Supplementary Material (ESI) for *PCCP*
Evaluation of the Field-Adapted ADMA Approach: Absolute and Relative Energies of Crambin

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Table S1: Results of the ADMA and FA-ADMA approaches for 16 proteins, selected as test cases for the evaluation of the methodology. The STO-3G basis set and surroundings of 4 Å were used. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AKG	-6747.33250543	0.05983961	0.04191574	0.04170690
1CMR	-13868.53189850	0.11025690	0.08143860	0.08092090
1CNL	-5764.91797185	0.03803796	0.03121957	0.03090054
1CNR	-17775.22180290	0.13349930	0.11046660	0.10965420
1EDN	-9839.46446225	0.07304331	0.05884642	0.05848951
1FGD	-7512.31620690	0.07769149	0.03760269	0.03746869
1GIB	-9935.89211088	0.10466867	0.06832312	0.06805180
1GRM	-12227.05264500	0.07728070	0.07721510	0.07676450
1HCW	-8394.69165937	0.08438467	0.06188042	0.06151916
1LFC	-11198.87428030	0.09723270	0.06354760	0.06309600
1M2C	-7019.17869883	0.05843786	0.04441716	0.04413558
1OMG	-10985.51373010	0.09391070	0.07016590	0.06986740
1PEN	-6723.33774734	0.05903606	0.04001925	0.03972270
1RPB	-8432.14950919	0.05557736	0.05331517	0.05301915
1TER	-9578.80398501	0.09581660	0.06351451	0.06305840
1VTP	-9885.60187070	0.08494238	0.04547242	0.04481692
2ETI	-11845.17035950	0.08695190	0.06681770	0.06643800
Max. Error		0.13349930	0.11046660	0.10965420
RMS Error		0.08493782	0.06270749	0.06422532

Table S2: Results of the ADMA and FA-ADMA approaches for 16 proteins, selected as test cases for the evaluation of the methodology. The STO-3G basis set and surroundings of 5 Å were used. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AKG	-6747.33250543	0.01873061	0.00812306	0.00801515
1CMR	-13868.53189850	0.03436740	0.01713210	0.01660440
1CNL	-5764.91797185	0.00874957	0.00530843	0.00520443
1CNR	-17775.22180290	0.03380820	0.02000550	0.01914750
1EDN	-9839.46446225	0.02282985	0.01268606	0.01233545
1FGD	-7512.31620690	0.04062519	0.00910497	0.00879200
1GIB	-9935.89211088	0.03072156	0.01025008	0.00990004
1GRM	-12227.05264500	0.01844980	0.01939280	0.01882650
1HCW	-8394.69165937	0.02571985	0.01168979	0.01144846
1LFC	-11198.87428030	0.04015750	0.01270800	0.01226710
1M2C	-7019.17869883	0.02154198	0.01142384	0.01118870
1OMG	-10985.51373010	0.03011690	0.01190420	0.01150630
1PEN	-6723.33774734	0.01853148	0.00687526	0.00669168
1RPB	-8432.14950919	0.01423703	0.01278205	0.01239493
1TER	-9578.80398501	0.03818876	0.01064071	0.01044736
1VTP	-9885.60187070	0.03854608	0.00970214	0.00940290
2ETI	-11845.17035950	0.02724900	0.01277130	0.01248320
Max. Error		0.04062519	0.02000550	0.01914750
RMS Error		0.02878453	0.01251903	0.01251626

Table S3: Results of the FA-ADMA approaches using an empirical energy-based scaling factor for 16 proteins, selected as test cases for the evaluation of the methodology. The STO-3G basis set and surroundings of 4 Å were used. For the FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AKG	-6747.33250543	0.00098486	0.00104125
1CMR	-13868.53189850	-0.00269115	-0.00266369
1CNL	-5764.91797185	-0.00375178	-0.00384420
1CNR	-17775.22180290	0.00263799	0.00252432
1EDN	-9839.46446225	-0.00084206	-0.00081219
1FGD	-7512.31620690	-0.00796881	-0.00780751
1GIB	-9935.89211088	0.00804974	0.00816899
1GRM	-12227.05264500	0.00304298	0.00307301
1HCW	-8394.69165937	0.06308447	0.06272956
1LFC	-11198.87428030	-0.00438740	-0.00439878
1M2C	-7019.17869883	0.00183720	0.00183154
1OMG	-10985.51373010	0.00352524	0.00365858
1PEN	-6723.33774734	-0.00076608	-0.00079834
1RPB	-8432.14950919	0.00216381	0.00219925
1TER	-9578.80398501	0.00540729	0.00532772
1VTP	-9885.60187070	-0.01449602	-0.01476293
2ETI	-11845.17035950	-0.00503788	-0.00495196
Max. Error		0.06308447	0.06272956
RMS Error		0.01618322	0.01611454

