Supplemental Information

Table S1: Binding energies of the ions in 30 metalloproteins computed from B3LYP/CEP-121, DFTB3/3OB approximations, and the Drude and C36 force fields.

Ion	PDB	B3LYP/CEP-121	DFTB3/3OB	Drude	C36	$\Delta E/E$ (%)		
						DFTB3/3OB	Drude	C36
K^+	1J5Y	-121	-118	-110	-125	-2	-9	3
	1JF8	-196	-210	-200	-233	7	2	19
	1NI4	-74	-78	-67	-83	5	-9	12
	2BFD	-148	-152	-145	-158	3	-2	7
	1P36	-189	-200	-192	-221	6	2	17
	1LJL	-196	-210	-199	-230	7	2	17
	1TYY	-105	-118	-106	-134	12	1	28
	1DTW	-143	-150	-142	-155	5	-1	8
	1V3Z	-66	-68	-54	-71	2	-18	8
	4LS7	-83	-97	-95	-102	16	14	23
Na^+	193L	-85	-78	-76	-85	-9	-11	0
	1E43	-159	-179	-171	-187	12	8	18
	1SFQ	-131	-128	-119	-133	-2	-9	2
	1GEN	-176	-206	-174	-197	17	-1	12
	3N0U	-61	-54	-54	-55	-12	-11	-10
	1L5B	-150	-149	-136	-149	-1	-9	-1
	1QNJ	-220	-237	-242	-274	8	10	25
	1QUS	-299	-323	-326	-364	8	9	22
	1S36	-169	-179	-168	-208	6	-1	23
	1SK4	-191	-185	-169	-193	-3	-12	1
Ca^{2+}	3LI3	-738	-748	-725	-857	1	-2	16
	1BLI	-629	-662	-689	-799	5	10	27
	2UUY	-786	-797	-752	-877	1	-4	12
	1A4V	-806	-841	-794	-966	4	-1	20
	4KTS	-789	-816	-778	-932	3	-1	18
	2AAA	-973	-1003	-937	-1126	3	-4	16
	3TZ1	-818	-841	-789	-963	3	-4	18
	1EXR	-734	-784	-712	-934	7	-3	27
	1RWY	-629	-678	-593	-826	8	-6	31
	3ICB	-709	-725	-676	-788	2	-5	11

Table S2: Binding energies ($\Delta_{Bind}E$) obtained in different functionals with the 6-311++G(2d,2p) basis set for 20 sodium complexes of 193L small model, mean (μ), standard deviation (σ), minimum (min.) and maximum (max.), and the absolute differences between min. and max values of $\Delta_{Bind}E$. All numbers expressed in kcal.mol^{-1}.

Frame	PBE	PW91	BLYP	TPSS	B3LYP	M11	B2PLYP
0	-35.94	-39.88	-38.61	-37.33	-37.35	-37.23	-35.84
1	-40.78	-41.59	-40.50	-39.63	-39.35	-39.20	-38.03
2	-40.63	-41.43	-40.28	-39.54	-38.82	-38.01	-36.76
3	-38.78	-39.64	-38.42	-37.66	-37.11	-36.50	-35.36
4	-34.39	-35.38	-34.05	-33.56	-33.03	-32.90	-31.97
5	-31.95	-32.93	-31.84	-31.00	-30.51	-29.36	-28.63
6	-42.37	-43.39	-42.06	-41.65	-41.63	-42.57	-41.48
7	-38.17	-39.84	-38.50	[a]	-39.37	-40.26	-39.33
8	-31.27	-32.74	-31.38	-30.92	-31.47	-31.14	-29.91
9	-37.51	-38.43	-35.00	-36.54	-36.62	-37.34	-36.23
10	-38.48	-39.29	-37.60	-37.17	-37.38	-37.92	[a]
11	-43.30	-44.25	-42.81	-42.70	-43.79	-45.14	-44.33
12	-43.21	-44.09	-42.88	-42.45	-43.49	-44.77	-43.76
13	-37.65	-38.54	-37.27	-36.75	-37.91	-38.05	-37.10
14	-46.24	-47.30	-46.02	-45.80	-47.54	-47.94	-46.85
15	-40.20	-41.15	-39.61	-39.44	-41.08	-41.64	-40.70
16	-50.20	-50.85	-49.66	-49.62	-50.71	-52.33	-51.20
17	-47.39	-48.22	-46.91	-46.94	-47.24	-48.33	-47.27
18	-43.75	-44.52	-43.44	-43.11	-43.40	-44.29	-43.26
19	-39.00	-39.97	-38.64	-38.07	-38.79	-39.32	-38.14
μ	*-40.1*	*-41.2*	*-39.8*	*-39.5*	*-39.8*	*-40.2*	*-39.3*
σ	*4.9*	*4.7*	*4.8*	*5.0*	*5.2*	*5.8*	*5.9*
min	*-50.2*	*-50.9*	*-49.7*	*-49.6*	*-50.7*	*-52.3*	*-51.2*
max	*-31.3*	*-32.7*	*-31.4*	*-30.9*	*-30.5*	*-29.4*	*-28.6*
δ	*18.9*	*18.1*	*18.3*	*18.7*	*20.2*	*23.0*	*22.6*

a - System not converged.

Table S3: Binding energies ($\Delta_{Bind}E$) obtained in different functionals with the 6-311++G(2d,2p) basis set for 20 calcium complexes of 2AAA small model, mean (μ), standard deviation (σ), minimum (min.) and maximum (max.), and the absolute differences between min. and max values of $\Delta_{Bind}E$. All numbers expressed in kcal.mol^{-1}.

Frame	PBE	PW91	BLYP	TPSS	B3LYP	M11	B2PLYP
0	-586.81	-588.06	-580.64	-588.36	-594.67	-603.48	-598.87
1	-598.29	-599.99	-592.22	[a]	-609.76	-619.84	-615.11
2	-587.73	-589.49	-581.98	-589.82	-598.11	-607.50	-602.50
3	-593.10	-594.06	-586.44	-599.00	-602.64	-611.17	-607.30
4	-594.30	-595.39	-585.85	-595.73	-603.90	-613.17	-608.91
5	-599.98	-600.71	-592.43	-601.20	-610.50	-621.00	-615.99
6	-596.91	-598.52	-590.42	-598.72	-607.27	-616.48	-612.21
7	-586.81	-589.43	-579.67	-589.49	-597.48	-607.67	-602.46
8	-592.34	-593.90	-585.63	-597.31	-602.34	-611.61	-607.09
9	-592.57	-594.25	-585.66	-598.53	-602.99	-612.40	-607.69
10	-600.21	-600.82	-592.53	-602.68	-612.11	-622.58	-618.25
11	-597.57	-598.73	-590.56	-599.97	-607.56	-617.50	-612.34
12	-592.46	-594.01	-586.15	-593.87	-601.33	-610.76	-606.14
13	[a]	-598.72	-589.72	-604.98	-608.48	-619.26	-614.01
14	-600.77	-601.74	-594.35	-602.55	-609.26	-620.81	-614.36
15	-595.53	-596.95	-588.04	-600.26	-605.09	-614.49	-610.15
16	-591.59	-593.61	-584.73	-593.72	-598.92	-608.86	-603.42
17	-601.80	-602.45	-595.04	-602.60	[a]	-622.30	-617.55
18	-595.69	-596.59	-587.56	-597.30	-606.34	-616.32	-611.96
19	-595.77	-597.89	-589.26	[a]	[a]	-618.40	-614.32
μ	*-594.75*	*-596.27*	*-587.94*	*-597.56*	*-604.38*	*-614.78*	*-610.03*
σ	*4.56*	*4.17*	*4.33*	*4.87*	*4.97*	*5.51*	*5.49*
min	*-601.80*	*-602.45*	*-595.04*	*-604.98*	*-612.11*	*-622.58*	*-618.25*
max	*-586.81*	*-588.06*	*-579.67*	*-588.36*	*-594.67*	*-603.48*	*-598.87*
δ	*14.99*	*14.39*	*15.37*	*16.62*	*17.44*	*19.10*	*19.38*

a - System not converged.

Table S4: Binding energies ($\Delta_{Bind}E$) obtained in different functionals with the 6-311++G(2d,2p) and CEP-121 basis set and with DFTB3/3OB for 20 sodium complexes of 193L small model, mean (μ), standard deviation (σ), minimum (min.) and maximum (max.), and the absolute differences between min. and max values of $\Delta_{Bind}E$. All numbers expressed in kcal.mol^{-1}.

FRAME	6-311++G(2d,2p)			6-31++G(d,p)		CEP-121		DFTB3/3OB
	PBE	B3LYP	M11	B3LYP	M11	B3LYP	M11	
0	-35.9	-37.4	-37.2	-37.8	-38.2	-41.0	-41.2	-43.8
1	-40.8	-39.4	-39.2	-39.6	-40.2	-43.1	-43.3	-44.4
2	-40.6	-38.8	-38.0	-39.4	-39.1	-43.9	-43.2	-44.3
3	-38.8	-37.1	-36.5	-37.5	-37.5	-40.8	-40.3	-43.1
4	-34.4	-33.0	-32.9	-33.7	-34.0	-37.2	-37.8	-36.5
5	-32.0	-30.5	-29.4	-30.7	-30.5	-34.2	-34.3	-36.4
6	-42.4	-41.6	-42.6	-42.2	-43.7	-45.8	-47.1	-46.4
7	-38.2	-39.4	-40.3	-39.6	-41.3	-42.4	-44.2	-45.1
8	-31.3	-31.5	-31.1	-31.1	-31.9	-34.3	-35.0	-38.6
9	-37.5	-36.6	-37.3	-37.0	-38.2	-39.3	-40.4	-43.3
10	-38.5	-37.4	-37.9	-37.3	-38.3	-37.7	-38.6	-48.1
11	-43.3	-43.8	-45.1	-43.9	-45.9	-45.6	-47.6	-52.3
12	-43.2	-43.5	-44.8	-43.9	-45.6	-46.4	-48.3	-48.6
13	-37.7	-37.9	-38.1	-37.3	-38.5	-38.2	-39.5	-45.4
14	-46.2	-47.5	-47.9	-47.1	-49.1	-51.1	-53.1	-52.0
15	-40.2	-41.1	-41.6	-40.8	-42.5	-43.6	-45.4	-48.9
16	-50.2	-50.7	-52.3	-51.1	-53.5	-54.7	-57.0	-56.6
17	-47.4	-47.2	-48.3	-47.7	-49.5	-51.2	-53.0	-52.5
18	-43.8	-43.4	-44.3	-44.2	-45.6	-47.8	-49.1	-47.5
19	-39.0	-38.8	-39.3	-38.8	-40.2	-41.5	-42.9	-44.2
μ	*-40.1*	*-39.8*	*-40.2*	*-40.0*	*-41.1*	*-43.0*	*-44.1*	*-45.9*
σ	*4.9*	*5.2*	*5.8*	*5.3*	*5.9*	*5.5*	*6.1*	*5.2*
min	*-50.2*	*-50.7*	*-52.3*	*-51.1*	*-53.5*	*-54.7*	*-57.0*	*-56.6*
max	*-31.3*	*-30.5*	*-29.4*	*-30.7*	*-30.5*	*-34.2*	*-34.3*	*-36.4*
δ	*18.9*	*20.2*	*23.0*	*20.4*	*23.0*	*20.5*	*22.8*	*20.3*

Table S5: Binding energies ($\Delta_{Bind}E$) obtained in different functionals with the 6-311++G(2d,2p) and CEP-121 basis set and with DFTB3/3OB for 20 calcium complexes of 2AAAL small model, mean (μ), standard deviation (σ), minimum (min.) and maximum (max.), and the absolute differences between min. and max values of $\Delta_{Bind}E$. All numbers expressed in kcal.mol^{-1}.

FRAME	6-311++G(2d,2p)			6-31++G(d,p)		CEP-121		DFTB3/3OB
	PBE	B3LYP	M11	B3LYP	M11	B3LYP	M11	
0	-586.8	-594.7	-603.5	-570.7	-588.3	-622.4	-637.0	-648.0
1	-598.3	-609.8	-619.8	-586.3	-605.3	-643.5	-659.1	-667.0
2	-587.7	-598.1	-607.5	-571.5	-590.1	-631.4	-646.2	-658.5
3	-593.1	-602.6	-611.2	-577.6	-595.3	-635.7	-650.6	-662.2
4	-594.3	-603.9	-613.2	-577.4	-596.3	-640.1	-655.7	-664.9
5	-600.0	-610.5	-621.0	-587.2	-606.2	-636.8	-652.2	-660.5
6	-596.9	-607.3	-616.5	-582.0	-600.3	-637.0	-652.1	-662.5
7	-586.8	-597.5	-607.7	-570.3	-589.9	-635.5	-651.4	-664.1
8	-592.3	-602.3	-611.6	-578.9	-596.9	-634.8	-649.5	-660.4
9	-592.6	-603.0	-612.4	-579.3	-598.0	-638.3	-653.6	-661.2
10	-600.2	-612.1	-622.6	-587.7	-607.1	-638.7	-654.3	-665.4
11	-597.6	-607.6	-617.5	-582.4	-601.2	-637.1	-652.4	-663.9
12	-592.5	-601.3	-610.8	-577.6	-596.1	-634.5	-649.6	-659.1
13	[a]	-608.5	-619.3	-582.9	-602.8	-640.3	-656.1	-667.9
14	-600.8	-609.3	-620.8	-587.9	-607.3	-631.7	-647.3	-655.4
15	-595.5	-605.1	-614.5	-581.6	-600.1	-636.3	-651.5	-661.8
16	-591.6	-598.9	-608.9	-575.6	-594.2	-626.9	-641.4	-651.9
17	-601.8	[a]	-622.3	[a]	-607.0	-643.9	-659.9	-671.4
18	-595.7	-606.3	-616.3	-580.3	-599.4	-643.4	-659.2	-668.7
19	-595.8	[a]	-618.4	-584.9	-603.6	-639.8	-655.4	-668.4
μ	*-594.7*	*-604.4*	*-614.8*	*-580.1*	*-599.3*	*-636.4*	*-651.7*	*-662.1*
σ	*4.6*	*5.0*	*5.5*	*5.5*	*5.9*	*5.4*	*5.7*	*5.8*
min	*-601.8*	*-612.1*	*-622.6*	*-587.9*	*-607.3*	*-643.9*	*-659.9*	*-671.4*
max	*-586.8*	*-594.7*	*-603.5*	*-570.3*	*-588.3*	*-622.4*	*-637.0*	*-648.0*
δ	*15.0*	*17.4*	*19.1*	*17.6*	*19.1*	*21.6*	*22.9*	*23.3*

a - System not converged

Table S6: mean (μ), standard deviation (σ) and min. max. differences between the new benchmark and Li et all[7] benchmark for 193L and 2AAA small model complex on B3LYP, M11 and DFTB3/3OB

Na^+ - 193L												
	B3LYP						M11					
	A	**B**	**C**	**D**	**E**	**F**	**A**	**B**	**C**	**D**	**E**	**F**
μ	0.2	3.2	3.0	6.1	5.9	2.9	0.9	3.8	2.9	5.7	4.7	1.8
σ	0.4	1.2	1.0	1.7	1.9	2.8	0.2	1.2	1.0	1.8	2.0	2.8
δ	1.4	4.8	4.0	7.2	8.0	11.0	0.9	4.6	3.8	7.0	7.9	11.1
Ca^{2+}- 2AAA												
	B3LYP						M11					
	A	**B**	**C**	**D**	**E**	**F**	**A**	**B**	**C**	**D**	**E**	**F**
μ	-24.5	31.4	55.9	56.9	81.5	25.8	-15.5	36.9	52.5	47.4	62.9	10.4
σ	1.5	4.1	5.1	4.7	5.8	1.6	1.1	4.3	5.1	4.8	5.7	1.6
δ	5.8	15.7	21.5	20.5	26.3	5.7	4.3	17.2	21.5	21.9	26.1	5.5

$\boldsymbol{A} = \Delta_{Bind}E^{6-311++G(2d,2p)} - \Delta_{Bind}E^{6-31++G(d,p)}$;$\boldsymbol{B} = \Delta_{Bind}E^{6-311++G(2d,2p)} - \Delta_{Bind}E^{CEP-121}$;
$\boldsymbol{C} = \Delta_{Bind}E^{6-31++G(d,p)} - \Delta_{Bind}E^{CEP-121}$;$\boldsymbol{D} = \Delta_{Bind}E^{6-311++G(2d,2p)} - \Delta_{Bind}E^{DFTB3OB}$
;$\boldsymbol{E} = \Delta_{Bind}E^{6-31++G(d,p)} - \Delta_{Bind}E^{DFTB3OB}$; $\boldsymbol{F} = \Delta_{Bind}E^{CEP-121} - \Delta_{Bind}E^{DFTB3OB}$.

