 | 206.108328 | 205.593426 | 206.814740 | 209.087135 | 208.292721 | 208.541468 | 207.971787 |
| 151 | 10.20 | 207.149732 | 205.619428 | 207.149234 | 209.035823 | 208.078584 | 208.314010 | 208.120948 |
| 152 | 10.28 | 207.359504 | 205.318367 | 206.773883 | 208.658450 | 207.794087 | 208.053897 | 207.791171 |

Table S17: Acid dissociation free energies calculated for the Ph-$NH_2$ subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | $r^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 153 | 0.28 | 186.352434 | 185.918123 | 190.501609 | 190.092091 | 188.573829 | 188.203735 | 189.819965 |
| 154 | 0.98 | 187.614365 | 187.339686 | 191.611497 | 191.136015 | 190.222450 | 190.032994 | 192.376690 |
| 155 | 2.04 | 191.657059 | 191.023414 | 195.888287 | 195.319056 | 193.530950 | 193.067341 | 193.933827 |
| 156 | 2.10 | 191.858795 | 191.428060 | 196.298579 | 195.792173 | 193.868773 | 193.466474 | 194.206269 |
| 157 | 2.16 | 191.510344 | 191.022385 | 195.875417 | 195.355095 | 193.488552 | 193.089035 | 193.860989 |
| 158 | 2.30 | 190.689464 | 189.693007 | 194.277294 | 193.496736 | 191.859737 | 191.742566 | 192.929457 |
| 159 | 2.32 | 190.415432 | 189.828727 | 194.399550 | 193.618925 | 192.065918 | 191.934243 | 193.117128 |
| 160 | 2.38 | 190.842596 | 189.956817 | 194.560882 | 193.827607 | 192.123648 | 192.001087 | 193.131425 |
| 161 | 2.45 | 189.554222 | 190.219545 | 194.654795 | 194.078453 | 192.443135 | 192.204487 | 193.122634 |
| 162 | 2.62 | 194.690857 | 190.812244 | 195.479375 | 195.062860 | 193.158640 | 192.930137 | 193.253127 |
| 163 | 2.96 | 191.232249 | 192.055582 | 196.542434 | 195.953707 | 194.152998 | 193.881475 | 194.302432 |
| 164 | 3.05 | 192.691402 | 192.564900 | 196.999123 | 196.455229 | 194.658868 | 194.467920 | 195.098420 |
| 165 | 3.32 | 194.033200 | 192.464149 | 196.990180 | 196.456369 | 194.591375 | 194.415943 | 194.841082 |
| 166 | 3.38 | 191.820806 | 192.645312 | 197.168956 | 196.547337 | 194.668107 | 194.450409 | 194.783292 |
| 167 | 3.56 | 192.531694 | 192.728222 | 197.163498 | 196.618027 | 194.804096 | 194.599016 | 195.223503 |
| 168 | 3.78 | 194.762281 | 193.451676 | 198.140076 | 197.642821 | 195.567227 | 195.355253 | 195.626544 |
| 169 | 3.81 | 194.220926 | 193.165135 | 197.593920 | 197.046057 | 195.264519 | 195.091429 | 195.431216 |
| 170 | 4.05 | 194.298369 | 193.848024 | 198.415374 | 197.923407 | 195.873345 | 195.724966 | 195.801258 |
| 171 | 4.17 | 194.953193 | 194.430868 | 198.952124 | 198.413019 | 196.380197 | 196.175725 | 196.262374 |
| 172 | 4.17 | 194.684914 | 194.278093 | 198.797094 | 198.335221 | 196.237144 | 196.004869 | 196.118692 |
| 173 | 4.20 | 194.753281 | 194.150250 | 198.693086 | 198.178903 | 196.095540 | 195.873846 | 196.008273 |
| 174 | 4.36 | 194.775272 | 194.044623 | 198.533093 | 197.931533 | 195.964487 | 195.791857 | 196.169753 |
| 175 | 4.38 | 195.822700 | 194.176737 | 198.678079 | 198.143214 | 196.193666 | 195.971592 | 196.275742 |
| 176 | 4.40 | 194.378135 | 194.323279 | 198.646092 | 198.299945 | 196.328950 | 196.274743 | 195.960799 |
| 177 | 4.47 | 196.700665 | 194.654769 | 199.115231 | 198.724586 | 196.756076 | 196.508005 | 196.823669 |
| 178 | 4.49 | 196.405521 | 194.523212 | 198.991885 | 198.549811 | 196.701224 | 196.455912 | 196.719847 |
| 179 | 4.52 | 193.037499 | 194.317726 | 198.594989 | 198.085386 | 196.366146 | 196.104195 | 196.454543 |
| 180 | 4.64 | 195.957433 | 194.502122 | 198.974994 | 198.420989 | 196.526243 | 196.363521 | 196.621676 |
| 181 | 4.67 | 195.089093 | 194.691317 | 199.156655 | 198.563246 | 196.642274 | 196.497927 | 196.725906 |
| 182 | 4.72 | 196.971706 | 195.059484 | 199.515060 | 199.076705 | 197.182708 | 196.905277 | 197.162978 |
| 183 | 5.07 | 195.168492 | 195.176196 | 199.518231 | 198.940599 | 197.144803 | 196.989605 | 197.237486 |
| 184 | 5.25 | 195.691837 | 196.133112 | 200.435560 | 200.027464 | 198.044452 | 197.771375 | 198.047211 |
| 185 | 5.29 | 195.488759 | 196.002540 | 200.296759 | 199.873124 | 197.916370 | 197.629734 | 197.930709 |
| 186 | 5.50 | 195.497038 | 196.214509 | 200.477383 | 200.044710 | 198.220842 | 197.941816 | 198.126742 |

