Supporting Information

Benchmark assessment of molecular geometries and energies from small molecule force fields

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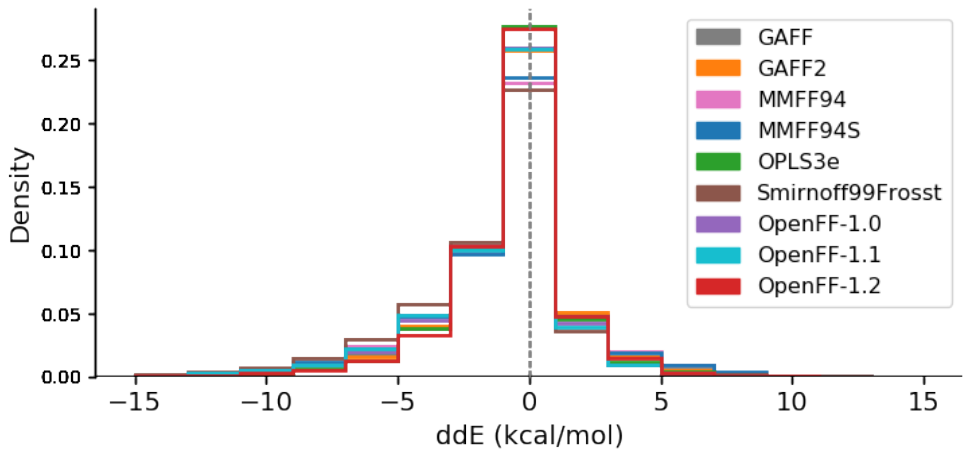


Figure S.1: Histograms of the relative conformer energy differences as computed in equation 2 (main text) for each force field relative to QM. Each molecular structure, including different conformers of the same molecule, is counted separately. Since the global minimum molecular structures were set to zero deliberately and add a constant offset to the central bin, they are removed from the counts. A force field having higher agreement with QM would have a higher bin centered at ddE = 0 kcal/mol.

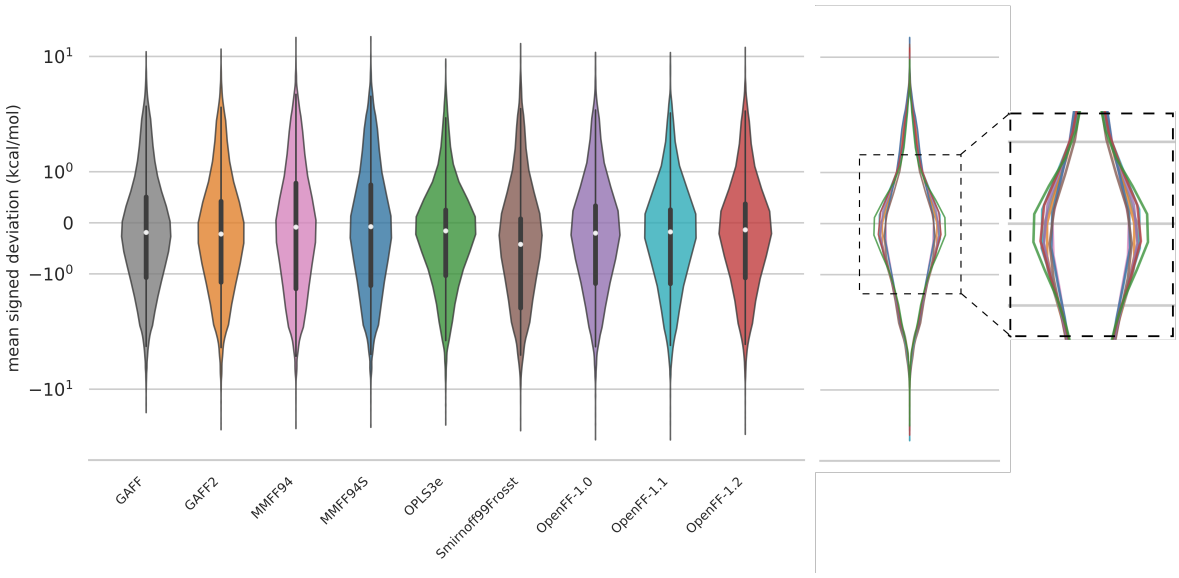
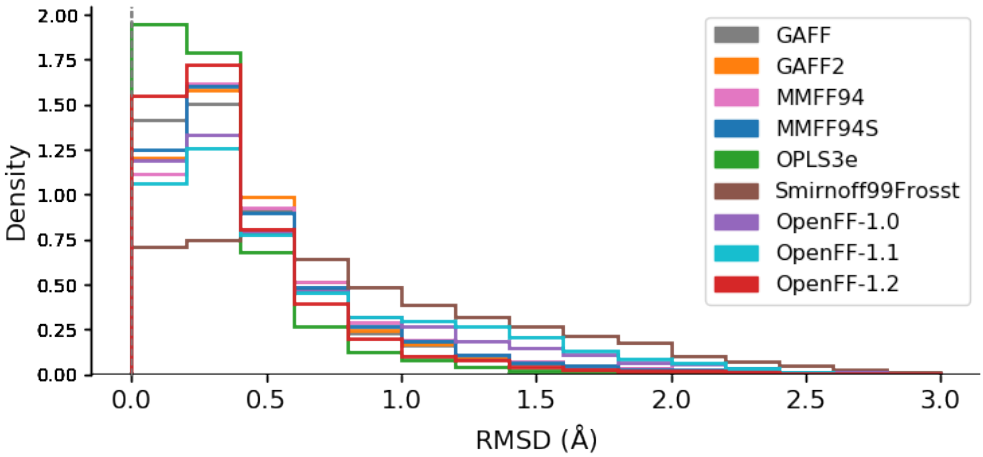
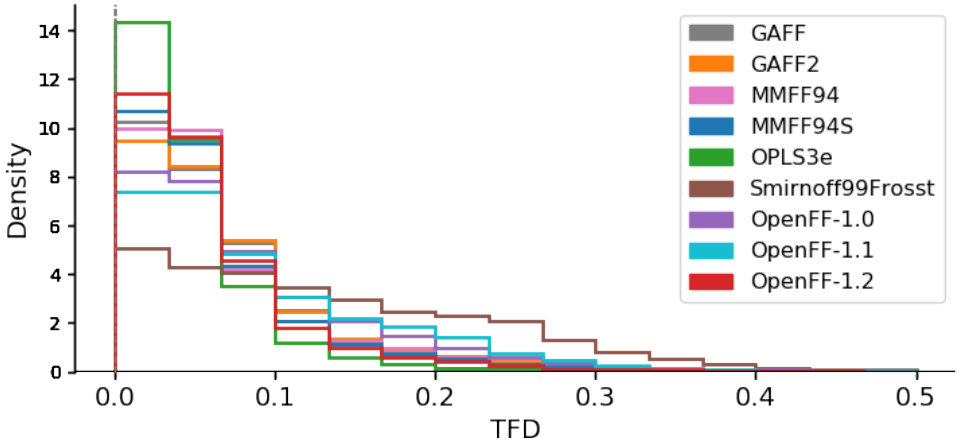


