Supplementary Information

TS1: Mean absolute error, root mean square error, R-squared correlation, and spearman rank between relative conformer energies predicted by ANI and MP2 for each molecule in the conformer test set. Energy range is the difference between the highest and lowest energy conformer as predicted by MP2.

Molecule	MAE (kcal/mol)	RMSE (kcal/mol)	R_2	Spearman Rank	Energy Range (kcal/mol)
omegacsd_FABSOQ10	1.092	1.329	0.365	0.467	1.262
omegacsd_DIAVER	1.272	1.527	0.754	0.527	4.762
omegacsd_CDBMPI10	1.556	1.981	0.589	0.571	6.125
omegacsd_GALSEM	1.918	2.535	0.422	0.318	7.416
astex_1n2j	1.428	1.922	0.781	0.922	8.088
omegapdb_1m5f	1.433	1.753	0.739	0.854	8.798
omegapdb_1v2k	1.213	1.583	0.853	0.901	8.958
astex_1of1	1.870	1.870	0.869	0.911	10.252
omegacsd_SEYMIS	2.700	4.341	0.235	0.484	10.491
omegacsd_FIBREN	2.304	2.843	0.785	0.871	10.613
omegapdb_1qxw	2.376	3.296	0.466	0.675	10.745
omegacsd_SPIRIL	1.581	1.960	0.820	0.837	11.107
omegacsd_CUHNEY10	1.542	2.121	0.785	0.794	11.107
omegapdb_2f7p	1.537	1.879	0.837	0.910	11.689
omegacsd_CEJTIU	3.239	4.264	0.705	0.901	12.056
omegapdb_2byh	3.100	4.156	0.421	0.650	12.216
omegapdb_1z1r	3.342	4.155	0.629	0.808	13.824
omegapdb_1gs5	1.978	3.354	0.694	0.827	14.936
astex_1meh	1.551	1.914	0.947	0.958	15.013
omegapdb_1xom	1.414	1.712	0.917	0.896	15.102

TS2: DFT@ANI

Mean absolute error, root mean square error, R-squared correlation, and spearman rank between relative conformer energies predicted by ANI and DFT for each molecule in the conformer test set. The structures were optimized using ANI-2x and single point calculation on those structures were performed with ωb97x/6-31g*. Energy range is the difference between the highest and lowest energy conformer as predicted by DFT.

Molecule	MAE (kcal/mol)	RMSE (kcal/mol)	R_2	Spearman Rank	Energy Range (kcal/mol)
omegacsd_FABSOQ10	0.973	1.167	0.471	0.692	2.596
omegacsd_DIAVER	1.218	1.442	0.674	0.855	4.557
omegacsd_CDBMPI10	1.332	1.623	0.707	0.462	4.756
Omegacsd_GALSEM	1.044	1.328	0.797	0.768	6.662
omegapdb_1v2k	0.909	1.099	0.926	0.946	8.732
omegacsd_SEYMIS	0.838	1.062	0.936	0.967	9.120
astex_1n2j	1.368	1.708	0.842	0.928	10.574
omegapdb_1m5f	1.399	1.745	0.795	0.854	11.020
astex_1of1	0.537	0.700	0.982	0.982	11.618
omegapdb_2f7p	1.183	1.531	0.894	0.940	12.207
omegacsd_SPIRIL	2.219	2.716	0.818	0.809	12.567
omegacsd_FIBREN	2.015	2.462	0.813	0.938	13.063
omegapdb_1qxw	2.838	3.490	0.649	0.777	13.212
omegacsd_CEJTIU	0.705	0.873	0.988	0.926	14.155
omegapdb_1xom	0.836	1.053	0.972	0.931	14.582
omegacsd_CUHNEY10	1.397	1.792	0.957	0.877	15.657
omegapdb_1gs5	1.014	1.247	0.969	0.979	15.989
omegapdb_2byh	2.624	3.234	0.675	0.824	16.724
omegapdb_1z1r	1.888	2.363	0.900	0.947	18.865
astex_1meh	2.017	3.009	0.873	0.916	20.207

TS3: ANI@DFT

Mean absolute error, root mean square error, R-squared correlation, and spearman rank between relative conformer energies predicted by ANI and DFT for each molecule in the conformer test set. The structures were optimized using ωb97x/6-31g* and single point calculation on those structures were performed with ANI-2x. Energy range is the difference between the highest and lowest energy conformer as predicted by DFT.