Table S18: Acid dissociation free energies calculated for the Ph-COOH subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 187 | 2.17 | 195.593567 | 192.544080 | 194.131094 | 196.380730 | 195.259439 | 195.007026 | 194.847357 |
| 188 | 2.94 | 195.895702 | 194.479705 | 195.960207 | 198.027235 | 197.128882 | 197.124409 | 196.240295 |
| 189 | 2.95 | 195.535872 | 192.550045 | 194.496704 | 195.378276 | 193.762134 | 195.139789 | 194.659183 |
| 190 | 2.98 | 197.099556 | 194.635076 | 196.275048 | 198.212432 | 196.857458 | 196.905173 | 196.162863 |
| 191 | 3.27 | 196.440701 | 195.249445 | 196.545804 | 198.654662 | 197.819287 | 197.692827 | 196.866082 |
| 192 | 3.45 | 196.986370 | 194.750711 | 196.392409 | 198.394074 | 197.156717 | 196.943227 | 196.468812 |
| 193 | 3.46 | 197.899793 | 195.596055 | 197.201981 | 199.231243 | 198.111047 | 197.939219 | 197.366377 |
| 194 | 3.51 | 197.735929 | 195.161528 | 196.816027 | 198.863780 | 197.601974 | 197.401534 | 196.825259 |
| 195 | 3.54 | 197.999338 | 195.409908 | 197.044377 | 199.104897 | 197.823876 | 197.614199 | 197.061466 |
| 196 | 3.77 | 198.091297 | 196.174383 | 197.357330 | 199.462400 | 198.508515 | 198.560171 | 197.610272 |
| 197 | 3.83 | 198.036197 | 195.533359 | 197.172165 | 199.274165 | 197.984870 | 197.776183 | 197.187298 |
| 198 | 3.87 | 197.908003 | 195.655625 | 197.264981 | 199.342779 | 198.052238 | 197.838347 | 197.211545 |
| 199 | 3.91 | 198.032368 | 195.904056 | 197.068309 | 199.109113 | 198.344541 | 198.451497 | 197.348222 |
| 200 | 3.99 | 198.729355 | 195.740632 | 197.363103 | 199.485730 | 198.166584 | 197.967542 | 197.292710 |
| 201 | 4.08 | 198.641259 | 196.229263 | 197.855069 | 199.980228 | 198.638817 | 198.428678 | 197.707353 |
| 202 | 4.09 | 198.361167 | 195.494009 | 196.621369 | 198.882721 | 198.042130 | 198.077713 | 196.825011 |
| 203 | 4.09 | 198.685519 | 196.067369 | 197.698475 | 199.820042 | 198.471160 | 198.262409 | 197.540213 |
| 204 | 4.14 | 198.520598 | 196.021934 | 197.596123 | 199.710525 | 198.446139 | 198.239135 | 197.576068 |
| 205 | 4.17 | 198.571529 | 196.062118 | 197.691920 | 199.823306 | 198.456048 | 198.253627 | 197.525179 |
| 206 | 4.21 | 198.001872 | 195.205792 | 196.353425 | 198.614193 | 197.767267 | 197.830152 | 196.474136 |
| 207 | 4.24 | 199.191224 | 196.340598 | 197.948618 | 200.066568 | 198.745040 | 198.567333 | 197.876445 |
| 208 | 4.34 | 199.100048 | 196.484473 | 198.044803 | 200.188864 | 198.864235 | 198.677088 | 197.986557 |
| 209 | 4.35 | 199.034183 | 196.381257 | 198.007029 | 200.104997 | 198.792321 | 198.611338 | 197.894593 |
| 210 | 4.35 | 199.051093 | 196.525333 | 198.106532 | 200.226503 | 198.928613 | 198.759182 | 198.032216 |
| 211 | 4.45 | 199.357707 | 196.916548 | 198.480738 | 200.682125 | 199.255111 | 199.039896 | 198.270377 |
| 212 | 4.47 | 199.272296 | 196.758994 | 198.331906 | 200.515455 | 199.129737 | 198.924348 | 198.146680 |
| 213 | 4.58 | 199.251745 | 196.945246 | 198.494937 | 200.688812 | 199.314401 | 199.096561 | 198.315641 |
| 214 | 4.92 | 197.224953 | 194.686107 | 196.360924 | 198.378938 | 197.074146 | 196.834805 | 196.394891 |

Table S19: Acid dissociation free energies calculated for the R-C-H subset of TR224. Various levels of theory are shown. All DFT methods employ COSMO-RS implicit solvation, GFN2-xTB uses ALPB implicit solvation.