Figure S.2: Violin plots of the mean signed deviations of MM conformer energies relative to QM conformer energies as computed in main text (equation 3). The energy MSDs only take into account structures matched within 0.3 Å of the QM reference structure, so there are minor differences in the amount of data used to plot each violin. The number of structures are 10124 (GAFF), 9404 (GAFF2), 9097 (MMFF94), 9544 (MMFF94S), 13813 (OPLS3e), 5068 (SMIRNOFF99Frosst), 8898 (OpenFF-1.0), 8087 (OpenFF-1.1), and 11669 (OpenFF-1.2). The vertical axis is shown on a logarithmic scale. An overlay of the violin plots on the right panel better shows the subtle distinctions between the force fields in the most populated region, near zero error.



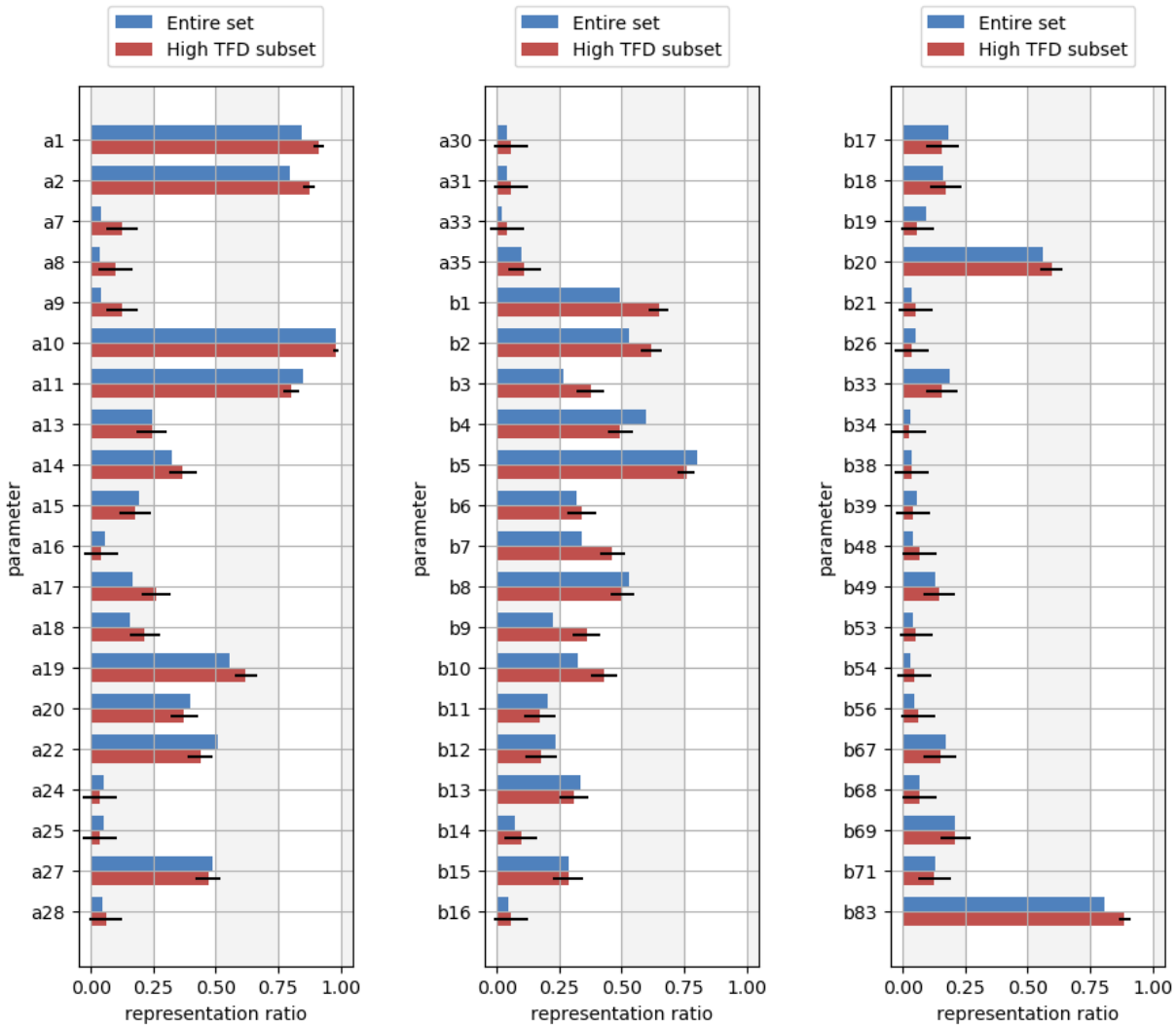
(a)



(b)

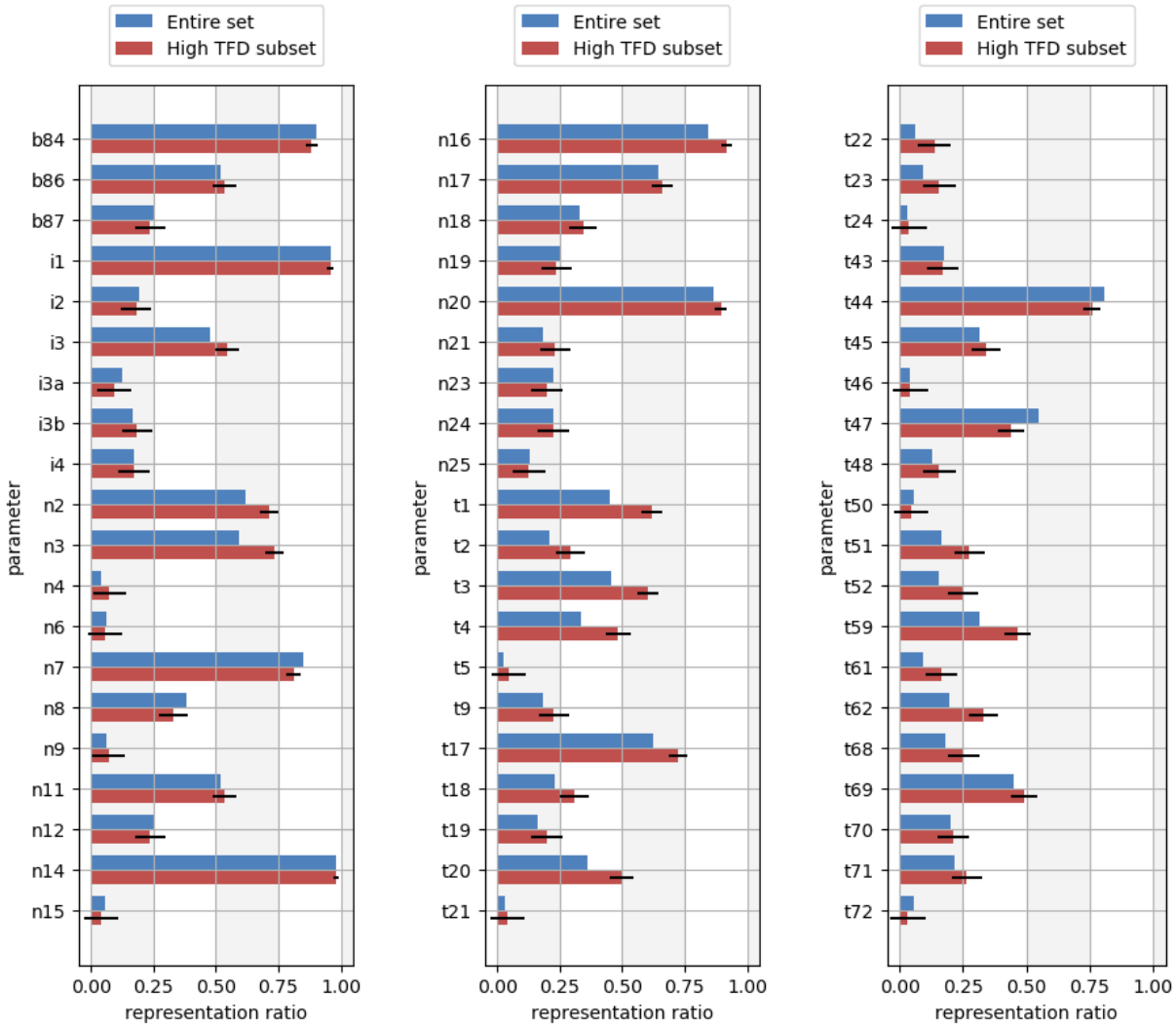
Figure S.3: Histograms of the RMSD and TFD values between force field structures as compared to QM structures. Values closer to zero indicate higher geometric similarity for both RMSD and TFD.