Molecule	MAE (kcal/mol)	RMSE (kcal/mol)	R_2	Spearman Rank	Energy Range (kcal/mol)
omegacsd_FABSOQ10	1.076	1.305	0.141	0.250	2.205
omegacsd_DIAVER	0.518	0.648	0.835	0.960	3.394
omegacsd_CDBMPI10	0.916	1.104	0.823	0.724	5.036
omegacsd_SEYMIS	1.561	1.899	0.927	0.962	7.652
omegacsd_GALSEM	1.153	1.553	0.795	0.790	8.165
omegapdb_1v2k	1.030	1.271	0.891	0.911	8.190
omegapdb_1m5f	1.406	1.715	0.775	0.897	9.466
omegacsd_SPIRIL	1.553	1.980	0.837	0.861	9.808
astex_1n2j	1.113	1.361	0.895	0.934	10.655
omegapdb_1qxw	1.636	2.075	0.788	0.852	11.424
astex_1of1	0.596	0.749	0.982	0.971	11.594
omegacsd_FIBREN	2.067	2.675	0.836	0.953	12.298
omegapdb_2f7p	1.228	1.505	0.905	0.927	12.373
omegacsd_CEJTIU	0.933	1.151	0.980	0.864	12.907
omegacsd_CUHNEY10	1.020	1.268	0.966	0.889	13.376
omegapdb_2byh	2.466	3.131	0.619	0.833	13.980
omegapdb_1xom	1.010	1.262	0.961	0.897	15.533
omegapdb_1gs5	1.021	1.306	0.961	0.962	15.945
omegapdb_1z1r	2.396	2.912	0.816	0.885	16.596
astex_1meh	1.218	1.542	0.966	0.970	18.899

TS4: ANI@ANI_DFT@DFT

Mean absolute error, root mean square error, R-squared correlation, and spearman rank between relative conformer energies predicted by ANI and DFT for each molecule in the conformer test set. The conformers were optimized with each method and the correlation between the methods is shown below.

Molecule	MAE (kcal/mol)	RMSE (kcal/mol)	R_2	Spearman Rank
omegacsd_FABSOQ10	1.251	1.521	0.135	0.179
omegacsd_DIAVER	1.433	1.702	0.174	0.322
omegacsd_CDBMPI10	1.209	1.499	0.750	0.514
omegacsd_SEYMIS	0.828	1.004	0.963	0.967
omegacsd_GALSEM	1.965	2.526	0.400	0.385
omegapdb_1v2k	1.341	1.658	0.830	0.911
omegapdb_1m5f	1.590	1.955	0.689	0.847
omegacsd_SPIRIL	1.595	1.942	0.838	0.795
astex_1n2j	1.209	1.491	0.875	0.931
omegapdb_1qxw	2.124	2.662	0.651	0.752
astex_1of1	1.320	1.978	0.873	0.931
omegacsd_FIBREN	2.024	2.526	0.803	0.923
omegapdb_2f7p	1.198	1.511	0.903	0.933
omegacsd_CEJTIU	0.916	1.132	0.981	0.887
omegacsd_CUHNEY10	0.669	0.841	0.976	0.872
omegapdb_2byh	2.932	3.871	0.468	0.672
omegapdb_1xom	1.109	1.412	0.954	0.895
omegapdb_1gs5	1.114	1.413	0.953	0.981
omegapdb_1z1r	3.673	4.757	0.599	0.761
astex_1meh	1.454	1.911	0.947	0.945

