Supporting Information for: Interaction energies in Complexes of Zn and Amino-Acids: a Comparison of Ab-Initio and Force Field based calculations

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Emma Ahlstrand,[†,‡] Kersti Hermansson,[¶] and Ran Friedman[*,†,‡]

Department of Chemistry and Biomedical Sciences, Linnæus University, 391 82 Kalmar, Sweden, Linnæus University Centre for Biomaterials Chemistry, and Department of Chemistry, Ångström Laboratory, Uppsala University, BOX 538, 751 21 Uppsala, Sweden

E-mail: ran.friedman@lnu.se

[*]To whom correspondence should be addressed
[†]Linnæus University
[‡]Linnæus University
[¶]Uppsala University

Table S1: Charges and atom types used in calculation with Amber99SB, OPLS-AA and CHARMM27 for acetate. For O1, O2 and C1, the charges were selected to be the same as for ASP and GLU in Gromacs/aminoacids.rtp for the respective force field. The three hydrogens were set to have equal charges; for OPLS-AA according to atom type HC, and for Amber99SB according to the HC in GLU. For CHARMM the atom type HA was used, but the charge for the HA was modified from +0.09 to +0.06, in order to avoid a large negative charge on the C2 carbon. The rows in which the Zn interacting atoms are described are marked in gray.

	Amber99SB		OPLS-AA		CHARMM27	
Atom	Atomtype	charge	Atomtype	charge	Atomtype	charge
O1	O2	–0.8188	O2 (opls-272)	–0.8000	OC	–0.7600
O2	O2	–0.8188	O2 (opls-272)	–0.8000	OC	–0.7600
C1	C	+0.8054	C_3 (opls-271)	+0.7000	CC	+0.6200
C2	CT	–0.1159	CT (opls-135)	–0.2800	CT3	–0.2800
H1	HC	–0.0173	HC (opls-140)	+0.0600	HA	+0.0600
H2	HC	–0.0173	HC (opls-140)	+0.0600	HA	+0.0600
H3	HC	–0.0173	HC (opls-140)	+0.0600	HA	+0.0600

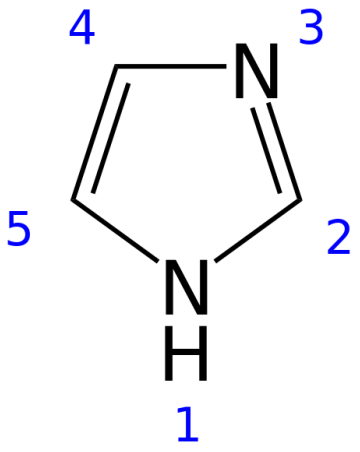

Figure S1: Numbering of atoms in imidazole

Table S2: Charges and atom types used in calculation with Amber99SB, OPLS-AA and CHARMM27 for imidazole. The Amber99SB charges follows HID in aminoacids.rtp, except for the H2 where the charge was +0.01 higher to enforce an overall neutral charge for imidazole. For OPLS-AA, the parameters optimised by McDonald and Jorgensen[1] were used. For CHARMM27 the atomtypes and the charges were according to Gromacs/aminoacids.rtp,[2,3] for all atoms except for C4, where +0.21 was added to the atom charge. The row in which the Zn interacting atom is described is marked in gray.

	Amber99SB		OPLS-AA		CHARMM27	
Atom	Atomtype	charge	Atomtype	charge	Atomtype	charge
N1	NA	–0.3811	NA (opls-557)	–0.2570	NR1	–0.3600
C2	CV	+0.1292	CR (opls-558)	+0.2750	CPH2	+0.2500
N3	NB	–0.5727	NB (opls-559)	–0.5630	NR2	–0.7000
C4	CR	+0.2057	CV (opls-560)	+0.1850	CPH1	+0.1600
C5	CC	–0.0266	CW (opls-561)	–0.2860	CPH1	–0.0500
H1	H	+0.3649	H (opls-562)	+0.3060	H	+0.3100
H2	H4	+0.1247	HA (opls-563)	+0.0780	HR1	+0.1300
H4	H5	+0.1392	HA (opls-564)	+0.0750	HR1	+0.1300
H5	H5	+0.0167	HA (opls-565)	+0.1870	HR1	+0.1300

Table S3: Charges and atomtypes used in calculation with Amber99SB, OPLS-AA and CHARMM27 for methoxide. The charges were calculated with the CHarges from ELectrostatic Potentials using a Grid (CHELPG)[4] method at the M06/def2TZVP-level. The row in which the Zn interacting atom is described is marked in gray.