In the same format as Figure 6 of main text, the following figures display representation ratios for all parameters of the Parsley force field. The blue bars represent the parameter ratios from the full molecule set, and the red bars represent the parameter ratios from only the set of molecules with TFD values greater than 0.12. Error bars denote the 95% confidence interval determined from the one-sample Z-test for proportions. Figure 6 is reproduced here for ease of reference.



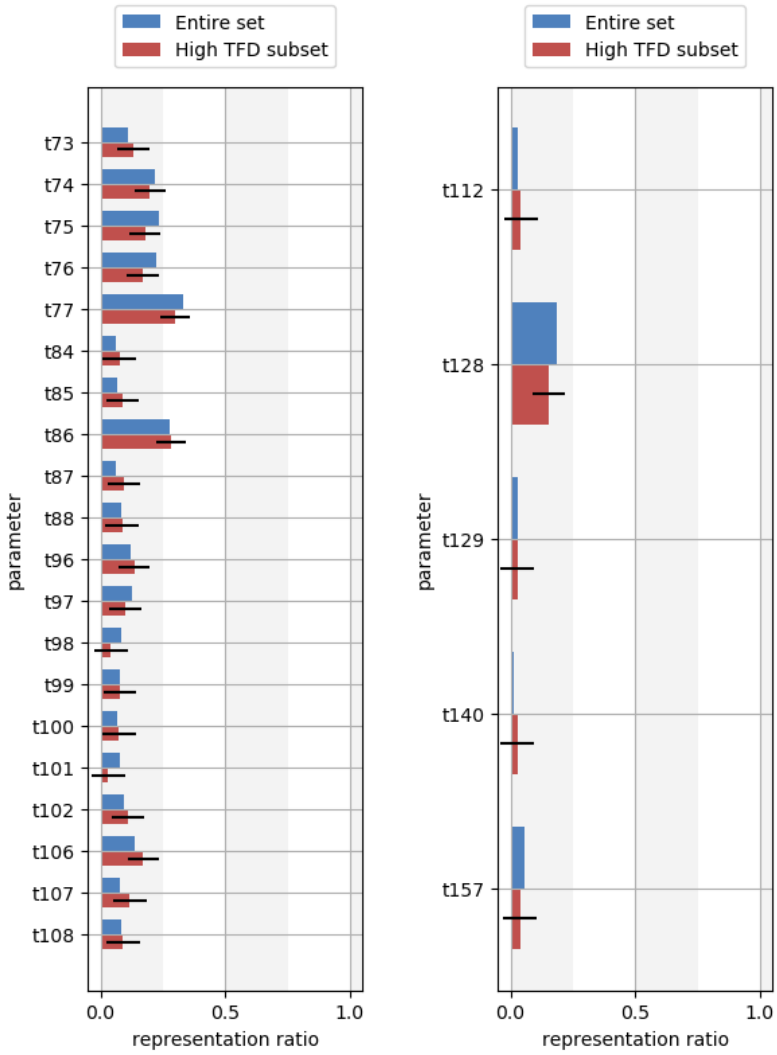
(a) (b) (c)

Figure S.4



(a) (b) (c)

Figure S.5


Entire set
High TFD subset
t73
t74
t75
t76
t77
t84
t85
t86
t87
t88
t96
t97
t98
t99
t100
t101
t102
t106
t107
t108
parameter
0.0
0.5
1.0
representation ratio
Entire set
High TFD subset
t112
t128
t129
t140
t157
parameter
0.0
0.5
1.0
representation ratio

(a) (b)

