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Fitting quantum machine learning potentials to experimental free energy data: Predicting tautomer ratios in solution

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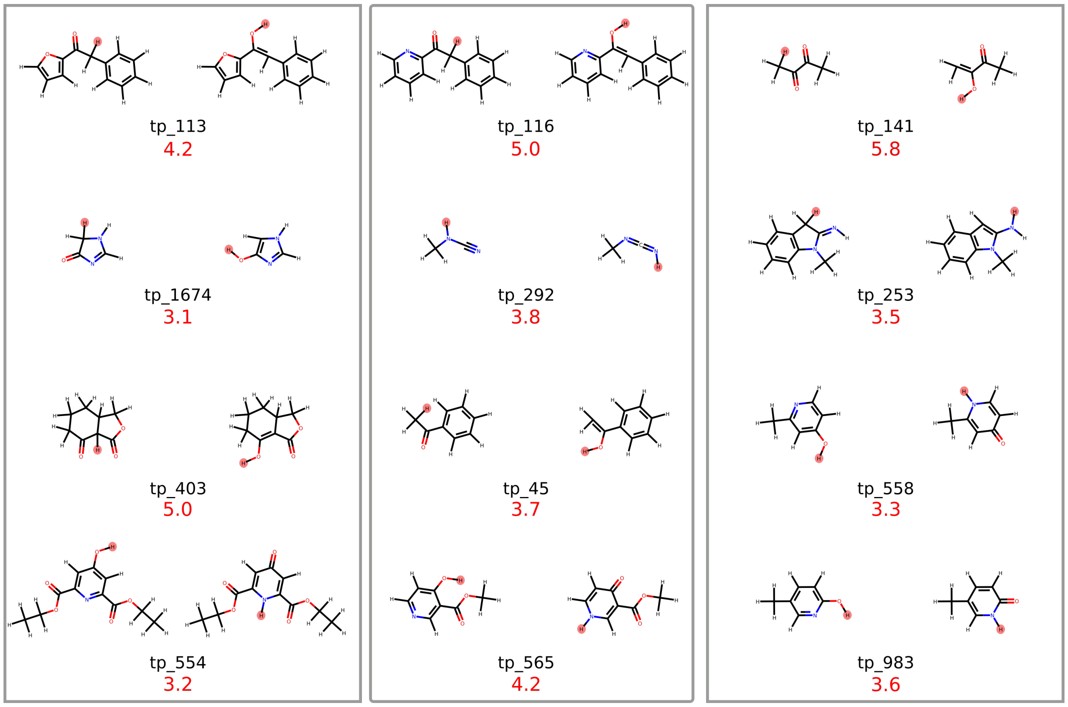


Figure S.I.1. Molecules for which the RRHO approximation introduces an error of more than 3 kcal/mol are shown. Absolute error is shown in red (value in kcal/mol) The hydrogen that changes position is highlighted in red.

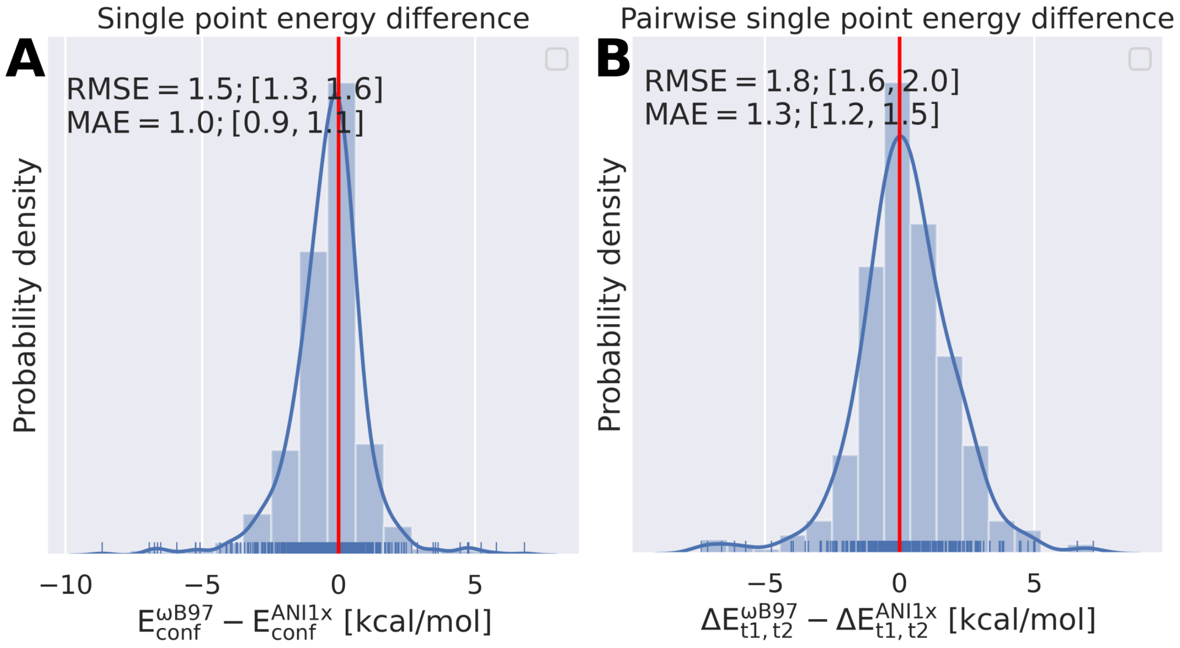


Figure S.I.2. The single point energy deviation between the ANI-1x and its corresponding level of theory is shown for the individual molecules of the tautomer set (A) and for the tautomer pairs (B).

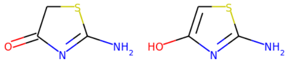
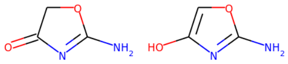
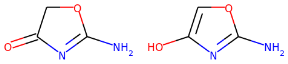
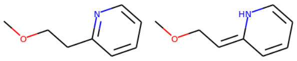
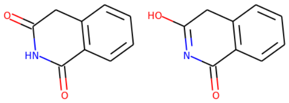
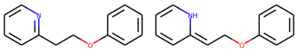
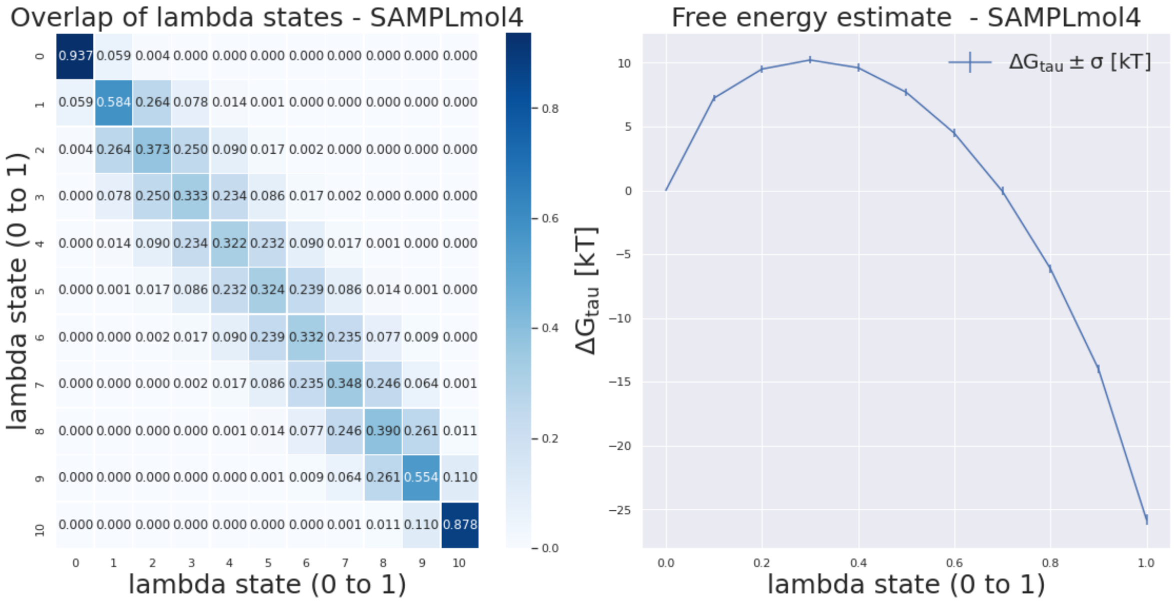
name		ΔG_{solv}^{exp}	ΔG_{solv}^{calc}
tp_1668		5.5	15.9
tp_1669		9.5	21.5
tp_1670		6.8	17.6
tp_1559		2.7	18.9
tp_331		2.2	12.8
tp_853		1.4	18.6

Table S.I.1. 5 out of the 6 tautomer pairs with the highest absolute error have common scaffolds. Tautomer pairs with absolute errors above 10 kcal/mol are shown.