	Amber99SB		OPLS-AA		CHARMM27	
Atom	Atomtype	charge	Atomtype	charge	Atomtype	charge
C1	CT	+0.5280	CT (opls-157)	+0.5280	CT3	+0.5280
H1	H1	–0.1800	HC (opls-156)	–0.1800	HA	–0.1800
H2	H1	–0.1800	HC (opls-156)	–0.1800	HA	–0.1800
H3	H1	–0.1800	HC (opls-156)	–0.1800	HA	–0.1800
O1	OH	–0.9880	OH (opls-154)	–0.9880	OC	–0.9880

Table S4: Distances (Å) between Zn and liganding atoms for the model systems (S1-S10) with Stote and Karplus[5] parameters for Zn and different force fields.

Zn systems				**QM**	**MM**		
Name	Ligands	Atom	n	MP2	OPLS-AA	Amber99SB	CHARMM27
S1	Imi_4	N (Imi)	4	2.01(0.0)	2.03(0.01)	2.10(0.01)	2.10(0.00)
S2	Imi_3Ace	N (Imi)	3	2.01, 2.03, 2.06	2.07, 2.07, 2.08	2.12, 2.13, 2.14	2.12, 2.12, 2.14
		O (Ace)	1-2	1.96, 2.57	1.92, 1.95	1.94, 1.95	1.98, 1.99
S3	Imi_3Meo	N (Imi)	3	2.03, 2.03, 2.04	2.03, 2.04, 2.04	2.10, 2.11, 2.12	2.11, 2.12, 2.12
		O (Meo)	1	1.87	1.91	1.89	1.85
S4	Imi_3Water	N (Imi)	3	1.97, 1.98, 1.98	2.02, 2.03, 2.03	2.09, 2.10, 2.10	2.09, 2.10, 2.10
		O (Wa)	1	2.13	1.98	2.04	2.05
S5	Imi_2Ace	N (Imi)	2	2.03, 2.03	2.03, 2.04	2.10, 2.10	2.10, 2.10
		O (Ace)	2	1.97, 1.97	1.90, 1.91	1.92, 1.92	1.95, 1.96
S6	Imi_2Water_2	N (Imi)	2	1.97, 1.97	2.03, 2.04	2.10, 2.10	2.10, 2.10
		O (Wa)	2	2.09, 2.10	1.97, 1.98	2.04, 2.04	2.05, 2.05
S7	$AceWater_2$	O (Wa)	2	2.02, 2.03	1.97, 1.98	2.04, 2.05	2.04, 2.05
		O (Ace)	2	2.00, 2.00	1.91, 1.92	1.93, 1.93	1.94, 1.94
S8	$AceWater_4$	O (Wa)	4	2.14(0.07)	2.05(0.02)	2.10(0.01)	2.10(0.01)
		O (Ace)	2	2.03, 2.09	1.96, 1.97	1.96, 1.96	1.98, 1.98
S9	$AceWater_5$	O (Wa)	5	2.17(0.02)	2.07(0.01)	2.17(0.04)	2.16(0.01)
		O (Ace)	1-2	1.97, 2.97	1.93, 2.87	2.04, 2.04	2.07, 2.07
S10	$Water_6$	O (Wa)	6	2.12(0.00)	2.06(0.01)	2.11(0.01)	2.10(0.00)

Table S5: Interaction energies ($\triangle E^{int,shell}$, see Eq. 1) calculated with and without BSSE (CP) correction in vacuum for the Zn model systems (S1-S10). Interaction energies where the ligands were in the same geometry as in the complex ($\triangle E^{int,a}$) rather than at the optimal isolated ligand geometries ($\triangle E^{int}$, Eq. 2) were calculated for complexes S2, S6, and S10. Interaction energies were calculated with MP2 and the aug-cc-pTZV basis set unless otherwise stated.