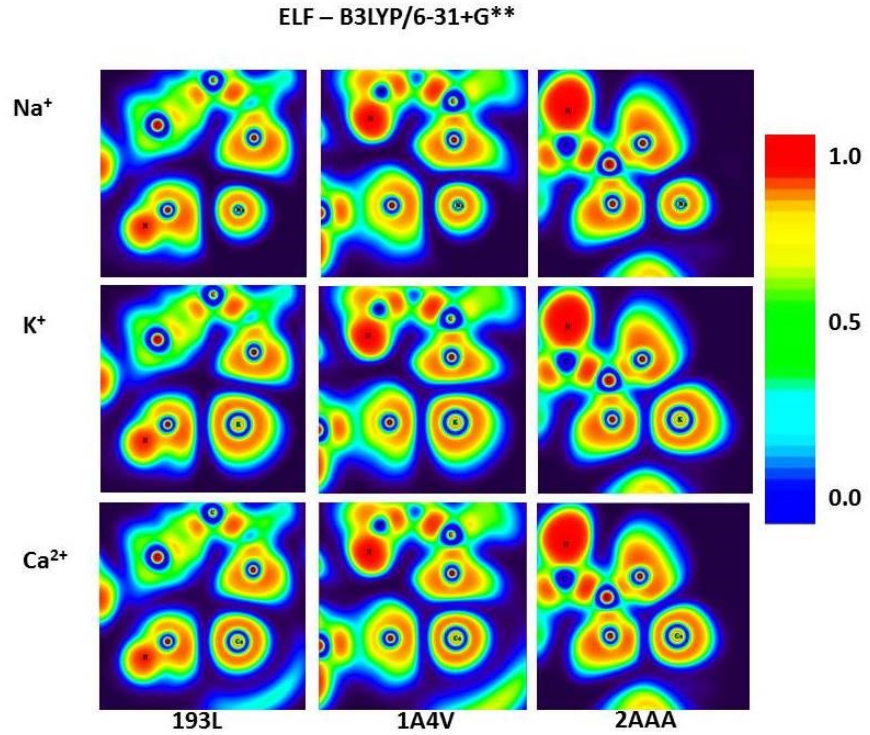

Figure S1: Electronic localize function (ELF) for small models of 193L, 1A4V and 2AAA model complex probed with Na^+, K^+ and Ca^{2+} in B3LYP/6-31+G**

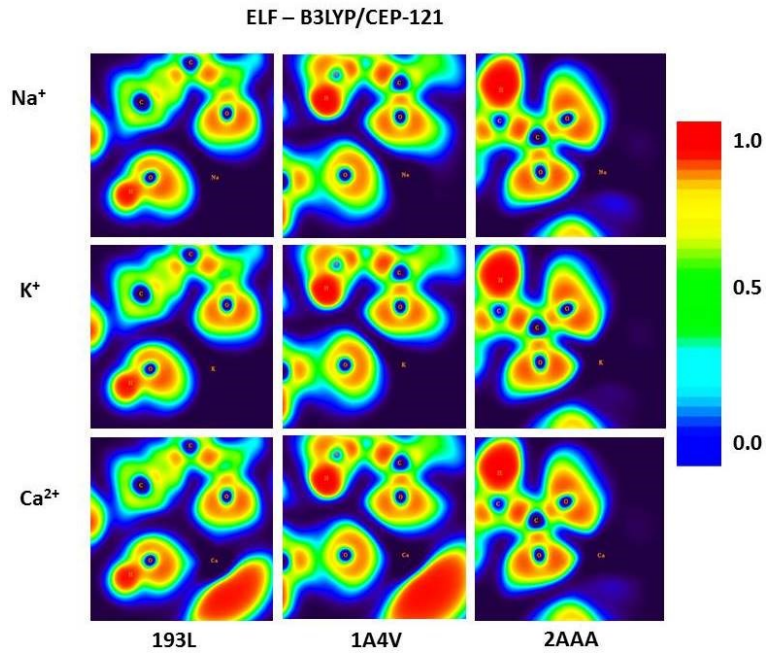

Figure S2: Electronic localize function (ELF) for small models of 193L, 1A4V and 2AAA model complex probed with Na^{+}, K^{+} and Ca^{2+} in B3LYP/CEP-121.

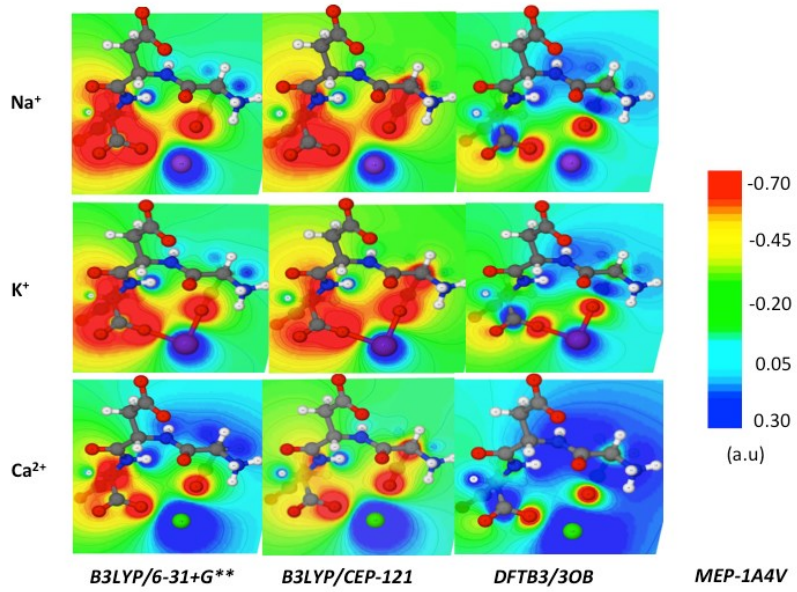

Figure S3: Molecular electrostatic map plotted in a plane for small model of 1A4V.

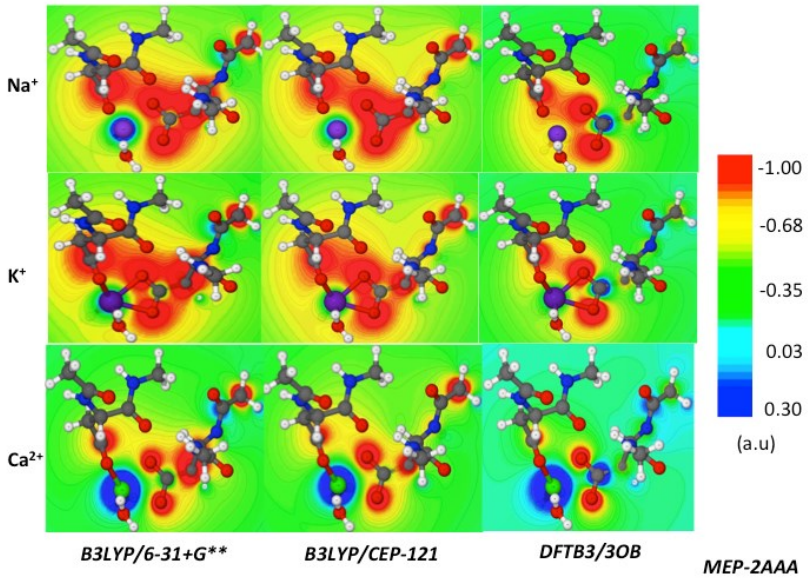

Figure S4: Molecular electrostatic map plotted in a plane for small model of 2AAA.

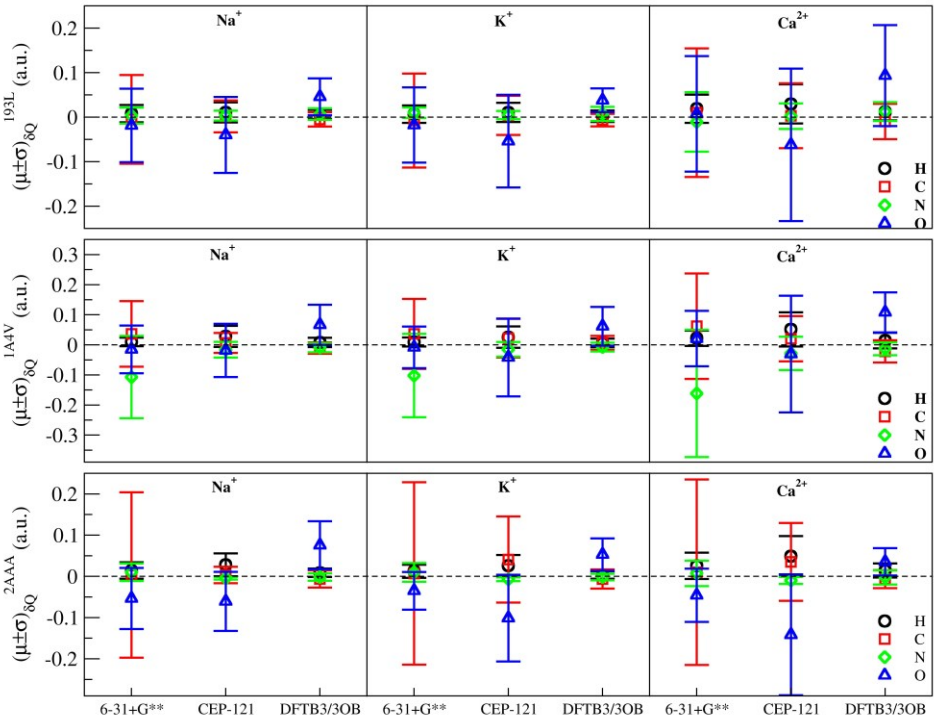

Figure S5: Mean and standard deviations of the Mulliken charge differences per atom type of the ligands in the small models of 193L, 1A4V and 2AAA evaluated in B3LYP/6-31+G**, B3LYP/CEP-121 and DFTB3/3OB, sampled with different cations in the binding sites.

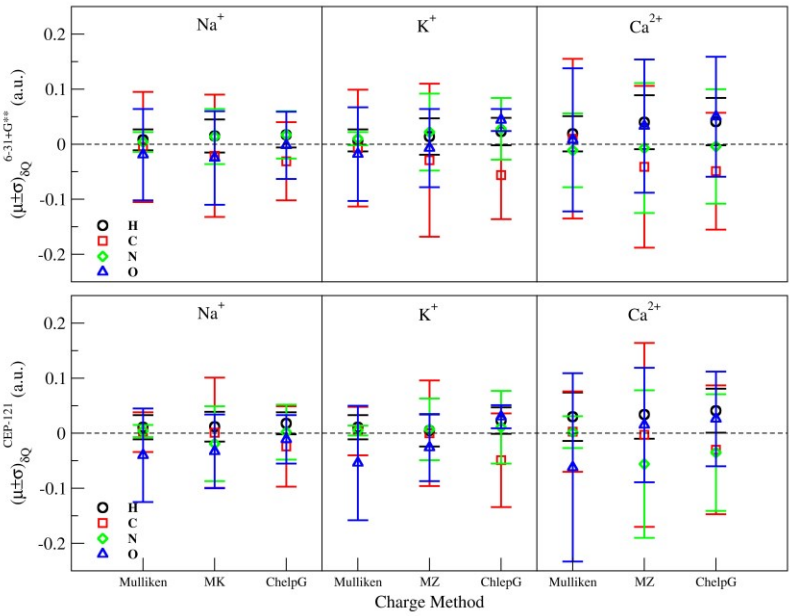

Figure S6: Mean and standard deviations of the Mulliken, Merz-Kollman and ChelpG charge differences per atom type of the ligands in the small models of 193L evaluated in B3LYP/6-31+G** and B3LYP/CEP-121, with different cations in the binding sites.

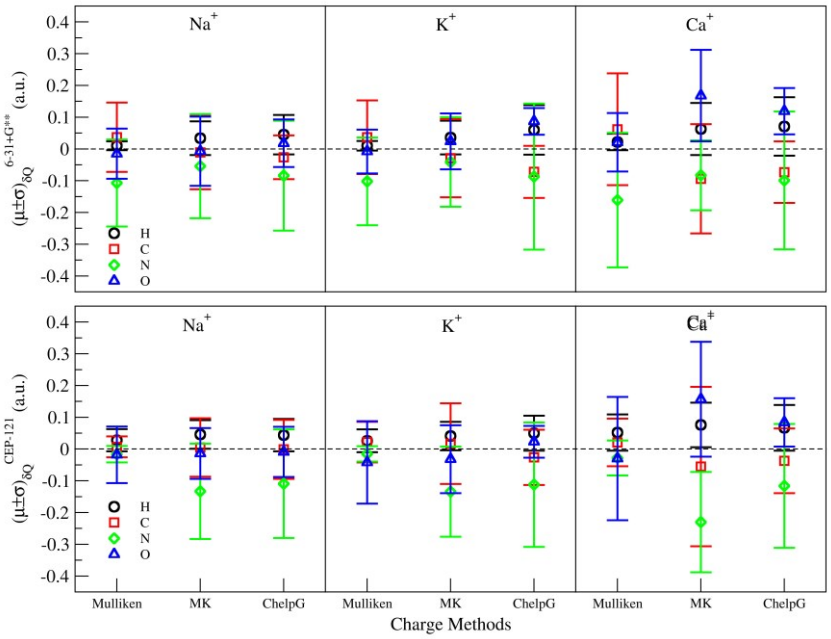

Figure S7: Mean and standard deviations of the Mulliken, Merz-Kollman and ChelpG charge differences per atom type of the ligands in the small models 1A4V evaluated in B3LYP/6-31+G** and B3LYP/CEP-121, with different cations in the binding sites.

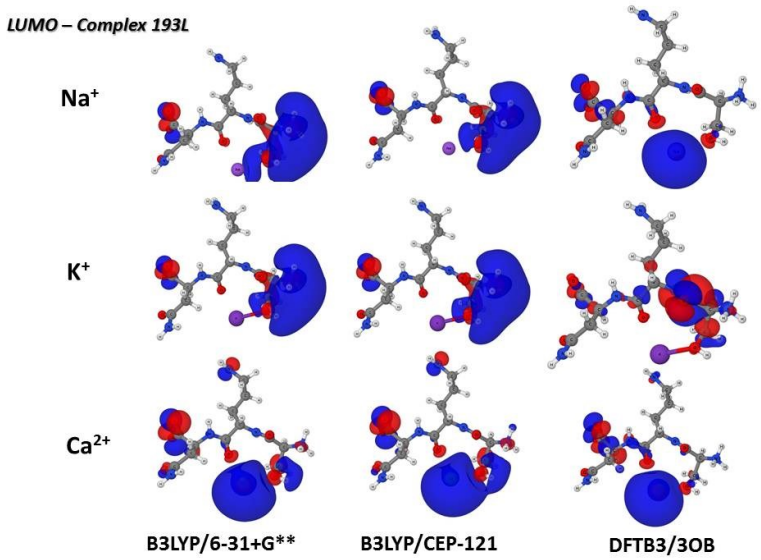

Figure S8: Lowest unoccupied molecular orbital (LUMO) for small model 193L complex with Na^+, K^+ and Ca^{2+} on its binding site obtained from DFT and DFTB3/3OB levels of theory.

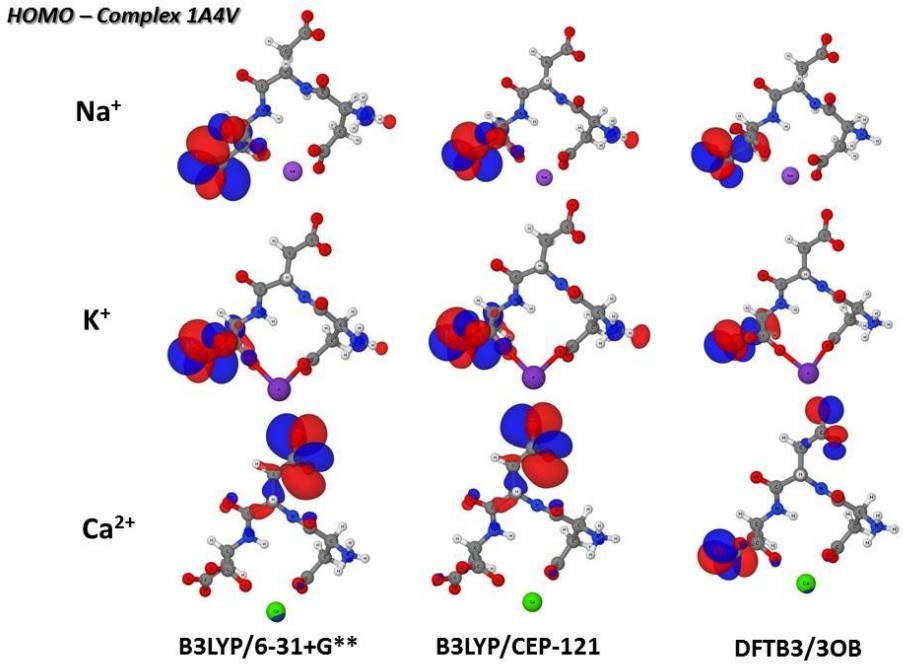

Figure S9: Highest occupied molecular orbitals (HOMO) for small model 1A4V complex with Na^+, K^+ and Ca^{2+} on its binding site obtained from DFT and DFTB3/3OB levels of theory.