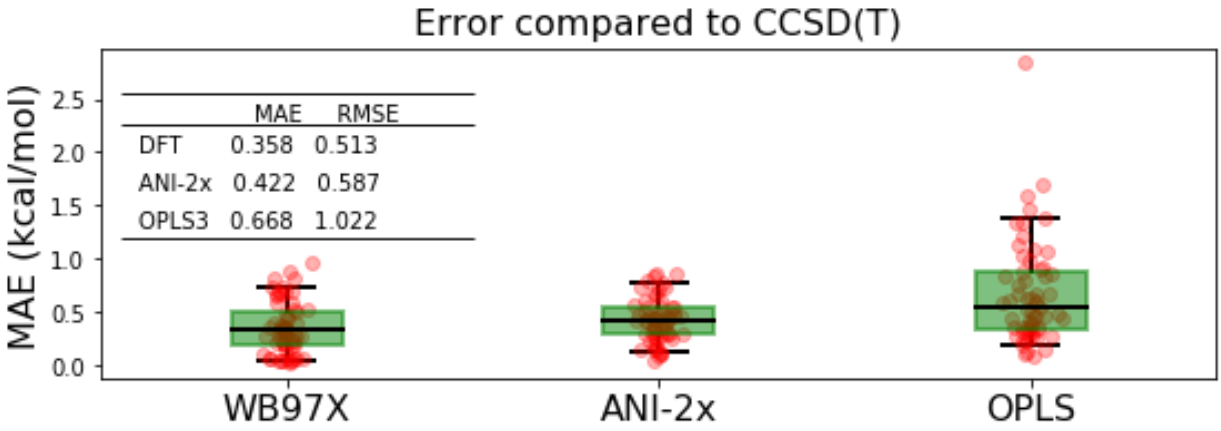
TS5: MAE and RMSE comparing ANI-2x to DFT interaction energies including deformation energy for the X40 dataset and the dataset from Halgren.

Error Metric	Halgren	X40
MAE	1.25	1.30
RMSE	1.81	1.89

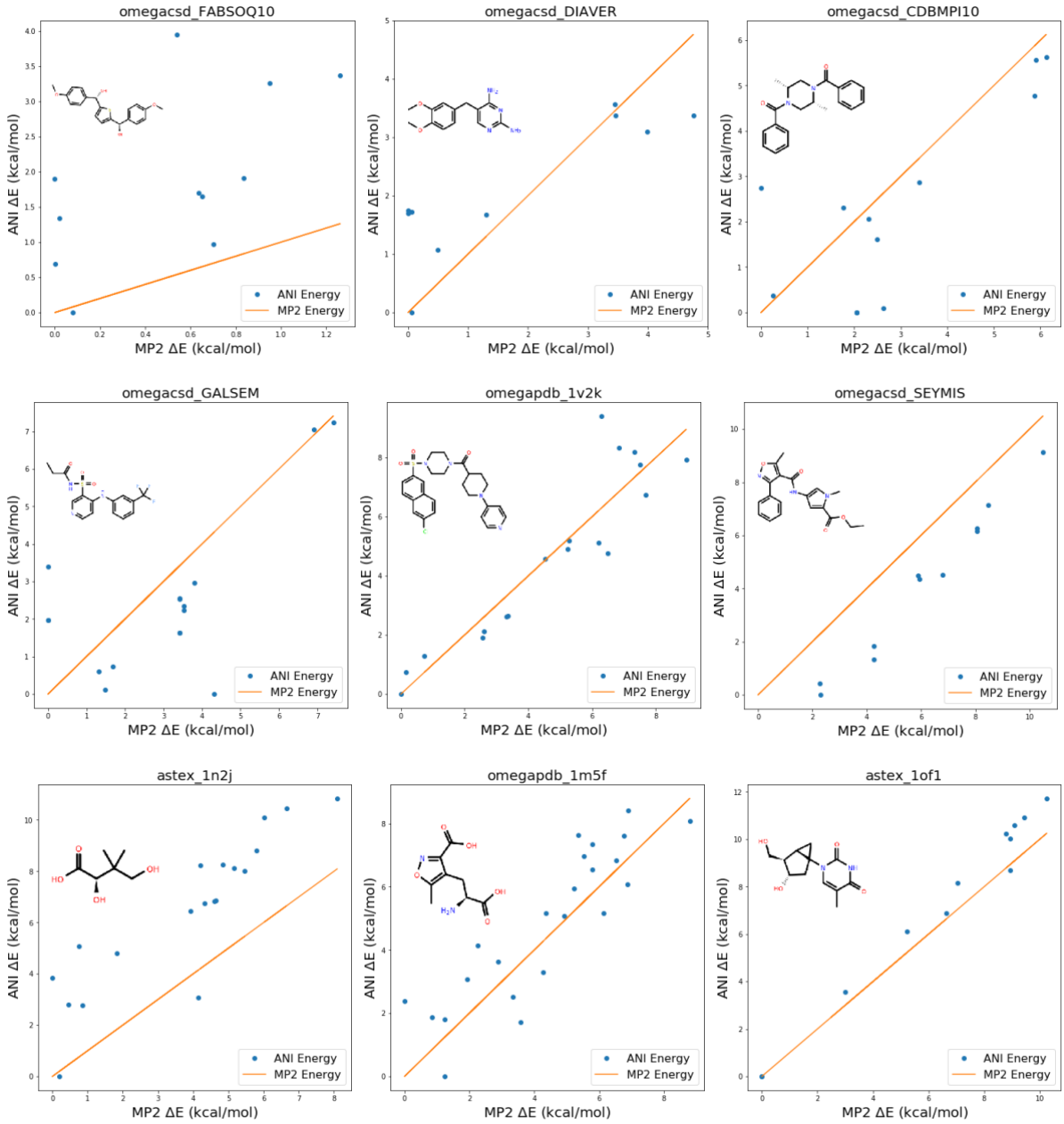
TS6: MAE and RMSE comparing ANI-2x to DFT interaction energies for the X40 dataset, separated by interaction type and whether or not deformation energy was included in the interaction energy values. The number of systems from the X40 dataset for each interaction type is also reported.

