Supporting information

Validation of linear scaling semiempirical LocalSCF method

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Table 1S. LocalSCF energy convergence settings (1 eV = 23.0627 kcal/mol) with keyword values marked in bold.

Option	Keyword	eV	kcal/mol
LMO refining gradient norm	grnorm	**0.00050**	0.0115
Maximum component of gradient for LMO refining	gelmax	**0.00200**	0.0461
LMO refining total energy change	destop	0.00004	**0.0001**
Maximal permitted non-orthogonality	sijcrt=0.001	-	-
LMO expansion gradient threshold	thrder1	**0.04000**	0.9225
Total energy change between expansions	deestop	0.02170	**0.5000**

Table 2S. **AM1** total (Et) and conformational (Ec) energies, kcal/mol, obtained with default program settings LSCFR (L), MOZ12 (Z), and MOPAC (M), and differences between the linear scaling and MOPAC energies, for 20 insulin conformations (1247 atoms).

Conf	Et(L)	Et(Z)	Et(M)	ΔEt(L)	ΔEt(Z)	Ec(L)	Ec(Z)	Ec(M)	ΔEc(L)	ΔEc(Z)
1	-7859.73	-7866.73	-7866.30	6.57	-0.43					
2	-7808.01	-7815.22	-7814.45	6.43	-0.77	-51.72	-51.52	-51.86	-0.14	-0.34
3	-7883.81	-7891.53	-7890.54	6.73	-0.99	75.80	76.31	76.10	0.30	-0.21
4	-7838.84	-7846.53	-7845.51	6.67	-1.03	-44.97	-44.99	-45.04	-0.07	-0.04
5	-7777.99	-7786.06	-7784.70	6.71	-1.36	-60.85	-60.48	-60.81	0.05	-0.33
6	-7842.35	-7849.25	-7849.19	6.84	-0.07	64.36	63.20	64.49	0.12	1.29
7	-7900.92	-7908.24	-7907.94	7.02	-0.31	58.57	58.99	58.75	0.18	-0.24
8	-7871.47	-7879.05	-7878.29	6.82	-0.76	-29.45	-29.20	-29.65	-0.20	-0.45
9	-7864.70	-7873.22	-7871.67	6.97	-1.55	-6.78	-5.82	-6.62	0.16	-0.80
10	-7889.75	-7897.31	-7896.69	6.93	-0.62	25.06	24.08	25.02	-0.04	0.94
11	-7944.17	-7953.49	-7952.30	8.13	-1.18	54.42	56.18	55.62	1.20	-0.57
12	-7878.29	-7886.17	-7885.26	6.97	-0.91	-65.89	-67.32	-67.05	-1.16	0.27
13	-7895.03	-7902.26	-7902.03	7.00	-0.23	16.74	16.09	16.78	0.03	0.68
14	-7860.07	-7867.09	-7867.11	7.04	0.02	-34.97	-35.17	-34.93	0.04	0.24
15	-7982.52	-7988.87	-7989.38	6.86	0.51	122.46	121.78	122.27	-0.18	0.49
16	-7970.14	-7977.65	-7976.99	6.85	-0.66	-12.39	-11.22	-12.39	-0.01	-1.17
17	-7903.43	-7911.07	-7910.33	6.91	-0.73	-66.71	-66.58	-66.66	0.05	-0.07
18	-7848.29	-7856.44	-7855.14	6.85	-1.30	-55.14	-54.63	-55.20	-0.06	-0.57
19	-8005.24	-8013.12	-8012.40	7.16	-0.72	156.95	156.68	157.26	0.31	0.58
20	-7960.22	-7968.14	-7967.33	7.12	-0.81	-45.03	-44.97	-45.07	-0.04	-0.10

Table 3S. **AM1** RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ).