	0	1	2	3	4	5	6	7	8	9	10
0	0.937	0.059	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	0.059	0.584	0.264	0.078	0.014	0.001	0.000	0.000	0.000	0.000	0.000
2	0.004	0.264	0.373	0.250	0.090	0.017	0.002	0.000	0.000	0.000	0.000
3	0.000	0.078	0.250	0.333	0.234	0.086	0.017	0.002	0.000	0.000	0.000
4	0.000	0.014	0.090	0.234	0.322	0.232	0.090	0.017	0.001	0.000	0.000
5	0.000	0.001	0.017	0.086	0.232	0.324	0.239	0.086	0.014	0.001	0.000
6	0.000	0.000	0.002	0.017	0.090	0.239	0.332	0.235	0.077	0.009	0.000
7	0.000	0.000	0.000	0.002	0.017	0.086	0.235	0.348	0.246	0.064	0.001
8	0.000	0.000	0.000	0.000	0.001	0.014	0.077	0.246	0.390	0.261	0.011
9	0.000	0.000	0.000	0.000	0.000	0.001	0.009	0.064	0.261	0.554	0.110
10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.011	0.110	0.878

Figure S.I.3. Alchemical free energy overlap and accumulated free energy estimates (with the accumulated free energy uncertainty added) are shown.

tautomer pair	ΔG^{calc}_{solv} [kcal/mol]	ΔG^{calc}_{vac} [kcal/mol]	ΔG^{exp}_{solv} [kcal/mol]
tp_113	4.0 ± 0.2	9.0 ± 0.2	8.0
tp_1000	-0.8 ± 0.2	3.5 ± 0.2	-2.6
tp_1001	-4.5 ± 0.2	-1.8 ± 0.2	-3.7
SAMPLmol4	-6.3 ± 0.2	2.4 ± 0.2	-2.3
SAMPLmol2	-7.6 ± 0.2	-2.7 ± 0.2	-6.1
tp_1072	5.0 ± 0.2	3.4 ± 0.2	0.3
	MAE: 2.8 kcal/mol	MAE: 3.4 kcal/mol	

Table S.I.2. Performing the above described alchemical simulations inside a 16 Å water droplet to model the solvent effects directly shows for 6 selected tautomer pairs an improvement of the mean absolute error by ≈ 0.5 kcal/mol. The alchemical free energy calculation was performed using 11 equidistant lambda states and 200 decorrelated snapshots per lambda state. Samples were drawn from 100 ps simulations.

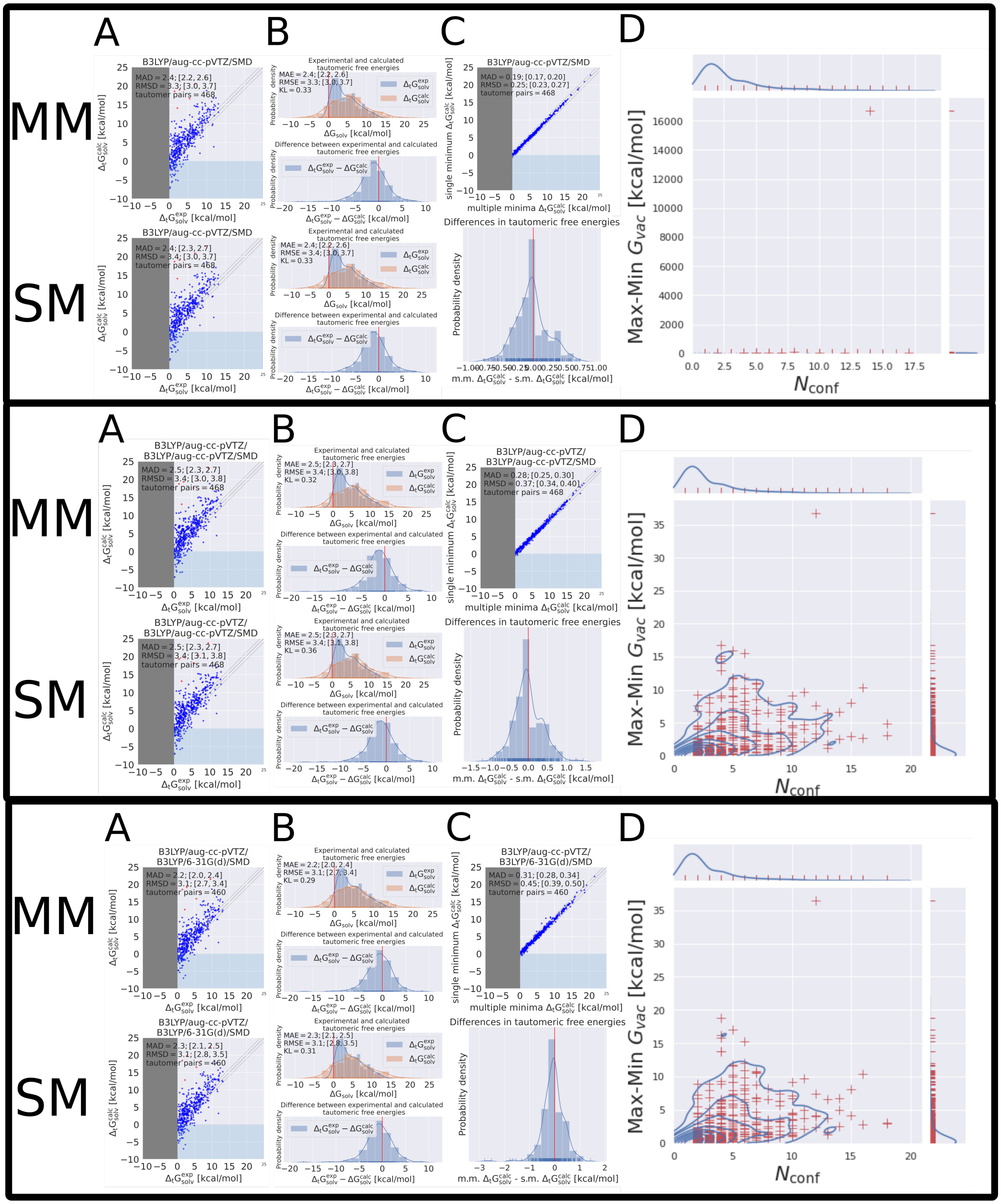


Figure S.I.4. Each of the three blocks show the QM calculations done with different level of theory indicated by the title in the plots in column **A**. In each block the top penal shows the results obtained with multiple minimum conformations, the bottom penal shows the results obtain with a single conformation. Column **D** shows the difference between the multiple minimum and single minimum approach and **E** show the the number of minimum conformations against the difference between the lowest and highest energy for each tautomer. These results were obtained without the additional structure symmetry correction.