Table S4: Results of the FA-ADMA approach using an empirical number-of-electrons-based scaling factor for 16 proteins, selected as test cases for the evaluation of the methodology. The STO-3G basis set and surroundings of 4 Å were used. For the FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AKG	-6747.33250543	0.00458259	0.00461772
1CMR	-13868.53189850	0.00040674	0.00041857
1CNL	-5764.91797185	0.00051004	0.00039170
1CNR	-17775.22180290	0.00208003	0.00197593
1EDN	-9839.46446225	0.00190046	0.00191569
1FGD	-7512.31620690	-0.00841859	-0.00825185
1GIB	-9935.89211088	0.01473198	0.01481088
1GRM	-12227.05264500	-0.00949415	-0.00937812
1HCW	-8394.69165937	0.06001546	0.05964872
1LFC	-11198.87428030	-0.00836603	-0.00834768
1M2C	-7019.17869883	0.00544961	0.00542268
1OMG	-10985.51373010	0.00977910	0.00987522
1PEN	-6723.33774734	0.00311620	0.00306081
1RPB	-8432.14950919	0.00402509	0.00405117
1TER	-9578.80398501	0.00699866	0.00691187
1VTP	-9885.60187070	-0.02050575	-0.02073009
2ETI	-11845.17035950	0.00058146	0.00063461
Max. Error		0.06001546	0.05964872
RMS Error		0.01662793	0.01656165

Table S5: Results of the FA-ADMA approach using an empirical energy-based scaling factor for 16 proteins, selected as test cases for the evaluation of the methodology. The STO-3G basis set and surroundings of 5 Å were used. For the FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AKG	-6747.33250543	0.00000836	0.00014707
1CMR	-13868.53189850	0.00045308	0.00043227
1CNL	-5764.91797185	-0.00162476	-0.00151806
1CNR	-17775.22180290	-0.00137191	-0.00158023
1EDN	-9839.46446225	0.00085261	0.00086163
1FGD	-7512.31620690	0.00007027	0.00003187
1GIB	-9935.89211088	-0.00169935	-0.00168623
1GRM	-12227.05264500	0.00468791	0.00456851
1HCW	-8394.69165937	0.01207359	0.01182597
1LFC	-11198.87428030	-0.00076035	-0.00079193
1M2C	-7019.17869883	0.00298221	0.00300362
1OMG	-10985.51373010	-0.00130756	-0.00130393
1PEN	-6723.33774734	-0.00121058	-0.00114842
1RPB	-8432.14950919	0.00264111	0.00256218
1TER	-9578.80398501	-0.00087926	-0.00072251
1VTP	-9885.60187070	-0.00218681	-0.00212473
2ETI	-11845.17035950	-0.00147432	-0.00132948
Max. Error		0.01207359	0.01182597
RMS Error		0.00345940	0.00338994

Table S6: Results of the FA-ADMA approach using an empirical number-of-electrons-based scaling factor for 16 proteins, selected as test cases for the evaluation of the methodology. The STO-3G basis set and surroundings of 5 Å were used. For the FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AKG	-6747.33250543	0.00067543	0.00079444
1CMR	-13868.53189850	0.00096697	0.00093180
1CNL	-5764.91797185	-0.00081785	-0.00073519
1CNR	-17775.22180290	-0.00161665	-0.00181585
1EDN	-9839.46446225	0.00132585	0.00132137
1FGD	-7512.31620690	-0.00007586	-0.00010911
1GIB	-9935.89211088	-0.00044087	-0.00046517
1GRM	-12227.05264500	0.00209508	0.00205582
1HCW	-8394.69165937	0.01130135	0.01106351
1LFC	-11198.87428030	-0.00163812	-0.00164192
1M2C	-7019.17869883	0.00365016	0.00365188
1OMG	-10985.51373010	-0.00014243	-0.00017328
1PEN	-6723.33774734	-0.00048657	-0.00044584
1RPB	-8432.14950919	0.00294912	0.00286160
1TER	-9578.80398501	-0.00063370	-0.00048353
1VTP	-9885.60187070	-0.00345991	-0.00335812
2ETI	-11845.17035950	-0.00044224	-0.00032774
Max. Error		0.01130135	0.01106351
RMS Error		0.00322008	0.00316234

Table S7: Results of the ADMA and FA-ADMA approaches for 36 conformations of Crambin taken from the Protein Data Bank. The STO-3G basis set and surroundings of 4 Å were used. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AB1	-17773.1693654	0.1271413	0.1044217	0.1038555
1CBN_a	-17775.0246715	0.1264248	0.1044292	0.1038750
1CBN_b	-17772.9825348	0.1255662	0.1035151	0.1030314
1CCM_1	-17778.9389824	0.1419161	0.1120126	0.1111651
1CCM_2	-17778.9451434	0.1338091	0.1085057	0.1078928
1CCM_3	-17779.0970346	0.1407511	0.1138682	0.1132955
1CCM_4	-17778.9902866	0.1509856	0.1183800	0.1175932
1CCM_5	-17779.0747182	0.1452762	0.1177325	0.1168828
1CCM_6	-17779.0630271	0.1440769	0.1130198	0.1122976
1CCM_7	-17779.1144058	0.1438010	0.1157957	0.1149080
1CCM_8	-17779.1166939	0.1361501	0.1109743	0.1102873
1CCN	-17779.0862163	0.1450300	0.1185537	0.1174207
1CNR	-17775.2180243	0.1297207	0.1066880	0.1058756
1CRN	-17779.4071714	0.1388397	0.1135899	0.1130081
CXR_1	-17777.9782345	0.1297262	0.1049232	0.1042163
CXR_2	-17778.0330661	0.1370047	0.1119985	0.1113772
CXR_3	-17778.0851568	0.1230760	0.1011516	0.1004501
CXR_4	-17778.0143655	0.1358444	0.1035533	0.1028628
CXR_5	-17777.9901074	0.1250528	0.1005859	0.0999077
CXR_6	-17777.8545734	0.1506958	0.1050117	0.1043951
CXR_7	-17777.9789726	0.1366158	0.1119161	0.1110919
CXR_8	-17778.0873908	0.1356840	0.1090762	0.1078844
CXR_9	-17778.0083623	0.1300949	0.1070786	0.1064993
CXR_10	-17778.1996836	0.1300536	0.1076854	0.1069228
1EJG_a	-17779.4683544	0.1413259	0.1155077	0.1146153
1EJG_b	-17777.2394182	0.1457005	0.1201720	0.1194074
1JXT_a	-17775.5722082	0.1279010	0.1049810	0.1042169
1JXT_b	-17773.4038398	0.1275044	0.1044714	0.1038078
1JXU_a	-17775.4997448	0.1296700	0.1072087	0.1066550
1JXU_b	-17773.3106015	0.1289652	0.1065253	0.1060282
1JXW_a	-17775.6578167	0.1277258	0.1048687	0.1041198
1JXW_b	-17773.4525187	0.1267601	0.1038387	0.1031579

Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1JXX_a	-17775.5075278	0.1272992	0.1046416	0.1039365
1JXX_b	-17773.2535053	0.1273013	0.1046000	0.1039556
1JXY_a	-17775.4350333	0.1260804	0.1034971	0.1028736
1JXY_b	-17773.2067176	0.1254710	0.1028493	0.1022844
Max. Error		0.1509856	0.1201720	0.1194074
RMS Error		0.1342614	0.1086765	0.1079634

Table S8: Results of the FA-ADMA approach using the energy-based and the empirical number-of-electrons-based scaling factor for 36 conformations of Crambin. The STO-3G basis set and surroundings of 4 Å were used. For the FA-ADMA calculations, the errors compared to the direct calculations are given.

		Energy-based Scaling		Number-of-electrons-based Scaling	
Molecule	Hartree-Fock Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AB1	-17773.1693654	-0.0033945	-0.0032620	-0.0037068	-0.0035664
1CBN_a	-17775.0246715	-0.0033982	-0.0032537	-0.0039574	-0.0038033
1CBN_b	-17772.9825348	-0.0043000	-0.0040850	-0.0046134	-0.0043905
1CCM_1	-17778.9389824	0.0041615	0.0040128	0.0036260	0.0034868
1CCM_2	-17778.9451434	0.0006545	0.0007405	0.0001191	0.0002145
1CCM_3	-17779.0970346	0.0060161	0.0061423	0.0054816	0.0056172
1CCM_4	-17778.9902866	0.0105286	0.0104407	0.0099934	0.0099149
1CCM_5	-17779.0747182	0.0098806	0.0097297	0.0093459	0.0092045
1CCM_6	-17779.0630271	0.0051679	0.0051446	0.0046332	0.0046193
1CCM_7	-17779.1144058	0.0079435	0.0077547	0.0074091	0.0072297
1CCM_8	-17779.1166939	0.0031221	0.0031340	0.0025877	0.0026090
1CCN	-17779.0862163	0.0107017	0.0102676	0.0101671	0.0097424
1CNR	-17775.2180243	-0.0011406	-0.0012543	-0.0016986	-0.0018027
1CRN	-17779.4071714	0.0057359	0.0058530	0.0052033	0.0053298
CXR_1	-17777.9782345	-0.0029222	-0.0029302	-0.0032053	-0.0032056
CXR_2	-17778.0330661	0.0041528	0.0042304	0.0038700	0.0039553
CXR_3	-17778.0851568	-0.0066944	-0.0066971	-0.0069769	-0.0069718

		Energy-based Scaling		Number-of-electrons-based Scaling	
Molecule	**Hartree-Fock Energy (Hartree)**	**Error of FA-ADMA Energy, Mulliken charges (Hartree)**	**Error of FA-ADMA Energy, Löwdin charges (Hartree)**	**Error of FA-ADMA Energy, Mulliken charges (Hartree)**	**Error of FA-ADMA Energy, Löwdin charges (Hartree)**
CXR_4	-17778.0143655	-0.0042923	-0.0042839	-0.0045752	-0.0045591
CXR_5	-17777.9901074	-0.0072596	-0.0072389	-0.0075426	-0.0075142
CXR_6	-17777.8545734	-0.0028329	-0.0027507	-0.0031168	-0.0030268
CXR_7	-17777.9789726	0.0040708	0.0039454	0.0037876	0.0036700
CXR_8	-17778.0873908	0.0012302	0.0007372	0.0009477	0.0004625
CXR_9	-17778.0083623	-0.0007669	-0.0006474	-0.0010499	-0.0009226
CXR_10	-17778.1996836	-0.0001613	-0.0002250	-0.0004431	-0.0004991
1EJG_a	-17779.4683544	0.0076534	0.0074599	0.0071211	0.0069370
1EJG_b	-17777.2394182	0.0123312	0.0122654	0.0120435	0.0119855
1JXT_a	-17775.5722082	-0.0028498	-0.0029151	-0.0034056	-0.0034614
1JXT_b	-17773.4038398	-0.0033462	-0.0033112	-0.0036571	-0.0036141
1JXU_a	-17775.4997448	-0.0006216	-0.0004766	-0.0011779	-0.0010233
1JXU_b	-17773.3106015	-0.0012917	-0.0010902	-0.0016032	-0.0013937
1JXW_a	-17775.6578167	-0.0029626	-0.0030127	-0.0035179	-0.0035585
1JXW_b	-17773.4525187	-0.0039792	-0.0039614	-0.0042898	-0.0042640
1JXX_a	-17775.5075278	-0.0031888	-0.0031951	-0.0037450	-0.0037418
1JXX_b	-17773.2535053	-0.0032167	-0.0031624	-0.0035285	-0.0034663
1JXY_a	-17775.4350333	-0.0043328	-0.0042576	-0.0048895	-0.0048047
1JXY_b	-17773.2067176	-0.0049671	-0.0048334	-0.0052792	-0.0051375
Max. Error		0.0123312	0.0122654	0.0120435	0.0119855
RMS Error		0.0053782	0.0053054	0.0052947	0.0044363