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(M)	Δμ(L)	Δμ(Z)
1	0.0002	0.0001	0.0006	0.0004	253.33	253.34	253.28	0.05	0.21
2	0.0002	0.0001	0.0006	0.0003	259.15	259.14	259.10	0.06	0.12
3	0.0002	0.0001	0.0006	0.0003	250.09	249.99	250.00	0.09	0.15
4	0.0002	0.0001	0.0005	0.0004	224.07	224.02	224.02	0.05	0.07
5	0.0002	0.0001	0.0006	0.0004	259.18	259.24	259.13	0.05	0.15
6	0.0002	0.0001	0.0005	0.0003	211.81	211.76	211.75	0.06	0.06
7	0.0002	0.0001	0.0005	0.0003	207.32	207.18	207.22	0.11	0.09
8	0.0002	0.0001	0.0005	0.0004	247.39	247.44	247.32	0.08	0.13
9	0.0002	0.0001	0.0006	0.0004	275.46	275.45	275.36	0.11	0.11
10	0.0002	0.0001	0.0006	0.0004	225.83	225.80	225.74	0.09	0.12
11	0.0003	0.0002	0.0005	0.0004	234.92	235.00	234.81	0.11	0.20
12	0.0002	0.0001	0.0005	0.0003	202.73	202.75	202.67	0.06	0.16
13	0.0002	0.0001	0.0005	0.0003	194.59	194.55	194.51	0.08	0.11
14	0.0002	0.0001	0.0006	0.0003	155.62	155.62	155.58	0.05	0.11
15	0.0002	0.0001	0.0005	0.0003	145.24	145.30	145.19	0.06	0.13
16	0.0002	0.0001	0.0006	0.0003	151.29	151.29	151.23	0.06	0.11
17	0.0002	0.0001	0.0005	0.0003	174.45	174.51	174.40	0.06	0.12
18	0.0002	0.0001	0.0006	0.0004	161.91	161.99	161.83	0.07	0.20
19	0.0002	0.0001	0.0006	0.0004	197.49	197.50	197.42	0.07	0.08
20	0.0002	0.0001	0.0006	0.0004	138.38	138.49	138.34	0.05	0.16

Table 4S. **AM1** RMS errors for bond orders (B) and geometry gradients for non-hydrogen (%∇n) and hydrogen (%∇h) atoms.

Conf	B(L)	B(Z)	%∇n(L)	%∇h(L)	%∇n(Z)	%∇h(Z)
1	0.0001	0.0001	0.40	0.87	0.57	0.70
2	0.0001	0.0001	0.46	0.92	0.55	0.69
3	0.0001	0.0000	0.39	0.83	0.59	0.78
4	0.0001	0.0000	0.38	1.04	0.50	0.74
5	0.0001	0.0001	0.35	0.93	0.65	1.04
6	0.0001	0.0000	0.40	1.15	0.66	0.83
7	0.0001	0.0001	0.38	1.05	0.58	0.93
8	0.0001	0.0000	0.43	0.91	0.71	0.80
9	0.0001	0.0000	0.45	0.99	0.57	0.95
10	0.0001	0.0000	0.38	0.93	0.62	0.97
11	0.0001	0.0000	0.68	1.96	0.74	0.94
12	0.0001	0.0001	0.37	1.18	0.51	1.17
13	0.0001	0.0001	0.40	1.03	0.59	0.79
14	0.0001	0.0001	0.47	1.03	0.69	1.03
15	0.0001	0.0001	0.41	0.83	0.49	0.64
16	0.0001	0.0000	0.36	1.43	0.62	1.15
17	0.0001	0.0000	0.41	0.87	0.55	0.86
18	0.0001	0.0001	0.35	1.02	0.59	0.90
19	0.0001	0.0000	0.35	1.08	0.53	0.95
20	0.0001	0.0000	0.37	0.89	0.52	0.81

Table 5S. **MNDO** total (Et) and conformational (Ec) energies, kcal/mol, obtained with default program settings LSCFR (L), MOZ12 (Z), and MOPAC (M), and differences between the linear scaling and MOPAC energies, for 20 insulin conformations (1247 atoms).