Zn systems		with BSSE corr.	without BSSE corr.		
Name	Ligands	$\triangle E^{int,shell}$	$\triangle E^{int,shell}$	$\triangle E^{int}$	$\triangle E^{int,a}$
S1	Imi_4	-438	-444	-428	
S2	Imi_3Ace	-606	-612*	-586	-596*
S3	Imi_3Meo	-619		-600	
S4	Imi_3Wa	-409	-412	-399	
S5	Imi_2Ace	-571	-568	-568	
S6	Imi_2Wa_2	-376	-376	-366	-372
S7	$AceWa_2$	-513	-506	-496	
S8	$AceWa_4$	-555	-548	-537	
S9	$AceWa_5$	-554	-567	-553	
S10	Wa_6	-357	-347	-342	-343

*Acetate atoms were calculated at the MP2/aug-cc-pDZV level.

Table S6: Distances between Zn and its liganding atoms for the model system S9 with different LJ-parameters (Stote and Karplus (Stote),[5] Li *et al.* (Li),[6] Sakharov and Lim (Sak.)[7]) for Zn.

Zn systems					MM (OPLS-AA)
Name	Ligands	LJ	Atom	n	Bond length (Å)
S1	Imi_4	Stote CHARMM	N (Imi)	4	2.10(0.00)
		Li Amber	N (Imi)	4	1.88(0.01)
		Sak CHARMM27	N (Imi)	4	1.92(0.01)
S2	Imi_3Ace	Stote CHARMM	N (Imi)	3	2.12, 2.12, 2.14
			O (Ace)	2	1.98, 1.99
		Li Amber	N (Imi)	3	1.94, 1.94, 2.00
			O (Ace)	2	1.75, 1.76
		Sak CHARMM	N (Imi)	3	1.96, 1.97, 2.00
			O (Ace)	2	1.81, 1.84
S3	Imi_3Meo	Stote CHARMM	N (Imi)	3	2.11, 2.12, 2.12
			O (Meo)	1	1.85
		Li Amber	N (Imi)	3	1.89, 1.89, 1.90
			O (Meo)	1	1.70
		Sak CHARMM	N (Imi)	3	1.93, 1.93, 1.94
			O (Meo)	1	1.69
S6	Imi_3Water	Stote CHARMM	N (Imi)	3	2.09, 2.10, 2.10
			O (Wa)	1	2.05
		Li Amber	N (Imi)	3	1.88, 1.88, 1.89
			O (Wa)	1	1.82
		Sak CHARMM27	N (Imi)	3	1.91, 1.92, 1.92
			O (Wa)	1	1.88
S9	$AceWater_5$	Stote CHARMM	O (Wa)	5	2.16(0.01)
			O (Ace)	2	2.07, 2.07
		Li Amber	O (Wa)	5	1.97(0.01)
			O (Ace)	2	1.79, 2.81
		Sak CHARMM27	O (Wa)	5	1.98(0.00)
			O (Ace)	2	1.80, 2.90

Table S7: Interaction energies divided into components according to the LMOEDA-scheme in vacuum and in PCM (water and THF). All values are in kcal/mol. Interaction energies, $\triangle E^{int}$, were calculated using MP2/aug-cc-pTZV on Zn and MP2/aug-cc-pDZV on all other atoms unless otherwise stated. Interaction free energies, $\triangle G^{int}$, were calculated using MP2/aug-cc-pDZV on all atoms.