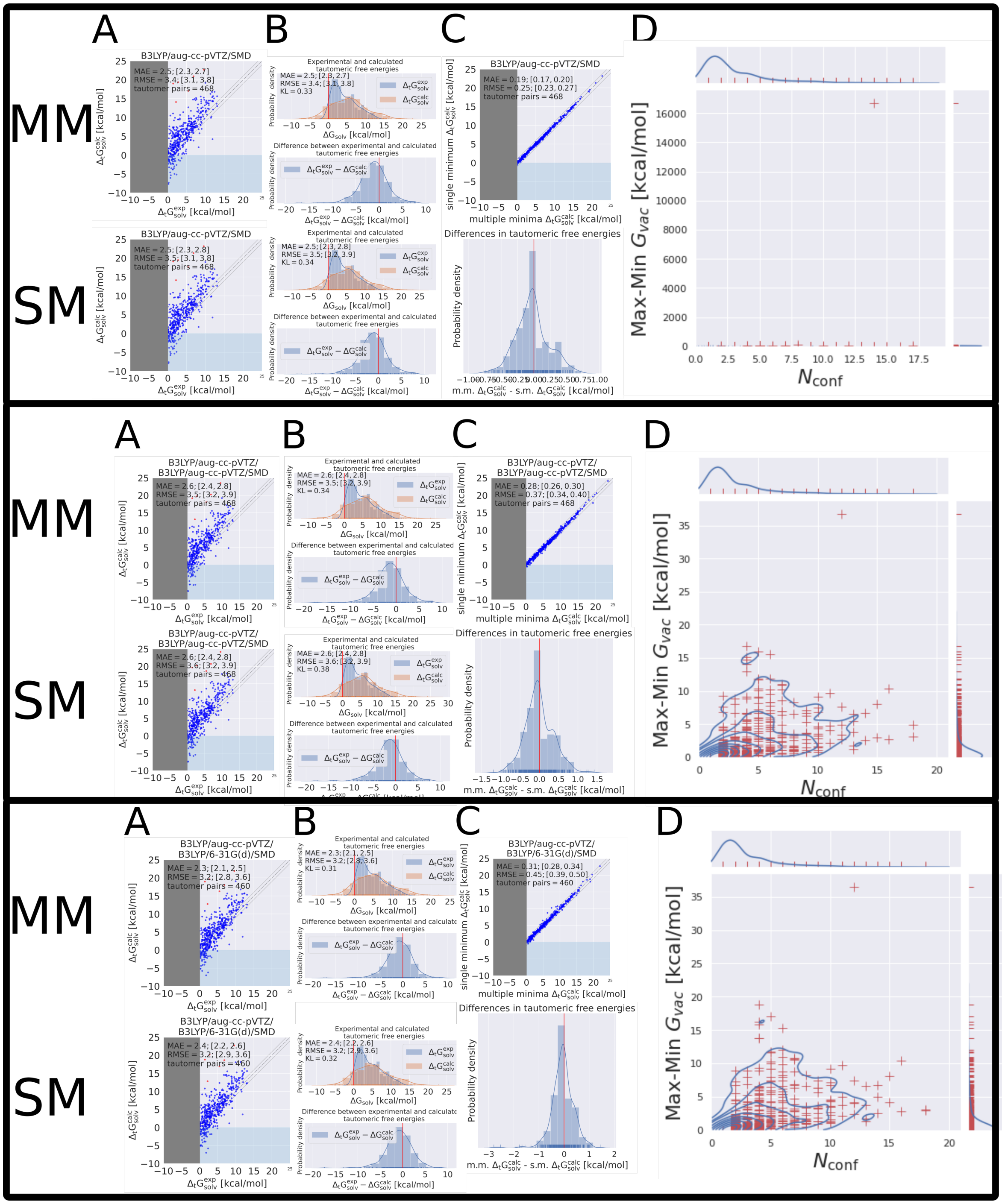
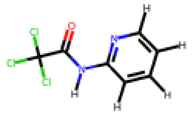


Figure S.I.5. Each of the three blocks show the QM calculations done with different level of theory indicated by the title in the plots in column **A**. In each block the top penal shows the results obtained with multiple minimum conformations, the bottom penal shows the results obtain with a single conformation. Column **D** shows the difference between the multiple minimum and single minimum approach and **E** show the the number of minimum conformations against the difference between the lowest and highest energy for each tautomer. These results were obtained **with** structure symmetry correction.



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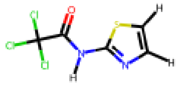

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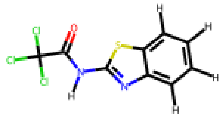

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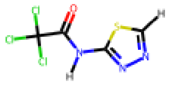

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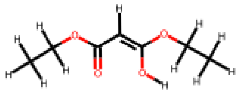

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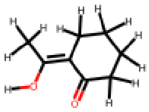

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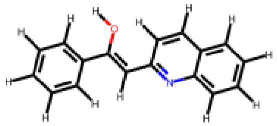

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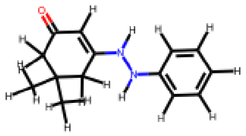

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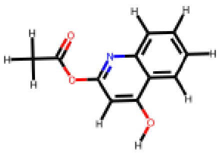

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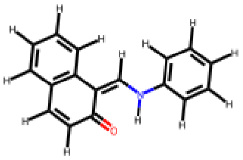

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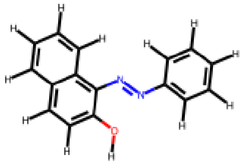

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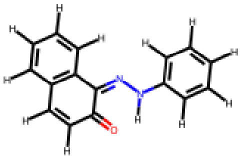

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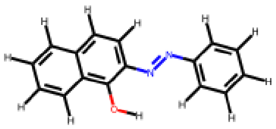

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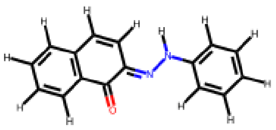

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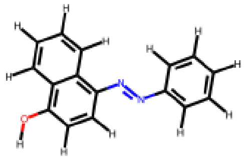

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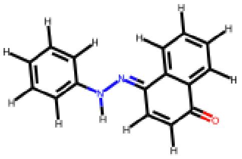

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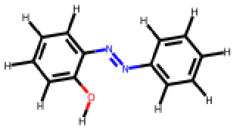
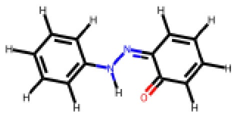


tp_867-t1



tp_867-t2

Figure S.I.6. Molecules for which the difference between their highest and lowest free energy at a minimum conformation was higher than 10 kcal/mol, calculated with B3LYP/aug-cc-pVTZ. Names are in accordance with Figure S.I.13 and S.I.14.