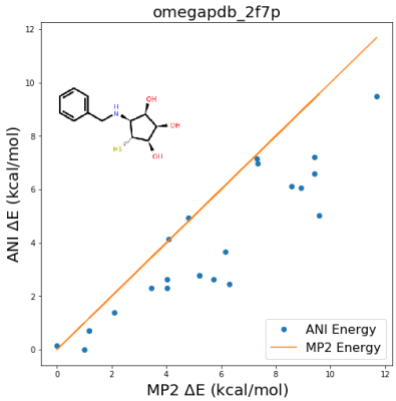
	Error Metric	London Dispersion	Induction	Dipole-dipole Interaction	Stacking	Halogen Bonds	Hydrogen Bonds
Number of Systems		2	4	2	2	4	8
No Deformation Energy	**MAE**	0.60	0.90	0.32	1.43	1.07	2.59
	RMSE	0.66	1.06	0.33	1.90	1.24	3.73
Including Deformation Energy	**MAE**	0.58	0.89	0.32	1.03	1.06	2.10
	RMSE	0.64	1.06	0.32	1.34	1.23	2.81

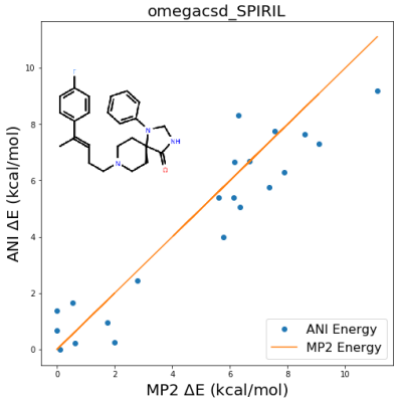
FS1: Each red point represents the MAE across all 36 conformers compared to benchmark CCSD(T)/CBS data for one molecule in the genentech benchmark. The boxes extend to include 50% of the points and the whiskers extend to include 90% of the points. The middle line represents the median value. The table shows the MAE and RMSE of each method across all conformers of all molecules.