Figure S.6

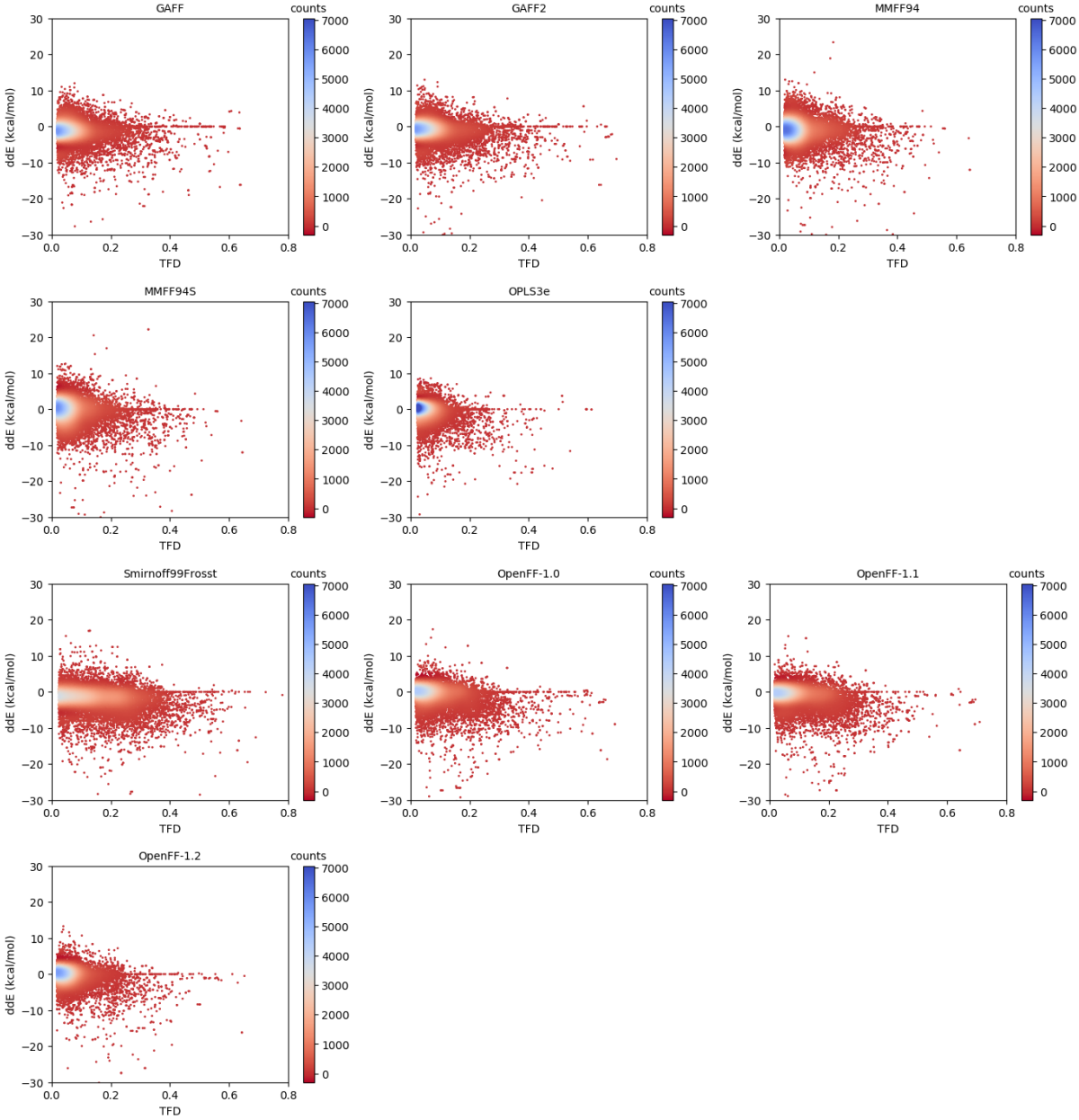


Figure S.7: Scatter plots of relative conformer energies versus TFD scores. The points are colored by the interpolated density of points in a certain area. Blue indicates region of high density, that is, high compactness of points in that area. A force field having better agreement in both relative energies and geometries with the QM reference would have more points around the origin (ddE = 0, TFD = 0). The vertical axis is represented on linear scale; the same plots with logarithmic scaling can be found in the main text (Figure 6).