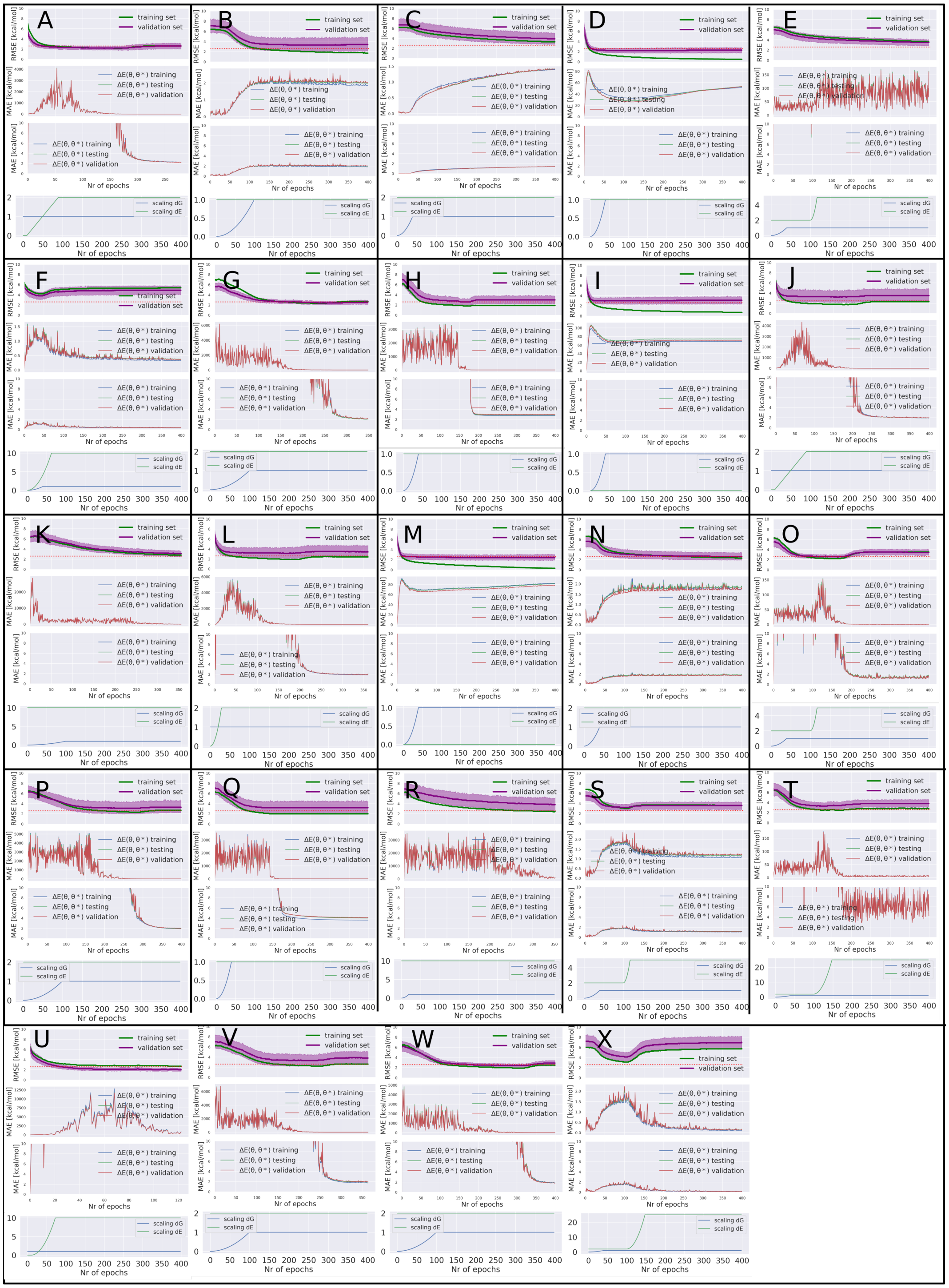


Figure S.I.7. The top panel of the figure shows the RMSE of the training/validation set. The red dotted line indicates the validation set performance of final results shown in Figure 8. The two middle panels show the $\Delta E(\theta, \theta^*)$ for the coordinate sets in the training (blue), validation (red) and test set (green). The top middle panel shows the full range of the values on the y-axis, while the bottom middle panel is limited to the interval [0,10] kcal/mol. The bottom panel shows the scaling variables used to scale the two terms (free energy and energy deviation) of the molecular loss function. In addition to the scaling variables used in the loss function there were three hyper parameters controlling the performance of the optimizer: the learning rate (LR) for the SGD and AdamW optimizer (optimizing the bias and the weight of the neural net) and the weight decay. The following list contains the LR for the training runs shown, if weight decay or a learning rate reduction method was used it is explicitly mentioned. **A, H, J, K, L, M, R, U, V, W**: AdamW: LR of 1e-4, SGD: LR of 1e-4. **B** : LR AdamW: 1e-4, LR SGD: 1e-9. **F, I, N, X, S**: LR AdamW: 1e-4, LR SGD: 0. **D**: LR AdamW 1e-5, LR SGD: 0. **O**: LR AdamW 1e-4, LR SGD: 1e-6. **E** : LR AdamW 1e-5, LR SGD: 1e-6. **G** : LR AdamW 1e-4, LR SGD: 1e-4, weight decay: 1e-05. **Q** : LR AdamW 1e-4, LR SGD: 1e-4, with LRReduction on Plateau for AdamW. **T** : LR AdamW 1e-4, LR SGD: 1e-6, weight decay: 1e-9.

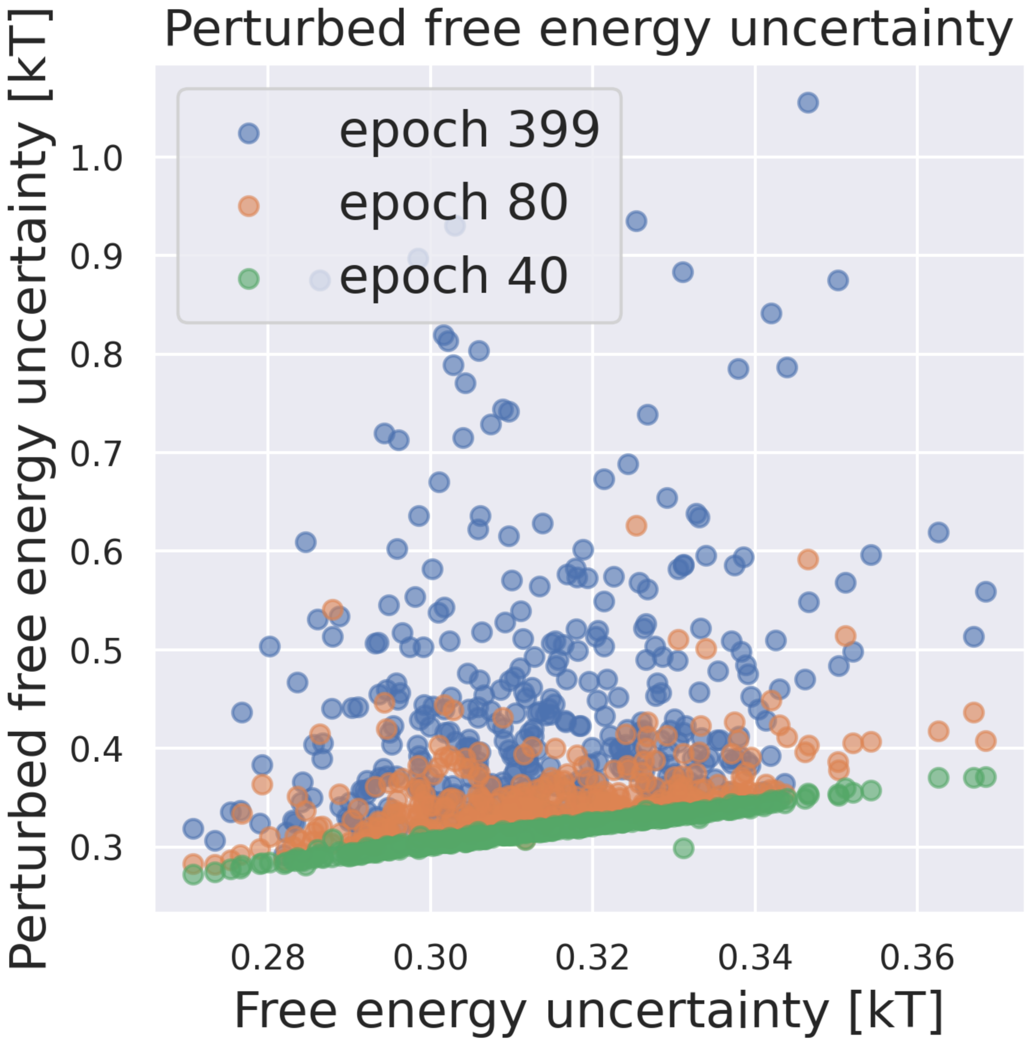


Figure S.I.8. Perturbed free energy uncertainty increases with the number of training epochs. The free energy estimate uncertainty was calculated using the MBAR implementation in pyMBAR.