Table S9: Results of the ADMA and FA-ADMA approaches for 36 conformations of Crambin taken from the Protein Data Bank. The STO-3G basis set and surroundings of 5 Å were used. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AB1	-17773.1693654	0.0324268	0.0185690	0.0178603
1CBN_a	-17775.0246715	0.0335884	0.0207274	0.0198489
1CBN_b	-17772.9825348	0.0327290	0.0198529	0.0190974
1CCM_1	-17778.9389824	0.0424654	0.0231341	0.0225757
1CCM_2	-17778.9451434	0.0409650	0.0258011	0.0250742
1CCM_3	-17779.0970346	0.0420022	0.0255194	0.0250240
1CCM_4	-17778.9902866	0.0457784	0.0246286	0.0239945
1CCM_5	-17779.0747182	0.0448360	0.0273232	0.0264198
1CCM_6	-17779.0630271	0.0443872	0.0238944	0.0231286
1CCM_7	-17779.1144058	0.0430608	0.0251169	0.0243526
1CCM_8	-17779.1166939	0.0402561	0.0235467	0.0231089
1CCN	-17779.0862163	0.0428410	0.0251868	0.0245321
1CNR	-17775.2180243	0.0338026	0.0200013	0.0191416
1CRN	-17779.4071714	0.0396542	0.0238342	0.0230642
CXR_1	-17777.9782345	0.0339882	0.0190791	0.0183686
CXR_2	-17778.0330661	0.0379074	0.0200191	0.0193329
CXR_3	-17778.0851568	0.0335301	0.0200257	0.0192097
CXR_4	-17778.0143655	0.0454740	0.0213176	0.0205657
CXR_5	-17777.9901074	0.0348308	0.0184000	0.0177516
CXR_6	-17777.8545734	0.0509316	0.0204733	0.0196157
CXR_7	-17777.9789726	0.0364679	0.0201794	0.0194893
CXR_8	-17778.0873908	0.0392405	0.0217954	0.0209086
CXR_9	-17778.0083623	0.0378838	0.0206256	0.0199230
CXR_10	-17778.1996836	0.0349034	0.0200799	0.0192828
1EJG_a	-17779.4683544	0.0370580	0.0219887	0.0212738
1EJG_b	-17777.2394182	0.0366628	0.0218730	0.0211785
1JXT_a	-17775.5722082	0.0336223	0.0198847	0.0190217
1JXT_b	-17773.4038398	0.0327410	0.0189717	0.0182287
1JXU_a	-17775.4997448	0.0340419	0.0203611	0.0196100
1JXU_b	-17773.3106015	0.0330540	0.0195204	0.0188457
1JXW_a	-17775.6578167	0.0340975	0.0201780	0.0194562
1JXW_b	-17773.4525187	0.0331726	0.0192614	0.0186479

Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1JXX_a	-17775.5075278	0.0339891	0.0202317	0.0193641
1JXX_b	-17773.2535053	0.0335097	0.0196591	0.0188996
1JXY_a	-17775.4350333	0.0334417	0.0198154	0.0189834
1JXY_b	-17773.2067176	0.0324761	0.0188384	0.0181210
Max. Error		0.0509316	0.0273232	0.0264198
RMS Error		0.0378587	0.0215095	0.0207827

Table S10: Results of the FA-ADMA approach using the energy-based and the empirical number-of-electrons-based scaling factor for 36 conformations of Crambin. The STO-3G basis set and surroundings of 5 Å were used. For the FA-ADMA calculations, the errors compared to the direct calculations are given.

		Energy-based Scaling		Number-of-electrons-based Scaling	
Molecule	Hartree-Fock Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
1AB1	-17773.1693654	-0.0027588	-0.0029343	-0.0030017	-0.0030531
1CBN_a	-17775.0246715	-0.0006026	-0.0009479	-0.0008947	-0.0011145
1CBN_b	-17772.9825348	-0.0014747	-0.0016970	-0.0017178	-0.0018160
1CCM_1	-17778.9389824	0.0017994	0.0017744	0.0015120	0.0016123
1CCM_2	-17778.9451434	0.0044664	0.0042729	0.0041790	0.0041108
1CCM_3	-17779.0970346	0.0041845	0.0042225	0.0038973	0.0040606
1CCM_4	-17778.9902866	0.0032938	0.0031931	0.0030065	0.0030311
1CCM_5	-17779.0747182	0.0059883	0.0056183	0.0057011	0.0054564
1CCM_6	-17779.0630271	0.0025596	0.0023271	0.0022723	0.0021652
1CCM_7	-17779.1144058	0.0037820	0.0035511	0.0034948	0.0033892
1CCM_8	-17779.1166939	0.0022118	0.0023074	0.0019246	0.0021455
1CCN	-17779.0862163	0.0038519	0.0037306	0.0035647	0.0035687
1CNR	-17775.2180243	-0.0013289	-0.0016554	-0.0016208	-0.0018218
1CRN	-17779.4071714	0.0024989	0.0022623	0.0022121	0.0021008
CXR_1	-17777.9782345	-0.0022545	-0.0024316	-0.0024916	-0.0025448
CXR_2	-17778.0330661	-0.0013145	-0.0014674	-0.0015516	-0.0015805
CXR_3	-17778.0851568	-0.0013080	-0.0015906	-0.0015450	-0.0017037