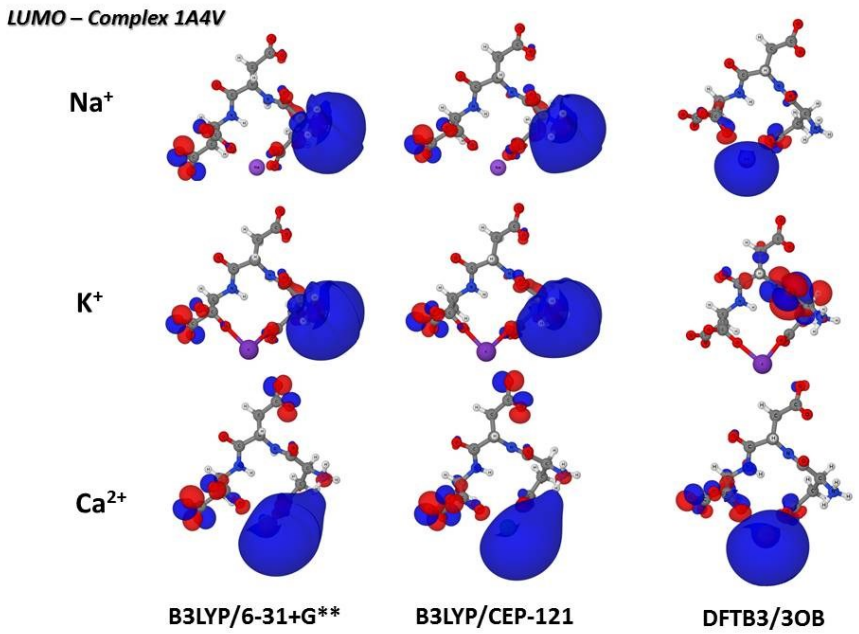

Figure S10: Lowest unoccupied molecular orbitals (LUMO) for small model 1A4V complex probed with Na^+, K^+ and Ca^{2+} on its bind site for DFT and DFTB3/3OB level of theory.

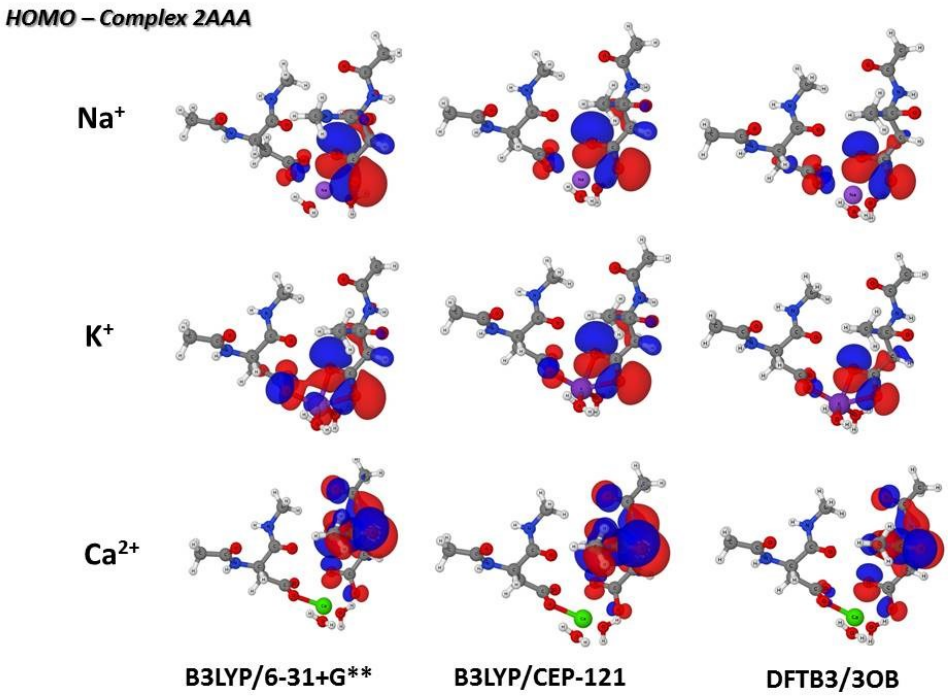

Figure S11: Highest occupied molecular orbital (HOMO) for small model 2AAA complex with Na^+, K^+ and Ca^{2+} on its binding site obtained from DFT and DFTB3/3OB levels of theory.

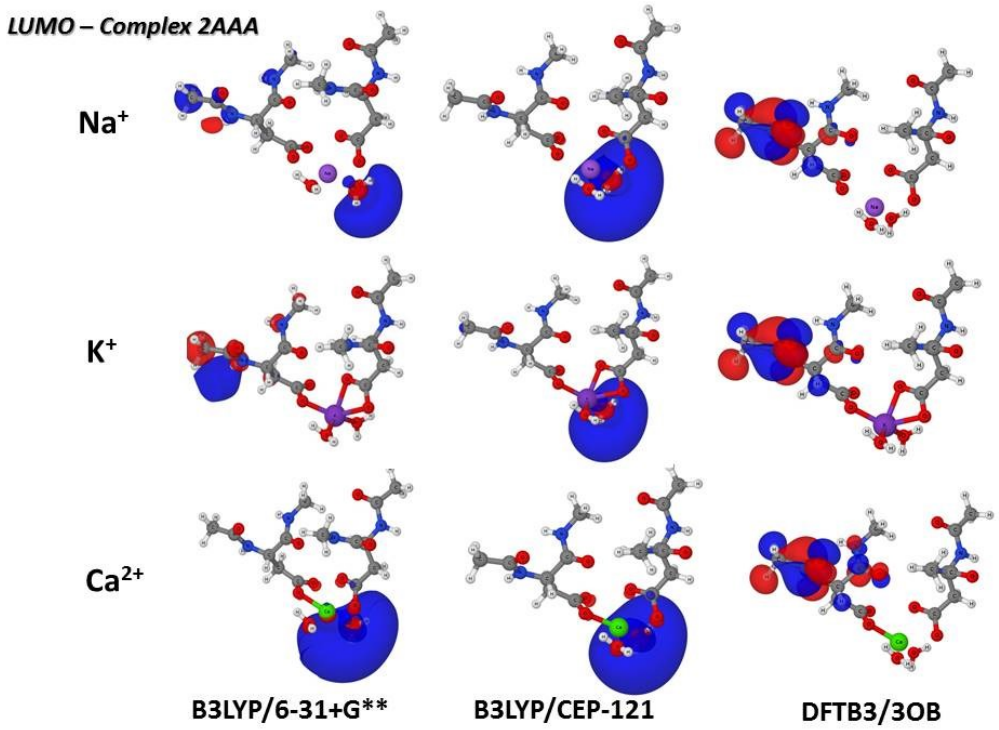

Figure S12: Lowest unoccupied molecular (LUMO) for small model 2AAA complex probed with Na^+, K^+ and Ca^{2+} on its bind site for DFT and DFTB3/3OB level of theory.

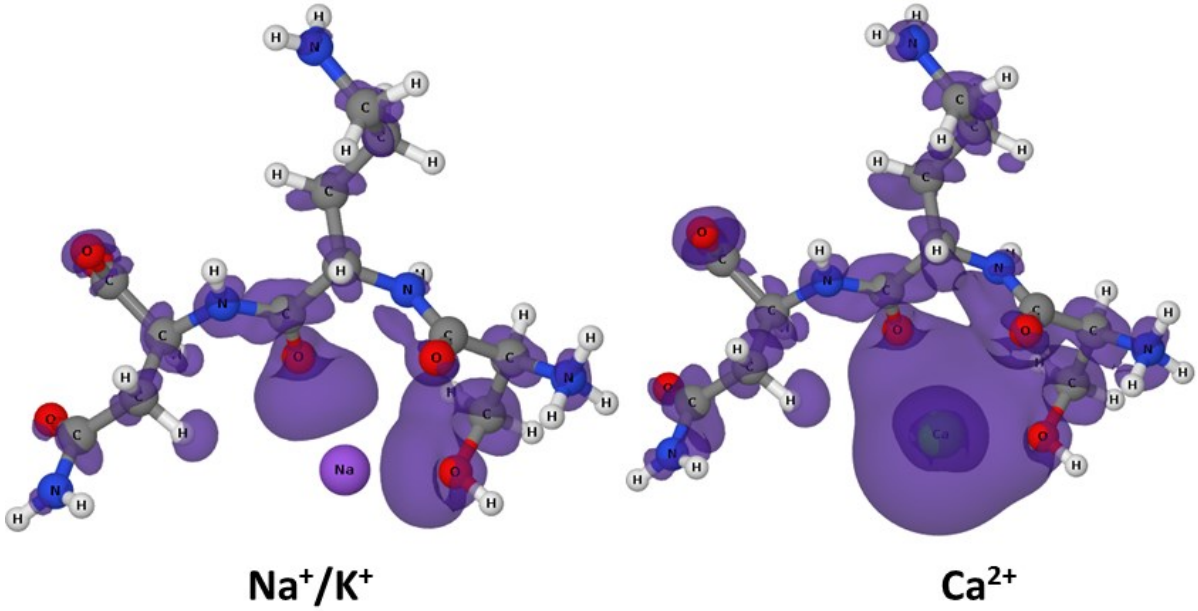

Figure S13: Electronic density perturbation (δρ) for the small model of 193L ligand - Na^+, K^+ and Ca^{2+} complex, evaluated to B3LYP/6-31+G**, B3LYP/CEP-121 and DFTB3/3OB methods. All isodensities envelopes (η) are equal to 0.05.

Basis Set and Functional Validation.

To provide a validation of the functionals and the basis sets used in the energetic calculations of this work, the atomization energies of a set of 22 small molecules and the binding energies of a set of 30 small simple reactions involving the cations Na^+, K^+ and Ca^{2+} were investigated. The Gaussian version 4 composite method (G4) was used as a reference/standard method to calibrate the functionals PBE, BLYP, PBE0, B3LYP, TPSS, M11, B2PLYP, B2T-PLYP, B2K-PLYP and B2GP-PLYP on the basis sets Def2-SVP, 6-31+G**, 6-31++G**, 6-311++G(2d,2p), CEP-121 (SBKJC-ECPs) and SDD (Stuttgart-ECPs). For the binding energy training set Grimme's D3 dispersion scheme was also employed, although it should not be so important for such small molecular systems. In both the atomization energy and the binding energy calculations the G4 molecular optimized geometries were used rather then the local method/basis optimized structures. This validation was done in both NWChem and GAMESS packages because of some numerical problems found in some cases. To guarantee the transferability between functionals, basis sets and softwares, a reference radial grid of 200 points, angular grid of 1202 points and a density convergence criteria of 1.0e-8 was used in all DFT calculations in both softwares (very fine integration grid and tight convergence criteria). G4 calculations were done in Gaussian09-A2 software and the integration and optimization criteria were set at a very accurate level, no constraint nor point symmetry was employed for the systems during the G4 calculations.

In **Table S7** are presented the experimental atomization enthalpies, free energies and entropic component calculated using the experimental standard formation thermodynamic functions. G4 presented a mean absolute deviation of 2.1 kcal/mol for a set of 22 atomization enthalpies with a standard deviation of 2.2 kcal/mol, the free atomization energies mean and standard deviation are 2.0 and 1.8 kcal/mol respectively, and the mean absolute deviation of the entropic factor are below 1.0 kcal/mol. Large deviations were obtained for Ca_2, KOH, NaCN and KCN, more then 4.0 kcal/mol as shown in **Table S7**. For all the other cases the atomization enthalpy deviations are close to the value of 2.0 kcal/mol. As it is shown in **Table S7,** G4 atomization enthalpies are very close to the experimental values with a precision around 2.0 kcal/mol which is quite good considering that this training set contains heavy atoms like Ca and K and the atomization energies involved differences between closed- and open-shell systems.

Table S7: Standard experimental atomization enthalpies ($\Delta_{atom}H^o$), free energies ($\Delta_{atom}G^o$), entropic component ($-T\Delta_{atom}S^o$), the associated G4 absolute deviations to these thermodynamics potential functions and the mean (μ) and standard deviations (σ) over all the 22 molecules. All values are expressed in kcal/mol. * http://webbook.nist.gov/chemistry/

	Experimental*			G4 Absolute Deviations		
Molecules	$\Delta_{atom}H^o$	$\Delta_{atom}G^o$	$-T\,\Delta_{atom}S^o$	$\Delta_{atom}H^o$	$\Delta_{atom}G^o$	$-T\,\Delta_{atom}S^o$
Na_2	17.3	11.8	5.5	1.08	1.03	0.05
K_2	13.0	7.9	5.1	0.33	0.32	0.02
Ca_2	3.3	-0.4	3.7	4.58	4.42	0.16
NaH	48.0	42.3	5.7	2.81	2.83	0.02
KH	44.0	38.5	5.5	2.60	2.60	0.01
NaF	114.0	107.3	6.8	0.06	0.53	0.47
KF	118.3	111.8	6.6	2.32	1.86	0.47
CaF	126.5	120.5	6.0	1.62	2.09	0.47
CaF_2	267.9	253.8	14.2	0.19	1.65	1.83
NaCl	98.0	91.7	6.3	0.12	0.31	0.43
KCl	101.6	95.4	6.2	1.03	0.59	0.44
CaCl	96.5	90.9	5.6	1.97	2.41	0.45
$CaCl_2$	213.2	199.3	13.9	0.08	1.82	1.90
NaO	65.2	59.1	6.1	1.06	0.93	0.14
KO	63.8	57.9	5.9	1.80	1.86	0.06
CaO	91.5	84.7	6.9	1.89	2.48	0.59
CaS	79.2	72.7	6.4	0.28	0.19	0.47
NaOH	184.6	170.2	14.3	1.80	0.03	1.84
KOH	180.2	166.3	13.9	4.68	4.94	0.25
CaOH	200.5	186.6	13.9	1.08	0.06	1.01
NaCN	287.4	271.6	15.8	8.83	6.90	1.93
KCN	286.5	271.0	15.6	6.56	4.07	2.49

μ	***2.1***	***2.0***	***0.7***
σ	***2.2***	***1.8***	***0.8***

The G4 composite method can be considered a good theoretical reference for our validations; however, in the G4 protocol there are some parameters fitted to get the smallest deviation with experimental results such as high-level correlation (HLC) due to open-shell systems, spin-orbit coupling and harmonic frequencies scaling factors. These factors in the G4 method can be considered empirical terms and in a straight interpretation do not reflect directly the electronic structure or perturbation to the electronic structure. Because of this in all our validations we excluded all empirical contributions to the G4 energies and thermal corrections due to rigid body and vibrational motions, leaving only the real electronic G4 energies that are related strictly to the dynamic correlation effects and the completeness of the basis set.

Figure S14 presents the mean and the standard absolute deviation of the atomization energies of the same 22 small molecules shown in **Table S7**, considering the G4 method as the standard reference. First of all, neither of the pseudopotential basis sets(CEP-121 and SDD) are good enough to reproduce the predicted atomization energies on the same accuracy level as G4. The typical mean absolute deviation in all evaluated functionals for CEP-121 and SDD is around 25 kcal/mol. This large deviation can be associated with the absence of polarization and diffuse extra functions in these ECPs basis sets. Polarization and diffuse functions may take an important role in the prediction of atomization energies. When an all-electron basis set is employed, the typical mean absolute deviation stays below 10 kcal/mol in most cases of tested functionals, or close to this value. The Def2-SVP basis set has almost the same size as 6-31++G** but the atomization energies predicted with Def2-SVP are much better. The 6-311++G(2d,2p) basis can be considered the best basis set to reproduce, for all functionals, the same predicted atomization energies as the G4 method. As can be shown in **Figure S14**, B3LYP and PBE0 presented better performance than M11 and the double hybrid functionals are not so much better than B3LYP or PBE0. The mean absolute deviation of B3LYP and PBE0 on 6-311++G(2d,2p) lies below 5 kcal/mol. On **Tables S8** to **S13** are presented all individual values of the deviation from G4 atomization energies. The values obtained with the 6-31+G** are numerically similar to 6-31++G** and they are only presented in **Table S9**. This means that the extra diffuse function for H atoms does not change significantly the results obtained with 6-31++G**, the extra polarization p function of H atoms has a more important role in predicting the atomization energies.