a)	Imi_4	$ZnImi_3Ace$	Imi_3Meo	Imi_3Wa	Imi_2Ace	Imi_2Wa_2	$AceWa_2$	$AceWa_4$	$AceWa_5$	Wa_6
Vacuum	S1	S2	S3	S4*	S5*	S6	S7*	S8*	S9*	S10*
Electrostatic	-317	-481	-526	-316	-478	-287	-453	-466	-462	-270
Exchange	-84	-72	-99	-92	-80	-79	-69	-59	-59	-54
Repulsion	211	181	251	235	202	197	172	144	145	129
Polarisation	-218	-208	-218	-208	-194	-186	-149	-164	-168	-154
MP2 Dispersion	-26	-18	-20	-23	-22	-22	-15	-11	-9	-8
Total $\triangle E^{int}$	-433	-600	-613	-405	-571	-376	-513	-555	-554	-357
b)										
PCM water	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
Electrostatic	-343	-539	-572	-345	-547	-319	-489	-487	-478	-275
Exchange	-85	-74	-99	-95	-94	-81	-73	-59	-59	-54
Repulsion	213	185	252	240	236	204	181	145	146	129
Polarisation	-192	-153	-173	-180	-143	-155	-115	-140	-150	-146
MP2 Dispersion	-25	-20	-21	-23	-21	-18	-13	-10	-8	-6
Desolvation	61	234	225	74	271	81	286	221	202	13
Total $\triangle G^{int}$	-371	-368	-388	-330	-297	-290	-223	-332	-349	-339
c)										
PCM THF	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
Electrostatic	-339	-530	-565	-341	-538	-314	-484	-484	-476	-274
Exchange	-85	-74	-99	-94	-93	-81	-72	-59	-59	-54
Repulsion	213	185	252	239	234	203	180	145	146	129
Polarisation	-195	-161	-179	-184	-151	-160	-119	-143	-152	-147
MP2 Dispersion	-25	-20	-21	-23	-21	-18	-13	-9	-8	-5
Desolvation	53	204	197	65	237	71	251	194	177	11
Total $\triangle G^{int}$	-379	-397	-416	-339	-330	-300	-258	-358	-373	-340

*aug-cc-pTZV on all atoms

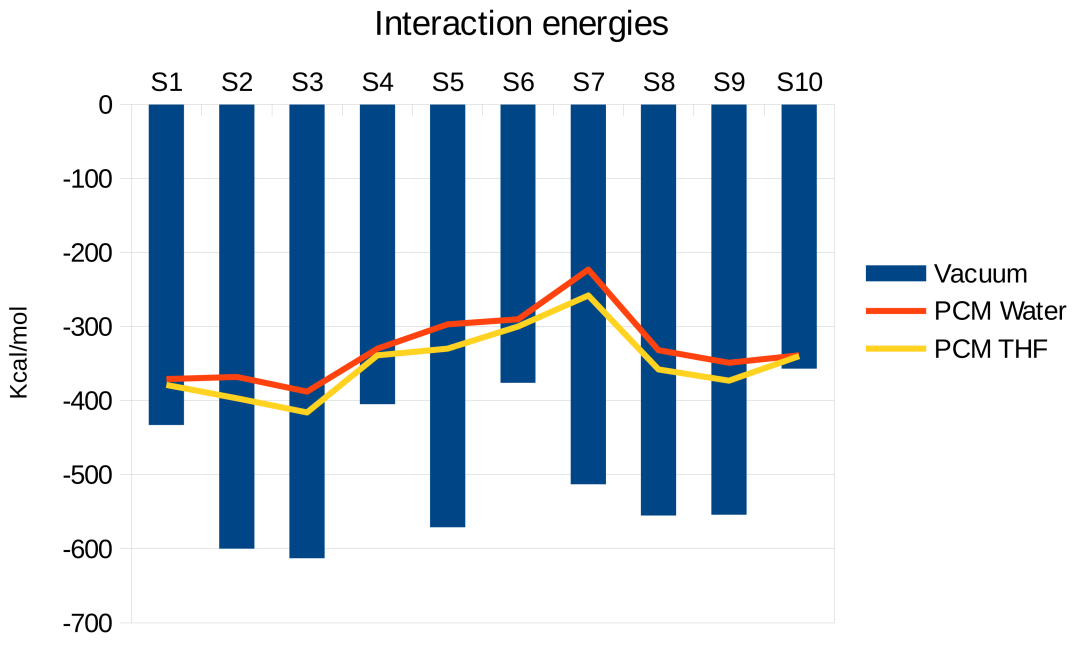

Figure S2: Visualisation of interaction energies, ΔE^{int}, and interaction free energies, ΔG^{int}, as presented in Table S7.