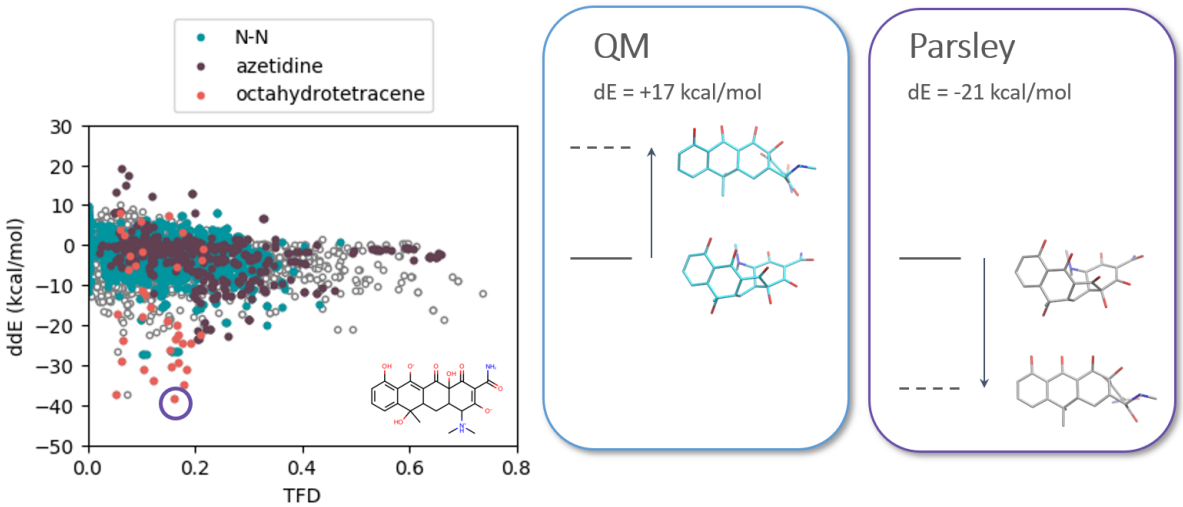


Figure S.8: An example of an outlying ddE result (for OpenFF-1.0) of the substituted octahydrotetracene structure (circled in the scatter plot). The two panels on the right show the four structures and energy differences that go into computing the ddE value of -38 kcal/mol. Energy bands are not drawn to scale. The solid band represents the energy of the reference conformer as it has the lowest QM energy for all the conformers of this molecule. The dashed band shows the energy of the example structure relative to the reference conformer. QM predicts that this conformation should be higher in energy by +17 kcal/mol, but OpenFF-1.0 evaluates the energy difference to be −21 kcal/mol relative to the reference.