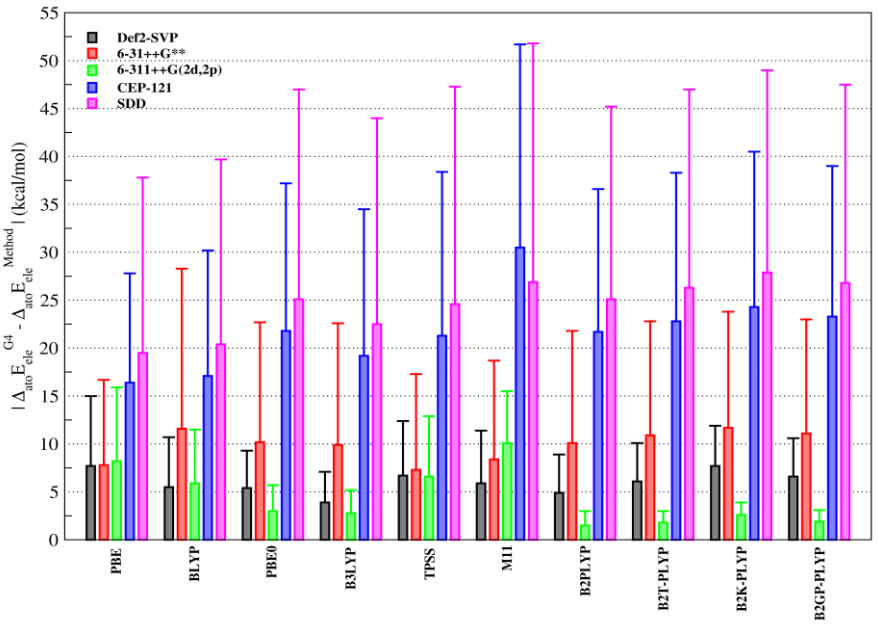

Figure S14: mean and standard absolute deviations of the atomization energies of 22 small molecular system considering G4 method as standard reference.

The atomization energies training set was used in principal to check the quality of the G4 method as a theoretical reference for calculations involving the atomic species Na, K and Ca. A very large basis set and a high level of dynamic electronic correlation are needed to reproduce very accurate atomization energies. Hence, this training set was also used to show the main response of different functionals in different basis sets (all-electron and ECPs) to predict the atomization energies. Our calculations show that B3LYP and PBE0 are good functionals to be used although today many papers support M11 and double hybrids as new standard reference functional. We observed that good results were had when a large basis set was used rather than M11 or a double hybrid functional.

A second more realistic training set to predict binding energies was investigated with the same functionals and the same basis sets used in the atomization energy calculations. The binding energies in the gas phase of the ions Na^+, K^+ and Ca^{2+} (A) with one ligand (M=OH^-, H_2O, CH_3OH, CH_3SH, CO, OCH_2, $CH_3CO_2^-$, NH_3, PH_3 and NMA), coordinated by the most electronegative atom, were calculated based on the chemical reaction presented on **Eq. S1**. This second training set tries to mimic the same type of chemical coordination present in the biological ion-protein ligands. **Figure S15** shows that the mean absolute deviation for all functionals and all basis sets stays close to or below 10 kcal/mol. Differently from the atomization results, the Def2-SVP basis set presented the worst results compared to G4. The basis sets 6-31+G**, 6-31++G**, CEP-121 and DFTB3/3OB method have the same average tendencies with mean absolute deviations close to or below 5 kcal/mol, as presented on **Figure S15**. It seems that the binding energy prediction is less sensitive to the type of the basis set but the 6-311++G(2d,2p) presented the best performance for the prediction of G4 binding energies on all functionals, **Figure S15** and **S16**.

$$A + M = [A \cdots M] \qquad \text{S1}$$

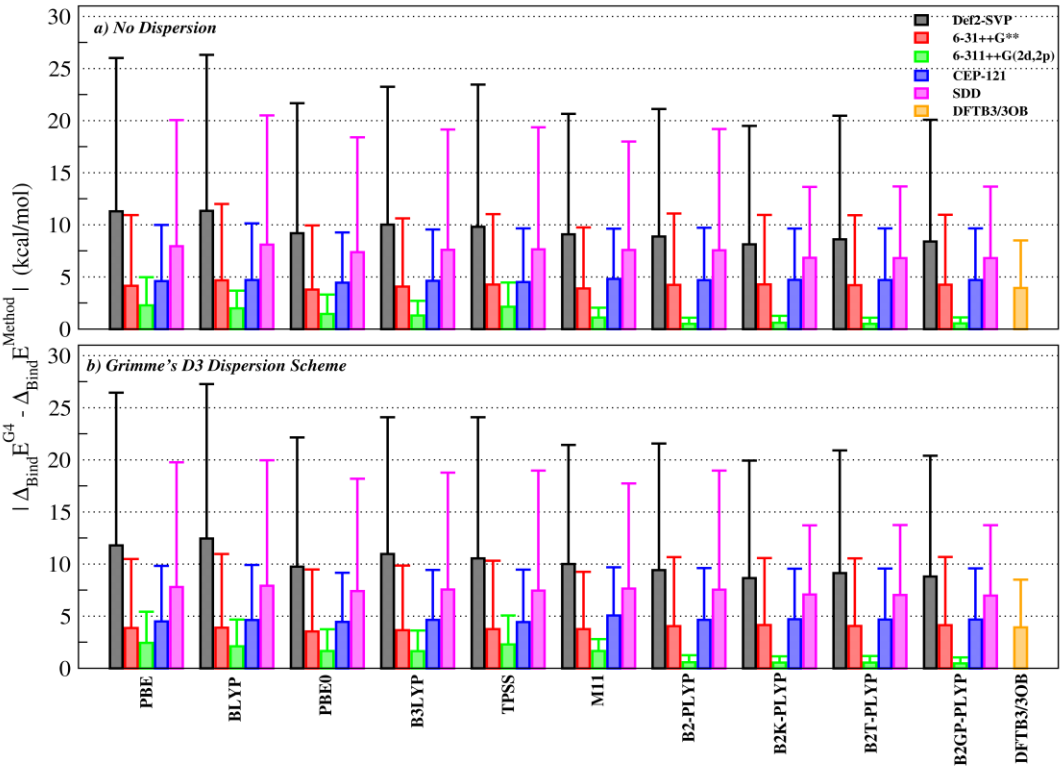

Figure S15: mean and standard absolute deviations of the binding energies of 30 small reactions considering G4 method as standard reference.

Figure S16 shows, on a better precision scale, how similar are the mean absolute deviations between the 6-31+G**, 6-31++G** and CEP-121 basis sets for all functionals and the DFTB3/3OB method. The double hybrid functional with the 6-311++G(2d,2p) basis presented the best quality results for the prediction of the G4 binding energies for the studied systems. Only with the 6-311++G(2d,2p) basis set was it possible to get some differences amongst all employed functionals, for the other basis sets all the functionals presented the same trends. From **Table S14** to **S25** are presented the individual values for each ion, ligand, functional and basis set. The large dispersion of the data is especially due to the Ca^{2+} ion in the complexes with NMA, $CH_3CO_2^-$ and OH^-. The deviation of some Ca^{2+} complexes is larger than 20 kcal/mol as presented in **Tables S14** to **S25** to the 6-31+G**, 6-31++G** and CEP-121 basis set. The mean absolute deviation of CEP-121 is a little larger than the results obtained for 6-31+G** and 6-31++G** but the standard absolute deviation of CEP-121 is around 1 kcal/mol lower than 6-31+G** and 6-31++G** results. B3LYP results are very close to those obtained with M11 for 6-311++G(2d,2p) and only around 0.5 kcal/mol worse than those obtained with a double hybrid functional. The average trends observed for 6-31+G**, 6-31++G** and CEP-121 are almost the same over all functionals, no improvements were observed in using M11 or a double hybrid functional with this basis set to predict the G4 binding energies of the studied systems.

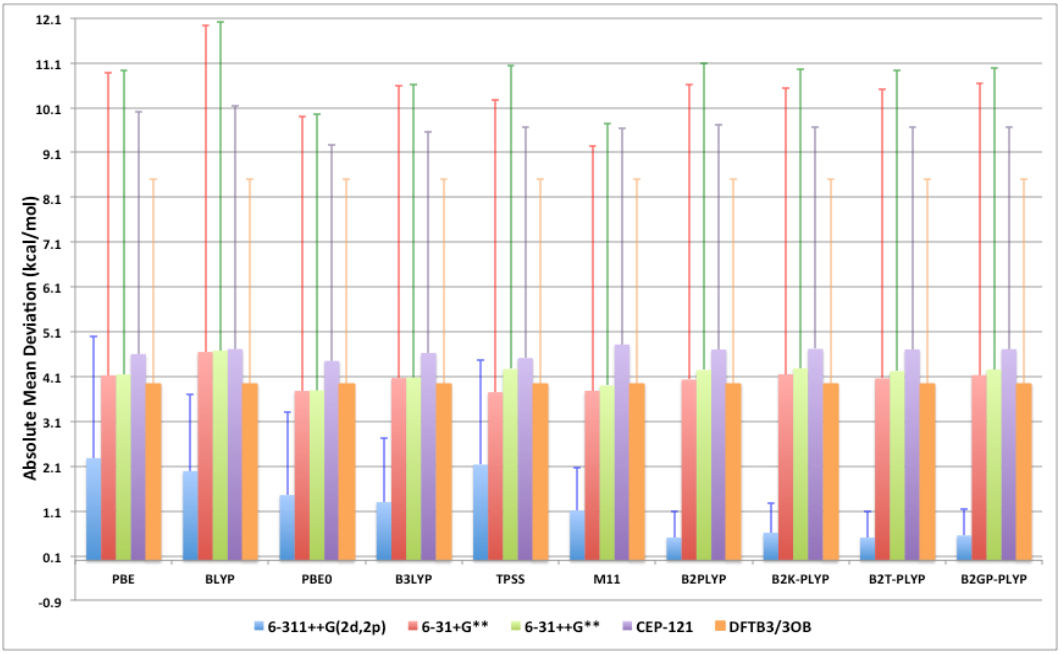

Figure S16: mean and standard absolute deviations of the binding energies of 30 small reactions considering G4 method as standard reference.

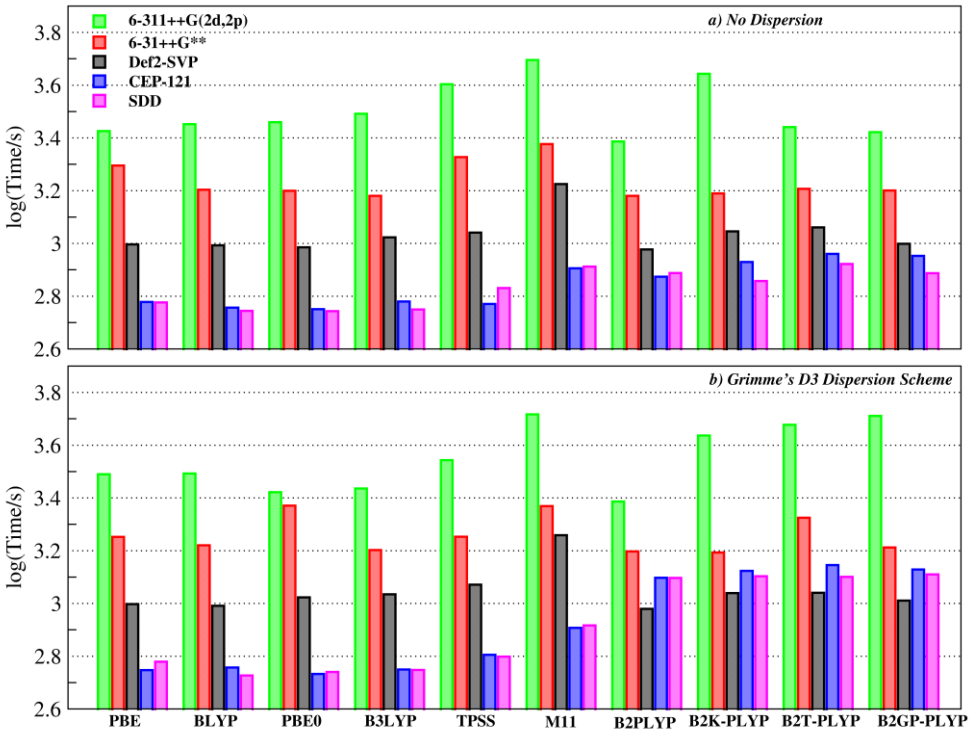

Figure S17: Logarithmic total cpu and I/O time to calculate all binding energies in the training set in different functionals and basis set used in this work.

Table S8: Atomization energies on G4 electronic reference and their absolute deviation on different functionals on Def2-SVP basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the Def2-SVP basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

	$G4_{ele}$	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2T-PLYP	B2K-PLYP	B2GP-PLYP
Na_2	18.20	0.37	0.23	2.35	0.98	1.03	3.01	2.36	2.84	3.81	3.23
K_2	12.41	0.76	0.28	0.97	0.93	1.93	0.81	1.24	1.56	2.11	1.76
Ca_2	2.35	3.50	0.19	2.50	0.43	3.41	0.20	0.49	0.51	0.40	0.44
NaH	43.46	1.81	1.93	3.77	1.25	3.32	2.94	2.19	2.89	4.32	3.49
KH	39.29	0.70	1.91	2.25	1.54	5.23	7.40	2.15	2.80	4.21	3.40
NaF	112.27	3.42	3.37	11.10	7.85	5.52	0.45	9.06	10.04	10.84	10.22
KF	114.07	2.97	4.36	10.12	8.17	4.36	3.22	10.19	11.18	12.11	11.43
CaF	125.15	14.03	10.64	4.36	4.68	11.09	10.47	0.49	1.89	3.40	2.41
CaF_2	263.76	16.13	10.93	0.03	1.86	12.20	18.88	4.58	6.79	8.94	7.44
NaCl	96.30	3.92	6.55	4.93	6.01	1.52	2.20	7.28	7.48	7.85	7.61
KCl	98.91	4.58	8.58	4.81	7.26	1.35	4.80	8.89	9.01	9.36	9.15
CaCl	95.72	8.27	2.43	6.00	1.98	9.40	9.40	2.60	3.00	3.78	3.37
$CaCl_2$	210.47	9.87	0.33	7.01	0.44	13.90	17.67	5.59	6.14	7.30	6.65
NaO	60.99	1.78	2.70	6.49	2.62	1.75	1.09	6.59	8.05	9.99	8.76
KO	62.41	0.08	0.56	7.46	5.03	2.72	1.07	9.03	10.27	11.98	10.88
CaO	88.93	27.74	22.57	6.07	8.07	21.16	9.30	0.78	3.40	8.40	5.07
CaS	74.36	16.83	9.37	7.57	3.98	17.76	10.76	5.09	7.39	11.07	8.84
NaOH	183.39	4.30	5.51	13.22	9.13	9.48	1.45	11.88	13.33	14.93	13.79
KOH	185.49	3.91	6.45	12.63	9.73	8.46	1.02	13.21	14.69	16.43	15.22
CaOH	199.08	14.04	9.16	3.40	4.25	8.09	10.65	2.30	4.03	6.16	4.76
NaCN	273.80	14.76	7.37	0.18	0.35	1.52	4.68	1.02	3.36	5.71	3.93
KCN	275.12	14.84	6.45	0.65	0.07	2.47	8.61	1.27	3.51	5.76	4.05
μ		7.7	5.5	5.4	3.9	6.7	5.9	4.9	6.1	7.7	6.6
σ		7.3	5.2	3.9	3.2	5.7	5.5	4.0	4.0	4.2	4.0

Table S9: Atomization energies on G4 electronic reference and their absolute deviation on different functionals on 6-31+G** basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-31+G** basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