		Energy-based Scaling		Number-of-electrons-based Scaling	
Molecule	**Hartree-Fock Energy (Hartree)**	**Error of FA-ADMA Energy, Mulliken charges (Hartree)**	**Error of FA-ADMA Energy, Löwdin charges (Hartree)**	**Error of FA-ADMA Energy, Mulliken charges (Hartree)**	**Error of FA-ADMA Energy, Löwdin charges (Hartree)**
CXR_4	-17778.0143655	-0.0000160	-0.0002346	-0.0002531	-0.0003477
CXR_5	-17777.9901074	-0.0029336	-0.0030486	-0.0031707	-0.0031618
CXR_6	-17777.8545734	-0.0008601	-0.0011844	-0.0010974	-0.0012977
CXR_7	-17777.9789726	-0.0011542	-0.0013109	-0.0013913	-0.0014241
CXR_8	-17778.0873908	0.0004617	0.0001083	0.0002247	-0.0000048
CXR_9	-17778.0083623	-0.0007080	-0.0008772	-0.0009451	-0.0009904
CXR_10	-17778.1996836	-0.0012539	-0.0015177	-0.0014908	-0.0016306
1EJG_a	-17779.4683544	0.0006534	0.0004718	0.0003666	0.0003104
1EJG_b	-17777.2394182	0.0005403	0.0003792	0.0003023	0.0002651
1JXT_a	-17775.5722082	-0.0014460	-0.0017757	-0.0017374	-0.0019417
1JXT_b	-17773.4038398	-0.0023564	-0.0025662	-0.0025990	-0.0026847
1JXU_a	-17775.4997448	-0.0009695	-0.0011873	-0.0012610	-0.0013534
1JXU_b	-17773.3106015	-0.0018075	-0.0019491	-0.0020503	-0.0020677
1JXW_a	-17775.6578167	-0.0011528	-0.0013413	-0.0014441	-0.0015072
1JXW_b	-17773.4525187	-0.0020667	-0.0021470	-0.0023093	-0.0022655
1JXX_a	-17775.5075278	-0.0010989	-0.0014332	-0.0013904	-0.0015993
1JXX_b	-17773.2535053	-0.0016688	-0.0018951	-0.0019116	-0.0020138
1JXY_a	-17775.4350333	-0.0015151	-0.0018138	-0.0018067	-0.0019800
1JXY_b	-17773.2067176	-0.0024894	-0.0026736	-0.0027323	-0.0027924
Max. Error		0.0059883	0.0056183	0.0057011	0.0054564
RMS Error		0.0023469	0.0023715	0.0023423	0.0020809

Table S11 Maximum errors and root mean square errors of the total energy calculated by the ADMA and FA-ADMA approaches for 36 structures of the protein Crambin with different parent molecule sizes for the surroundings

Surroundings		ADMA Energy	FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges
4 Å	Max. Error (Hartree)	0,1509856	0,1201720	0,1194074
	RMS Error (Hartree)	0,1342614	0,1086765	0,1079634
5 Å	Max. Error (Hartree)	0,0509316	0,0273232	0,0264198
	RMS Error (Hartree)	0,0378587	0,0215095	0,0207827

Table S12: Maximum errors and root mean square errors of the total energy calculated by the FA-ADMA approach using empirical scaling factors for 36 structures of the protein Crambin with different sizes of the surroundings.

		Energy-based Scaling		Number-of-electrons-based Scaling	
Surroundings		FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges	FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges
4 Å	Max. Error (Hartree)	0,0123312	0,0122654	0,0120435	0,0119855
	RMS Error (Hartree)	0,0053782	0,0053054	0,0052947	0,0044363
5 Å	Max. Error (Hartree)	0,0059883	0,0056183	0,0057011	0,0054564
	RMS Error (Hartree)	0,0023469	0,0023715	0,0023423	0,0020809

Table S13: Maximum errors and root mean square errors of the relative energy calculated by the ADMA and FA-ADMA approach for 36 structures of the protein Crambin with different sizes of the surroundings.

Surroundings		ADMA Energy	FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges
4 Å	Max. Error (Hartree)	0,0279096	0,0195861	0,0194997
	RMS Error (Hartree)	0,0113276	0,0076589	0,0075557
5 Å	Max. Error (Hartree)	0,0185048	0,0089232	0,0086682
	RMS Error (Hartree)	0,0069146	0,0033681	0,0033970

Table S14: Maximum errors and root mean square errors of the relative energy calculated by the FA-ADMA approach using empirical scaling factors for 36 structures of the protein Crambin with different sizes of the surroundings.

