

Supporting Information

Selection of theory/level in *ab initio* calculations

For the *ab initio* gas-phase cluster calculations, the B3PW91 approximation with the LANLD2Z basis set yields results at the same accuracy level as other all-electron calculations. Table S1 provides a comparison of the theory/level dependence of the *ab initio* gas-phase cluster calculations.

Since we had about 300 binding sites, the criteria for the choice of theory/level are meant to balance accuracy and computational cost. We examined the accuracy of the MP2 and the B3LYP wave-function approximations, which have been widely used on small molecular complexes in the gas phase. We applied these approximations to systems containing an ion (Na^+ , K^+ , Ca^{2+}) with either one H_2O or NH_3 molecule. To calculate the binding energies of the above reference system, we used all-electron Gaussian basis sets including 6-31G, 6-311G with extra diffuse (sp) and polarization (p,d,f) functions, and Def2-TZVP, which were compared with effective core potentials (ECP) LANL2DZ, SDDALL and CEP-121. All calculations were performed with removal of the BSSE to enhance the accuracy of binding energies, which are shown in Tables S2 to S6.

The binding energy differences between the two approximations are shown in Table S3. Most of the cases have differences below 2.0 kcal/mol, except for the Ca^{2+} - NH_3 complex. The inclusion of extra diffuse functions in the all-electron treatment reduces the differences. For example, the binding energy $\langle E \rangle$ for 6-31G** changes from -1.1 kcal.mol⁻¹ to -0.5 kcal.mol⁻¹ in 6-31+G**, and for 6-311G** the change goes from -1.7 kcal.mol⁻¹ to -1.1 kcal.mol⁻¹ in 6-311+G**. This suggests that we can enhance the accuracy in B3LYP calculations by such an inclusion of extra diffuse functions.

For such small complexes, the differences when using ECP are from 4.0 (K^+ and Ca^{2+}) to 10.0 (Na) kcal/mol with high deviations (~ 6.0 kcal/mol) for SDDALL and LANL2DZ, but only a deviation of 0.2 kcal/mol for CEP-121.

For a final test of evaluating the performance and accuracy, we used the largest basis set 6-311+G(2df,2p) as an energy reference to compute the energy differences for the two approximations. Tables 4-5 show that 6-31+G** and 6-311+G** yield the highest accuracy for both MP2 and B3LYP. The inclusion of extra diffuse functions can enhance the accuracy for basis sets 6-31G** and 6-311G** (no 'plus'), e.g., in the sodium complex, the differences were reduced from |-6.1| to |-1.4| kcal/mol and from |-4.9| to |-1.3| kcal/mol for 6-31G** and 6-311G**, respectively. In terms of the computational cost, 6-31+G* is cheaper than 6-311+G(2df,2p). To this end, B3LYP with ECP performs with higher accuracy than MP2 with ECP, especially for sodium complexes. In terms of both computational cost and accuracy, B3LYP with CEP-121 is both reasonably accurate and reasonably efficient for all of the small complexes.

For a further rigorous validation of using B3LYP with CEP-121 (see Figures 3-5), we tested the performance of B3LYP, M11, MP2 using CEP-121 against that of B3LYP, M11, MP2 and RIMP2 using 6-31++G** for larger complexes (40-80 atoms). For MP2/6-31++G** level in Ca^{2+} complex we included 6 (n-1)p electrons inside the MP2 active space to get good agreement between all tested methods for all basis sets. For consistency, the 6 (n-1)p electrons of Na and K were also included in the active MP2 space. The full-electron and effective-core-potential approximations applied to 20 frames of binding sites 193L having Na^+ , 1NI4 having K^+ , and 2AAA and 1A4V having Ca^{2+} . Within an uncertainty of less than 10 kcal/mol, the results from

using CEP-121 are identical to the results from using 6-31++G** (Figures 3-5). However, for calcium binding sites, different basis sets and different approximations can yield differences of binding energies between the two basis sets as large as 20-60 kcal/mol, depending on the number of atoms and net charges. Note that there are constant shifts even within QM calculations, especially in calcium-binding sites.

We found that the sums of separated interaction energies between water, ligands and ions are different from the interaction energies between the combined ligands forming binding sites and ions by 20-30 kcal/mol (see Table S7). This indicates that the pairwise additivity can add up at least 20 kcal/mol to the uncertainty in the parameterization of classical force fields.

In conclusion, for small systems like gas-phase clusters, we used B3PW91 with LAND2DZ to produce the results in the main text. For many and large systems like the truncated ion-binding sites, we found that the B3LYP functional with basis set CEP-121 yields consistent and reliable results in comparison with all-electron calculations, while it is computationally less expensive than using the LAND2DZ basis set and other all-electron approximations.