	$G4_{ele}$	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2T-PLYP	B2K-PLYP	B2GP-PLYP
Na_2	18.20	0.44	0.62	2.30	1.16	0.96	3.67	2.32	2.78	3.73	3.16
K_2	12.41	0.74	0.30	1.03	1.00	2.06	0.67	2.17	2.59	3.40	2.92
Ca_2	2.35	1.49	2.06	0.97	1.87	1.33	0.85	2.24	2.28	2.32	2.29
NaH	43.46	0.65	2.76	2.52	2.12	4.76	5.10	1.48	2.19	3.67	2.81
KH	39.29	0.86	1.78	2.78	1.12	4.92	6.21	3.12	3.89	5.53	4.59
NaF	112.27	1.17	0.96	5.53	2.42	0.32	8.87	1.57	2.32	2.54	2.21
KF	114.07	1.21	2.52	7.29	5.20	2.09	8.16	4.61	5.29	5.51	5.19
CaF	125.15	13.59	17.06	17.25	18.07	14.91	5.71	16.88	16.99	16.35	16.59
CaF_2	263.76	15.14	20.15	23.47	22.76	16.81	3.06	19.97	20.49	19.68	19.84
NaCl	96.30	3.03	5.69	3.62	4.60	1.28	3.15	4.96	5.05	5.18	5.06
KCl	98.91	3.68	7.18	3.82	5.65	1.50	4.25	6.91	7.00	7.32	7.12
CaCl	95.72	10.99	16.93	9.95	14.63	9.73	5.45	14.81	14.48	13.95	14.26
$CaCl_2$	210.47	18.31	28.32	17.00	24.08	14.93	6.30	24.16	23.75	23.15	23.48
NaO	60.99	5.19	5.90	2.06	1.63	2.46	7.35	0.69	1.91	3.34	2.37
KO	62.41	2.31	1.98	4.26	1.62	0.20	7.42	3.58	4.59	5.75	4.94
CaO	88.93	36.17	38.96	55.10	51.48	41.53	49.15	45.75	49.00	51.70	49.44
CaS	74.36	19.77	25.42	25.83	28.35	19.75	24.94	30.73	32.07	33.89	32.68
NaOH	183.39	3.01	1.72	5.83	1.58	1.45	11.00	2.74	4.06	5.20	4.28
KOH	185.49	1.46	0.83	7.05	3.74	2.39	10.34	5.34	6.67	7.93	6.94
CaOH	199.08	11.00	15.76	17.01	16.92	15.07	2.80	17.96	18.68	19.02	18.63
NaCN	273.80	11.19	3.88	3.46	2.89	0.79	4.37	3.75	6.05	8.26	6.55
KCN	275.12	10.73	2.70	3.32	3.55	0.61	6.09	4.47	6.69	8.84	7.17
μ		7.8	9.3	10.1	9.8	7.3	8.4	10.0	10.9	11.6	11.0
σ		8.9	10.9	12.5	12.7	10.0	10.3	11.6	11.9	12.1	11.9

Table S10: Atomization energies on G4 electronic reference and their absolute deviation on different functionals on 6-31++G** basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-31++G** basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

	$G4_{ele}$	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2T-PLYP	B2K-PLYP	B2GP-PLYP
Na_2	18.20	0.44	0.62	2.30	1.16	0.96	3.67	2.32	2.78	3.73	3.16
K_2	12.41	0.74	0.30	1.03	1.00	2.06	0.67	2.17	2.59	3.40	2.92
Ca_2	2.35	1.49	2.06	0.97	1.87	1.33	0.85	2.24	2.28	2.32	2.29
NaH	43.46	1.40	2.05	2.94	1.68	4.29	4.71	1.65	2.30	3.68	2.88
KH	39.29	0.99	1.75	2.57	1.36	5.00	6.48	2.60	3.30	4.81	3.95
NaF	112.27	1.17	0.96	5.53	2.42	0.32	8.87	1.57	2.32	2.54	2.21
KF	114.07	1.21	2.52	7.29	5.20	2.09	8.16	4.61	5.29	5.51	5.19
CaF	125.15	13.59	68.89	17.25	18.07	14.91	5.71	16.88	16.99	16.35	16.59
CaF_2	263.76	15.14	20.15	23.47	22.76	16.81	3.06	19.97	20.49	19.68	19.84
NaCl	96.30	3.03	5.69	3.62	4.60	1.28	3.15	4.96	5.05	5.18	5.06
KCl	98.91	3.68	7.18	3.82	5.65	1.50	4.25	6.91	7.00	7.32	7.12
CaCl	95.72	10.99	16.93	9.95	14.63	9.73	5.45	14.81	14.48	13.95	14.26
$CaCl_2$	210.47	18.31	28.32	17.00	24.08	14.93	6.30	24.16	23.75	23.15	23.48
NaO	60.99	5.19	5.90	2.06	1.63	2.46	7.34	0.69	1.90	3.34	2.37
KO	62.41	2.31	1.98	4.26	1.62	0.20	7.41	3.58	4.59	5.75	4.94
CaO	88.93	36.17	38.96	55.10	51.48	41.53	49.16	45.75	49.00	51.70	49.44
CaS	74.36	19.77	25.42	25.83	28.35	19.75	24.94	30.73	32.07	33.89	32.68
NaOH	183.39	1.98	0.68	6.59	2.39	2.16	10.10	3.22	4.48	5.51	4.65
KOH	185.49	0.41	1.89	7.82	4.57	3.10	9.34	5.89	7.16	8.34	7.40
CaOH	199.08	12.08	16.85	17.81	17.77	15.81	3.80	18.56	19.22	19.48	19.14
NaCN	273.80	11.19	3.88	3.46	2.89	0.79	4.37	3.75	6.05	8.26	6.55
KCN	275.12	10.73	2.70	3.32	3.55	0.61	6.09	4.47	6.69	8.84	7.17
μ		7.8	11.6	10.2	9.9	7.3	8.4	10.1	10.9	11.7	11.1
σ		8.9	16.7	12.5	12.7	10.0	10.3	11.7	11.9	12.1	11.9

Table S11: Atomization energies on G4 electronic reference and their absolute deviation on different functionals on 6-31++G(2d,2p) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-31++G(2d,2p) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

	$G4_{ele}$	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2T-PLYP	B2K-PLYP	B2GP-PLYP
Na_2	18.20	0.73	0.73	2.64	1.43	0.40	3.13	2.19	2.61	3.40	2.92
K_2	12.41	0.93	0.18	0.80	0.83	2.43	0.28	1.22	1.57	2.17	1.79
Ca_2	2.35	3.53	0.20	2.38	0.53	3.44	0.09	1.18	1.25	1.30	1.27
NaH	43.46	1.02	2.39	2.67	2.01	4.29	5.33	0.26	0.79	1.83	1.21
KH	39.29	1.64	4.18	0.15	3.88	7.78	10.37	0.87	0.32	0.82	0.16
NaF	112.27	1.65	1.37	5.12	1.94	0.34	9.28	1.13	1.90	2.16	1.80
KF	114.07	6.92	5.42	0.51	1.76	6.16	13.75	0.74	0.25	0.97	0.37
CaF	125.15	12.56	8.66	4.07	3.88	10.73	12.94	0.30	0.80	1.74	1.06
CaF_2	263.76	14.95	9.52	0.39	2.13	12.75	23.20	1.39	3.20	4.47	3.43
NaCl	96.30	1.68	4.44	2.29	3.27	0.02	4.86	2.45	2.39	2.12	2.22
KCl	98.91	1.12	2.46	0.48	1.22	3.38	8.67	1.65	1.68	1.67	1.64
CaCl	95.72	6.73	0.60	4.79	0.54	7.53	8.26	2.27	2.41	2.57	2.49
$CaCl_2$	210.47	6.26	3.98	3.88	2.62	9.30	13.07	5.34	5.46	5.52	5.45
NaO	60.99	5.96	6.51	1.28	2.35	3.25	7.76	0.51	0.66	1.96	1.06
KO	62.41	8.79	8.18	1.59	4.20	6.85	10.84	0.09	1.32	2.83	1.82
CaO	88.93	30.81	25.17	9.50	11.08	25.44	17.22	6.08	2.25	1.87	0.99
CaS	74.36	19.24	11.77	9.74	6.26	19.88	11.88	0.71	2.69	5.51	3.75
NaOH	183.39	2.87	1.69	5.84	1.40	1.52	10.19	1.51	2.73	3.60	2.81
KOH	185.49	7.92	5.68	1.61	2.04	4.02	14.37	0.40	1.03	2.30	1.29
CaOH	199.08	13.73	8.81	3.51	4.39	8.93	14.53	0.07	1.54	2.98	1.94
NaCN	273.80	14.70	7.61	0.19	0.72	2.27	9.00	0.71	1.51	3.43	1.86
KCN	275.12	17.21	9.39	2.58	2.73	5.50	13.19	1.94	0.30	2.34	0.72
μ		8.2	5.9	3.0	2.8	6.6	10.1	1.5	1.8	2.6	1.9
σ		7.7	5.6	2.7	2.4	6.3	5.4	1.5	1.2	1.3	1.2

Table S12: Atomization energies on G4 electronic reference and their absolute deviation on different functionals on CEP-121 (SBKJC-ECPs) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the CEP-121 (SBKJC-ECPs) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

	$G4_{ele}$	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2T-PLYP	B2K-PLYP	B2GP-PLYP
Na_2	18.20	6.80	5.51	6.83	4.99	0.91	87.70	6.16	6.47	7.20	6.77
K_2	12.41	7.64	6.55	7.96	6.39	2.23	1.36	7.89	8.29	9.16	8.65
Ca_2	2.35	1.31	2.13	0.62	2.05	1.28	2.26	3.07	3.19	3.40	3.28
NaH	43.46	4.60	1.26	6.29	0.71	0.78	43.17	4.41	5.34	7.39	6.22
KH	39.29	8.17	2.25	10.28	3.08	3.14	7.41	8.54	9.54	11.70	10.47
NaF	112.27	9.77	9.42	15.37	11.76	10.63	31.59	12.68	13.43	14.09	13.57
KF	114.07	16.06	15.91	21.04	17.70	16.53	19.05	18.73	19.36	19.89	19.46
CaF	125.15	9.68	11.53	13.66	12.66	13.60	19.30	12.76	12.99	12.82	12.82
CaF_2	263.76	15.54	17.19	22.89	18.83	22.10	25.03	19.05	19.72	19.83	19.54
NaCl	96.30	7.64	8.12	8.37	7.20	8.40	33.72	10.28	10.70	11.76	11.16
KCl	98.91	12.41	13.10	12.75	11.76	12.91	15.78	14.91	15.27	16.27	15.71
CaCl	95.72	18.72	21.76	19.18	20.73	23.24	30.65	23.25	23.34	23.74	23.55
$CaCl_2$	210.47	38.26	41.54	39.09	39.36	45.62	52.28	44.57	44.99	46.35	45.61
NaO	60.99	4.63	2.62	11.23	6.33	11.71	41.13	10.19	11.52	13.43	12.21
KO	62.41	12.74	10.86	19.47	14.69	19.53	12.00	18.94	20.20	22.05	20.88
CaO	88.93	41.68	40.82	62.52	54.93	55.71	71.38	47.31	50.96	53.77	51.43
CaS	74.36	36.13	37.33	44.66	42.41	45.89	51.57	47.32	49.41	52.53	50.57
NaOH	183.39	15.82	16.33	23.33	18.54	23.20	33.82	23.55	25.19	27.59	26.01
KOH	185.49	25.14	25.74	32.61	27.87	32.25	21.19	33.10	34.72	37.11	35.55
CaOH	199.08	16.56	19.65	22.59	20.69	27.66	18.23	24.86	25.96	27.46	26.45
NaCN	273.80	22.94	31.16	36.77	37.14	42.31	27.41	40.12	42.67	45.56	43.47
KCN	275.12	28.39	36.45	42.25	42.37	47.90	23.92	45.56	48.12	51.08	48.96
μ		16.4	17.1	21.8	19.2	21.3	30.5	21.7	22.8	24.3	23.3
σ		11.4	13.1	15.4	15.3	17.1	21.2	14.9	15.5	16.2	15.7

Table S13: Atomization energies on G4 electronic reference and their absolute deviation on different functionals on SDD (Stuttgart-ECPs) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the SDD

(Stuttgart-ECPs) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

	$G4_{ele}$	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2T-PLYP	B2K-PLYP	B2GP-PLYP
Na_2	18.20	7.79	6.60	8.00	6.21	1.86	0.46	7.93	8.33	9.24	8.71
K_2	12.41	5.13	4.06	5.24	3.69	0.23	66.58	5.01	5.34	6.12	5.66
Ca_2	2.35	1.37	2.15	0.67	2.05	1.04	1.39	3.05	3.17	3.37	3.25
NaH	43.46	2.84	2.85	4.88	2.03	2.32	1.18	3.60	4.62	6.83	5.57
KH	39.29	5.30	0.38	7.80	0.79	0.46	26.89	6.61	7.70	9.99	8.68
NaF	112.27	7.49	7.17	13.37	9.60	7.94	9.30	10.44	11.32	12.17	11.52
KF	114.07	16.12	16.04	21.40	17.87	16.29	15.79	18.66	19.42	20.12	19.57
CaF	125.15	32.29	34.58	35.89	35.33	35.70	38.19	34.80	34.96	34.66	34.74
CaF_2	263.76	47.94	50.17	55.40	51.82	53.19	51.24	51.23	51.90	51.97	51.70
NaCl	96.30	5.51	5.69	6.74	5.06	6.51	10.65	8.99	9.59	11.03	10.21
KCl	98.91	7.56	8.09	8.16	6.82	8.22	21.50	10.52	11.00	12.27	11.55
CaCl	95.72	20.38	23.46	20.99	22.47	25.12	32.30	25.55	25.74	26.40	26.06
$CaCl_2$	210.47	40.99	44.31	42.24	42.29	48.37	55.44	48.56	49.20	51.05	50.03
NaO	60.99	2.75	0.56	9.28	4.19	10.27	2.07	7.89	9.31	11.30	10.04
KO	62.41	10.27	8.30	16.56	11.65	17.58	28.19	15.33	16.64	18.48	17.31
CaO	88.93	73.28	72.59	93.57	86.19	86.85	95.10	77.41	80.92	83.39	81.23
CaS	74.36	41.83	43.11	50.17	47.97	51.60	55.40	52.95	55.03	58.19	56.21
NaOH	183.39	11.14	11.46	19.47	14.27	19.00	1.40	19.43	21.32	23.99	22.25
KOH	185.49	20.22	20.72	28.46	23.33	27.89	22.04	28.43	30.29	32.90	31.19
CaOH	199.08	31.29	34.52	37.59	35.81	43.05	25.83	39.67	40.87	42.43	41.39
NaCN	273.80	16.38	23.89	31.56	31.18	36.77	9.03	35.84	38.74	42.25	39.81
KCN	275.12	20.14	27.99	34.79	34.76	40.23	21.01	39.32	42.11	45.49	43.14
μ		19.5	20.4	25.1	22.5	24.6	26.9	25.1	26.3	27.9	26.8
σ		18.3	19.3	21.9	21.5	22.7	24.9	20.1	20.7	21.1	20.7

Table S14: Binding energies on G4 electronic reference and their absolute deviation on different functionals on Def2-SVP basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the Def2-SVP basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	43.7	45.9	38.0	41.5	39.9	38.1	39.9	37.9	39.1	38.6
	K^+	**-139.6**	43.3	44.0	37.5	39.7	39.6	36.8	37.9	35.9	37.1	36.6
	Ca^{2+}	**-339.7**	66.2	66.2	55.4	58.3	61.0	49.2	52.0	47.3	50.1	49.0
H_2O	Na^+	**-24.8**	7.4	7.9	6.5	7.5	6.1	7.6	7.1	6.8	7.0	6.9
	K^+	**-17.6**	7.0	6.9	6.1	6.5	5.8	6.9	6.4	6.2	6.3	6.3
	Ca^{2+}	**-56.4**	14.0	14.0	10.9	12.0	11.9	11.0	10.2	9.1	9.8	9.5
CH_3OH	Na^+	**-26.9**	4.0	4.8	3.6	4.6	3.5	5.2	4.6	4.5	4.6	4.6
	K^+	**-19.2**	3.9	3.9	3.4	3.9	3.3	4.7	4.1	4.2	4.2	4.2
	Ca^{2+}	**-65.9**	10.7	11.4	7.2	8.9	9.8	7.7	7.1	5.9	6.6	6.3
CH_3SH	Na^+	**-18.2**	2.0	1.9	1.7	1.9	1.5	2.5	1.7	1.6	1.7	1.6
	K^+	**-12.6**	2.2	1.5	2.0	1.7	1.7	2.5	1.8	1.9	1.8	1.9
	Ca^{2+}	**-54.7**	9.5	8.8	5.5	6.0	7.5	3.1	2.6	1.0	2.0	1.6
CO	Na^+	**-11.2**	1.8	1.8	0.6	1.1	1.0	0.3	1.1	0.8	0.9	0.9
	K^+	**-6.7**	2.0	1.6	1.0	1.1	1.2	0.6	1.3	1.2	1.3	1.3
	Ca^{2+}	**-29.6**	5.7	5.2	2.3	2.9	4.0	0.5	2.3	1.4	1.8	1.7
OCH_2	Na^+	**-26.2**	1.9	2.5	2.4	3.2	1.6	4.4	3.1	3.2	3.2	3.2
	K^+	**-19.2**	2.1	2.1	2.5	2.7	1.7	4.0	2.9	3.1	3.0	3.0
	Ca^{2+}	**-65.7**	8.1	8.7	6.9	8.0	7.6	8.4	5.9	5.3	5.8	5.5
$CH_3CO_2^-$	Na^+	**-148.2**	12.3	13.4	10.6	12.4	10.4	12.2	11.8	11.2	11.6	11.4
	K^+	**-129.1**	12.5	12.2	11.1	11.5	10.9	12.8	11.3	11.1	11.2	11.2
	Ca^{2+}	**-322.4**	27.3	26.8	20.5	22.0	24.5	16.9	17.3	14.5	16.2	15.5
NH_3	Na^+	**-28.5**	6.8	7.0	5.8	6.5	5.3	5.9	6.0	5.6	5.9	5.7
	K^+	**-19.6**	6.2	5.7	5.4	5.4	4.9	5.5	5.3	5.2	5.3	5.2
	Ca^{2+}	**-64.6**	12.4	11.5	9.6	9.9	10.1	8.0	7.8	6.7	7.4	7.1
PH_3	Na^+	**-17.9**	1.3	0.9	1.1	1.0	0.8	1.0	0.8	0.7	0.8	0.8
	K^+	**-11.4**	1.5	0.5	1.5	0.8	1.0	1.2	1.0	1.1	1.0	1.1
	Ca^{2+}	**-51.0**	6.1	4.8	3.8	3.4	4.2	0.9	1.0	0.1	0.6	0.3
NMA	Na^+	**-41.9**	2.0	3.0	2.1	3.3	1.3	3.9	3.0	3.0	3.1	3.0
	K^+	**-31.8**	2.4	2.5	2.4	2.9	1.6	3.8	2.8	3.0	2.9	2.9
	Ca^{2+}	**-107.9**	12.7	13.1	8.4	10.2	11.1	7.3	6.6	4.9	6.0	5.5
		μ	11.3	11.4	9.2	10.0	9.8	9.1	8.9	8.1	8.6	8.4
		σ	14.7	15.0	12.5	13.2	13.6	11.6	12.2	11.4	11.9	11.7