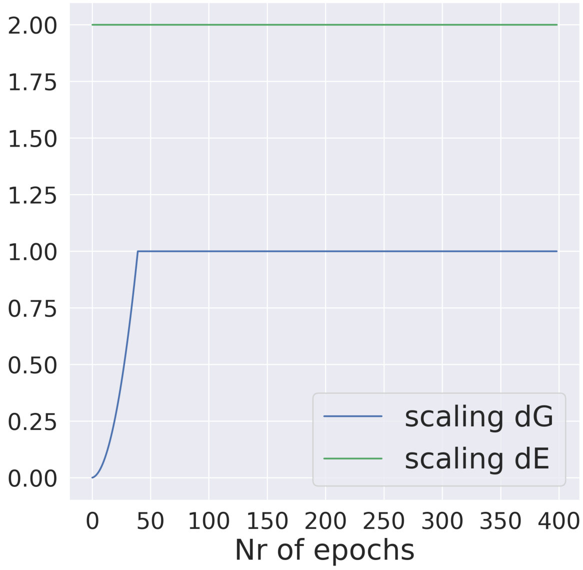


Figure S.I.9. The scaling factors for f(epoch) and g(epoch) used in the molecular loss function in the reported results in 8.

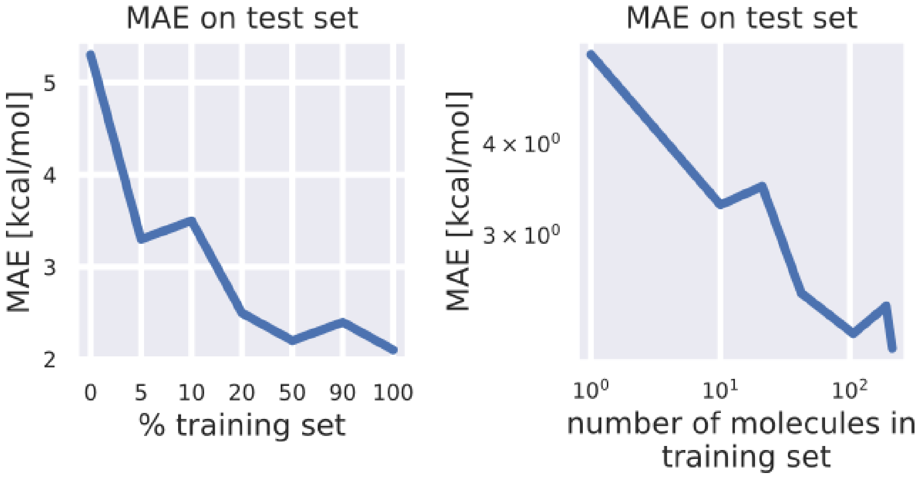


Figure S.I.10. The learning curve shows the performance of the optimized parameter set on a test set resulting from different retraining runs performed with increasing percentage of the training set. Scaling factors and learning rate were chosen as in Figure 8. The MAE was calculated with the parameter set with the best performance on the validation set. The training and validation set was kept constant, molecules from the training set were randomly selected.

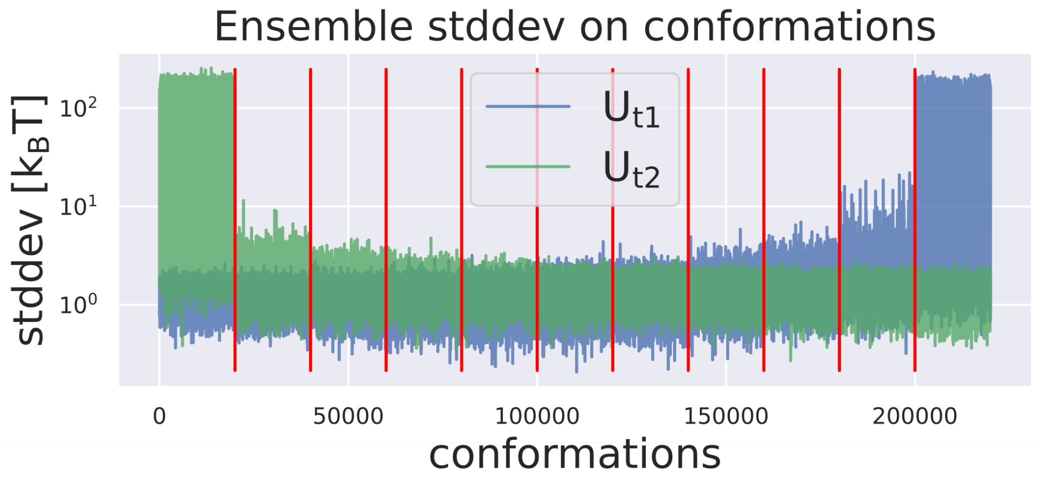


Figure S.I.11. The neural net ensemble standard deviation is plotted for the potential energy calculation with the end-point potential energy functions (U_{t1} and U_{t2}) on the conformations obtained along the alchemical path for the 11 λ states, starting with conformations from $\lambda = 0$. The red lines indicate the different states along the alchemical path starting at the left end with $\lambda = 0$ and ending at $\lambda = 1$ The slow increase of the standard deviation along the alchemical path indicates that ANI-1ccx is well suited to efficiently perform alchemical free energy calculations for tautomer pairs and the QML has confidence in the potential energy values even at $\lambda = 0.5$. The high standard deviation for U_{t1} on samples generated at $\lambda = 1$ and vice versa are to be expected since the dummy hydrogen of U_{t2} at $\lambda = 1$ is moving freely inside a spherical restraint; but this hydrogen is a real atom for U_{t1}.