| Nr. | exp. pKa | GFN2-xTB | r$^2$SCAN-3c | B97-3c | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ B97-D | PBE0-D3 | PW6B95-D3 | $\omega$B97X-V |
|---|---|---|---|---|---|---|---|---|
| 215 | 9.90 | 201.812041 | 203.531214 | 206.613864 | 207.523152 | 205.575771 | 205.944535 | 209.056243 |
| 216 | 10.40 | 199.331032 | 204.162891 | 206.424802 | 207.738451 | 206.655999 | 206.776807 | 209.759801 |
| 217 | 10.50 | 196.584359 | 204.004173 | 207.327558 | 208.412228 | 206.096227 | 206.579712 | 209.494424 |
| 218 | 11.50 | 198.202156 | 203.758310 | 206.988746 | 208.067598 | 205.839274 | 206.195696 | 209.508460 |
| 219 | 13.10 | 201.085907 | 205.600759 | 208.132871 | 209.079514 | 207.965298 | 208.390748 | 210.695094 |
| 220 | 14.80 | 210.016244 | 208.569445 | 210.609520 | 211.853374 | 210.759149 | 211.085392 | 213.417162 |
| 221 | 16.70 | 206.453168 | 209.447682 | 212.004739 | 212.732900 | 211.711031 | 212.118604 | 213.081832 |
| 222 | 18.30 | 210.682116 | 213.011765 | 215.893633 | 216.756786 | 215.176947 | 215.576407 | 215.972555 |
| 223 | 19.20 | 212.059500 | 214.049231 | 216.946529 | 217.760383 | 216.091307 | 216.488731 | 216.838420 |
| 224 | 19.30 | 211.829018 | 213.164619 | 215.708822 | 216.558276 | 215.306788 | 215.615683 | 216.385332 |

## 3.5 Appendix: Flexible drug molecules

Table S20: CFER parameters determined for r$^2$SCAN-3c/COSMO-RS, GFN2-xTB+$E_{mod}^{\mathrm{TB}}$/ALPB and B97-3c/COSMO-RS from the drug and SAMPL6 set.

| | CFER parameters | | | |
|---|---|---|---|---|
| | $c_1$ | $c_2$ | $c_3$ | $c_4$ |
| r$^2$SCAN-3c | 37659.112434 | -568.698226 | 2.858687 | -0.004782 |
| GFN2-xTB | 12284.084912 | -186.207085 | 0.938732 | -0.001573 |
| B97-3c | 34751.943849 | -515.624632 | 2.546401 | -0.004185 |

### 3.5.1 Appendix: Drug benchmark set

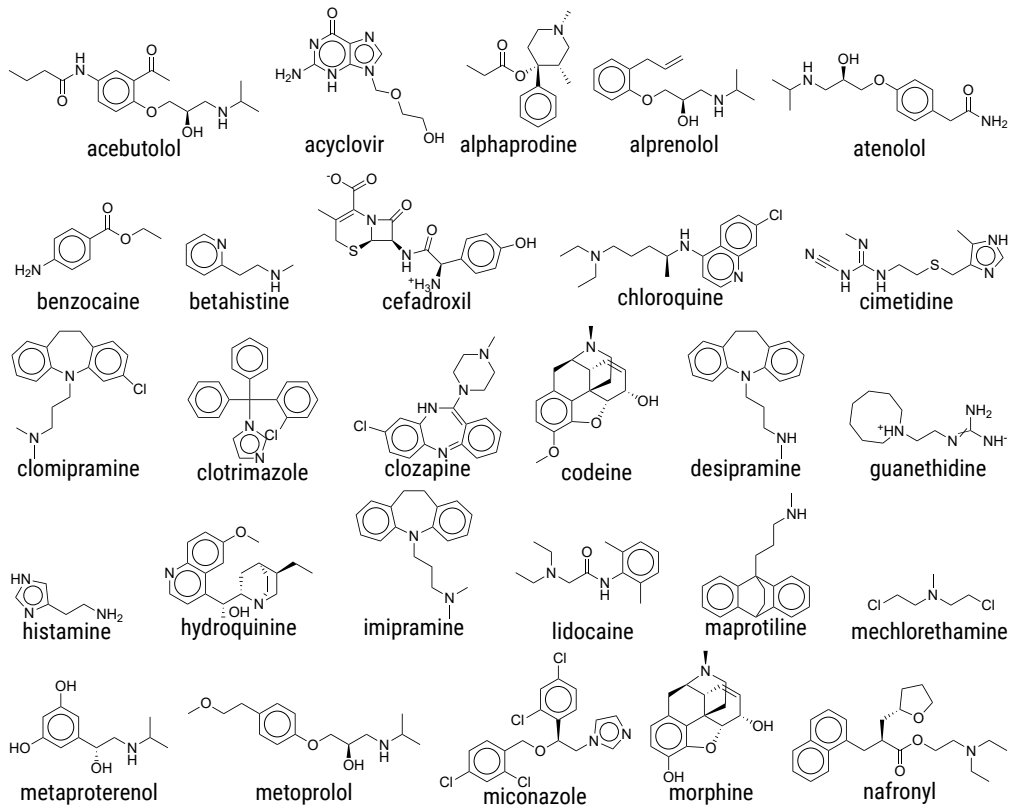


Figure S1: Investigated drug molecules in their neutral protonation state (pt. 1)