Supplementary Tables

	B3lyp/ 6-311++g(2df,2pd)	B3pw91/ LANL2DZ	* MP2/ 6-311++g(2df,2pd)	MP2/ 6-31+g(d)	MP2/ 6-31+g(d,p)
O₁-K⁺(Å)	2.53	2.53	2.53	2.59	2.59
O₂-K⁺(Å)	2.53	2.53	2.53	2.59	2.59
I.E. (kcal/mol)	-58.3	-57.4	-60.0	-60.0	-60.0

Table S1: Theory/basis set dependence in the *ab initio* gas-phase calculation of a model, which contains a K⁺ cation and 2 NMA molecules. * denotes the calculation in which the geometry was optimized at B3PW91/LANL2DZ, with Interaction Energy (I.E.) evaluated at MP2/6-311++g(2df,2pd).

	Basis	Na ⁺		K ⁺		Ca ²⁺		μ_1	σ_1
		H ₂ O	NH ₃	H ₂ O	NH ₃	H ₂ O	NH ₃		
ECP	SDDALL	10.1	9.8	0.0	-0.8	-2.5	-3.9	2.1	6.2
	LANL2DZ	9.3	9.4	-0.5	-0.6	-1.8	-3.0	2.1	5.7
	CEP-121	9.6	9.7	9.9	10.0	9.5	9.7	9.7	0.2
Full Electron	6-31G	-1.3	-1.7	-0.5	-0.9	-1.7	-3.1	-1.5	0.9
	6-31+G	-0.7	-1.4	-0.1	-0.6	-0.9	-2.4	-1.0	0.8
	6-31G**	-1.1	-1.4	0.2	-0.4	-1.6	-2.5	-1.1	0.9
	6-31+G**	-0.6	-0.9	0.6	0.2	-0.7	-1.5	-0.5	0.8
	6-311G	-1.2	-1.8	-0.3	-0.7	-2.0	-3.2	-1.5	1.0
	6-311+G	-0.8	-1.6	0.3	-0.4	-1.5	-2.9	-1.2	1.1
	6-311G**	-1.3	-1.6	0.0	-0.1	-3.6	-3.8	-1.7	1.6
	6-311+G**	-0.5	-1.2	0.7	0.3	-2.7	-3.4	-1.1	1.6
	6-311+G(2df,2p)	-0.9	-1.7	0.6	0.3	-2.4	-3.1	-1.2	1.5
	Def2TZV	-1.2	-2.0	-0.6	-1.1	-3.3	-3.4	-1.9	1.2
	μ_2	1.5	1.0	0.8	0.4	-1.2	-2.0	Statistics	
	σ_2	4.7	4.9	2.8	2.9	3.3	3.6		

Table S2: Differences ($\Delta\Delta_{\text{Bind}}E$) between the binding energies calculated with B3LYP and MP2, and average (μ_1 and μ_2) and standard deviation (σ_1 and σ_2) of the differences considering the same basis set over all complex ($\mu_1 \pm \sigma_1$) and considering the same complex over all basis set ($\mu_2 \pm \sigma_2$). All values are expressed in kcal/mol.

	Basis	Na ⁺		K ⁺		Ca ²⁺	
		H ₂ O	NH ₃	H ₂ O	NH ₃	H ₂ O	NH ₃
ECP	SDDALL	-21.0	-26.8	-14.2	-17.1	-59.2	-70.5
	LANL2DZ	-24.0	-22.9	-16.0	-14.5	-53.1	-55.7
	CEP-121	-23.0	-22.8	-14.1	-12.5	-53.6	-53.6
Full Electron	6-31G	-27.8	-28.7	-17.4	-16.9	-55.1	-59.1
	6-31+G	-23.3	-23.1	-14.5	-12.5	-49.9	-52.8
	6-31G**	-23.8	-26.6	-15.2	-16.8	-52.1	-58.5
	6-31+G**	-18.6	-22.0	-11.6	-12.9	-45.9	-53.2
	6-311G	-27.0	-27.5	-17.7	-16.9	-57.6	-60.6
	6-311+G	-23.3	-23.4	-15.1	-13.4	-53.4	-56.4
	6-311G**	-22.9	-25.1	-15.3	-16.2	-56.3	-62.5
	6-311+G**	-18.5	-21.4	-11.9	-13.0	-50.9	-58.5
	6-311+G(2df,2p)	-17.5	-20.6	-10.9	-12.1	-50.0	-58.0
	Def2-TZV	-23.6	-24.1	-14.7	-13.5	-50.8	-54.2

Table S3: Binding energies (interaction energies between ions and surroundings) obtained for molecular gas phase complexes using B3LYP wave function with different Gaussian basis sets. All values are expressed in kcal/mol.