Table S8: Partial atomic charges calculated with the MKS and Mulliken methods at the MP2/aug-cc-pVTZ level on the optimized Zn systems S1-S10.

a) MKS	Wa_6 S10	$AceWa_5$ S9	$AceWa_4$ S8	$AceWa_2$ S7	Imi_2Wa_2 S6	Imi_2Ace S5	Imi_3Wa S4	Imi_3Meo S3	Imi_3Ace S2	Imi_4 S1
Zn	+2.33	+1.08	+1.26	+1.17	+0.79	+0.83	+0.19	+0.24	+0.50	-0.42
Ligands	-1.17	**-0.76**	**-0.82**	**-0.75**	**-0.12**	**-0.11**	**+0.22**	**-0.03**	**-0.08**	**+0.27**
	-1.16	**-0.69**	**-0.75**	**-0.77**	**-0.08**	**-0.12**	**+0.08**	**+0.09**	**-0.11**	**+0.30**
	-1.17	-0.71	-0.72	-0.67	-0.74	**-0.69**	**+0.11**	**+0.05**	**+0.10**	**+0.29**
	-1.17	-0.79	-0.78	-0.66	-0.87	**-0.71**	-0.74	**-0.56**	**-0.75**	**+0.32**
	-1.11	-0.70	-0.75						**-0.73**	
	-1.17	-0.74	-0.76							
		-0.70								
b) Mulliken	S10	S9	S8	S7	S6	S5	S4	S3	S2	S1
Zn	+1.86	+2.16	+1.97	+1.49	+1.48	+1.74	+1.00	+1.60	+1.17	+1.17
Ligands	-0.30	**-0.86**	**-0.88**	**-0.74**	**-0.32**	**-0.31**	**+0.05**	**-0.45**	**-0.15**	**+0.22**
	-0.30	**-0.73**	**-0.84**	**-0.76**	**-0.19**	**-0.19**	**-0.10**	**-0.39**	**-0.14**	**+0.07**
	-0.30	-0.40	-0.38	-0.46	-0.42	**-0.88**	**-0.01**	**-0.37**	**+0.48**	**-0.01**
	-0.30	-0.61	-0.46	-0.48	-0.37	**-0.85**	-0.40	**-0.77**	**-0.90**	**+0.16**
	-0.30	-0.38	-0.47						**-0.65**	
	-0.30	-0.45	-0.28							
		-0.62								

Colour codes: **imidazole N**, **acetate O**, **methoxide O**, water O.

References

(1) McDonald, N. A.; Jorgensen, W. L. Development of an All-Atom Force Field for Heterocycles. Properties of Liquid Pyrrole, Furan, Diazoles, and Oxazoles. *J. Phys. Chem. B* **1998**, *102*, 8049–8059.

(2) Bjelkmar, P.; Larsson, P.; Cuendet, M. A.; Hess, B.; Lindahl, E. Implementation of the CHARMM Force Field in GROMACS: Analysis of Protein Stability Effects from Correction Maps, Virtual Interaction Sites, and Water Models. *J. Chem. Theory Comput.* **2010**, *6*, 459–466.

(3) MacKerell, A. D.; Banavali, N.; Foloppe, N. Development and current status of the CHARMM force field for nucleic acids. *Biopolymers* **2000**, *56*, 257–265.

(4) Breneman, C. M.; Wiberg, K. B. Determining atom-centered monopoles from molecular electrostatic potentials. The need for high sampling density in formamide conformational analysis. *J. Comput. Chem.* **1990**, *11*, 361–373.

(5) Stote, R. H.; Karplus, M. Zinc binding in proteins and solution: a simple but accurate nonbonded representation. *Proteins* **1995**, *23*, 12–31.

(6) Li, P.; Roberts, B. P.; Chakravorty, D. K.; Merz, K. M. Rational Design of Particle Mesh Ewald Compatible Lennard-Jones Parameters for +2 Metal Cations in Explicit Solvent. *J. Chem. Theory Comput.* **2013**, *9*, 2733–2748.

(7) Sakharov, D. V.; Lim, C. Zn Protein Simulations Including Charge Transfer and Local Polarization Effects. *J. Am. Chem. Soc.* **2005**, *127*, 4921–4929.