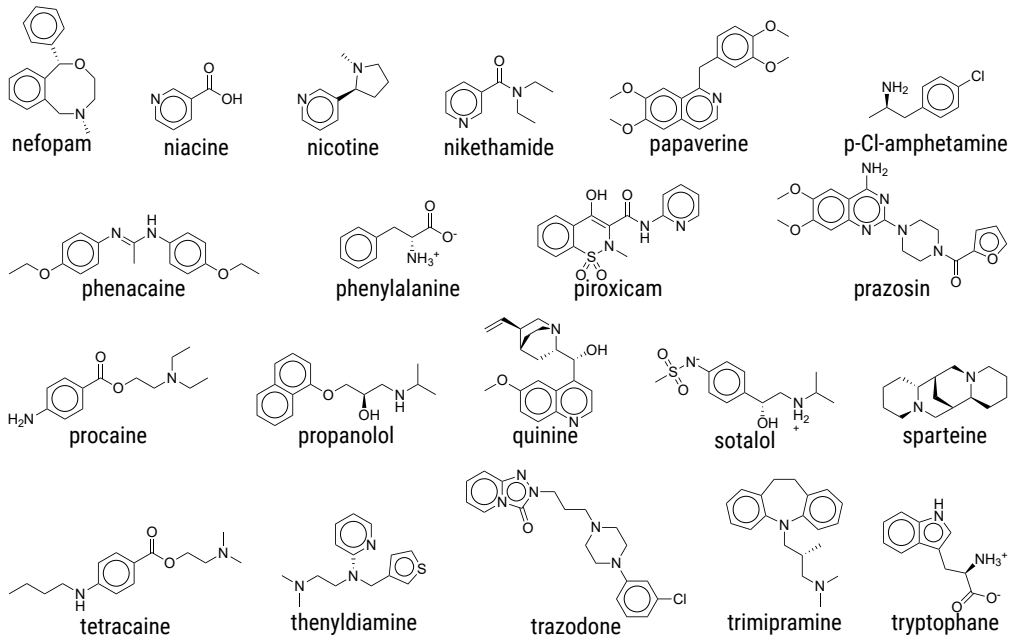


Figure S2: Investigated drug molecules in their neutral protonation state (pt. 2)

Table S21: Acid dissociation free energies for the flexible drug benchmark set at the r$^2$SCAN-3c/COSMO-RS, GFN2-xTB+$E_{mod}^{\mathrm{TB}}$/ALPB and B97-3c/COSMO-RS level.

| | | | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ | | |
|---|---|---|---|---|---|
| | | exp. p$K_a$ | r$^2$SCAN-3c | GFN2-xTB | B97-3c |
| 1 | acebutolol | 9.50 | 203.998707 | 205.860197 | 207.372498 |
| 2 | acyclovir | 2.20 | 193.537952 | 194.735579 | 196.478811 |
| 3 | alphaprodine | 8.70 | 201.323400 | 200.604678 | 204.752763 |
| 4 | alprenolol | 9.60 | 203.023857 | 202.389308 | 206.796334 |
| 5 | atenolol | 9.60 | 202.228354 | 202.096999 | 205.836038 |
| 6 | benzocaine | 2.50 | 190.092551 | 190.332008 | 194.721840 |
| 7 | betahistine | 10.00 | 203.299444 | 205.772887 | 206.920214 |
| 8 | betahistine+ | 3.90 | 195.966529 | 191.969840 | 198.939911 |
| 9 | cefadroxil- | 7.00 | 198.919657 | 196.614623 | – |
| 10 | chloroquine | 10.60 | 202.416045 | 205.017334 | 205.689354 |
| 11 | cimetidine0 | 6.80 | 207.180120[a] | 198.776353 | 209.662065[a] |
| 12 | clomipramine | 9.40 | 202.024218 | 202.836156 | 205.279785 |
| 13 | clotrimazole | 5.80 | 198.189084 | 197.644979 | 201.090956 |
| 14 | clozapine | 7.50 | 197.981240 | 198.344544 | 201.161951 |
| 15 | clozapine+ | 3.90 | 197.786666 | 199.394335 | 201.059971 |
| 16 | codeine | 8.10 | 200.208203 | 199.190383 | 203.789814 |
| 17 | desipramine | 10.30 | 202.842364 | 200.848801 | 206.500956 |
| 18 | guanethidine | 11.40 | 206.652562 | 207.892505 | 209.163574 |
| 19 | histamine | 9.70 | 202.509310 | 205.919226 | 206.529420 |
| 20 | hydroquinine | 9.10 | 202.078423 | 200.093147 | 205.810353 |
| 21 | hydroquinine+ | 4.10 | 197.535923 | 197.187386 | 200.556105 |
| 22 | imipramine | 9.60 | 202.094964 | 202.680539 | 205.520923 |
| 23 | labetalol | 9.30 | 201.255348 | 202.119568 | 205.264672 |
| 24 | lidocaine | 7.90 | 199.315283 | 200.462297 | 202.126331 |
| 25 | maprotiline | 10.30 | 202.912397 | 201.173762 | 206.569462 |
| 26 | mechlorethamine | 6.40 | 199.659045 | 196.842763 | 203.082943 |
| 27 | metaproterenol | 9.90 | 202.157590 | 202.727757 | 205.888678 |
| 28 | metoprolol | 9.60 | 202.354476 | 202.324562 | 205.981459 |
| 29 | miconazole | 6.40 | 198.888428 | 197.999825 | 201.487964 |
| 30 | morphine | 8.20 | 200.089781 | 199.087744 | 203.698130 |
| 31 | nafronyl | 9.10 | 201.368051 | 203.486634 | 204.838803 |
| 32 | nefopam | 8.50 | 201.101947 | 199.896133 | 204.512113 |
| 33 | niacine- | 4.80 | 198.139303 | 196.226316 | 200.727399 |
| 34 | nicotine | 8.10 | 199.950574 | 199.217766 | 203.361273 |
| 35 | nicotine+ | 4.80 | 196.049681 | 194.425384 | 198.801962 |
| 36 | nikethamide | 3.50 | 196.261462 | 194.280926 | 199.013279 |
| 37 | papaverine | 8.07 | 200.302895 | 200.118983 | 203.176066 |
| 38 | p-Cl-amphetamine | 9.90 | 201.462146 | 202.605859 | 205.622131 |
| 39 | phenacaine | 9.30 | 203.342334 | 201.367618 | 206.335734 |
| 40 | phenylalanine- | 8.90 | 200.257527 | 201.986584 | 204.182521 |
| 41 | piroxicam | 5.30 | 196.269551 | 196.566943 | 199.272837 |
| 42 | prazosin | 7.00 | 200.412901 | 195.957535 | 203.652849 |
| 43 | procaine | 9.10 | 202.487330 | 202.545609 | 205.990229 |
| 44 | procaine+ | 2.00 | 189.181533 | 188.538912 | 193.668393 |
| 45 | propanolol | 9.60 | 202.004559 | 206.336238 | 205.704995 |
| 46 | quinine | 8.50 | 201.399294 | 199.821850 | 205.092518 |
| 47 | sotalol | 9.30 | 201.737329 | 203.085999 | 205.437554 |
| 48 | sparteine | 12.00 | 207.046798 | 208.899822 | 210.762596 |
| 49 | tetracaine | 8.50 | 202.331854 | 201.834995 | 205.640921 |
| 50 | thenyldiamine | 8.90 | 203.381151 | 203.379449 | 207.017171 |
| 51 | trazodone | 6.80 | 198.663543 | 204.212586 | 203.128758 |
| 52 | trimipramine | 9.40 | 201.964598 | 198.617859 | 205.630875 |
| 53 | tryptophan- | 9.10 | 201.749066 | 202.988346 | 205.649437 |