	Basis	Na ⁺		K ⁺		Ca ²⁺		μ_1	σ_1
		H ₂ O	NH ₃	H ₂ O	NH ₃	H ₂ O	NH ₃		
ECP	SDDALL	10.1	9.8	0.0	-0.8	-2.5	-3.9	2.1	6.2
	LANL2DZ	9.3	9.4	-0.5	-0.6	-1.8	-3.0	2.1	5.7
	CEP-121	9.6	9.7	9.9	10.0	9.5	9.7	9.7	0.2
Full Electron	6-31G	-1.3	-1.7	-0.5	-0.9	-1.7	-3.1	-1.5	0.9
	6-31+G	-0.7	-1.4	-0.1	-0.6	-0.9	-2.4	-1.0	0.8
	6-31G**	-1.1	-1.4	0.2	-0.4	-1.6	-2.5	-1.1	0.9
	6-31+G**	-0.6	-0.9	0.6	0.2	-0.7	-1.5	-0.5	0.8
	6-311G	-1.2	-1.8	-0.3	-0.7	-2.0	-3.2	-1.5	1.0
	6-311+G	-0.8	-1.6	0.3	-0.4	-1.5	-2.9	-1.2	1.1
	6-311G**	-1.3	-1.6	0.0	-0.1	-3.6	-3.8	-1.7	1.6
	6-311+G**	-0.5	-1.2	0.7	0.3	-2.7	-3.4	-1.1	1.6
	6-311+G(2df,2p)	-0.9	-1.7	0.6	0.3	-2.4	-3.1	-1.2	1.5
	Def2TZV	-1.2	-2.0	-0.6	-1.1	-3.3	-3.4	-1.9	1.2
	μ_2	1.5	1.0	0.8	0.4	-1.2	-2.0	<i>Statistics</i>	
	σ_2	4.7	4.9	2.8	2.9	3.3	3.6		

Table S4: Differences ($\Delta\Delta_{\text{Bind}}E$) between the binding energies calculated with B3LYP and MP2, and average (μ_1 and μ_2) and standard deviation (σ_1 and σ_2) of the differences considering the same basis set over all complex ($\mu_1 \pm \sigma_1$) and considering the same complex over all basis set ($\mu_2 \pm \sigma_2$). All values are expressed in kcal/mol.

	Basis	Na ⁺		K ⁺		Ca ²⁺		μ_1	σ_1
		H ₂ O	NH ₃	H ₂ O	NH ₃	H ₂ O	NH ₃		
ECP	SDDALL	-14.4	-17.7	-2.7	-4.0	-9.1	-11.6	-9.9	5.8
	LANL2DZ	-16.6	-13.5	-4.0	-1.5	-3.8	2.3	-6.2	7.3
	CEP-121	-16.0	-13.6	-12.6	-10.2	-15.6	-8.3	-12.7	3.0
Full Electron	6-31G	-10.0	-8.1	-5.4	-3.7	-5.9	-1.1	-5.7	3.1
	6-31+G	-5.9	-2.8	-2.9	0.4	-1.5	4.6	-1.4	3.6
	6-31G**	-6.1	-6.3	-3.8	-4.0	-2.9	-1.1	-4.0	2.0
	6-31+G**	-1.4	-2.2	-0.8	-0.8	2.4	3.3	0.1	2.2
	6-311G	-9.2	-6.8	-5.9	-3.8	-8.0	-2.5	-6.0	2.5
	6-311+G	-6.0	-2.9	-3.8	-0.7	-4.4	1.5	-2.7	2.7
	6-311G**	-4.9	-4.6	-3.8	-3.8	-5.1	-3.7	-4.3	0.6
	6-311+G**	-1.3	-1.3	-1.1	-1.0	-0.7	-0.2	-0.9	0.4
	Def2-TZV	-5.7	-3.2	-2.6	-0.1	0.0	4.2	-1.2	3.4
μ_2	-8.1	-6.9	-4.1	-2.8	-4.5	-1.1	<i>Statistics</i>		
σ_2	5.2	5.3	3.0	2.9	4.8	5.0			

Table S5: Differences ($\Delta\Delta_{\text{Bind}}E_{\text{GBS}}$) between the binding energies calculated in each level and the value obtained with 6-311+G(2df,2p) basis set for MP2 wave function and average (μ_1 and μ_2) and standard deviation (σ_1 and σ_2) of the differences considering the same basis set over all complex ($\mu_1\pm\sigma_1$) and considering the same complex over all basis set ($\mu_2\pm\sigma_2$). All values are expressed in kcal/mol.