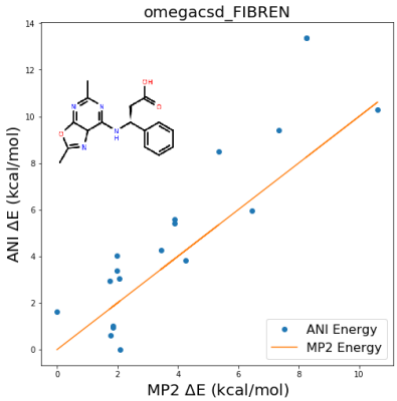


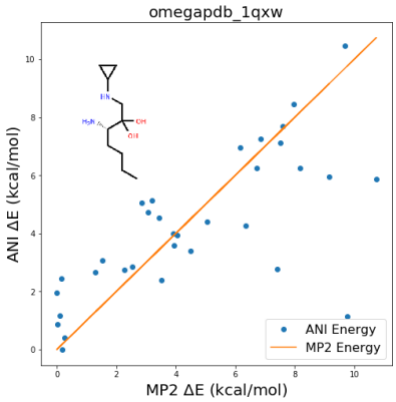
FS2: ANI-2x energies vs. MP2 energies for each of the molecules in the conformer test case. One conformation of each molecule is shown to help demonstrate the types of molecules studied.