[a] neglected outlier

Table S22: Minimum and maximum acid dissociation constants calculated for the flexible drug benchmark set at the B97-3c/COSMO-RS, r$^2$SCAN-3c/COSMO-RS and GFN2-xTB+$E^{\mathrm{TB}}_{mod}$/ALPB level. All pKa values in this table were obtained using the CFER parameters fitted on the TR224 set.

| | | | r$^2$SCAN-3c | | GFN2-xTB | | B97-3c | |
|---|---|---|---|---|---|---|---|---|
| | | exp. p$K_a$ | min. p$K_a$ | max. p$K_a$ | min. p$K_a$ | max. p$K_a$ | min. p$K_a$ | max. p$K_a$ |
| 1 | acebutolol | 9.50 | 8.93 | 11.60 | 7.26 | 14.13 | 9.45 | 12.57 |
| 2 | acyclovir | 2.20 | 2.42 | 4.53 | 1.75 | 6.96 | 2.43 | 4.84 |
| 3 | alphaprodine | 8.70 | 7.63 | 9.08 | 3.84 | 11.07 | 8.47 | 9.51 |
| 4 | alprenolol | 9.60 | 8.22 | 10.85 | 5.47 | 12.19 | 9.06 | 12.04 |
| 5 | atenolol | 9.60 | 7.71 | 10.31 | 4.75 | 12.31 | 8.57 | 11.35 |
| 6 | benzocaine | 2.50 | 1.33 | 2.00 | 0.94 | 1.94 | 2.06 | 2.79 |
| 7 | betahistine | 10.00 | 9.49 | 10.42 | 10.62 | 13.06 | 10.31 | 11.26 |
| 8 | betahistine+ | 3.90 | 4.07 | 4.94 | 1.28 | 2.70 | 4.26 | 5.18 |
| 9 | cefadroxil | 7.00 | 6.28 | 7.56 | 1.79 | 10.71 | – | – |
| 10 | chloroquine | 10.60 | 7.79 | 10.39 | 7.35 | 13.85 | 8.25 | 10.98 |
| 11 | cimetidine | 6.80 | 11.32[a] | 13.06[a] | 3.52 | 9.82 | 11.6[a] | 13.39[a] |
| 12 | clomipramine | 9.40 | 7.65 | 10.05 | 5.84 | 12.87 | 8.18 | 10.47 |
| 13 | clotrimazole | 5.80 | 5.46 | 6.74 | 4.61 | 6.83 | 5.65 | 6.93 |
| 14 | clozapine | 7.50 | 5.74 | 6.52 | 3.70 | 8.57 | 6.09 | 6.89 |
| 15 | clozapine+ | 3.90 | 4.78 | 6.31 | 4.07 | 9.03 | 5.30 | 6.80 |
| 16 | codeine | 8.10 | 6.81 | 8.66 | 4.27 | 9.15 | 7.49 | 9.38 |
| 17 | desipramine | 10.30 | 7.92 | 10.40 | 4.72 | 11.83 | 8.78 | 11.40 |
| 18 | guanethidine | 11.40 | 10.68 | 12.96 | 8.67 | 14.89 | 10.78 | 13.69 |
| 19 | histamine | 9.70 | 8.86 | 9.89 | 10.97 | 12.81 | 9.96 | 11.26 |
| 20 | hydroquinine | 9.10 | 7.64 | 10.11 | 4.10 | 10.42 | 8.67 | 11.11 |
| 21 | hydroquinine+ | 4.10 | 4.73 | 6.96 | 2.59 | 9.40 | 4.97 | 7.13 |
| 22 | imipramine | 9.60 | 7.80 | 9.81 | 5.77 | 12.95 | 8.33 | 10.42 |
| 23 | labetalol | 9.30 | 7.24 | 9.63 | 5.56 | 12.06 | 8.16 | 10.91 |
| 24 | lidocaine | 7.90 | 6.10 | 7.86 | 3.99 | 10.55 | 6.27 | 8.10 |