	Basis	Na ⁺		K ⁺		Ca ²⁺		μ_1	σ_1
		H ₂ O	NH ₃	H ₂ O	NH ₃	H ₂ O	NH ₃		
ECP	SDDALL	-3.4	-6.2	-3.4	-5.1	-9.2	-12.5	-6.6	3.6
	LANL2DZ	-6.5	-2.4	-5.2	-2.4	-3.2	2.3	-2.9	3.0
	CEP-121	-5.5	-2.3	-3.3	-0.4	-3.7	4.5	-1.8	3.5
Full Electron	6-31G	-10.3	-8.2	-6.5	-4.9	-5.2	-1.1	-6.0	3.1
	6-31+G	-5.7	-2.5	-3.7	-0.4	0.0	5.3	-1.2	3.8
	6-31G**	-6.2	-6.1	-4.3	-4.7	-2.1	-0.5	-4.0	2.3
	6-31+G**	-1.1	-1.4	-0.8	-0.9	4.1	4.8	0.8	2.8
	6-311G	-9.5	-6.9	-6.8	-4.8	-7.6	-2.6	-6.4	2.4
	6-311+G	-5.8	-2.8	-4.2	-1.4	-3.4	1.6	-2.7	2.6
	6-311G**	-5.4	-4.5	-4.4	-4.2	-6.3	-4.5	-4.9	0.8
	6-311+G**	-0.9	-0.8	-1.0	-0.9	-0.9	-0.5	-0.9	0.2
	Def2-TZV	-6.0	-3.6	-3.9	-1.4	-0.8	3.8	-2.0	3.4
μ_2	-5.5	-4.0	-3.9	-2.6	-3.2	0.1	<i>Statistics</i>		
σ_2	2.8	2.4	1.8	1.9	3.6	5.0			

Table S6: Differences ($\Delta\Delta_{\text{Bind}}E_{\text{GBS}}$) between the binding energies calculated in each level and the value obtained with 6-311+G(2df,2p) basis set for B3LYP wave function and average (μ_1 and μ_2) and standard deviation (σ_1 and σ_2) of the differences considering the same basis set over all complex ($\mu_1\pm\sigma_1$) and considering the same complex over all basis set ($\mu_2\pm\sigma_2$). All values are expressed in kcal/mol.

Binding Site	6-31++G**				CEP-121		
	B3LYP	M11	MP2	RIMP2	B3LYP	M11	MP2
193L (47 atoms)	-40±5	-41±6	-37±6	-23±7	-43±6	-44±6	-42±6
193L (53 atoms)	1±7	0±7	4±7	-14±8	-2±7	-4±7	-1±7
IN14 (55 atoms)	50±2	50±2	50±2	56±10	50±2	50±2	50±2
IN14 (78 atoms)	-24±7	-26±7	N/A	-22±10	-22±7	-23±7	N/A
1A4V (40 atoms)	-543±5	-540±8	-528±8	-532±10	-560±6	-549±8	-542±8
2AAA (53 atoms)	-580±6	-599±6	-568±6	-568±6	-636±5	-652±6	-629±5

Table S7: Binding energy (kcal/mol) in B3LYP, M11, MP2 and RI-MP2 using 6-31++G** and CEP-121 basis sets.