		Energy-based Scaling		Number-of-electrons-based Scaling	
Surroundings		FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges	FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges
4 Å	Max. Error (Hartree)	0,0195908	0,0195043	0,0195861	0,0194997
	RMS Error (Hartree)	0,0076469	0,0075439	0,0075829	0,0074802
5 Å	Max. Error (Hartree)	0,0089219	0,0086669	0,0088717	0,0086183
	RMS Error (Hartree)	0,0033654	0,0033944	0,0033452	0,0033750

Table S15: Maximum errors and root mean square errors of the relative energy calculated by the ADMA and FA-ADMA approaches for 10 NMR structures of the PDB entry 1CXR with various sizes of the surroundings and the STO-3G basis set.

Surroundings		ADMA Energy	FA-ADMA Energy, Mulliken charges	FA-ADMA Energy, Löwdin charges
4 Å	Max. Error (Hartree)	0.0276198	0.0114126	0.0114695
	RMS Error (Hartree)	0.0110106	0.0056667	0.0055992
5 Å	Max. Error (Hartree)	0.0174015	0.0033954	0.0031570
	RMS Error (Hartree)	0.0059887	0.0011267	0.0010781
6 Å	Max. Error (Hartree)	0.0118413	0.0010995	0.0013305
	RMS Error (Hartree)	0.0014559	0.0005595	0.0005816

Table S16: Maximum errors and root mean square errors of the relative energy calculated by the FA-ADMA approach using empirical scaling factors for 10 NMR structures of the PDB entry 1CXR with various sizes of the surroundings and the STO-3G basis set.

		Energy-based Scaling		Number-of-electrons-based Scaling	
Surroundings		FA-ADMA Energy, Mulliken charges	FA-ADMA Energy, Löwdin charges	FA-ADMA Energy, Mulliken charges	FA-ADMA Energy, Löwdin charges
4 Å	Max. Error (Hartree)	0.0114124	0.0114693	0.0114126	0.0114695
	RMS Error (Hartree)	0.0056667	0.0055992	0.0056667	0.0055992
5 Å	Max. Error (Hartree)	0.0033953	0.0031569	0.0033954	0.0031570
	RMS Error (Hartree)	0.0013844	0.0013147	0.0013844	0.0013147
6 Å	Max. Error (Hartree)	0.0010994	0.0013305	0.0010995	0.0013305
	RMS Error (Hartree)	0.0005594	0.0005816	0.0005595	0.0005816

Table S17: Maximum errors and root mean square errors of the relative energy calculated by the ADMA and FA-ADMA approaches for 8 NMR structures of the PDB entry 1CCM and the minimized mean structure of the PDB entry 1CCN with various sizes of the surroundings and the STO-3G basis set.

Surroundings		ADMA Energy	FA-ADMA Energy, Mulliken charges	FA-ADMA Energy, Löwdin charges
4 Å	Max. Error (Hartree)	0.0171765	0.0100480	0.0097004
	RMS Error (Hartree)	0.0072369	0.0050112	0.0048540
5 Å	Max. Error (Hartree)	0.0055223	0.0041891	0.0038441
	RMS Error (Hartree)	0.0025484	0.0018187	0.0016959

Table S18: Maximum errors and root mean square errors of the relative energy calculated by the FA-ADMA approach using empirical scaling factors for 8 NMR structures of the PDB entry 1CCM and the minimized mean structure of the PDB entry 1CCN with various sizes of the surroundings and the STO-3G basis set.

		Energy-based Scaling		Number-of-electrons-based Scaling	
Surroundings		FA-ADMA Energy, Mulliken charges	FA-ADMA Energy, Löwdin charges	FA-ADMA Energy, Mulliken charges	FA-ADMA Energy, Löwdin charges
4 Å	Max. Error (Hartree)	0.0100472	0.0097002	0.0100480	0.0097004
	RMS Error (Hartree)	0.0050110	0.0048539	0.0050112	0.0048540
5 Å	Max. Error (Hartree)	0.0041889	0.0038439	0.0041891	0.0038441
	RMS Error (Hartree)	0.0018187	0.0016959	0.0018187	0.0016959

Table S19: Results of the ADMA and FA-ADMA approach for 8 fictive reaction products of Crambin. The STO-3G basis set and surroundings of 4 Å were used. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy Mulliken charges (Hartree)	Error of FA-ADMA Energy Löwdin charges (Hartree)
1CNR	-17775,2180243	0,1297207	0,1066880	0,1058756
protonated GLU23	-17775,8007659	0,1408220	0,1074825	0,1064703
protonated ASP43	-17775,9169756	0,1247316	0,1066694	0,1059545
deprotonated TYR29	-17774,4622715	0,1312753	0,1065188	0,1056726
deprotonated TYR44	-17774,3954624	0,1370004	0,1067430	0,1059604
acetylated N-terminus	-17924,5407942	0,1257479	0,1081670	0,1074040
methylated C-terminus	-17814,3306537	0,1303286	0,1054034	0,1045989
amidated C-terminus	-17756,2620786	0,1311320	0,1051607	0,1044516
N-methylamidated C-terminus	-17794,8299989	0,1309251	0,1054003	0,1047735
Max. Error		0,1408220	0,1081670	0,1074040
RMS Error		0,1313831	0,1064746	0,1056884

Table S20: Results of the ADMA and FA-ADMA approach for 8 fictive reaction products of Crambin. The STO-3G basis set and surroundings of 5 Å were used. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given.

Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy Mulliken charges (Hartree)	Error of FA-ADMA Energy Löwdin charges (Hartree)
1CNR	-17775,2180243	0,0338026	0,0200013	0,0191416
protonated GLU23	-17775,8007659	0,0421181	0,0201157	0,0191652
protonated ASP43	-17775,9169756	0,0298818	0,0199830	0,0191540
deprotonated TYR29	-17774,4622715	0,0347075	0,0198603	0,0189629
deprotonated TYR44	-17774,3954624	0,0393569	0,0199332	0,0190624
acetylated N-terminus	-17924,5407942	0,0309433	0,0201490	0,0193567
methylated C-terminus	-17814,3306537	0,0350957	0,0200667	0,0191737
amidated C-terminus	-17756,2620786	0,0354910	0,0199681	0,0190352
N-methylamidated C-terminus	-17794,8299989	0,0351920	0,0199145	0,0190203
Max. Error		0,0421181	0,0201490	0,0193567
RMS Error		0,0353559	0,0199993	0,0191194

Table S21: Maximum errors and root mean square errors of the relative energy calculated by the ADMA and FA-ADMA approaches for 8 fictive reaction products of Crambin with various sizes of the surroundings and the STO-3G basis set.

Surroundings		ADMA Energy	FA-ADMA Energy, Mulliken charges	FA-ADMA Energy, Löwdin charges
4 Å	Max. Error (Hartree)	0.0160904	0.0030063	0.0029524
	RMS Error (Hartree)	0.0070841	0.0014200	0.0013498
5 Å	Max. Error (Hartree)	0.0122363	0.0002887	0.0003938
	RMS Error (Hartree)	0.0053345	0.0001347	0.0001641

Table S22: Results of the ADMA and FA-ADMA approach for 4 mutations of Crambin with different surroundings. The STO-3G basis set was used. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given.

Surroundings	Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy Mulliken charges (Hartree)	Error of FA-ADMA Energy Löwdin charges (Hartree)
4 Å	1CBN_a	-17775,0246715	0,1264248	0,1044292	0,1038750
	1CBN_b	-17772,9825348	0,1255662	0,1035151	0,1030314
	1CBN_ab	-17775,0086664	0,1263309	0,1043205	0,1038280
	1CBN_ba	-17772,9985102	0,1256097	0,1035828	0,1030097
	Max. Error		0,1264248	0,1044292	0,1038750
	RMS Error		0,1259835	0,1039627	0,1034369
5 Å	1CBN_a	-17775,0246715	0,0335884	0,0207274	0,0198489
	1CBN_b	-17772,9825348	0,0327290	0,0198529	0,0190974
	1CBN_ab	-17775,0086664	0,0330921	0,0202227	0,0193845
	1CBN_ba	-17772,9985102	0,0332146	0,0203526	0,0195534
	Max. Error		0,0335884	0,0207274	0,0198489
	RMS Error		0,0331574	0,0202913	0,0194730

Table S23: Maximum errors and root mean square errors of the relative energy calculated by the ADMA and FA-ADMA approaches for 4 mutations of Crambin with various sizes of the surroundings and the STO-3G basis set.

Surroundings		ADMA Energy	FA-ADMA Energy, Mulliken charges	FA-ADMA Energy, Löwdin charges
4 Å	**Max. Error (Hartree)**	0.0008586	0.0009141	0.0008653
	RMS Error (Hartree)	0.0006477	0.0006784	0.0006791
5 Å	**Max. Error (Hartree)**	0.0008594	0.0008745	0.0007515
	RMS Error (Hartree)	0.0005012	0.0005104	0.0004447

Table S24: Results of the ADMA and FA-ADMA approaches for 4 mutations of Crambin surroundings of 4 Å and various basis sets. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given. For comparison, errors of direct calculations using slightly smaller basis sets are also given using direct calculations with the basis set of the FA-ADMA calculations as reference.

Basis Set	Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
3-21G	1CBN_a	-17903.2603050	0.3326420	0.2963280	0.2850426
	1CBN_b	-17901.3360218	0.3313068	0.2939475	0.2836956
	1CBN_ab	-17903.2475909	0.3322071	0.2954964	0.2846347
	1CBN_ba	-17901.3496940	0.3314758	0.2944525	0.2837359
	Max. Error		0.3326420	0.2963280	0.2850426
	RMS Error		0.3319084	0.2950575	0.2842778
	1EJG_a	-17906.3509078	0.3527453	0.3069955	0.2975300
6-31G	1CBN_a	-17994.6040344	0.3146185	0.2837094	0.2659209
	1CBN_b	-17992.6694489	0.3127293	0.280199	0.2636880
	1CBN_ab	-17994.5922981	0.3137960	0.2824928	0.2650627
	1CBN_ba	-17992.6816390	0.3133811	0.2812456	0.2636847
	Max. Error		0.3146185	0.2837094	0.2659209
	RMS Error		0.3136320	0.2819148	0.2645908
	1EJG_a	-17997.5612124	0.3348905	0.2953343	0.2793449

Table S25: Maximum errors and root mean square errors of the relative energy calculated by the ADMA and FA-ADMA approach for 4 mutations of Crambin with surroundings of 4 Å and different basis sets. For comparison, the maximum errors and root mean square errors of direct calculations using slightly smaller basis sets are also given using direct calculations with the basis set of the FA-ADMA calculations as reference.