Conf	Et(L)	Et(Z)	Et(M)	ΔEt(L)	ΔEt(Z)	Ec(L)	Ec(Z)	Ec(M)	ΔEc(L)	ΔEc(Z)
1	-5206.10	-5209.47	-5209.28	3.18	-0.19					
2	-5233.89	-5237.68	-5237.08	3.19	-0.61	27.79	28.22	27.80	0.01	-0.42
3	-5102.82	-5106.92	-5106.20	3.38	-0.72	-131.07	-130.77	-130.88	0.20	-0.11
4	-5171.79	-5175.72	-5175.02	3.23	-0.70	68.97	68.81	68.82	-0.15	0.02
5	-5028.79	-5033.19	-5032.20	3.41	-0.99	-143.00	-142.54	-142.83	0.18	-0.29
6	-5042.56	-5045.52	-5045.87	3.32	0.35	13.76	12.34	13.67	-0.09	1.33
7	-5229.91	-5233.41	-5233.45	3.55	0.05	187.35	187.88	187.58	0.23	-0.30
8	-5211.53	-5215.16	-5214.91	3.38	-0.25	-18.37	-18.25	-18.54	-0.17	-0.29
9	-5174.28	-5179.45	-5178.14	3.86	-1.31	-37.25	-35.71	-36.77	0.48	-1.06
10	-5192.41	-5196.42	-5196.21	3.80	-0.22	18.13	16.98	18.07	-0.07	1.09
11	-5153.87	-5157.89	-5157.07	3.21	-0.81	-38.55	-38.54	-39.14	-0.59	-0.60
12	-5154.43	-5158.67	-5158.35	3.92	-0.32	0.57	0.78	1.28	0.71	0.50
13	-5095.15	-5098.35	-5098.53	3.38	0.19	-59.28	-60.33	-59.82	-0.54	0.50
14	-5133.23	-5136.76	-5137.07	3.84	0.31	38.08	38.42	38.54	0.46	0.12
15	-5263.76	-5266.45	-5267.15	3.39	0.70	130.53	129.69	130.09	-0.45	0.40
16	-5166.04	-5169.97	-5169.45	3.42	-0.52	-97.73	-96.48	-97.70	0.02	-1.22
17	-5140.37	-5144.24	-5143.77	3.40	-0.48	-25.67	-25.72	-25.68	-0.01	0.04
18	-5170.39	-5174.60	-5173.82	3.42	-0.78	30.03	30.35	30.05	0.02	-0.30
19	-5213.29	-5217.30	-5216.79	3.50	-0.52	42.89	42.71	42.97	0.08	0.26
20	-5207.67	-5212.22	-5211.68	4.01	-0.54	-5.61	-5.09	-5.10	0.51	-0.02

Table 6S. **MNDO** RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ).

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(M)	Δμ(L)	Δμ(Z)
1	0.0001	0.0001	0.0006	0.0004	253.98	254.04	253.97	0.02	0.22
2	0.0001	0.0001	0.0006	0.0003	258.60	258.63	258.57	0.03	0.13
3	0.0001	0.0001	0.0006	0.0003	250.75	250.72	250.72	0.04	0.15
4	0.0001	0.0001	0.0005	0.0003	223.52	223.53	223.51	0.02	0.06
5	0.0001	0.0001	0.0005	0.0004	259.65	259.76	259.63	0.03	0.17
6	0.0001	0.0001	0.0005	0.0003	211.59	211.57	211.55	0.04	0.06
7	0.0001	0.0001	0.0005	0.0003	208.54	208.44	208.50	0.06	0.10
8	0.0001	0.0001	0.0006	0.0003	247.87	247.96	247.82	0.05	0.14
9	0.0002	0.0001	0.0006	0.0003	275.81	275.85	275.75	0.07	0.13
10	0.0002	0.0001	0.0006	0.0003	227.10	227.10	227.04	0.07	0.12
11	0.0001	0.0001	0.0005	0.0003	234.52	234.68	234.49	0.04	0.20
12	0.0002	0.0001	0.0005	0.0003	202.84	202.91	202.83	0.02	0.14
13	0.0001	0.0001	0.0005	0.0003	195.50	195.48	195.45	0.05	0.09
14	0.0002	0.0001	0.0005	0.0003	157.22	157.23	157.19	0.03	0.09
15	0.0001	0.0001	0.0005	0.0003	146.42	146.49	146.39	0.03	0.12
16	0.0001	0.0001	0.0005	0.0003	151.58	151.61	151.55	0.04	0.11
17	0.0001	0.0001	0.0005	0.0003	174.16	174.23	174.13	0.03	0.11
18	0.0001	0.0001	0.0006	0.0004	162.15	162.25	162.10	0.05	0.19
19	0.0001	0.0001	0.0006	0.0003	197.45	197.50	197.42	0.03	0.08
20	0.0002	0.0001	0.0005	0.0003	137.53	137.65	137.50	0.04	0.16