	PDB	Ion	Binding Energy		
			C36	Drude	QM
1	1J5Y	K ⁺	-123±15	-107±13	-118±13
2	1JF8	K ⁺	-210±9	-191±7	-187±8
3	1NI4	K ⁺	-78±10	-68±6	-72±6
4	2BFD	K ⁺	-131±8	-133±5	-130±7
5	1P36	K ⁺	-236±11	-198±9	-194±7
6	1LJL	K ⁺	-205±8	-185±4	-184±4
7	1TYY	K ⁺	-135±8	-102±5	-100±5
8	1DTW	K ⁺	-136±7	132±6	-131±6
9	1V3Z	K ⁺	-53±11	-48±11	-53±13
10	4LS7	K ⁺	-69±7	-68±7	-61±4
11	193L	Na ⁺	-64±10	-64±9	-73±7
12	1E43	Na ⁺	-190±8	-175±8	-161±4
13	1SFQ	Na ⁺	-115±6	-110±6	-123±6
14	1GEN	Na ⁺	-230±6	-189±7	-192±4
15	3N0U	Na ⁺	-56±9	-47±10	-59±7
16	1L5B	Na ⁺	-123±10	-113±11	-131±7
17	1QNJ	Na ⁺	-239±12	-229±12	-205±9
18	1QUS	Na ⁺	-357±9	-325±10	-297±9
19	1S36	Na ⁺	-228±8	-178±9	-181±7
20	1SK4	Na ⁺	-173±11	-154±10	-177±8
21	3LI3	Ca ²⁺	-838±20	-682±18	-697±16
22	1BLI	Ca ²⁺	-750±18	-656±17	-595±15
23	2UUY	Ca ²⁺	-813±21	-732±19	-746±13
24	1A4V	Ca ²⁺	-944±16	-780±14	-793±9
25	4KTS	Ca ²⁺	-861±21	-732±20	-745±11
26	2AAA	Ca ²⁺	-10 ³ ±14	-887±14	-914±8
27	3TZ1	Ca ²⁺	-925±16	-781±15	-800±11
28	1EXR	Ca ²⁺	-893±14	-675±13	-710±8
29	1RWY	Ca ²⁺	-791±19	-575±20	-609±10
30	3ICB	Ca ²⁺	-791±14	-681±13	-704±7

Table S8: Binding energies of ions in binding sites of the enzymes without NBFIX for K-carbonyl oxygen atoms and Na-carbonyl oxygen atoms. NTER and CTER are used. Legends: C36 is CHARMM c36 force fields. L1, L2 and L3 are separated ligands around ions. Units are in kcal/mol.

	PDB	Ion	Binding Energy		
			C36	Drude	QM
1	1J5Y	K ⁺	-125±16	-110±11	-121±13
2	1JF8	K ⁺	-233±6	-200±4	-196±5
3	1NI4	K ⁺	-83±11	-67±4	-74±5
4	2BFD	K ⁺	-158±7	-145±5	-148±7
5	1P36	K ⁺	-221±11	-192±10	-189±10
6	1LJL	K ⁺	-230±6	-199±3	-196±5
7	1TYY	K ⁺	-134±8	-106±5	-105±6
8	1DTW	K ⁺	-155±7	-142±5	-143±5
9	1V3Z	K ⁺	-71±11	-54±6	-66±9
10	4LS7	K ⁺	-102±7	-95±10	-83±5
11	193L	Na ⁺	-85±8	-76±10	-85±7
12	1E43	Na ⁺	-187±7	-171±7	-159±5
13	1SFQ	Na ⁺	-133±6	-119±10	-131±7
14	1GEN	Na ⁺	-197±6	-174±4	-176±5
15	3N0U	Na ⁺	-55±9	-54±7	-61±7
16	1L5B	Na ⁺	-149±8	-136±5	-150±6
17	1QNJ	Na ⁺	-274±10	-242±7	-220±6
18	1QUS	Na ⁺	-364±9	-326±6	-299±9
19	1S36	Na ⁺	-208±7	-168±6	-169±7
20	1SK4	Na ⁺	-193±10	-169±9	-191±9
21	3LI3	Ca ²⁺	-857±17	-725±11	-738±14
22	1BLI	Ca ²⁺	-799±16	-689±16	-629±15
23	2UUY	Ca ²⁺	-877±20	-752±18	-786±12
24	1A4V	Ca ²⁺	-966±15	-794±10	-806±9
25	4KTS	Ca ²⁺	-932±20	-778±20	-789±8
26	2AAA	Ca ²⁺	-1126±16	-937±15	-973±12
27	3TZ1	Ca ²⁺	-963±16	-789±15	-818±11
28	1EXR	Ca ²⁺	-934±14	-712±13	-734±8
29	1RWY	Ca ²⁺	-826±17	-593±20	-629±10
30	3ICB	Ca ²⁺	-788±14	-676±13	-709±8

Table S9: Binding energies of ions in binding sites of the enzymes in which ACE and CT3 termini are used.