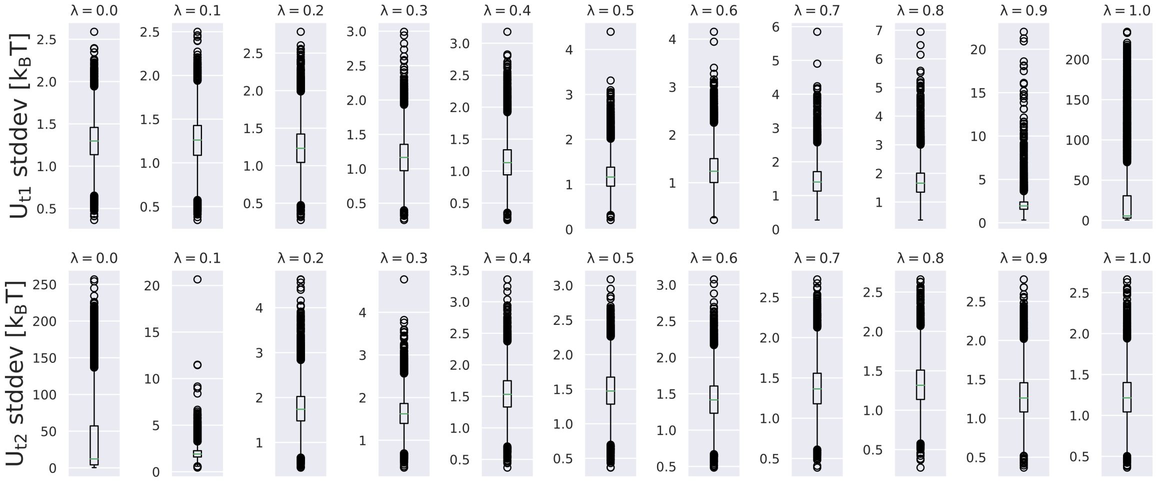
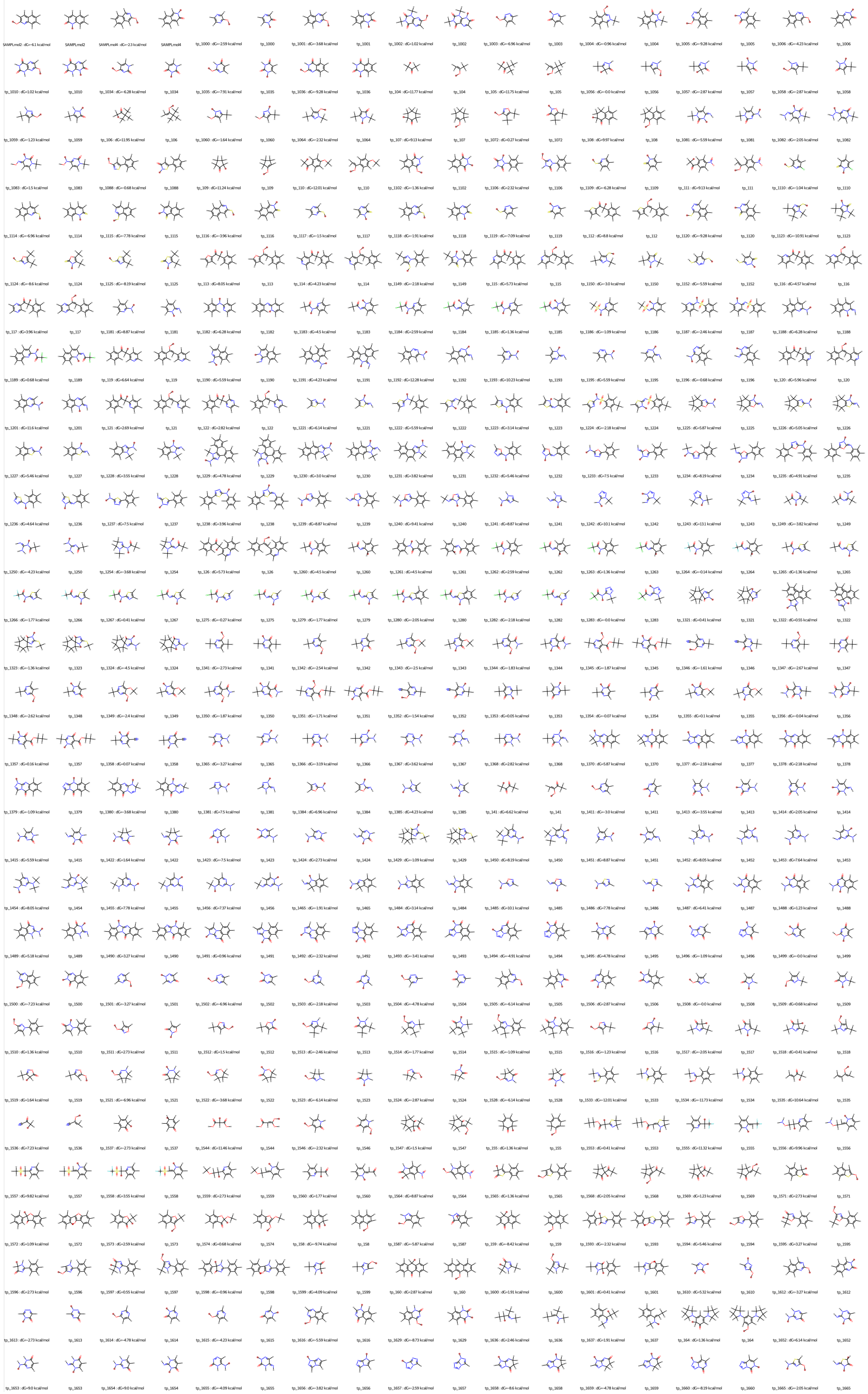


Figure S.I.12. The neural net ensemble standard deviation is plotted for the potential energy calculation with the end-point potential energy functions (U_{t1} and U_{t2}) on the conformations obtained along the alchemical path for the 11 λ states.