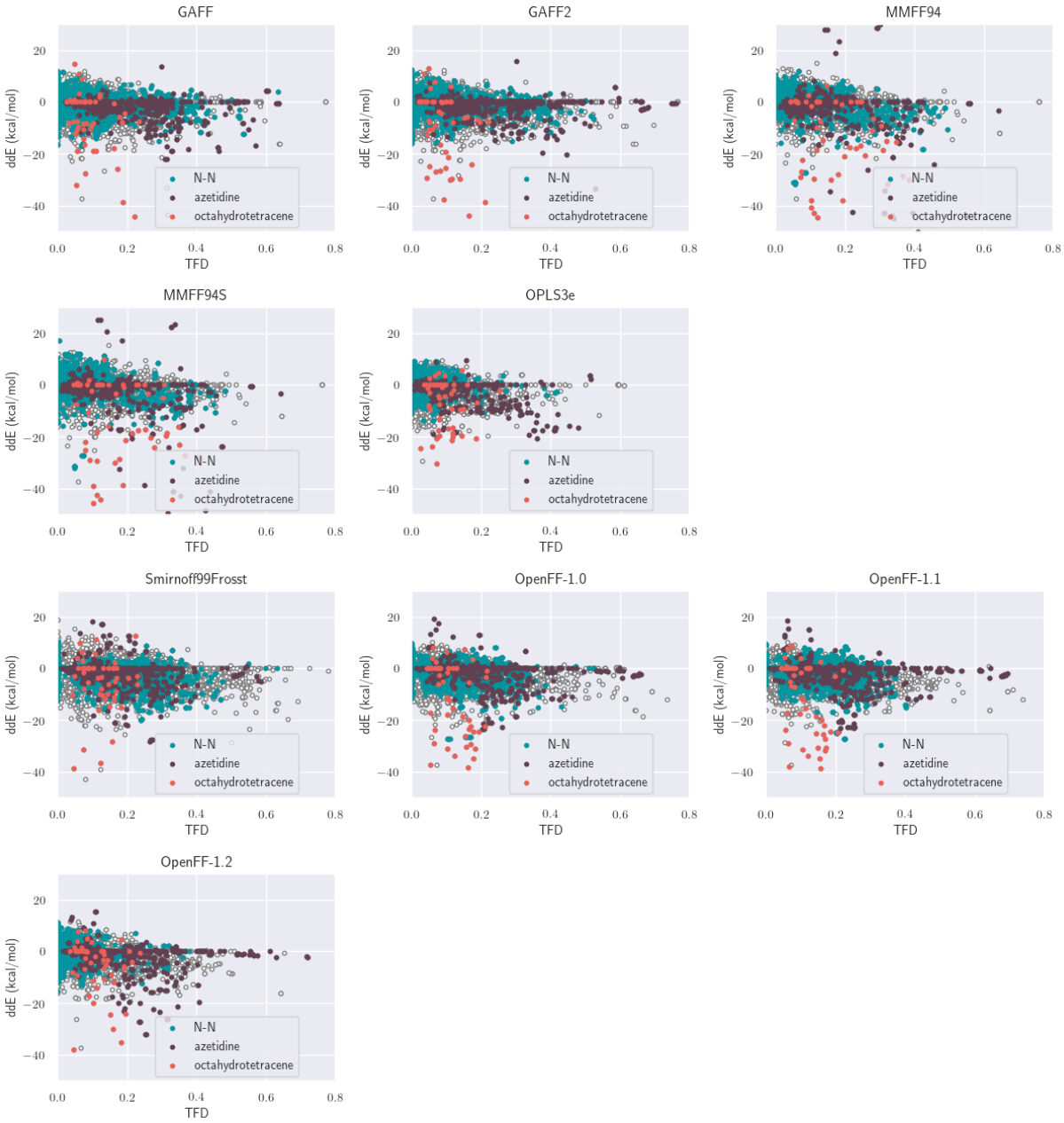


Figure S.9: Scatter plots of relative conformer energies versus TFD scores for all the force fields. Colors highlight particular chemical groups that appear to be systematic outliers in energies or geometries. Corresponding statistics (average and standard deviation) of the distributions are listed in Table 1 and illustrated in Figure S.10.

Table 1: Statistics of relative conformer energies and TFD scores considering different molecule sets for all force fields considered. The sets are either all molecules (22675 structures), molecules with N-N bonds (3824 structures), azetidines (543 structures), and octahydrotetracenes (50 structures). The subsequent table entries are the force field, the molecule set, the number of structures, the average relative conformer energies $\overline{\mathrm{dd}E}$, the standard deviation of relative conformer energies $\sigma(\mathrm{dd}E)$, the average torsion fingerprint score $\overline{\mathrm{TFD}}$, and the standard deviation of the torsion fingerprint scores $\sigma(\mathrm{TFD})$. The distributions are illustrated in Figure S.9 and the values are illustrated in Figure S.10.

Force Field	Set	Number Structures	$\overline{\mathrm{dd}E}$ [kcal/mol]	$\sigma(\mathrm{dd}E)$ [kcal/mol]	$\overline{\mathrm{TFD}}$	$\sigma(\mathrm{TFD})$
GAFF	all	22675	0.07	0.07	-0.82	2.84
GAFF	N-N	3824	0.08	0.09	-0.23	3.42
GAFF	azetidine	543	0.23	0.12	-2.29	4.13
GAFF	octahydrotetracene	50	0.09	0.05	-7.35	11.61
GAFF2	all	22675	0.08	0.08	-0.81	2.84
GAFF2	N-N	3824	0.08	0.09	-0.31	3.37
GAFF2	azetidine	543	0.23	0.15	-2.12	4.03
GAFF2	octahydrotetracene	50	0.09	0.05	-9.81	13.63
MMFF94	all	22675	0.07	0.07	-0.95	3.34
MMFF94	N-N	3824	0.07	0.07	-0.09	3.51
MMFF94	azetidine	543	0.16	0.11	-2.71	8.77
MMFF94	octahydrotetracene	50	0.17	0.09	-13.64	14.21
MMFF94S	all	22675	0.07	0.07	-0.88	3.27
MMFF94S	N-N	3824	0.06	0.07	0.22	3.70
MMFF94S	azetidine	543	0.16	0.11	-2.15	7.24
MMFF94S	octahydrotetracene	50	0.17	0.10	-13.62	14.52
OPLS3e	all	22675	0.05	0.05	-0.78	2.45
OPLS3e	N-N	3824	0.03	0.04	-0.35	2.77
OPLS3e	azetidine	543	0.12	0.10	-2.28	4.57
OPLS3e	octahydrotetracene	50	0.09	0.04	-7.18	9.12
Smirnoff99Frosst	all	22675	0.14	0.10	-1.55	3.25
Smirnoff99Frosst	N-N	3824	0.16	0.10	-2.09	3.56
Smirnoff99Frosst	azetidine	543	0.18	0.10	-1.93	5.50
Smirnoff99Frosst	octahydrotetracene	50	0.12	0.05	-5.44	10.56
OpenFF-1.0	all	22675	0.08	0.08	-1.10	2.88
OpenFF-1.0	N-N	3824	0.12	0.08	-1.27	3.38
OpenFF-1.0	azetidine	543	0.21	0.12	-2.28	5.21
OpenFF-1.0	octahydrotetracene	50	0.12	0.05	-11.39	13.77
OpenFF-1.1	all	22675	0.09	0.08	-1.19	2.89
OpenFF-1.1	N-N	3824	0.16	0.07	-1.66	3.46
OpenFF-1.1	azetidine	543	0.21	0.13	-2.46	5.23
OpenFF-1.1	octahydrotetracene	50	0.11	0.05	-11.69	13.92
OpenFF-1.2	all	22675	0.06	0.06	-0.70	2.53
OpenFF-1.2	N-N	3824	0.04	0.04	-0.36	2.94
OpenFF-1.2	azetidine	543	0.18	0.12	-2.26	5.60
OpenFF-1.2	octahydrotetracene	50	0.11	0.05	-5.61	10.16