Ion	PDB	Types of oxygen atoms		
		-OH	-C=O	-COO ⁻
K ⁺	1J5Y	0.00	1.81	0.00
	1JF8	0.29	2.81	1.24
	1N14	0.00	3.48	0.14
	2BFD	0.00	4.43	0.00
	1P36	0.52	0.10	1.10
	1LJL	0.62	3.15	1.00
	1TYY	0.05	4.62	0.67
	1DTW	0.10	4.57	0.00
	1V3Z	0.00	3.14	0.00
	4LS7	0.90	5.43	1.00
Na ⁺	193L	1.00	3.76	0.00
	1E43	0.00	1.00	4.14
	1SFQ	0.00	2.00	0.00
	1GEN	0.00	4.00	0.00
	3N0U	0.00	3.00	0.00
	1L5B	0.00	4.95	0.00
	1QNJ	0.00	4.00	3.00
	1QUS	1.00	1.00	3.95
	1S36	0.00	3.53	1.00
	1SK4	0.95	3.15	0.00
Ca ²⁺	3LI3	0.00	1.90	3.05
	1BLI	0.00	1.00	5.00
	2UUY	0.00	3.00	2.29
	1A4V	0.00	2.00	3.96
	4KTS	0.00	3.00	3.81
	2AAA	0.00	1.05	4.00
	3TZ1	1.00	1.00	4.00
	1EXR	0.00	1.00	5.00
	1RWY	0.95	1.00	5.05
	3ICB	0.00	5.00	2.00

Table S10: Types of oxygen atoms in the binding sites of ion-protein simulation systems, within a 3.0 Å cutoff the binding-ions. The values represent coordination numbers of an oxygen type around the bound ions in 20 frames extracted from 4-ns simulations.

Supplementary Figures

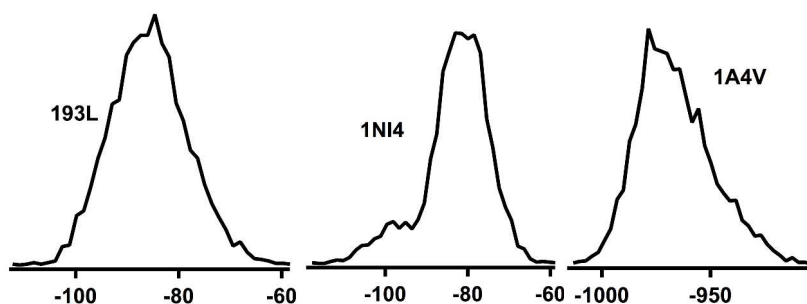


Figure S1. Histograms of binding energies of three binding sites, 193L, 1NI4 and 1A4V, evaluated using the CHARMM C36 force field.

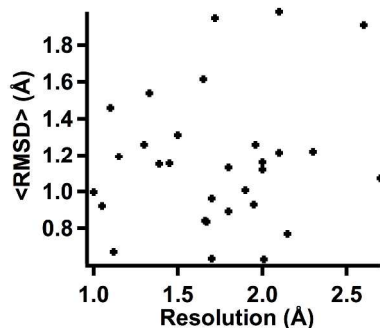


Figure S2. Resolution of the crystal structures against the averaged root-mean-square-deviation (RMSD) of the toy-model binding sites during 4 ns MD simulations. Most proteins have RMSD less than 2.6 Å, indicating significant conformation spaces for all proteins for estimating the binding energies between the ions and enzymes.

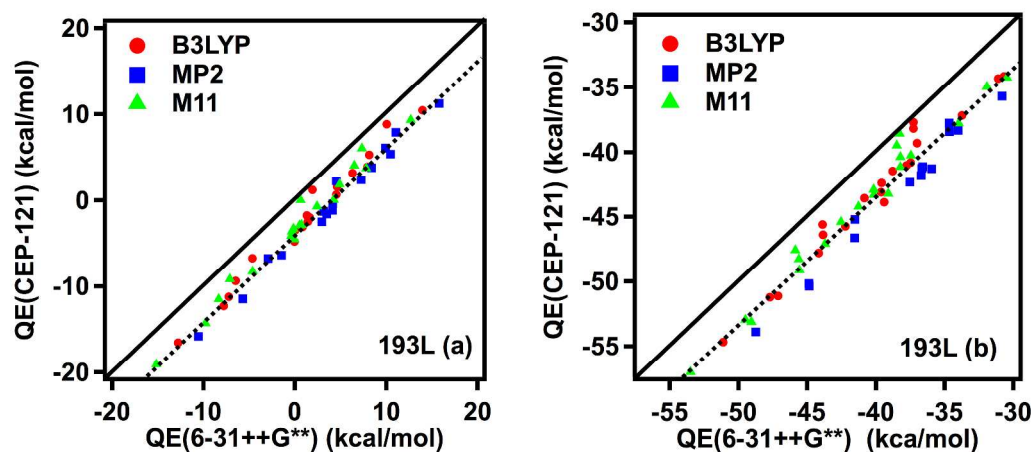


Figure S3. QM binding energies (QE) for Na^+ binding site 193L using effective core potential CEP-121 and full electron 6-31++G** basis sets.