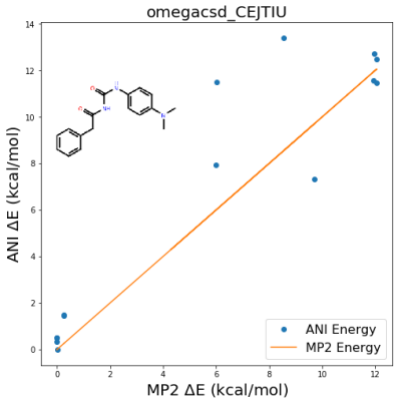


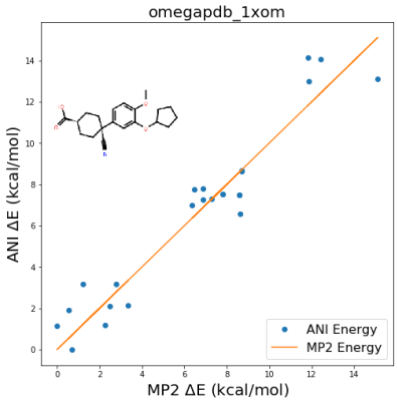

omegapdb_2f7p
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy

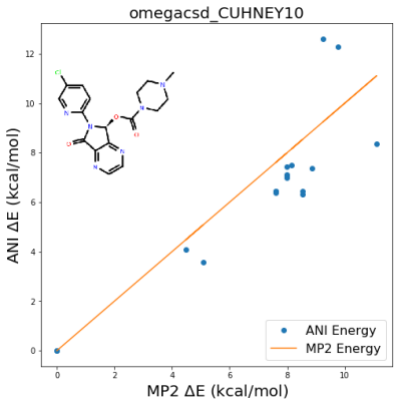

omegacsd_SPIRIL
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy

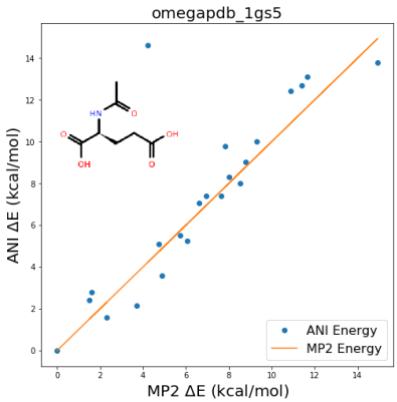

omegacsd_FIBREN
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy

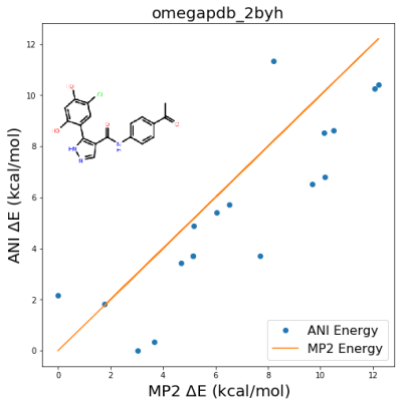

omegapdb_1qxw
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy

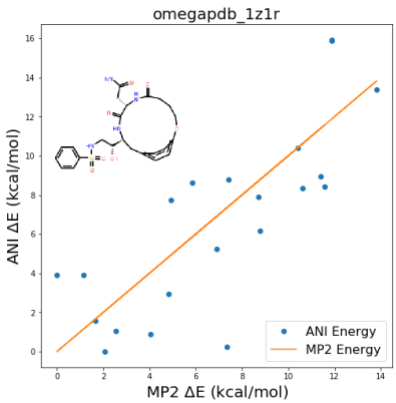

omegacsd_CEJTIU
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy

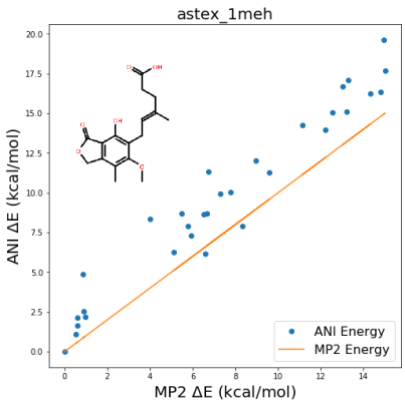

omegapdb_1xom
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy


omegacsd_CUHNEY10
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy

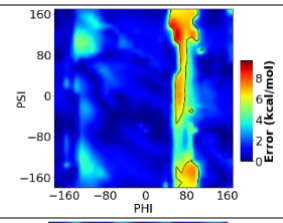
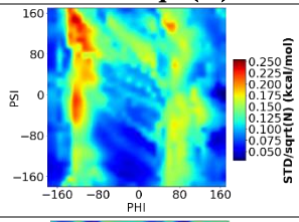
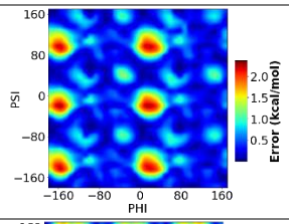
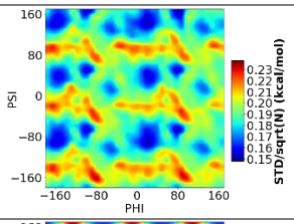
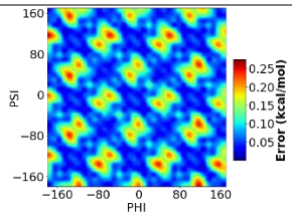
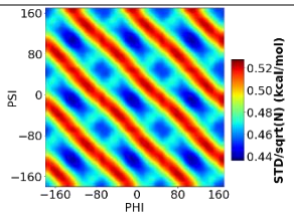
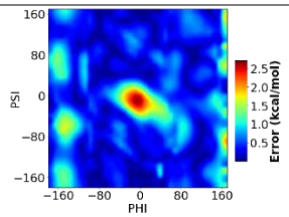
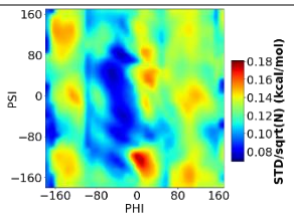

omegapdb_1gs5
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy


omegapdb_2byh
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy

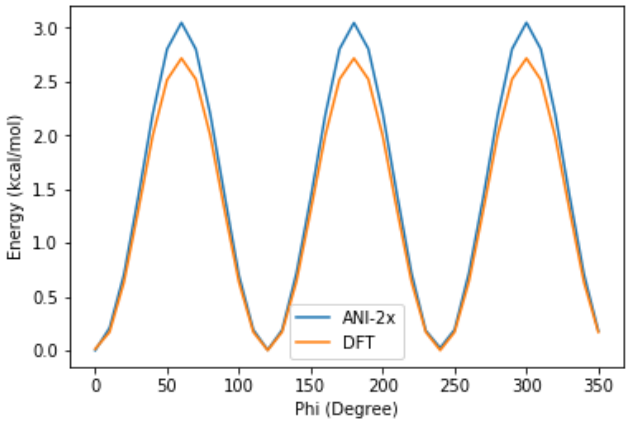

omegapdb_1z1r
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy


astex_1meh
ANI ΔE (kcal/mol)
MP2 ΔE (kcal/mol)
ANI Energy
MP2 Energy

FS3: ANI-2x error and ensemble standard deviation divided by the square root of number of atoms in the system for each of the molecules from the 2D torsion scan benchmark.