Table S15: Binding energies on G4 electronic reference and their absolute deviation on different functionals with Grimme's D3 dispersion scheme on Def2-SVP basis set and the mean absolute deviation (μ) and standard deviation (σ) for each

functional in the Def2-SVP basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	43.7	46.1	38.1	41.6	40.0	38.2	40.0	37.9	39.1	38.7
	K^+	**-139.6**	43.4	44.2	37.6	39.9	39.7	37.0	38.1	36.0	37.2	36.7
	Ca^{2+}	**-339.7**	66.5	67.0	55.8	59.1	61.5	49.9	52.5	47.8	50.6	49.3
H_2O	Na^+	**-24.8**	7.6	8.3	6.7	7.8	6.3	7.9	7.3	7.0	7.2	7.0
	K^+	**-17.6**	7.2	7.5	6.4	7.1	6.1	7.4	6.7	6.5	6.6	6.5
	Ca^{2+}	**-56.4**	14.7	15.8	11.8	13.7	13.1	12.6	11.1	10.1	10.7	10.2
CH_3OH	Na^+	**-26.9**	4.4	5.7	4.0	5.4	4.1	6.0	5.1	5.0	5.1	4.9
	K^+	**-19.2**	4.4	5.2	4.1	5.0	4.1	5.8	4.8	4.8	4.8	4.7
	Ca^{2+}	**-65.9**	11.8	13.9	8.5	11.1	11.5	9.8	8.3	7.2	7.9	7.3
CH_3SH	Na^+	**-18.2**	2.5	2.8	2.2	2.6	2.1	3.3	2.1	2.0	2.1	2.0
	K^+	**-12.6**	2.8	2.7	2.7	2.7	2.5	3.4	2.4	2.5	2.4	2.3
	Ca^{2+}	**-54.7**	10.4	10.8	6.5	7.6	8.8	4.7	3.5	1.9	2.9	2.2
CO	Na^+	**-11.2**	2.1	2.5	0.9	1.6	1.4	0.8	1.3	1.1	1.2	1.1
	K^+	**-6.7**	2.3	2.2	1.4	1.6	1.6	1.1	1.6	1.5	1.6	1.5
	Ca^{2+}	**-29.6**	5.9	5.8	2.6	3.4	4.4	1.0	2.6	1.7	2.2	1.9
OCH_2	Na^+	**-26.2**	2.2	3.2	2.8	3.8	2.0	4.9	3.4	3.5	3.5	3.4
	K^+	**-19.2**	2.6	3.2	3.0	3.6	2.4	4.8	3.4	3.6	3.5	3.4
	Ca^{2+}	**-65.7**	8.7	9.7	7.4	8.9	8.4	9.3	6.4	5.8	6.3	5.9
$CH_3CO_2^-$	Na^+	**-148.2**	12.5	14.0	10.9	12.8	10.8	12.6	12.0	11.4	11.8	11.6
	K^+	**-129.1**	12.9	13.0	11.5	12.2	11.4	13.4	11.7	11.4	11.6	11.4
	Ca^{2+}	**-322.4**	27.6	27.2	20.7	22.4	24.9	17.2	17.5	14.7	16.4	15.6
NH_3	Na^+	**-28.5**	7.0	7.4	6.0	6.8	5.5	6.3	6.2	5.8	6.1	5.9
	K^+	**-19.6**	6.5	6.4	5.8	6.1	5.3	6.2	5.7	5.6	5.7	5.5
	Ca^{2+}	**-64.6**	13.5	14.3	11.0	12.3	11.8	10.4	9.2	8.2	8.8	8.2
PH_3	Na^+	**-17.9**	1.6	1.6	1.5	1.6	1.2	1.7	1.2	1.1	1.2	1.0
	K^+	**-11.4**	1.9	1.4	1.9	1.6	1.6	2.0	1.4	1.6	1.5	1.4
	Ca^{2+}	**-51.0**	7.1	6.9	4.8	5.2	5.7	2.6	1.9	0.8	1.6	1.0
NMA	Na^+	**-41.9**	2.8	4.5	2.9	4.6	2.3	5.2	3.7	3.6	3.7	3.5
	K^+	**-31.8**	3.3	4.3	3.3	4.4	2.8	5.2	3.7	3.8	3.7	3.5
	Ca^{2+}	**-107.9**	14.1	16.2	9.9	12.7	13.2	9.8	8.0	6.3	7.4	6.5
		μ	11.8	12.5	9.8	11.0	10.6	10.0	9.4	8.7	9.1	8.8
		σ	14.6	14.8	12.4	13.1	13.6	11.4	12.1	11.3	11.8	11.6

Table S16: Binding energies on G4 electronic reference and their absolute deviation on different functionals on 6-31+G** basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-31+G** basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	1.15	0.30	2.59	2.08	0.77	4.05	2.43	3.11	2.80	2.86
	K^+	**-139.6**	1.92	3.90	0.44	1.96	2.06	0.35	1.91	1.32	1.57	1.54
	Ca^{2+}	**-339.7**	28.64	31.25	25.74	27.90	28.10	25.26	28.76	28.24	28.31	28.49
H_2O	Na^+	**-24.8**	0.64	0.23	1.23	1.13	0.48	2.68	1.59	1.88	1.76	1.75
	K^+	**-17.6**	0.66	0.21	1.15	0.66	0.63	2.78	1.43	1.81	1.61	1.60
	Ca^{2+}	**-56.4**	4.58	5.57	3.75	4.25	3.85	0.54	3.32	3.02	3.12	3.34
CH_3OH	Na^+	**-26.9**	0.16	0.07	0.24	0.59	0.41	2.64	1.56	1.87	1.71	1.65
	K^+	**-19.2**	0.42	0.94	0.04	0.23	0.32	2.35	1.13	1.56	1.31	1.24
	Ca^{2+}	**-65.9**	8.39	8.37	7.96	7.55	6.28	3.65	6.19	6.04	6.06	6.40
CH_3SH	Na^+	**-18.2**	0.07	0.68	0.10	0.36	0.12	0.77	0.36	0.50	0.44	0.34
	K^+	**-12.6**	0.12	1.13	0.09	0.71	0.19	0.95	0.00	0.14	0.07	0.06
	Ca^{2+}	**-54.7**	6.11	7.24	6.91	7.34	5.85	5.83	7.48	7.99	7.61	8.03
CO	Na^+	**-11.2**	0.09	0.63	0.74	0.84	0.15	0.82	0.27	0.31	0.30	0.37
	K^+	**-6.7**	0.02	0.78	0.46	0.83	0.00	0.44	0.12	0.02	0.10	0.14
	Ca^{2+}	**-29.6**	2.04	3.20	3.60	3.99	2.49	4.46	3.34	3.62	3.50	3.59
OCH_2	Na^+	**-26.2**	0.97	0.81	0.09	0.37	0.49	2.96	1.23	1.81	1.52	1.52
	K^+	**-19.2**	1.06	1.47	0.14	0.34	0.37	2.26	0.79	1.37	1.06	1.04
	Ca^{2+}	**-65.7**	8.63	8.60	6.57	6.45	7.18	2.54	6.13	5.54	5.74	5.88
$CH_3CO_2^-$	Na^+	**-148.2**	1.87	2.69	0.52	0.94	2.01	1.73	0.01	0.78	0.40	0.45
	K^+	**-129.1**	3.89	5.88	2.27	3.76	3.57	0.24	2.60	1.63	2.14	2.07
	Ca^{2+}	**-322.4**	23.28	25.70	21.14	22.99	23.03	20.28	23.63	23.09	23.20	23.32
NH_3	Na^+	**-28.5**	1.76	1.12	1.92	1.67	1.32	2.62	1.99	2.12	2.08	2.03
	K^+	**-19.6**	1.12	0.02	1.39	0.67	0.98	2.57	1.28	1.54	1.41	1.36
	Ca^{2+}	**-64.6**	3.51	5.00	3.33	4.23	2.88	0.65	3.18	3.18	3.11	3.51
PH_3	Na^+	**-17.9**	0.87	0.08	0.89	0.47	0.95	0.93	1.28	1.48	1.38	1.33
	K^+	**-11.4**	0.59	0.61	0.58	0.21	0.66	0.87	0.40	0.54	0.47	0.38
	Ca^{2+}	**-51.0**	2.11	3.52	2.83	3.58	2.11	3.05	3.41	3.81	3.51	3.91
NMA	Na^+	**-41.9**	1.35	1.07	0.58	0.04	0.69	3.22	1.26	1.87	1.53	1.46
	K^+	**-31.8**	2.02	2.47	1.24	1.35	1.03	1.94	0.08	0.67	0.34	0.24
	Ca^{2+}	**-107.9**	15.80	15.93	14.87	14.54	13.62	10.03	13.86	13.70	13.67	14.11
		μ	4.1	4.6	3.8	4.1	3.8	3.8	4.0	4.2	4.1	4.1
		σ	6.7	7.3	6.1	6.5	6.5	5.5	6.6	6.4	6.4	6.5

Table S17: Binding energies on G4 electronic reference and their absolute deviation on different functionals with Grimme's D3 dispersion scheme on 6-31+G** basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-31+G** basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	1.21	0.46	2.67	0.67	3.91	2.35	3.03	2.72	2.80	2.86
	K^+	**-139.6**	1.84	3.70	0.34	2.18	0.18	2.01	1.42	1.67	1.62	1.54
	Ca^{2+}	**-339.7**	28.31	30.43	25.33	28.62	25.97	29.19	28.67	28.74	28.82	28.49
H_2O	Na^+	**-24.8**	0.78	0.58	1.40	0.26	2.37	1.41	1.70	1.57	1.60	1.75
	K^+	**-17.6**	0.91	0.39	1.45	0.26	2.26	1.11	1.49	1.29	1.36	1.60
	Ca^{2+}	**-56.4**	3.86	3.78	2.86	4.98	2.08	4.26	3.97	4.06	4.05	3.34
CH_3OH	Na^+	**-26.9**	0.25	0.89	0.71	0.21	1.80	1.09	1.39	1.24	1.29	1.65
	K^+	**-19.2**	0.12	0.34	0.60	0.51	1.25	0.47	0.90	0.65	0.75	1.24
	Ca^{2+}	**-65.9**	7.25	5.82	6.67	7.96	5.82	7.43	7.28	7.31	7.32	6.40
CH_3SH	Na^+	**-18.2**	0.35	0.24	0.36	0.50	0.00	0.07	0.07	0.00	0.02	0.34
	K^+	**-12.6**	0.41	0.04	0.52	0.59	0.01	0.59	0.44	0.51	0.49	0.06
	Ca^{2+}	**-54.7**	5.20	5.32	5.91	7.16	7.43	8.37	8.88	8.50	8.68	8.03
CO	Na^+	**-11.2**	0.19	0.01	0.44	0.57	1.31	0.55	0.60	0.58	0.58	0.37
	K^+	**-6.7**	0.33	0.16	0.13	0.44	0.93	0.42	0.32	0.40	0.36	0.14
	Ca^{2+}	**-29.6**	1.79	2.58	3.30	2.88	5.01	3.66	3.93	3.82	3.83	3.59
OCH_2	Na^+	**-26.2**	0.66	0.11	0.43	0.95	2.37	0.89	1.47	1.18	1.27	1.52
	K^+	**-19.2**	0.62	0.45	0.38	1.03	1.43	0.27	0.86	0.54	0.65	1.04
	Ca^{2+}	**-65.7**	8.08	7.52	5.99	7.94	3.43	6.63	6.05	6.25	6.23	5.88
$CH_3CO_2^-$	Na^+	**-148.2**	1.62	2.16	0.24	2.37	1.33	0.25	0.52	0.14	0.26	0.45
	K^+	**-129.1**	3.54	5.12	1.86	4.09	0.33	2.99	2.02	2.53	2.36	2.07
	Ca^{2+}	**-322.4**	23.03	25.29	20.87	23.34	20.58	23.85	23.30	23.42	23.46	23.32
NH_3	Na^+	**-28.5**	1.93	1.55	2.14	1.05	2.23	1.77	1.89	1.86	1.86	2.03
	K^+	**-19.6**	1.41	0.70	1.75	0.53	1.94	0.90	1.16	1.03	1.07	1.36
	Ca^{2+}	**-64.6**	2.40	2.26	1.96	4.60	3.02	4.62	4.62	4.55	4.60	3.51
PH_3	Na^+	**-17.9**	1.18	0.83	1.24	0.47	0.27	0.94	1.14	1.04	1.08	1.33
	K^+	**-11.4**	0.98	0.30	1.03	0.06	0.11	0.04	0.10	0.03	0.05	0.38
	Ca^{2+}	**-51.0**	1.12	1.38	1.79	3.56	4.82	4.36	4.75	4.45	4.59	3.91
NMA	Na^+	**-41.9**	0.62	0.48	0.17	1.75	1.97	0.59	1.20	0.86	0.98	1.46
	K^+	**-31.8**	1.17	0.65	0.34	2.28	0.50	0.74	0.15	0.48	0.36	0.24
	Ca^{2+}	**-107.9**	14.34	12.91	13.30	15.70	12.52	15.25	15.08	15.05	15.12	14.11
		μ	3.8	3.9	3.5	4.3	3.9	4.2	4.3	4.2	4.3	4.1
		σ	6.6	7.0	5.9	6.7	5.8	6.8	6.6	6.7	6.7	6.5