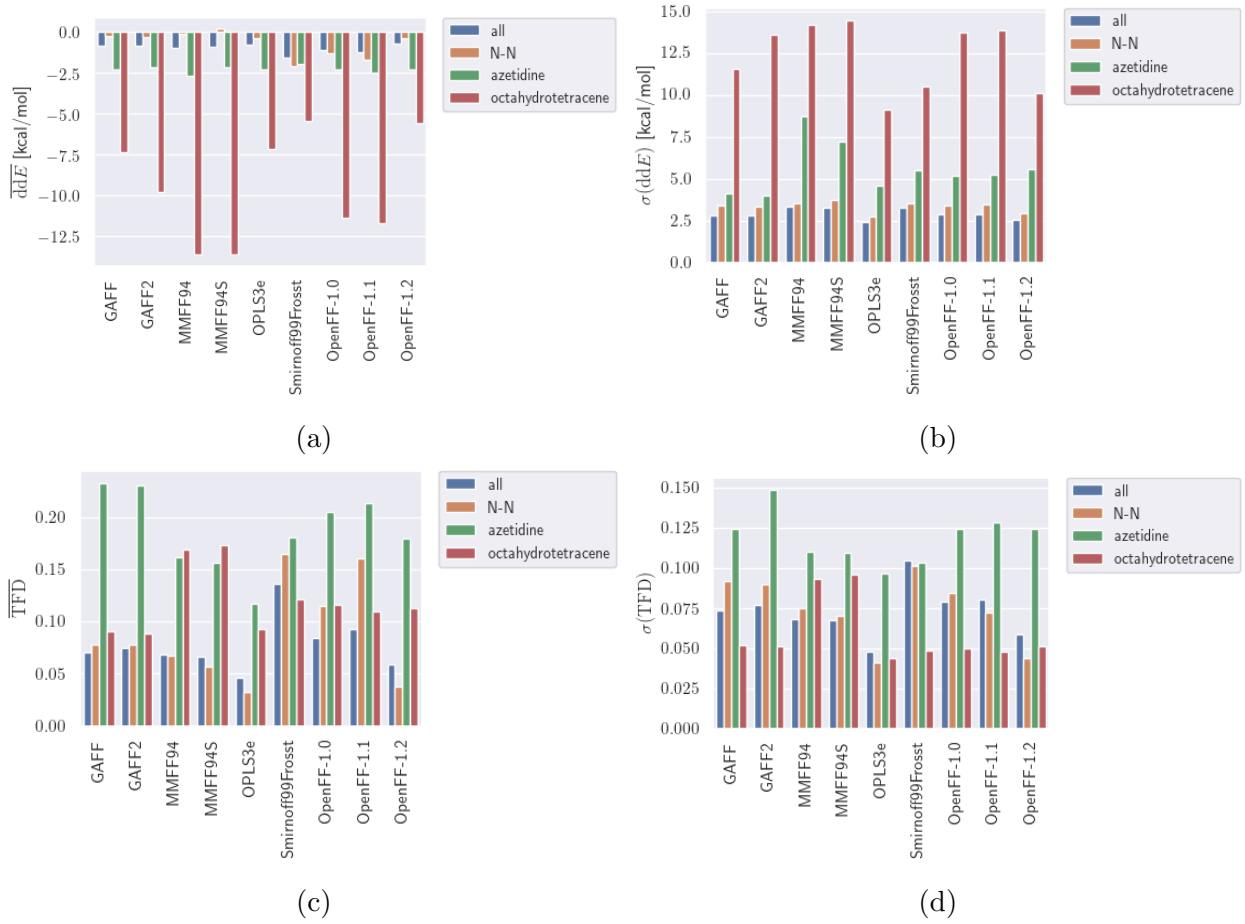


Figure S.10: Illustration of statistics of relative conformer energies and TFD scores considering different molecule sets for all force fields considered. The sets are either all structures (22675 structure, blue), molecules with N-N bonds (3824 structure, orange), azetidines (543 structure, green), and octahydrotetracenes (50 structure, red). The statistics are (a) the average relative conformer energies $\overline{\mathrm{dd}E}$, (b) the standard deviation of relative conformer energies $\sigma(\mathrm{dd}E)$, (c) the average torsion fingerprint score $\overline{\mathrm{TFD}}$, and (d) the standard deviation of the torsion fingerprint scores $\sigma(\mathrm{TFD})$. The corresponding values are listed in Table 1 and their distributions are illustrated in Figure S.9.