SAMPLmol2 : dG=−6.1 kcal/mol
SAMPLmol2
SAMPLmol4 : dG=−2.3 kcal/mol
SAMPLmol4
tp_1000 : dG=−2.59 kcal/mol
tp_1000
tp_1001 : dG=−3.68 kcal/mol
tp_1001
tp_1002 : dG=1.02 kcal/mol
tp_1002
tp_1003 : dG=−6.96 kcal/mol
tp_1003
tp_1004 : dG=−0.96 kcal/mol
tp_1004
tp_1005 : dG=−9.28 kcal/mol
tp_1005
tp_1006 : dG=−4.23 kcal/mol
tp_1006
tp_1010 : dG=1.02 kcal/mol
tp_1010
tp_1034 : dG=−6.28 kcal/mol
tp_1034
tp_1035 : dG=−7.91 kcal/mol
tp_1035
tp_1036 : dG=−9.28 kcal/mol
tp_1036
tp_104 : dG=11.77 kcal/mol
tp_104
tp_105 : dG=11.75 kcal/mol
tp_105
tp_1056 : dG=−0.0 kcal/mol
tp_1056
tp_1057 : dG=−2.87 kcal/mol
tp_1057
tp_1058 : dG=−2.87 kcal/mol
tp_1058
tp_1059 : dG=−1.23 kcal/mol
tp_1059
tp_106 : dG=11.95 kcal/mol
tp_106
tp_1060 : dG=−1.64 kcal/mol
tp_1060
tp_1064 : dG=−2.32 kcal/mol
tp_1064
tp_107 : dG=9.13 kcal/mol
tp_107
tp_1072 : dG=0.27 kcal/mol
tp_1072
tp_108 : dG=9.97 kcal/mol
tp_108
tp_1081 : dG=−5.59 kcal/mol
tp_1081
tp_1082 : dG=−2.05 kcal/mol
tp_1082
tp_1083 : dG=1.5 kcal/mol
tp_1083
tp_1088 : dG=−0.68 kcal/mol
tp_1088
tp_109 : dG=11.24 kcal/mol
tp_109
tp_110 : dG=12.01 kcal/mol
tp_110
tp_1102 : dG=−1.36 kcal/mol
tp_1102
tp_1106 : dG=2.32 kcal/mol
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tp_1109 : dG=−6.28 kcal/mol
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tp_1116
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tp_1118 : dG=−1.91 kcal/mol
tp_1118
tp_1119 : dG=−7.09 kcal/mol
tp_1119
tp_112 : dG=8.8 kcal/mol
tp_112
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tp_1123 : dG=−10.91 kcal/mol
tp_1123
tp_1124 : dG=−8.6 kcal/mol
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tp_1186
tp_1187 : dG=−2.46 kcal/mol
tp_1187
tp_1188 : dG=6.28 kcal/mol
tp_1188
tp_1189 : dG=0.68 kcal/mol
tp_1189
tp_119 : dG=6.64 kcal/mol
tp_119
tp_1190 : dG=5.59 kcal/mol
tp_1190
tp_1191 : dG=4.23 kcal/mol
tp_1191
tp_1192 : dG=12.28 kcal/mol
tp_1192
tp_1193 : dG=10.23 kcal/mol
tp_1193
tp_1195 : dG=5.59 kcal/mol
tp_1195
tp_1196 : dG=−0.68 kcal/mol
tp_1196
tp_120 : dG=5.96 kcal/mol
tp_120
tp_1201 : dG=11.6 kcal/mol
tp_1201
tp_121 : dG=2.69 kcal/mol
tp_121
tp_122 : dG=2.82 kcal/mol
tp_122
tp_1221 : dG=6.14 kcal/mol
tp_1221
tp_1222 : dG=5.59 kcal/mol
tp_1222
tp_1223 : dG=3.14 kcal/mol
tp_1223
tp_1224 : dG=−2.18 kcal/mol
tp_1224
tp_1225 : dG=5.87 kcal/mol
tp_1225
tp_1226 : dG=5.05 kcal/mol
tp_1226
tp_1227 : dG=5.46 kcal/mol
tp_1227
tp_1228 : dG=3.55 kcal/mol
tp_1228
tp_1229 : dG=4.78 kcal/mol
tp_1229
tp_1230 : dG=3.0 kcal/mol
tp_1230
tp_1231 : dG=3.82 kcal/mol
tp_1231
tp_1232 : dG=5.46 kcal/mol
tp_1232
tp_1233 : dG=7.5 kcal/mol
tp_1233
tp_1234 : dG=8.19 kcal/mol
tp_1234
tp_1235 : dG=4.91 kcal/mol
tp_1235
tp_1236 : dG=4.64 kcal/mol
tp_1236
tp_1237 : dG=7.5 kcal/mol
tp_1237
tp_1238 : dG=3.96 kcal/mol
tp_1238
tp_1239 : dG=8.87 kcal/mol
tp_1239
tp_1240 : dG=9.41 kcal/mol
tp_1240
tp_1241 : dG=8.87 kcal/mol
tp_1241
tp_1242 : dG=10.1 kcal/mol
tp_1242
tp_1243 : dG=13.1 kcal/mol
tp_1243
tp_1249 : dG=−3.82 kcal/mol
tp_1249
tp_1250 : dG=−4.23 kcal/mol
tp_1250
tp_1254 : dG=−3.68 kcal/mol
tp_1254
tp_126 : dG=5.73 kcal/mol
tp_126
tp_1260 : dG=4.5 kcal/mol
tp_1260
tp_1261 : dG=4.5 kcal/mol
tp_1261
tp_1262 : dG=2.59 kcal/mol
tp_1262
tp_1263 : dG=1.36 kcal/mol
tp_1263
tp_1264 : dG=−0.14 kcal/mol
tp_1264
tp_1265 : dG=1.36 kcal/mol
tp_1265
tp_1266 : dG=−1.77 kcal/mol
tp_1266
tp_1267 : dG=0.41 kcal/mol
tp_1267
tp_1275 : dG=−0.27 kcal/mol
tp_1275
tp_1279 : dG=−1.77 kcal/mol
tp_1279
tp_1280 : dG=−2.05 kcal/mol
tp_1280
tp_1282 : dG=−2.18 kcal/mol
tp_1282
tp_1283 : dG=−0.0 kcal/mol
tp_1283
tp_1321 : dG=0.41 kcal/mol
tp_1321
tp_1322 : dG=0.55 kcal/mol
tp_1322
tp_1323 : dG=−1.36 kcal/mol
tp_1323
tp_1324 : dG=−4.5 kcal/mol
tp_1324
tp_1341 : dG=−2.73 kcal/mol
tp_1341
tp_1342 : dG=−2.54 kcal/mol
tp_1342
tp_1343 : dG=−2.5 kcal/mol
tp_1343
tp_1344 : dG=−1.83 kcal/mol
tp_1344
tp_1345 : dG=−1.87 kcal/mol
tp_1345
tp_1346 : dG=−1.61 kcal/mol
tp_1346
tp_1347 : dG=−2.67 kcal/mol
tp_1347
tp_1348 : dG=−2.62 kcal/mol
tp_1348
tp_1349 : dG=−2.4 kcal/mol
tp_1349
tp_1350 : dG=−1.87 kcal/mol
tp_1350
tp_1351 : dG=−1.71 kcal/mol
tp_1351
tp_1352 : dG=−1.54 kcal/mol
tp_1352
tp_1353 : dG=0.05 kcal/mol
tp_1353
tp_1354 : dG=−0.07 kcal/mol
tp_1354
tp_1355 : dG=0.1 kcal/mol
tp_1355
tp_1356 : dG=−0.04 kcal/mol
tp_1356
tp_1357 : dG=0.16 kcal/mol
tp_1357
tp_1358 : dG=0.07 kcal/mol
tp_1358
tp_1365 : dG=−3.27 kcal/mol
tp_1365
tp_1366 : dG=−3.19 kcal/mol
tp_1366
tp_1367 : dG=3.62 kcal/mol
tp_1367
tp_1368 : dG=2.82 kcal/mol
tp_1368
tp_1370 : dG=5.87 kcal/mol
tp_1370
tp_1377 : dG=−2.18 kcal/mol
tp_1377
tp_1378 : dG=2.18 kcal/mol
tp_1378
tp_1379 : dG=−1.09 kcal/mol
tp_1379
tp_1380 : dG=−3.68 kcal/mol
tp_1380
tp_1381 : dG=7.5 kcal/mol
tp_1381
tp_1384 : dG=6.96 kcal/mol
tp_1384
tp_1385 : dG=4.23 kcal/mol
tp_1385
tp_141 : dG=6.62 kcal/mol
tp_141
tp_1411 : dG=−3.0 kcal/mol
tp_1411
tp_1413 : dG=−3.55 kcal/mol
tp_1413
tp_1414 : dG=2.05 kcal/mol
tp_1414
tp_1415 : dG=5.59 kcal/mol
tp_1415
tp_1422 : dG=1.64 kcal/mol
tp_1422
tp_1423 : dG=−7.5 kcal/mol
tp_1423
tp_1424 : dG=2.73 kcal/mol
tp_1424
tp_1429 : dG=−1.09 kcal/mol
tp_1429
tp_1450 : dG=8.19 kcal/mol
tp_1450
tp_1451 : dG=8.87 kcal/mol
tp_1451
tp_1452 : dG=8.05 kcal/mol
tp_1452
tp_1453 : dG=7.64 kcal/mol
tp_1453
tp_1454 : dG=8.05 kcal/mol
tp_1454
tp_1455 : dG=7.78 kcal/mol
tp_1455
tp_1456 : dG=7.37 kcal/mol
tp_1456
tp_1465 : dG=−1.91 kcal/mol
tp_1465
tp_1484 : dG=3.14 kcal/mol
tp_1484
tp_1485 : dG=10.1 kcal/mol
tp_1485
tp_1486 : dG=7.78 kcal/mol
tp_1486
tp_1487 : dG=6.41 kcal/mol
tp_1487
tp_1488 : dG=1.23 kcal/mol
tp_1488
tp_1489 : dG=5.18 kcal/mol
tp_1489
tp_1490 : dG=3.27 kcal/mol
tp_1490
tp_1491 : dG=0.96 kcal/mol
tp_1491
tp_1492 : dG=−2.32 kcal/mol
tp_1492
tp_1493 : dG=−3.41 kcal/mol
tp_1493
tp_1494 : dG=−4.91 kcal/mol
tp_1494
tp_1495 : dG=4.78 kcal/mol
tp_1495
tp_1496 : dG=−1.09 kcal/mol
tp_1496
tp_1499 : dG=−0.0 kcal/mol
tp_1499
tp_1500 : dG=−7.23 kcal/mol
tp_1500
tp_1501 : dG=−3.27 kcal/mol
tp_1501
tp_1502 : dG=−6.96 kcal/mol
tp_1502
tp_1503 : dG=−2.18 kcal/mol
tp_1503
tp_1504 : dG=−4.78 kcal/mol
tp_1504
tp_1505 : dG=−6.14 kcal/mol
tp_1505
tp_1506 : dG=2.87 kcal/mol
tp_1506
tp_1508 : dG=−0.0 kcal/mol
tp_1508
tp_1509 : dG=0.68 kcal/mol
tp_1509
tp_1510 : dG=1.36 kcal/mol
tp_1510
tp_1511 : dG=2.73 kcal/mol
tp_1511
tp_1512 : dG=1.5 kcal/mol
tp_1512
tp_1513 : dG=−2.46 kcal/mol
tp_1513
tp_1514 : dG=−1.77 kcal/mol
tp_1514
tp_1515 : dG=−1.09 kcal/mol
tp_1515
tp_1516 : dG=−1.23 kcal/mol
tp_1516
tp_1517 : dG=−2.05 kcal/mol
tp_1517
tp_1518 : dG=0.41 kcal/mol
tp_1518
tp_1519 : dG=1.64 kcal/mol
tp_1519
tp_1521 : dG=−6.96 kcal/mol
tp_1521
tp_1522 : dG=−3.68 kcal/mol
tp_1522
tp_1523 : dG=−6.14 kcal/mol
tp_1523
tp_1524 : dG=−2.87 kcal/mol
tp_1524
tp_1528 : dG=−6.14 kcal/mol
tp_1528
tp_1533 : dG=−12.01 kcal/mol
tp_1533
tp_1534 : dG=−11.73 kcal/mol
tp_1534
tp_1535 : dG=10.64 kcal/mol
tp_1535
tp_1536 : dG=7.23 kcal/mol
tp_1536
tp_1537 : dG=−2.73 kcal/mol
tp_1537
tp_1544 : dG=11.46 kcal/mol
tp_1544
tp_1546 : dG=−2.32 kcal/mol
tp_1546
tp_1547 : dG=1.5 kcal/mol
tp_1547
tp_155 : dG=1.36 kcal/mol
tp_155
tp_1553 : dG=0.41 kcal/mol
tp_1553
tp_1555 : dG=11.32 kcal/mol
tp_1555
tp_1556 : dG=9.96 kcal/mol
tp_1556
tp_1557 : dG=9.82 kcal/mol
tp_1557
tp_1558 : dG=3.55 kcal/mol
tp_1558
tp_1559 : dG=2.73 kcal/mol
tp_1559
tp_1560 : dG=1.77 kcal/mol
tp_1560
tp_1564 : dG=8.87 kcal/mol
tp_1564
tp_1565 : dG=1.36 kcal/mol
tp_1565
tp_1568 : dG=2.05 kcal/mol
tp_1568
tp_1569 : dG=1.23 kcal/mol
tp_1569
tp_1571 : dG=2.73 kcal/mol
tp_1571
tp_1572 : dG=1.09 kcal/mol
tp_1572
tp_1573 : dG=2.59 kcal/mol
tp_1573
tp_1574 : dG=0.68 kcal/mol
tp_1574
tp_158 : dG=−9.74 kcal/mol
tp_158
tp_1587 : dG=−5.87 kcal/mol
tp_1587
tp_159 : dG=−8.42 kcal/mol
tp_159
tp_1593 : dG=−2.32 kcal/mol
tp_1593
tp_1594 : dG=5.46 kcal/mol
tp_1594
tp_1595 : dG=3.27 kcal/mol
tp_1595
tp_1596 : dG=2.73 kcal/mol
tp_1596
tp_1597 : dG=0.55 kcal/mol
tp_1597
tp_1598 : dG=−0.96 kcal/mol
tp_1598
tp_1599 : dG=4.09 kcal/mol
tp_1599
tp_160 : dG=2.87 kcal/mol
tp_160
tp_1600 : dG=1.91 kcal/mol
tp_1600
tp_1601 : dG=0.41 kcal/mol
tp_1601
tp_1610 : dG=5.32 kcal/mol
tp_1610
tp_1612 : dG=−3.27 kcal/mol
tp_1612
tp_1613 : dG=−2.73 kcal/mol
tp_1613
tp_1614 : dG=−4.78 kcal/mol
tp_1614
tp_1615 : dG=−4.23 kcal/mol
tp_1615
tp_1616 : dG=−5.59 kcal/mol
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tp_1637
tp_164 : dG=1.36 kcal/mol
tp_164
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tp_1652
tp_1653 : dG=9.0 kcal/mol
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tp_1654 : dG=9.0 kcal/mol
tp_1654
tp_1655 : dG=−4.09 kcal/mol
tp_1655
tp_1656 : dG=−3.82 kcal/mol
tp_1656
tp_1657 : dG=−2.59 kcal/mol
tp_1657
tp_1658 : dG=−8.6 kcal/mol
tp_1658
tp_1659 : dG=−4.78 kcal/mol
tp_1659
tp_1660 : dG=−8.19 kcal/mol
tp_1660
tp_1665 : dG=−2.05 kcal/mol
tp_1665