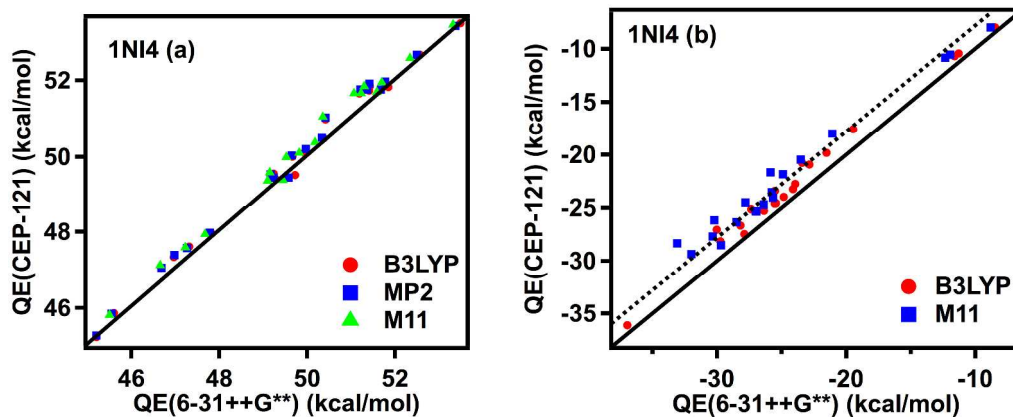


Figure S4. QM binding energies (QE) for K^+ 1NI4 with 53 (a) and 78 (b) atoms at B3LYP and M11 in ECPs CEP-121 and full electron 6-31++G** basis sets.

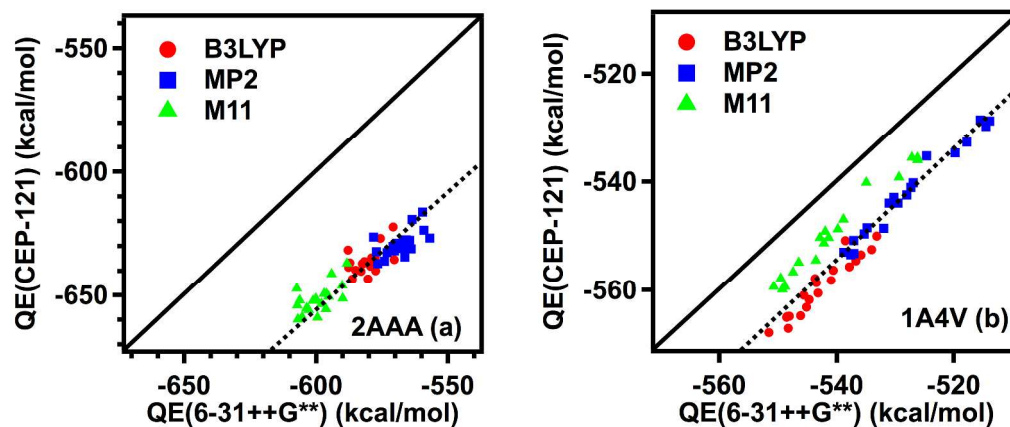


Figure S5. QM bind energies (QE) for calcium complex 2AAA (a) and 1A4V (b) at B3LYP, M11 and MP2 in ECPs CEP-121 and full electron 6-31++G** basis sets.

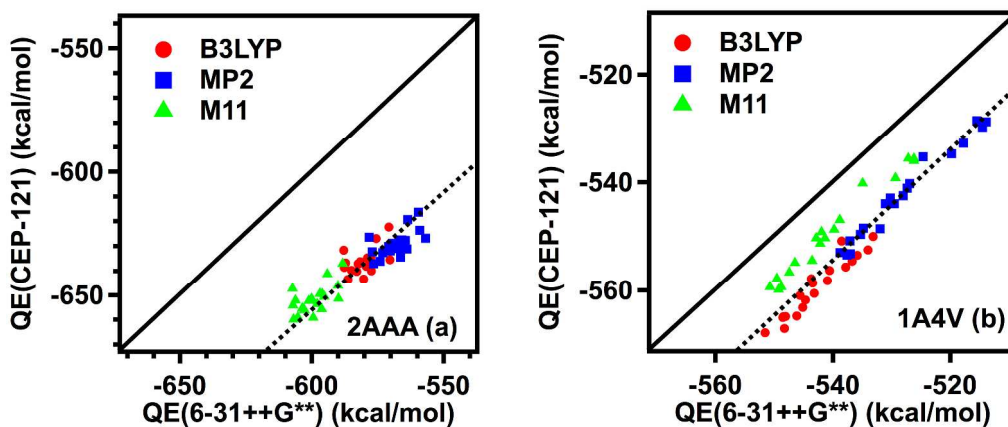


Figure S6. QM binding energies (QE) for Ca^{2+} 2AAA (a) and 1A4V (b) at B3LYP, M11 and MP2 in ECPs CEP-121 and full electron 6-31++G** basis sets.