Table S18: Binding energies on G4 electronic reference and their absolute deviation on different functionals on 6-31++G** basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-31++G** basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	0.9	0.1	2.4	1.9	0.5	3.9	2.2	2.9	2.6	2.7
	K^+	**-139.6**	2.2	4.1	0.6	2.2	2.4	0.0	2.2	1.6	1.9	1.8
	Ca^{2+}	**-339.7**	28.9	31.5	26.0	28.1	28.9	26.1	29.5	28.9	29.0	29.1
H_2O	Na^+	**-24.8**	0.6	0.2	1.2	1.1	0.2	2.3	1.4	1.6	1.5	1.5
	K^+	**-17.6**	0.6	0.3	1.1	0.6	0.2	2.2	1.1	1.4	1.2	1.3
	Ca^{2+}	**-56.4**	4.6	5.6	3.8	4.3	5.0	2.2	4.3	4.0	4.1	4.1
CH_3OH	Na^+	**-26.9**	0.2	0.1	0.2	0.6	0.2	1.8	1.1	1.4	1.2	1.3
	K^+	**-19.2**	0.4	1.0	0.1	0.2	0.5	1.2	0.5	0.9	0.6	0.7
	Ca^{2+}	**-65.9**	8.4	8.4	8.0	7.6	8.0	5.8	7.4	7.3	7.3	7.3
CH_3SH	Na^+	**-18.2**	0.1	0.7	0.1	0.4	0.5	0.0	0.1	0.1	0.0	0.1
	K^+	**-12.6**	0.1	1.1	0.1	0.7	0.6	0.0	0.6	0.4	0.5	0.5
	Ca^{2+}	**-54.7**	6.1	7.2	6.9	7.3	7.1	7.4	8.3	8.8	8.4	8.6
CO	Na^+	**-11.2**	0.1	0.6	0.7	0.8	0.6	1.3	0.6	0.6	0.6	0.6
	K^+	**-6.7**	0.0	0.8	0.5	0.8	0.4	0.9	0.4	0.3	0.4	0.4
	Ca^{2+}	**-29.6**	2.0	3.2	3.6	4.0	2.9	5.0	3.7	3.9	3.8	3.8
OCH_2	Na^+	**-26.2**	1.0	0.8	0.1	0.4	1.0	2.4	0.9	1.5	1.2	1.3
	K^+	**-19.2**	1.1	1.5	0.2	0.4	1.1	1.4	0.3	0.9	0.5	0.6
	Ca^{2+}	**-65.7**	8.7	8.6	6.6	6.5	8.0	3.5	6.7	6.1	6.3	6.3
$CH_3CO_2^-$	Na^+	**-148.2**	2.0	2.8	0.6	1.0	2.5	1.3	0.3	0.5	0.1	0.2
	K^+	**-129.1**	4.0	6.0	2.3	3.8	4.2	0.4	3.1	2.1	2.6	2.4
	Ca^{2+}	**-322.4**	23.4	25.9	21.2	23.1	23.5	20.7	23.9	23.4	23.5	23.5
NH_3	Na^+	**-28.5**	1.7	1.1	1.8	1.6	1.0	2.1	1.7	1.8	1.8	1.8
	K^+	**-19.6**	1.0	0.1	1.3	0.6	0.4	1.8	0.8	1.1	0.9	1.0
	Ca^{2+}	**-64.6**	3.6	5.0	3.4	4.3	4.7	3.1	4.7	4.7	4.6	4.7
PH_3	Na^+	**-17.9**	0.9	0.1	0.9	0.5	0.5	0.3	1.0	1.2	1.1	1.1
	K^+	**-11.4**	0.6	0.6	0.6	0.2	0.0	0.1	0.0	0.1	0.0	0.1
	Ca^{2+}	**-51.0**	2.1	3.5	2.8	3.6	3.5	4.8	4.3	4.7	4.4	4.5
NMA	Na^+	**-41.9**	1.3	1.1	0.6	0.0	1.7	2.0	0.6	1.2	0.9	1.0
	K^+	**-31.8**	2.0	2.5	1.3	1.4	2.3	0.5	0.7	0.1	0.5	0.3
	Ca^{2+}	**-107.9**	15.8	15.9	14.8	14.5	15.7	12.5	15.2	15.0	15.0	15.1
		μ	4.1	4.7	3.8	4.1	4.3	3.9	4.2	4.3	4.2	4.3
		σ	6.8	7.3	6.2	6.5	6.8	5.8	6.8	6.7	6.7	6.7

Table S19: Binding energies on G4 electronic reference and their absolute deviation on different functionals with Grimme's D3 dispersion scheme on 6-31++G** basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-31++G** basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	1.0	0.2	2.5	2.0	0.5	4.0	2.3	3.0	2.7	2.7
	K^+	**-139.6**	2.1	3.9	0.5	2.0	2.3	0.2	2.1	1.5	1.8	1.7
	Ca^{2+}	**-339.7**	28.6	30.7	25.5	27.4	28.4	25.4	29.0	28.5	28.6	28.8
H_2O	Na^+	**-24.8**	0.7	0.6	1.4	1.4	0.4	2.6	1.5	1.8	1.7	1.7
	K^+	**-17.6**	0.9	0.3	1.4	1.2	0.6	2.7	1.4	1.8	1.6	1.6
	Ca^{2+}	**-56.4**	3.9	3.8	2.9	2.7	3.9	0.6	3.4	3.1	3.2	3.4
CH_3OH	Na^+	**-26.9**	0.2	0.9	0.7	1.4	0.4	2.7	1.6	1.9	1.7	1.7
	K^+	**-19.2**	0.1	0.3	0.6	0.9	0.3	2.3	1.1	1.6	1.3	1.2
	Ca^{2+}	**-65.9**	7.3	5.8	6.7	5.3	6.3	3.6	6.2	6.0	6.0	6.4
CH_3SH	Na^+	**-18.2**	0.3	0.2	0.4	0.4	0.1	0.8	0.4	0.5	0.5	0.4
	K^+	**-12.6**	0.4	0.0	0.5	0.3	0.2	1.0	0.0	0.2	0.1	0.0
	Ca^{2+}	**-54.7**	5.2	5.3	5.9	5.7	5.8	5.8	7.4	7.9	7.5	7.9
CO	Na^+	**-11.2**	0.2	0.0	0.4	0.3	0.2	0.8	0.3	0.3	0.3	0.4
	K^+	**-6.7**	0.3	0.2	0.1	0.3	0.0	0.4	0.1	0.0	0.1	0.1
	Ca^{2+}	**-29.6**	1.8	2.6	3.3	3.4	2.5	4.5	3.3	3.6	3.5	3.6
OCH_2	Na^+	**-26.2**	0.7	0.1	0.4	1.0	0.5	3.0	1.3	1.9	1.6	1.6
	K^+	**-19.2**	0.7	0.5	0.3	0.5	0.4	2.2	0.8	1.4	1.0	1.0
	Ca^{2+}	**-65.7**	8.1	7.6	6.0	5.5	7.2	2.6	6.2	5.6	5.8	5.9
$CH_3CO_2^-$	Na^+	**-148.2**	1.8	2.3	0.3	0.6	2.2	1.7	0.1	0.7	0.3	0.4
	K^+	**-129.1**	3.7	5.3	1.9	3.1	3.7	0.2	2.7	1.7	2.2	2.1
	Ca^{2+}	**-322.4**	23.2	25.4	21.0	22.7	23.2	20.4	23.7	23.2	23.3	23.4
NH_3	Na^+	**-28.5**	1.9	1.5	2.0	2.0	1.2	2.5	1.9	2.0	2.0	1.9
	K^+	**-19.6**	1.3	0.6	1.7	1.3	0.9	2.5	1.2	1.4	1.3	1.3
	Ca^{2+}	**-64.6**	2.5	2.3	2.1	1.8	3.0	0.8	3.3	3.3	3.2	3.6
PH_3	Na^+	**-17.9**	1.2	0.8	1.2	1.1	1.0	0.9	1.3	1.5	1.4	1.4
	K^+	**-11.4**	1.0	0.3	1.0	0.6	0.6	0.9	0.4	0.6	0.5	0.4
	Ca^{2+}	**-51.0**	1.1	1.4	1.8	1.8	2.1	3.0	3.3	3.7	3.4	3.8
NMA	Na^+	**-41.9**	0.6	0.5	0.2	1.2	0.7	3.2	1.3	1.9	1.6	1.5
	K^+	**-31.8**	1.2	0.7	0.3	0.2	1.0	1.9	0.1	0.7	0.4	0.3
	Ca^{2+}	**-107.9**	14.3	12.9	13.3	12.0	13.6	10.0	13.8	13.7	13.6	14.1
		μ	3.9	3.9	3.5	3.7	3.8	3.8	4.0	4.2	4.1	4.1
		σ	6.6	7.1	5.9	6.2	6.6	5.5	6.6	6.4	6.5	6.5

Table S20: Binding energies on G4 electronic reference and their absolute deviation on different functionals on 6-311++G*(2d,2p) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-311++G(2d,2p) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	1.04	0.35	2.36	2.03	0.65	2.70	1.65	2.05	1.94	1.93
	K^+	**-139.6**	4.02	1.99	4.39	3.09	3.65	4.36	2.31	2.53	2.49	2.46
	Ca^{2+}	**-339.7**	12.11	8.65	8.89	7.22	11.01	2.45	2.15	0.29	1.57	0.97
H_2O	Na^+	**-24.8**	0.87	1.16	0.44	0.38	1.33	0.27	0.31	0.11	0.18	0.17
	K^+	**-17.6**	0.16	0.92	0.10	0.24	0.63	1.01	0.01	0.28	0.13	0.18
	Ca^{2+}	**-56.4**	2.21	1.18	1.07	0.93	1.47	0.90	0.40	0.74	0.48	0.61
CH_3OH	Na^+	**-26.9**	1.32	1.10	1.07	0.53	1.36	0.22	0.31	0.15	0.20	0.20
	K^+	**-19.2**	0.59	1.00	0.51	0.50	0.73	0.87	0.10	0.17	0.02	0.08
	Ca^{2+}	**-65.9**	3.27	3.15	0.89	1.76	3.31	1.10	0.09	0.68	0.18	0.40
CH_3SH	Na^+	**-18.2**	0.48	1.13	0.54	0.81	0.80	0.91	0.90	0.90	0.86	0.89
	K^+	**-12.6**	0.37	1.36	0.43	1.00	0.75	0.45	0.82	0.65	0.74	0.71
	Ca^{2+}	**-54.7**	6.03	4.58	2.57	2.29	4.69	0.82	0.60	1.88	1.07	1.43
CO	Na^+	**-11.2**	0.21	0.39	0.48	0.61	0.21	1.55	0.27	0.30	0.30	0.29
	K^+	**-6.7**	0.28	0.56	0.23	0.63	0.14	0.87	0.15	0.04	0.13	0.08
	Ca^{2+}	**-29.6**	3.00	1.55	0.54	0.07	2.08	2.38	0.10	0.33	0.15	0.18
OCH_2	Na^+	**-26.2**	1.73	1.52	0.79	0.39	1.74	0.75	0.33	0.02	0.11	0.09
	K^+	**-19.2**	1.01	1.35	0.36	0.41	1.13	1.24	0.12	0.30	0.09	0.15
	Ca^{2+}	**-65.7**	2.01	1.88	1.23	1.82	2.04	2.16	0.10	0.41	0.10	0.29
$CH_3CO_2^-$	Na^+	**-148.2**	1.85	2.77	0.49	0.97	2.22	0.35	0.68	0.11	0.34	0.29
	K^+	**-129.1**	0.03	2.20	0.97	0.51	0.25	2.57	0.07	0.65	0.28	0.40
	Ca^{2+}	**-322.4**	8.18	4.59	5.44	3.57	7.53	0.93	0.10	1.06	0.24	0.64
NH_3	Na^+	**-28.5**	0.05	0.55	0.01	0.10	0.71	0.24	0.16	0.10	0.09	0.11
	K^+	**-19.6**	0.26	0.75	0.30	0.24	0.33	0.60	0.04	0.18	0.07	0.11
	Ca^{2+}	**-64.6**	4.10	2.44	2.51	1.84	2.90	0.61	0.29	0.25	0.11	0.06
PH_3	Na^+	**-17.9**	0.09	0.60	0.18	0.17	0.00	0.83	0.26	0.22	0.19	0.22
	K^+	**-11.4**	0.25	1.32	0.14	0.84	0.44	0.56	0.62	0.41	0.52	0.48
	Ca^{2+}	**-51.0**	4.27	2.55	2.61	1.75	3.29	0.50	0.09	0.76	0.29	0.52
NMA	Na^+	**-41.9**	2.24	1.98	1.46	0.91	2.55	0.04	0.99	0.72	0.80	0.80
	K^+	**-31.8**	1.21	1.66	0.76	0.78	1.58	0.77	0.60	0.23	0.41	0.36
	Ca^{2+}	**-107.9**	5.19	4.55	1.91	2.60	4.59	0.32	0.69	2.01	1.14	1.54
		μ	2.3	2.0	1.5	1.3	2.1	1.1	0.5	0.6	0.5	0.6
		σ	2.7	1.7	1.9	1.4	2.3	0.9	0.6	0.6	0.6	0.6

Table S21: Binding energies on G4 electronic reference and their absolute deviation on different functionals with Grimme's D3 dispersion scheme on 6-311++G(2d,2p) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the 6-311++G(2d,2p) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	1.10	0.50	2.44	2.17	0.75	2.84	1.73	2.13	2.02	1.99
	K^+	**-139.6**	4.10	2.19	4.49	3.27	3.77	4.53	2.41	2.64	2.59	2.54
	Ca^{2+}	**-339.7**	12.45	9.47	9.30	7.96	11.53	3.16	2.59	0.72	2.00	1.30
H_2O	Na^+	**-24.8**	0.73	0.81	0.26	0.06	1.11	0.59	0.13	0.08	0.01	0.03
	K^+	**-17.6**	0.08	0.32	0.40	0.32	0.25	1.53	0.32	0.60	0.45	0.42
	Ca^{2+}	**-56.4**	2.94	2.96	1.96	2.55	2.60	2.44	0.55	0.20	0.46	0.10
CH_3OH	Na^+	**-26.9**	0.91	0.13	0.59	0.31	0.74	1.06	0.16	0.33	0.27	0.16
	K^+	**-19.2**	0.05	0.29	0.13	0.65	0.09	1.96	0.55	0.82	0.67	0.57
	Ca^{2+}	**-65.9**	4.41	5.70	2.17	3.99	5.00	3.27	1.34	0.56	1.06	0.51
CH_3SH	Na^+	**-18.2**	0.06	0.21	0.07	0.02	0.18	0.15	0.47	0.46	0.43	0.57
	K^+	**-12.6**	0.17	0.19	0.18	0.04	0.04	0.50	0.23	0.07	0.15	0.27
	Ca^{2+}	**-54.7**	6.95	6.50	3.57	3.92	5.99	0.78	0.29	0.99	0.17	0.78
CO	Na^+	**-11.2**	0.50	0.23	0.17	0.10	0.21	1.06	0.01	0.02	0.02	0.08
	K^+	**-6.7**	0.59	0.06	0.10	0.08	0.29	0.38	0.15	0.26	0.17	0.14
	Ca^{2+}	**-29.6**	3.25	2.17	0.84	0.62	2.47	1.83	0.42	0.02	0.17	0.05
OCH_2	Na^+	**-26.2**	1.42	0.81	0.45	0.22	1.28	1.34	0.01	0.36	0.23	0.16
	K^+	**-19.2**	0.57	0.34	0.15	0.50	0.47	2.08	0.40	0.81	0.61	0.54
	Ca^{2+}	**-65.7**	2.56	2.96	1.82	2.76	2.80	3.05	0.40	0.09	0.40	0.06
$CH_3CO_2^-$	Na^+	**-148.2**	1.60	2.24	0.21	0.50	1.86	0.74	0.42	0.15	0.07	0.10
	K^+	**-129.1**	0.32	1.44	1.38	0.18	0.27	3.15	0.32	1.04	0.68	0.69
	Ca^{2+}	**-322.4**	8.43	5.00	5.71	3.96	7.84	1.23	0.31	0.85	0.02	0.49
NH_3	Na^+	**-28.5**	0.13	0.12	0.20	0.29	0.44	0.16	0.07	0.12	0.13	0.06
	K^+	**-19.6**	0.55	0.03	0.66	0.41	0.12	1.24	0.34	0.56	0.45	0.40
	Ca^{2+}	**-64.6**	5.21	5.18	3.87	4.32	4.63	2.98	1.72	1.18	1.55	1.03
PH_3	Na^+	**-17.9**	0.40	0.15	0.52	0.44	0.47	0.16	0.08	0.13	0.15	0.03
	K^+	**-11.4**	0.14	0.41	0.30	0.05	0.16	0.20	0.18	0.03	0.08	0.16
	Ca^{2+}	**-51.0**	5.26	4.69	3.65	3.50	4.74	1.26	0.85	0.18	0.65	0.17
NMA	Na^+	**-41.9**	1.51	0.43	0.70	0.34	1.49	1.21	0.32	0.05	0.13	0.32
	K^+	**-31.8**	0.35	0.15	0.15	0.73	0.34	2.21	0.22	0.59	0.41	0.24
	Ca^{2+}	**-107.9**	6.65	7.58	3.47	5.14	6.66	2.81	0.69	0.62	0.25	0.53
		μ	2.4	2.1	1.7	1.6	2.3	1.7	0.6	0.6	0.5	0.5
		σ	3.0	2.6	2.1	2.0	2.8	1.1	0.7	0.6	0.6	0.6