Figure S.I.13. The full tautomer set is shown (part 1). The hydrogen that is moved in the reaction is highlighted in red, ΔG indicates the experimental free energy difference in solution.

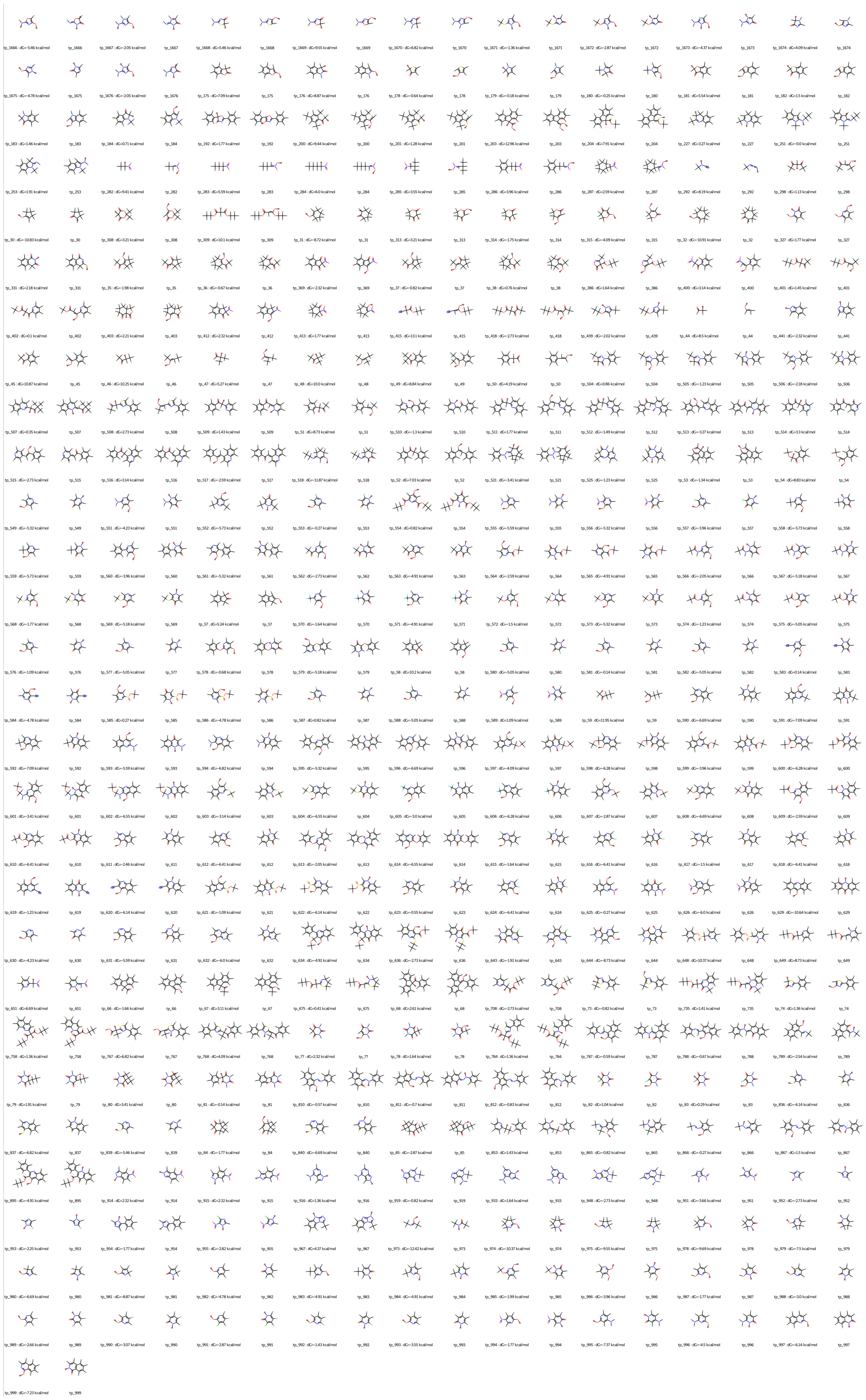

Figure S.I.14. The full tautomer set is shown (part 2). The hydrogen that is moved in the reaction is highlighted in red, ΔG indicates the experimental free energy difference in solution.