Name	Error	STD/sqrt(N)
Cysteine-Dipeptide		
DDT		
Hexafluoroacetone		
Bendamustine		

FS4: HCCH ethyl rotation relaxed scan with ANI-2x and ωb97x/6-31g*. ANI has an MAE of 0.15 kcal/mol and an RMSE of 0.18 kcal/mol.



Methods:

The bond lengths, angles, and dihedrals analyzed during the conformer search and score test were attained by iterating over all bonds using the RDKit software package. RMSD calculations were performed using open babel's python implementation pybel and exclude hydrogens.

ANI-2x contains an ensemble of 8 models. Each model contains a separate atomic network for each species. Table S4 shows details for these networks.

TS7:

		Hydrogen		
	Layer 1	Layer 2	Layer 3	Layer 4
Nodes	256	192	160	1
Activation	CELU	CELU	CELU	Linear
Regularization	L2 (5.0E-3)	L2(1.0E-6)	L2(1.0E-6)	None
		Carbon		
Nodes	224	192	160	1
Activation	CELU	CELU	CELU	Linear
Regularization	L2(5.0E-3)	L2(1.0E-6)	L2(1.0E-6)	None
		Nitrogen		
Nodes	192	160	128	1
Activation	CELU	CELU	CELU	Linear
Regularization	L2(5.0E-3)	L2(1.0E-6)	L2(1.0E-6)	None
		Oxygen		
Nodes	192	160	128	1
Activation	CELU	CELU	CELU	Linear
Regularization	L2(5.0E-3)	L2(1.0E-6)	L2(1.0E-6)	None
		Sulfur/Fluorine/Chlorine		
Nodes	160	128	96	1
Activation	CELU	CELU	CELU	Linear
Regularization	L2(5.0E-3)	L2(1.0E-6)	L2(1.0E-6)	None

TS8: Comprehensive Machine-learning Potential version 2 (COMP6v2) benchmark.

BENCHMARK	# OF MOLECULES	# OF CONFORMATIONS	AVERAGE ATOMS/MOLECULE (STDV.)
S66X8	66	528	20(7)
TRIPEPTIDES	345	3536	51(7)
MD BENCHMARK	14	1791	75(73)
GDB-12TO13	2000	24000	26(3)
GDB-10TO11	1746	41670	21(3)
GDB-07TO09	2625	63000	16(3)
DRUGBANK	1451	23203	44(18)

TS9: Validation RMSE for energy and forces for each ensemble member.

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**	**Average**
Energy RMSE (kcal/mol)	1.792	1.796	1.817	1.776	1.802	1.804	1.791	1.833	1.800
Force RMSE (kcal/mol/A)	3.695	3.692	3.684	3.679	3.689	3.710	3.667	3.714	3.691

The ANI model atomic environment vector (AEV) is computed using the in-house NeuroChem software suite. These AEVs are computed identically to those published in the ANI-1 work.7 In this work the atomic elements C, H, N, and O are described by the AEVs (using the parameters below) yielding a total of 384 AEV elements per atom. The AEV parameters used to train each model are supplied below.

Radial Parameters:

- Radial Cutoff= 5.1 $\AA$
- η_{Radial}= 19.70000
- $R_{SRadial}$=[8.0000000e+01, 1.0687500e+00, 1.3375000e+00, 1.6062500e+00, 1.8750000e+00, 2.1437500e+00, 2.4125000e+00, 2.6812500e+00, 2.9500000e+00, 3.2187500e+00, 3.4875000e+00, 3.7562500e+00, 4.0250000e+00, 4.2937500e+00, 4.5625000e+00, 4.8312500e+00] $\AA$

Angular Parameters:

- Angular Cutoff= 3.5 $\AA$
- $\eta_{Angular}$= 12.50000
- $R_{sRadial}$=[8.0000000e-01, 1.1375000e+00, 1.4750000e+00, 1.8125000e+00, 2.1500000e+00, 2.4875000e+00, 2.8250000e+00, 3.1625000e+00]
- ζ= 14.10000
- θs=[3.9269908e-01, 1.1780972e+00, 1.9634954e+00, 2.7488936e+00]