| 25 | maprotiline | 10.30 | 7.98 | 10.76 | 4.32 | 11.78 | 8.84 | 11.59 |
| 26 | mechlorethamine | 6.40 | 5.95 | 8.23 | 2.21 | 6.11 | 6.45 | 8.62 |
| 27 | metaproterenol | 9.90 | 7.63 | 10.10 | 5.53 | 12.01 | 8.54 | 11.31 |
| 28 | metoprolol | 9.60 | 7.81 | 10.39 | 5.03 | 12.12 | 8.53 | 11.62 |
| 29 | miconazole | 6.40 | 5.75 | 7.77 | 3.37 | 11.44 | 5.30 | 8.08 |
| 30 | morphine | 8.20 | 6.96 | 8.57 | 4.17 | 8.95 | 7.61 | 9.26 |
| 31 | nafronyl | 9.10 | 7.29 | 9.67 | 6.36 | 12.33 | 7.92 | 10.39 |
| 32 | nefopam | 8.50 | 7.37 | 9.27 | 4.15 | 9.68 | 7.90 | 10.21 |
| 33 | niacine | 4.80 | 6.18 | 6.18 | 4.57 | 4.57 | 6.16 | 6.16 |
| 34 | nicotine | 8.10 | 7.09 | 8.85 | 4.33 | 9.26 | 7.65 | 9.58 |
| 35 | nicotine+ | 4.80 | 3.61 | 5.18 | 2.17 | 5.57 | 3.53 | 5.27 |
| 36 | nikethamide | 3.50 | 4.22 | 5.69 | 1.59 | 6.46 | 4.30 | 5.78 |
| 37 | papaverine | 8.07 | 7.19 | 8.74 | 4.91 | 10.67 | 7.48 | 8.91 |
| 38 | p-Cl-amphetamine | 9.90 | 7.74 | 9.10 | 5.98 | 12.26 | 8.91 | 10.39 |
| 39 | phenacaine | 9.30 | 8.34 | 10.76 | 5.93 | 10.65 | 8.74 | 11.58 |
| 40 | phenylalanine | 8.90 | 7.26 | 8.54 | 6.04 | 10.38 | 8.19 | 9.52 |
| 41 | piroxicam | 5.30 | 4.92 | 5.68 | 2.50 | 7.23 | 5.16 | 6.15 |
| 42 | prazosin | 7.00 | 6.85 | 8.38 | 1.77 | 9.38 | 7.29 | 8.94 |
| 43 | procaine | 9.10 | 7.93 | 10.54 | 4.73 | 12.42 | 8.42 | 11.24 |
| 44 | procaine+ | 2.00 | 0.58 | 2.12 | 0.93 | 3.40 | 0.86 | 3.09 |
| 45 | propanolol | 9.60 | 7.27 | 10.27 | 4.85 | 14.01 | 8.13 | 11.28 |
| 46 | quinine | 8.50 | 7.16 | 9.68 | 4.14 | 9.84 | 8.00 | 10.67 |
| 47 | sotalol | 9.30 | 7.36 | 10.04 | 5.42 | 12.29 | 8.11 | 11.25 |
| 48 | sparteine | 12.00 | 12.24 | 12.24 | 10.61 | 15.57 | 13.33 | 13.33 |
| 49 | tetracaine | 8.50 | 7.71 | 10.17 | 4.55 | 10.70 | 8.12 | 10.70 |
| 50 | thenyldiamine | 8.90 | 8.63 | 10.78 | 5.85 | 12.07 | 9.50 | 11.73 |
| 51 | trazodone | 6.80 | 5.46 | 7.73 | 5.80 | 13.21 | 6.32 | 9.08 |
| 52 | trimipramine | 9.40 | 7.88 | 9.98 | 3.47 | 13.01 | 8.41 | 10.91 |
| 53 | tryptophane | 9.10 | 7.69 | 9.82 | 6.88 | 12.45 | 8.61 | 10.98 |
| | MAD | – | 1.23 | 0.92 | 3.25 | 2.58 | 0.82 | 1.57 |
| | RMSD | – | 1.40 | 1.13 | 3.57 | 2.92 | 0.96 | 1.73 |