Basis Set		ADMA Energy	FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges	STO-3G	3-21G
3-21G	Max. Error (Hartree)	0,0013352	0,0023805	0,0013470	0,1178535	
	RMS Error (Hartree)	0,0008856	0,0015066	0,0009469	0,0939718	
	Error in Energy Difference of 1EJG_a and 1CBN_a	0,0201033	0,0106675	0,0124874	1,3530801	
6-31G	Max. Error (Hartree)	0,0018892	0,0035104	0,0022362	0,1075512	0,0127622
	RMS Error (Hartree)	0,0011189	0,0021520	0,0015552	0,0845913	0,0094717
	Error in Energy Difference of 1EJG_a and 1CBN_a	0,0202720	0,0116249	0,0134240	1,4865049	0,1334248

Basis Set	Molecule	Hartree-Fock Energy (Hartree)	Error of Hartree-Fock Energy with STO-3G basis set (Hartree)	Error of Hartree-Fock Energy with 3-21G basis set (Hartree)
3-21G	1CBN_a	-17903.2603050	128.2356335	
	1CBN_b	-17901.3360218	128.3534870	
	1CBN_ab	-17903.2475909	128.2389245	
	1CBN_ba	-17901.3496940	128.3511838	
	Max. Error		128.3534870	
	RMS Error		128.2948201	
	1EJG_a	-17906.3509078	126.8825534	
6-31G	1CBN_a	-17994.6040344	219.5793629	91.3437294
	1CBN_b	-17992.6694489	219.6869141	91.3334271
	1CBN_ab	-17994.5922981	219.5836317	91.3447072
	1CBN_ba	-17992.6816390	219.6831288	91.3319450
	Max. Error		219.6869141	91.3447072
	RMS Error		219.6332655	91.3384524
	1EJG_a	-17997.5612124	218.0928580	91.2103046

Table S26: Results of the ADMA and FA-ADMA approaches for Crambin – ethanol and Crambin – water complexes with various surroundings. The STO-3G basis set was used. For the ADMA and FA-ADMA calculations, the errors compared to the direct calculations are given.

Surroundings	Molecule	Hartree-Fock Energy (Hartree)	Error of ADMA Energy (Hartree)	Error of FA-ADMA Energy, Mulliken charges (Hartree)	Error of FA-ADMA Energy, Löwdin charges (Hartree)
4 Å	1CBN_a	-17775.0246715	0.1264248	0.1044292	0.1038750
	1CBN_a + ethanol	-17927.1543796	0.1266343	0.1046714	0.1041142
	1CBN_a after minimization	-17779.5277300	0.1381029	0.1136976	0.1131059
	1CBN_a after MD	-17778.6441290	0.1369154	0.1144788	0.1140308
	1CBN_a + water (1)	-17853.6426890	0.1366918	0.1145232	0.1140667
	1CBN_a + water (2)	-17853.6375766	0.1366719	0.1145401	0.1141440
	1CBN_a + water (3)	-17853.6276959	0.1367519	0.1145094	0.1140624
	1CBN + 3 water (1…3)	-18003.6081438	0.1366869	0.1148006	0.1144471
	1CBN + 21 water	-19353.1082861	0.1400108	0.1167970	0.1168482
	Max. Error		0.1400108	0.1167970	0.1168482
	RMS Error		0.1350675	0.1125770	0.1121644
5 Å	1CBN_a	-17775.0246715	0.0335884	0.0207274	0.0198489
	1CBN_a + ethanol	-17927.1543796	0.0336139	0.0207806	0.0199010
	1CBN_a after minimization	-17779.5277300	0.0377671	0.0229919	0.0223802
	1CBN_a after MD	-17778.6441290	0.0386753	0.0248397	0.0240860
	1CBN_a + water (1)	-17853.6426890	0.0385557	0.0248556	0.0241201
	1CBN_a + water (2)	-17853.6375766	0.0384074	0.0248308	0.0240878
	1CBN_a + water (3)	-17853.6276959	0.0387468	0.0249271	0.0241985
	1CBN + 3 water (1…3)	-18003.6081438	0.0383903	0.0249155	0.0242099
	1CBN + 21 water	-19353.1082861	0.0390609	0.0253704	0.0248129
	Max. Error		0.0390609	0.0253704	0.0248129
	RMS Error		0.0374800	0.0238683	0.0231430

Table S27: Maximum errors and root mean square errors of the relative energy calculated by the ADMA and FA-ADMA approach for Crambin – ethanol and Crambin – water complexes with different sizes of the surroundings and the STO-3G basis set.

Surroundings		ADMA Energy	FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges
4 Å	Max. Error (Hartree)	0,0135860	0,0123678	0,0129732
	RMS Error (Hartree)	0,0069551	0,0064774	0,0066353
5 Å	Max. Error (Hartree)	0,0054725	0,0046430	0,0049640
	RMS Error (Hartree)	0,0031033	0,0026196	0,0027238

Table S28: Maximum errors and root mean square errors of the relative energy calculated by the ADMA and FA-ADMA approach for Crambin – water complexes with different sizes of the surroundings and the STO-3G basis set.

Surroundings		ADMA Energy	FA-ADMA Energy Mulliken charges	FA-ADMA Energy Löwdin charges
4 Å	Max. Error (Hartree)	0,0033389	0,0023182	0,0028174
	RMS Error (Hartree)	0,0018906	0,0012961	0,0015727
5 Å	Max. Error (Hartree)	0,0006706	0,0005396	0,0007269
	RMS Error (Hartree)	0,0003540	0,0002922	0,0003956