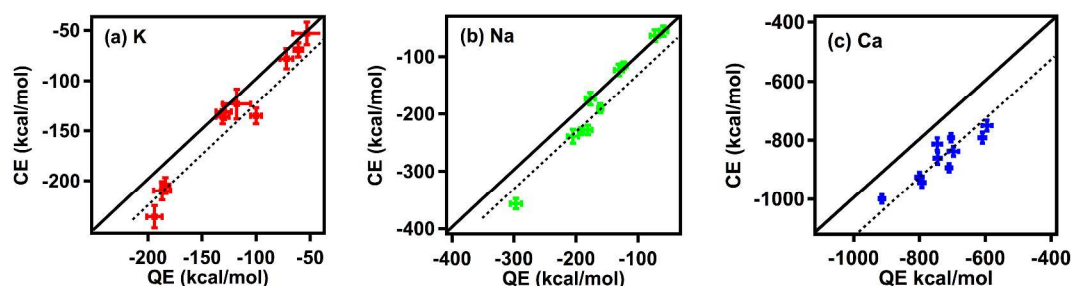


Figure S7. Classical binding energy (CE) computed without NBFIX versus QM binding energy (QE). NTER and CTER termini are used. The solid line represent the agreement between classical and QM binding energies. The dash line crosses the rest of the data points, which are off the solid line. The dash line denotes the region, where the rest of the data points are located.

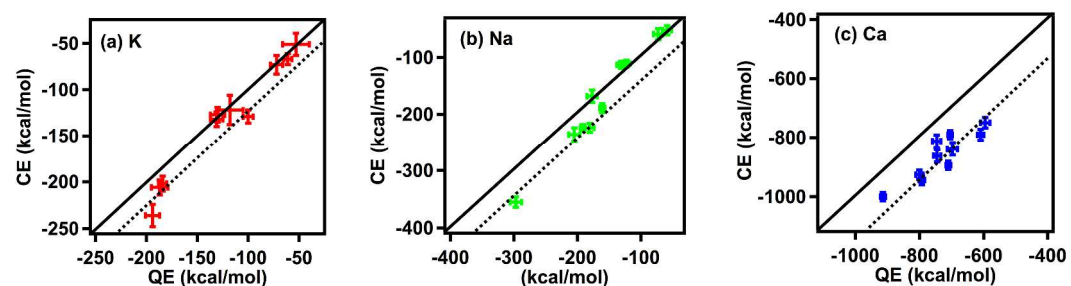


Figure S8. Classical binding energy (CE) computed with NBFIX versus QM binding energy (QE). NTER and CTER termini are used. The solid line represent the agreement between classical and QM binding energies. The dash line crosses the rest of the data points, which are off the solid line.

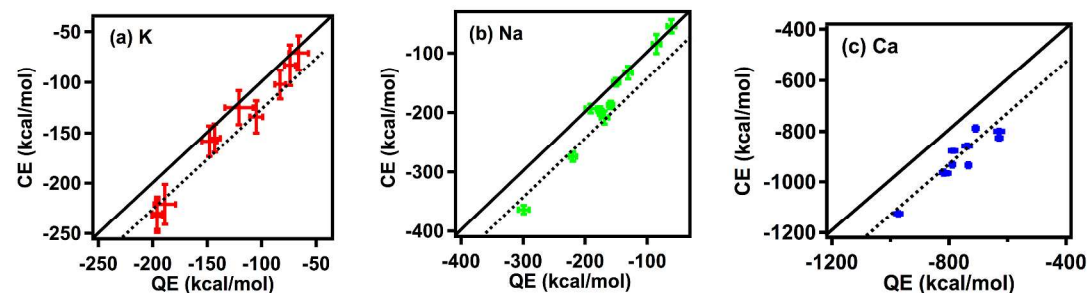


Figure S9. Classical binding energy (CE) versus QM binding energy (QE). ACE and CT3 termini are used. The solid line represent the agreement between classical and QM binding energies. The dash line crosses the rest of the data points, which are off the solid line.