[a] neglected outlier

### 3.5.2 Appendix: SAMPL6 benchmark set

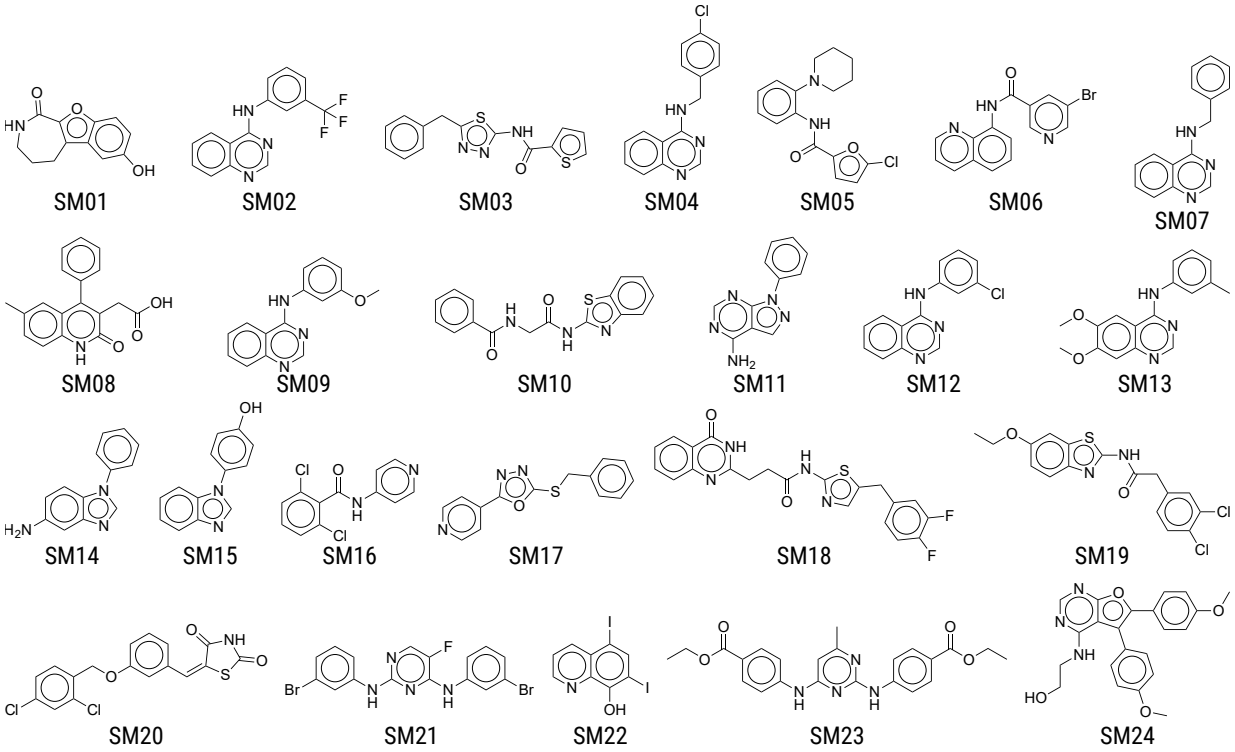


Figure S3: Investigated SAMPL6 molecules in their neutral protonation state

Table S23: Acid dissociation free energies for the SAMPL6 benchmark set at the r$^2$SCAN-3c/COSMO-RS, GFN2-xTB+$E_{mod}^{\mathrm{TB}}$/ALPB and B97-3c/COSMO-RS level.

| | | | $\frac{\Delta G'_{diss}}{RT\ln(10)}$ | | |
|---|---|---|---|---|---|
| | | exp. p$K_a$ | r$^2$SCAN-3c | GFN2-xTB | B97-3c |
| 1 | SM01- | 9.53 | 204.873812 | 205.840476 | 206.124628 |
| 2 | SM02 | 5.03 | 198.268219 | 196.235418 | 201.237057 |
| 3 | SM03- | 7.02 | 199.798406 | 192.099444 | 202.804185 |
| 4 | SM04 | 6.02 | 198.914314 | 198.113983 | 201.700387 |
| 5 | SM05 | 4.59 | 195.792115 | 187.282571 | 199.433817 |
| 6 | SM06 | 3.03 | 193.373074 | 193.566269 | 196.514900 |
| 7 | SM06- | 11.74 | 207.109076 | 206.161299 | 209.349298 |
| 8 | SM07 | 6.08 | 199.083159 | 197.851320 | 201.993863 |
| 9 | SM08- | 4.22 | 195.583327 | 193.591560 | 197.612225 |
| 10 | SM09 | 5.37 | 198.589074 | 196.967774 | 201.548259 |
| 11 | SM10- | 9.02 | 201.601089 | 192.243970 | 204.497921 |
| 12 | SM11 | 3.89 | 195.432361 | 192.575935 | 198.262989 |
| 13 | SM12 | 5.28 | 198.181950 | 197.073423 | 201.130245 |
| 14 | SM13 | 5.77 | 199.453897 | 197.661042 | 202.278515 |
| 15 | SM14+ | 2.58 | 190.727305 | 189.962271 | 195.137044 |
| 16 | SM14 | 5.30 | 198.753585 | 200.324025 | 201.776296 |
| 17 | SM15 | 4.70 | 197.245681 | 195.917449 | 200.248178 |
| 18 | SM15- | 8.94 | 204.140073 | 205.221013 | 205.506767 |
| 19 | SM16 | 5.37 | 198.551263 | 198.524350 | 201.257822 |
| 20 | SM16- | 10.65 | 204.243065 | 199.121457 | 206.322877 |
| 21 | SM17 | 3.16 | 196.602559 | 195.948580 | 199.256822 |
| 22 | SM18 | 2.15 | 192.568925 | 191.328006 | 196.596531 |
| 23 | SM18_2 | 9.58 | 203.343184 | 203.755478 | 204.765284 |
| 24 | SM18- | 11.02 | 203.901229 | 193.945662 | 206.037370 |
| 25 | SM19- | 9.56 | 203.134766 | 196.349667 | 205.916339 |
| 26 | SM20- | 5.70 | 198.744610 | 188.908059 | 201.788779 |
| 27 | SM21 | 3.86 | 195.570797 | 189.335496 | 198.671954 |
| 28 | SM22 | 2.40 | 193.626473 | 187.303665 | 196.667554 |
| 29 | SM22- | 7.43 | 201.186391 | 200.328920 | 203.166492 |
| 30 | SM23 | 4.52 | 196.821424 | 195.738072 | 199.830464 |
| 31 | SM24 | 2.60 | 193.653266 | 192.941149 | 195.872067 |