Table S22: Binding energies on G4 electronic reference and their absolute deviation on different functionals on CEP-121 (SBKJC-ECPs) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the CEP-121 (SBKJC-ECPs) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	19.59	20.09	17.20	17.87	18.33	17.54	17.25	16.48	16.90	16.74
	K^+	**-139.6**	8.23	8.69	5.75	6.36	7.15	5.68	5.50	4.70	5.14	4.97
	Ca^{2+}	**-339.7**	2.01	1.94	3.11	3.04	2.90	2.59	4.23	4.93	4.48	4.67
H_2O	Na^+	**-24.8**	6.82	6.61	7.01	6.77	6.53	8.23	6.81	6.92	6.86	6.88
	K^+	**-17.6**	4.01	3.86	4.09	3.95	3.78	4.90	3.91	3.94	3.93	3.93
	Ca^{2+}	**-56.4**	6.57	6.21	6.80	6.45	6.17	8.61	6.13	6.11	6.15	6.12
CH_3OH	Na^+	**-26.9**	3.98	4.29	4.59	4.73	4.34	5.77	5.28	5.63	5.41	5.50
	K^+	**-19.2**	1.44	1.67	1.88	2.00	1.73	2.67	2.34	2.56	2.43	2.48
	Ca^{2+}	**-65.9**	0.34	1.26	0.94	1.64	1.06	2.28	1.99	2.22	2.09	2.14
CH_3SH	Na^+	**-18.2**	0.54	0.72	0.02	0.31	0.79	0.03	0.20	0.01	0.11	0.08
	K^+	**-12.6**	1.59	1.74	1.19	1.42	1.76	1.31	1.45	1.37	1.40	1.40
	Ca^{2+}	**-54.7**	13.32	13.17	12.91	12.90	13.76	13.64	13.44	13.56	13.44	13.51
CO	Na^+	**-11.2**	0.94	1.23	1.52	1.73	1.01	1.55	1.26	1.20	1.30	1.23
	K^+	**-6.7**	1.38	1.58	1.89	2.00	1.49	2.04	1.72	1.73	1.77	1.74
	Ca^{2+}	**-29.6**	5.58	6.13	7.00	7.30	5.80	7.49	6.61	6.70	6.76	6.69
OCH_2	Na^+	**-26.2**	1.18	1.59	2.59	2.67	1.72	3.76	2.86	3.32	3.09	3.16
	K^+	**-19.2**	0.52	0.28	0.65	0.64	0.05	1.47	0.79	1.14	0.97	1.02
	Ca^{2+}	**-65.7**	1.02	0.24	1.88	2.01	0.23	3.53	1.93	2.65	2.36	2.41
$CH_3CO_2^-$	Na^+	**-148.2**	2.83	2.91	1.83	2.20	2.42	1.04	2.11	1.79	1.94	1.90
	K^+	**-129.1**	8.71	8.80	7.43	7.87	8.04	6.32	8.06	7.77	7.88	7.87
	Ca^{2+}	**-322.4**	22.40	22.33	20.44	20.94	21.31	19.45	22.27	22.17	22.07	22.19
NH_3	Na^+	**-28.5**	5.08	4.68	5.08	4.70	4.72	5.95	4.70	4.74	4.71	4.72
	K^+	**-19.6**	1.85	1.63	1.77	1.58	1.58	2.33	1.46	1.41	1.44	1.43
	Ca^{2+}	**-64.6**	0.39	1.00	0.64	1.15	1.04	0.58	1.69	1.92	1.77	1.83
PH_3	Na^+	**-17.9**	0.69	0.08	1.03	0.26	0.03	0.54	0.56	0.77	0.64	0.69
	K^+	**-11.4**	0.67	1.23	0.42	0.99	1.12	0.84	0.94	0.86	0.90	0.88
	Ca^{2+}	**-51.0**	7.94	9.21	7.79	9.00	9.38	8.87	9.07	9.02	9.05	9.03
NMA	Na^+	**-41.9**	0.94	1.17	2.46	2.35	1.49	3.87	2.58	3.11	2.84	2.92
	K^+	**-31.8**	1.97	1.87	0.59	0.78	1.46	0.33	0.65	0.23	0.43	0.38
	Ca^{2+}	**-107.9**	5.56	5.23	3.01	3.25	4.24	1.29	3.32	2.62	2.93	2.86
		μ	4.6	4.7	4.5	4.6	4.5	4.8	4.7	4.7	4.7	4.7
		σ	5.4	5.4	4.8	4.9	5.2	4.8	5.0	4.9	5.0	5.0

Table S23: Binding energies on G4 electronic reference and their absolute deviation on different functionals with Grimme's D3 dispersion scheme on CEP-121 (SBKJC-ECPs) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the CEP-121 (SBKJC-ECPs) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	19.65	20.24	17.28	18.01	18.43	17.67	17.33	16.56	16.98	16.81
	K^+	**-139.6**	8.31	8.89	5.85	6.54	7.28	5.85	5.61	4.80	5.25	5.05
	Ca^{2+}	**-339.7**	1.68	1.12	2.70	2.29	2.38	1.88	3.79	4.49	4.04	4.34
H_2O	Na^+	**-24.8**	6.96	6.96	7.18	7.09	6.75	8.55	7.00	7.11	7.05	7.02
	K^+	**-17.6**	4.25	4.46	4.40	4.50	4.15	5.42	4.23	4.26	4.25	4.17
	Ca^{2+}	**-56.4**	7.30	8.00	7.70	8.07	7.29	10.16	7.07	7.05	7.09	6.83
CH_3OH	Na^+	**-26.9**	4.39	5.25	5.07	5.56	4.96	6.61	5.75	6.10	5.88	5.85
	K^+	**-19.2**	1.98	2.95	2.52	3.14	2.56	3.76	3.00	3.21	3.08	2.97
	Ca^{2+}	**-65.9**	1.48	3.81	2.23	3.87	2.75	4.44	3.23	3.46	3.33	3.05
CH_3SH	Na^+	**-18.2**	0.12	0.20	0.45	0.48	0.18	0.73	0.24	0.42	0.33	0.24
	K^+	**-12.6**	1.05	0.57	0.58	0.37	0.97	0.37	0.87	0.78	0.81	0.96
	Ca^{2+}	**-54.7**	12.40	11.25	11.92	11.28	12.45	12.04	12.55	12.66	12.55	12.86
CO	Na^+	**-11.2**	0.65	0.61	1.22	1.21	0.59	1.06	0.98	0.92	1.02	1.03
	K^+	**-6.7**	1.08	0.96	1.56	1.45	1.06	1.55	1.42	1.43	1.47	1.52
	Ca^{2+}	**-29.6**	5.33	5.51	6.70	6.75	5.41	6.94	6.30	6.39	6.45	6.45
OCH_2	Na^+	**-26.2**	1.48	2.30	2.93	3.28	2.18	4.35	3.20	3.66	3.44	3.41
	K^+	**-19.2**	0.09	0.74	1.16	1.55	0.61	2.30	1.30	1.66	1.49	1.41
	Ca^{2+}	**-65.7**	0.47	0.83	2.46	2.95	0.99	4.42	2.43	3.15	2.86	2.76
$CH_3CO_2^-$	Na^+	**-148.2**	2.58	2.38	1.55	1.72	2.05	0.64	1.85	1.52	1.68	1.71
	K^+	**-129.1**	8.36	8.03	7.03	7.17	7.52	5.75	7.67	7.38	7.49	7.58
	Ca^{2+}	**-322.4**	22.15	21.92	20.17	20.54	21.00	19.16	22.06	21.96	21.86	22.04
NH_3	Na^+	**-28.5**	5.25	5.11	5.29	5.09	4.99	6.35	4.92	4.96	4.93	4.89
	K^+	**-19.6**	2.15	2.35	2.13	2.23	2.04	2.96	1.84	1.79	1.82	1.72
	Ca^{2+}	**-64.6**	0.73	1.74	0.73	1.33	0.68	2.95	0.25	0.48	0.33	0.74
PH_3	Na^+	**-17.9**	0.99	0.67	1.38	0.87	0.50	1.20	0.90	1.11	0.98	0.95
	K^+	**-11.4**	0.28	0.31	0.02	0.20	0.52	0.08	0.50	0.41	0.46	0.56
	Ca^{2+}	**-51.0**	6.96	7.08	6.75	7.26	7.93	7.11	8.12	8.07	8.10	8.35
NMA	Na^+	**-41.9**	1.67	2.72	3.22	3.60	2.55	5.12	3.25	3.78	3.51	3.40
	K^+	**-31.8**	1.11	0.06	0.31	0.73	0.22	1.76	0.17	0.59	0.39	0.22
	Ca^{2+}	**-107.9**	4.10	2.21	1.45	0.71	2.17	1.20	1.94	1.23	1.55	1.85
		μ	4.5	4.6	4.5	4.7	4.4	5.1	4.7	4.7	4.7	4.7
		σ	5.3	5.3	4.7	4.8	5.0	4.6	5.0	4.9	4.9	4.9

Table S24: Binding energies on G4 electronic reference and their absolute deviation on different functionals on SDD (Stuttgart-ECPs) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the SDD (Stuttgart-ECPs) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	1.96	3.05	0.77	0.83	0.98	3.95	0.60	14.12	14.11	14.07
	K^+	**-139.6**	12.84	13.88	10.24	11.77	11.82	7.99	11.60	0.47	0.29	0.31
	Ca^{2+}	**-339.7**	51.13	53.04	46.37	49.17	49.29	42.36	49.18	10.52	10.85	10.82
H_2O	Na^+	**-24.8**	4.39	3.79	5.49	4.74	4.52	6.94	5.04	8.37	8.24	8.28
	K^+	**-17.6**	2.31	1.82	3.20	2.60	2.44	4.21	2.84	5.34	5.21	5.26
	Ca^{2+}	**-56.4**	1.88	2.96	0.13	1.41	1.61	2.11	1.03	10.89	10.62	10.71
CH_3OH	Na^+	**-26.9**	3.88	4.09	4.76	4.76	4.30	5.64	5.24	5.96	5.74	5.83
	K^+	**-19.2**	1.53	1.65	2.27	2.22	1.89	2.83	2.61	2.87	2.66	2.74
	Ca^{2+}	**-65.9**	6.58	5.95	5.20	4.94	5.65	4.25	4.28	3.59	3.16	3.32
CH_3SH	Na^+	**-18.2**	0.37	0.41	0.11	0.03	0.69	0.28	0.11	1.55	1.46	1.49
	K^+	**-12.6**	0.40	0.49	0.02	0.15	0.62	0.28	0.07	1.05	0.98	1.00
	Ca^{2+}	**-54.7**	14.55	14.27	14.09	13.97	15.03	15.20	14.28	10.71	10.68	10.71
CO	Na^+	**-11.2**	1.24	1.45	1.97	2.04	1.33	1.97	1.60	1.69	1.76	1.70
	K^+	**-6.7**	0.91	1.08	1.45	1.52	0.97	1.46	1.17	1.60	1.66	1.61
	Ca^{2+}	**-29.6**	6.68	7.27	8.05	8.38	6.65	7.98	7.48	7.56	7.76	7.61
OCH_2	Na^+	**-26.2**	1.63	1.90	3.16	3.07	2.23	4.21	3.24	7.92	7.83	7.82
	K^+	**-19.2**	0.00	0.16	1.25	1.13	0.51	1.94	1.34	4.90	4.78	4.80
	Ca^{2+}	**-65.7**	8.87	8.34	5.76	5.95	7.51	4.06	5.75	11.96	11.69	11.71
$CH_3CO_2^-$	Na^+	**-148.2**	6.36	6.90	4.52	5.43	5.68	4.34	5.30	10.95	11.19	11.13
	K^+	**-129.1**	11.74	12.18	9.67	10.56	10.96	9.16	10.55	12.24	12.48	12.43
	Ca^{2+}	**-322.4**	48.11	48.75	44.84	46.25	46.71	45.13	46.88	36.11	36.46	36.42
NH_3	Na^+	**-28.5**	9.60	9.37	9.13	8.97	8.85	10.11	8.88	8.22	8.22	8.23
	K^+	**-19.6**	5.88	5.61	5.64	5.41	5.36	6.30	5.33	4.11	4.10	4.11
	Ca^{2+}	**-64.6**	2.93	2.13	2.62	1.92	1.87	3.97	1.68	3.33	3.29	3.31
PH_3	Na^+	**-17.9**	1.13	0.56	1.41	0.82	0.37	0.77	1.00	0.56	0.53	0.54
	K^+	**-11.4**	1.15	0.63	1.37	0.85	0.51	0.87	0.90	0.16	0.18	0.17
	Ca^{2+}	**-51.0**	8.07	9.22	7.97	9.07	9.72	9.30	9.10	8.98	8.92	8.94
NMA	Na^+	**-41.9**	1.63	1.93	3.06	3.04	2.01	4.40	3.22	6.32	6.18	6.20
	K^+	**-31.8**	1.33	1.13	0.07	0.14	0.98	0.85	0.05	2.97	2.78	2.82
	Ca^{2+}	**-107.9**	19.51	19.01	17.08	17.16	18.43	15.27	16.89	0.34	0.72	0.62
		μ	8.0	8.1	7.4	7.6	7.7	7.6	7.6	6.8	6.8	6.8
		σ	12.1	12.4	11.0	11.5	11.7	10.4	11.6	6.8	6.9	6.9

Table S25: Binding energies on G4 electronic reference and their absolute deviation on different functionals with Grimme's D3 dispersion scheme on SDD (Stuttgart-ECPs) basis set and the mean absolute deviation (μ) and standard deviation (σ) for each functional in the SDD (Stuttgart-ECPs) basis set. All values are expressed in kcal/mol. G4 optimized molecular structure were used in all calculations.

Ligand	Ion	G4	PBE	BLYP	PBE0	B3LYP	TPSS	M11	B2PLYP	B2K-PLYP	B2T-PLYP	B2GP-PLYP
OH^-	Na^+	**-156.5**	1.9	2.9	0.8	0.7	0.9	4.1	0.5	14.2	14.2	14.1
	K^+	**-139.6**	12.8	13.7	10.1	11.6	11.7	7.8	11.5	0.6	0.4	0.4
	Ca^{2+}	**-339.7**	50.8	52.2	46.0	48.4	48.8	41.7	48.7	10.1	10.4	10.5
H_2O	Na^+	**-24.8**	4.5	4.1	5.7	5.1	4.8	7.3	5.2	8.6	8.4	8.4
	K^+	**-17.6**	2.6	2.4	3.5	3.1	2.8	4.7	3.2	5.7	5.5	5.5
	Ca^{2+}	**-56.4**	1.2	1.2	0.8	0.2	0.5	3.7	0.1	11.8	11.6	11.4
CH_3OH	Na^+	**-26.9**	4.3	5.1	5.2	5.6	4.9	6.5	5.7	6.4	6.2	6.2
	K^+	**-19.2**	2.1	2.9	2.9	3.4	2.7	3.9	3.3	3.5	3.3	3.2
	Ca^{2+}	**-65.9**	5.4	3.4	3.9	2.7	4.0	2.1	3.0	4.8	4.4	4.2
CH_3SH	Na^+	**-18.2**	0.0	0.5	0.6	0.8	0.1	0.5	0.5	2.0	1.9	1.8
	K^+	**-12.6**	0.1	0.7	0.6	0.9	0.2	0.7	0.5	1.6	1.6	1.4
	Ca^{2+}	**-54.7**	13.6	12.4	13.1	12.3	13.7	13.6	13.4	9.8	9.8	10.1
CO	Na^+	**-11.2**	1.0	0.8	1.7	1.5	0.9	1.5	1.3	1.4	1.5	1.5
	K^+	**-6.7**	0.6	0.5	1.1	1.0	0.5	1.0	0.9	1.3	1.4	1.4
	Ca^{2+}	**-29.6**	6.4	6.7	7.8	7.8	6.3	7.4	7.2	7.2	7.4	7.4
OCH_2	Na^+	**-26.2**	1.9	2.6	3.5	3.7	2.7	4.8	3.6	8.3	8.2	8.1
	K^+	**-19.2**	0.4	1.2	1.8	2.0	1.2	2.8	1.9	5.4	5.3	5.2
	Ca^{2+}	**-65.7**	8.3	7.3	5.2	5.0	6.8	3.2	5.3	12.5	12.2	12.1
$CH_3CO_2^-$	Na^+	**-148.2**	6.1	6.4	4.2	5.0	5.3	3.9	5.0	10.7	10.9	10.9
	K^+	**-129.1**	11.4	11.4	9.3	9.9	10.4	8.6	10.2	11.8	12.1	12.1
	Ca^{2+}	**-322.4**	47.9	48.3	44.6	45.9	46.4	44.8	46.7	35.9	36.3	36.3
NH_3	Na^+	**-28.5**	9.8	9.8	9.3	9.4	9.1	10.5	9.1	8.4	8.4	8.4
	K^+	**-19.6**	6.2	6.3	6.0	6.1	5.8	6.9	5.7	4.5	4.5	4.4
	Ca^{2+}	**-64.6**	4.0	4.9	4.0	4.4	3.6	6.3	3.1	4.8	4.7	4.4
PH_3	Na^+	**-17.9**	1.4	1.3	1.8	1.4	0.9	1.4	1.3	0.9	0.9	0.8
	K^+	**-11.4**	1.5	1.5	1.8	1.6	1.1	1.6	1.3	0.6	0.6	0.5
	Ca^{2+}	**-51.0**	7.1	7.1	6.9	7.3	8.3	7.5	8.2	8.0	8.0	8.2
NMA	Na^+	**-41.9**	2.4	3.5	3.8	4.3	3.1	5.6	3.9	7.0	6.9	6.7
	K^+	**-31.8**	0.5	0.7	0.8	1.4	0.3	2.3	0.9	3.8	3.6	3.4
	Ca^{2+}	**-107.9**	18.1	16.0	15.5	14.6	16.4	12.8	15.5	1.0	0.7	0.4
		μ	7.8	7.9	7.4	7.6	7.5	7.7	7.6	7.1	7.0	7.0
		σ	12.0	12.1	10.8	11.2	11.5	10.1	11.4	6.6	6.7	6.7