Table S24: Minimum and maximum acid dissociation constants calculated for the SAMPL6 benchmark set at the B97-3c/COSMO-RS, r$^2$SCAN-3c/COSMO-RS and GFN2-xTB+$E_{mod}^{TB}$/ALPB level. All pKa values in this table were obtained using the CFER parameters fitted on the TR224 set.

| | | | r$^2$SCAN-3c | | GFN2-xTB | | B97-3c | |
|---|---|---|---|---|---|---|---|---|
| | | exp. p$K_a$ | min. p$K_a$ | max. p$K_a$ | min. p$K_a$ | max. p$K_a$ | min. p$K_a$ | max. p$K_a$ |
| 1 | SM01- | 9.53 | 10.78 | 10.82 | 9.82 | 13.95 | 9.96 | 9.99 |
| 2 | SM02 | 5.03 | 6.13 | 7.33 | 2.77 | 5.93 | 6.24 | 7.33 |
| 3 | SM03- | 7.02 | 6.32 | 8.01 | 1.64 | 3.24 | 6.52 | 8.62 |
| 4 | SM04 | 6.02 | 6.37 | 7.01 | 3.73 | 8.58 | 6.38 | 7.26 |
| 5 | SM05 | 4.59 | 4.17 | 5.54 | 0.93 | 2.06 | 4.76 | 6.28 |
| 6 | SM06 | 3.03 | 2.54 | 3.46 | 1.41 | 4.30 | 2.93 | 3.66 |
| 7 | SM06- | 11.74 | 11.97 | 13.17 | 9.82 | 12.87 | 12.01 | 14.05 |
| 8 | SM07 | 6.08 | 6.46 | 7.06 | 3.69 | 8.02 | 6.73 | 7.37 |
| 9 | SM08- | 4.22 | 4.21 | 4.76 | 1.64 | 3.43 | 3.37 | 4.37 |
| 10 | SM09 | 5.37 | 5.47 | 7.39 | 3.15 | 7.20 | 5.97 | 7.41 |
| 11 | SM10- | 9.02 | 7.83 | 9.37 | 1.28 | 6.05 | 7.96 | 9.54 |
| 12 | SM11 | 3.89 | 4.44 | 4.44 | 2.61 | 2.61 | 4.53 | 4.53 |
| 13 | SM12 | 5.28 | 5.96 | 7.15 | 3.34 | 7.31 | 6.20 | 7.14 |
| 14 | SM13 | 5.77 | 6.57 | 7.42 | 3.28 | 7.58 | 7.00 | 7.54 |
| 15 | SM14+ | 2.58 | 1.86 | 1.93 | 1.18 | 2.12 | 2.59 | 2.69 |
| 16 | SM14 | 5.30 | 6.50 | 7.02 | 6.34 | 8.38 | 6.78 | 7.23 |
| 17 | SM15 | 4.70 | 5.28 | 5.90 | 3.60 | 5.28 | 5.54 | 6.11 |
| 18 | SM15- | 8.94 | 10.05 | 10.38 | 9.58 | 10.75 | 9.32 | 9.61 |
| 19 | SM16 | 5.37 | 6.35 | 7.57 | 5.36 | 8.32 | 6.38 | 7.21 |
| 20 | SM16- | 10.65 | 9.19 | 11.48 | 4.75 | 10.02 | 9.41 | 11.78 |
| 21 | SM17 | 3.16 | 4.65 | 5.56 | 2.65 | 6.36 | 4.78 | 5.56 |
| 22 | SM18 | 2.15 | 2.13 | 3.68 | 0.93 | 5.50 | 2.18 | 4.42 |
| 23 | SM18_2 | 9.58 | 8.78 | 10.61 | 5.07 | 12.23 | 7.97 | 10.61 |
| 24 | SM18- | 11.02 | 9.16 | 10.98 | 1.08 | 7.94 | 8.85 | 11.00 |
| 25 | SM19- | 9.56 | 8.34 | 10.77 | 1.99 | 6.79 | 8.50 | 10.98 |
| 26 | SM20- | 5.70 | 5.56 | 7.50 | 0.93 | 3.36 | 5.90 | 7.89 |
| 27 | SM21 | 3.86 | 3.98 | 5.52 | 0.94 | 2.59 | 4.12 | 5.94 |
| 28 | SM22 | 2.40 | 3.38 | 3.38 | 1.02 | 1.02 | 3.54 | 3.54 |
| 29 | SM22- | 7.43 | 8.26 | 8.26 | 7.27 | 7.27 | 7.85 | 7.85 |
| 30 | SM23 | 4.52 | 4.36 | 6.59 | 2.68 | 7.24 | 4.57 | 6.91 |
| 31 | SM24 | 2.60 | 2.66 | 4.12 | 1.20 | 5.33 | 2.32 | 4.04 |
| | MAD | – | 0.71 | 1.27 | 2.72 | 2.08 | 0.73 | 1.37 |
| | RMSD | – | 0.86 | 1.41 | 3.61 | 2.33 | 0.91 | 1.55 |