Table 7S. **MNDO** RMS errors for bond orders (B) and geometry gradients for non-hydrogen (%∇n) and hydrogen (%∇h) atoms, in units of kcal/mol.

Conf	B(L)	B(Z)	%∇n(L)	%∇h(L)	%∇n(Z)	%∇h(Z)
1	0.0001	0.0001	0.32	0.57	0.63	0.68
2	0.0001	0.0001	0.28	0.60	0.57	0.72
3	0.0001	0.0001	0.47	1.32	0.61	0.62
4	0.0001	0.0001	0.25	0.58	0.60	0.76
5	0.0001	0.0001	0.25	0.74	0.51	1.12
6	0.0001	0.0001	0.30	0.72	0.65	0.81
7	0.0001	0.0001	0.31	0.76	0.62	0.74
8	0.0001	0.0001	0.26	0.77	0.78	0.86
9	0.0002	0.0001	0.48	0.95	0.55	0.66
10	0.0002	0.0001	0.48	1.07	0.56	0.70
11	0.0001	0.0001	0.27	0.63	0.54	0.80
12	0.0002	0.0001	0.51	1.49	0.54	0.83
13	0.0001	0.0001	0.30	0.70	0.57	0.69
14	0.0002	0.0001	0.46	1.45	0.59	0.78
15	0.0001	0.0001	0.31	0.70	0.71	0.68
16	0.0001	0.0001	0.26	0.80	0.62	1.02
17	0.0002	0.0001	0.34	0.58	0.63	1.78
18	0.0002	0.0001	0.25	0.59	0.67	0.82
19	0.0001	0.0001	0.27	0.75	0.60	0.83
20	0.0002	0.0001	0.50	1.39	0.52	0.79

Table 8S. **PM3** total (Et) and conformational (Ec) energies, kcal/mol, obtained with default program settings LSCFR (L), MOZ12 (Z), and MOPAC (M), and differences between the linear scaling and MOPAC energies, for 20 insulin conformations (1247 atoms).

Conf	Et(L)	Et(Z)	Et(M)	ΔEt(L)	ΔEt(Z)	Ec(L)	Ec(Z)	Ec(M)	ΔEc(L)	ΔEc(Z)
1	-7458.96	-7466.94	-7467.04	8.08	0.10					
2	-7407.71	-7415.77	-7415.62	7.91	-0.15	-51.26	-51.17	-51.42	-0.16	-0.24
3	-7500.01	-7508.86	-7508.36	8.35	-0.50	92.30	93.10	92.74	0.44	-0.35
4	-7414.76	-7423.25	-7422.88	8.11	-0.37	-85.25	-85.62	-85.49	-0.24	0.13
5	-7432.01	-7440.77	-7440.02	8.01	-0.76	17.25	17.53	17.14	-0.11	-0.39
6	-7488.99	-7496.74	-7497.33	8.34	0.60	56.98	55.96	57.32	0.34	1.36
7	-7506.56	-7514.83	-7515.13	8.57	0.30	17.58	18.10	17.80	0.22	-0.30
8	-7446.50	-7454.81	-7454.59	8.08	-0.22	-60.06	-60.03	-60.55	-0.48	-0.52
9	-7485.24	-7494.65	-7493.72	8.48	-0.93	38.74	39.84	39.13	0.39	-0.71
10	-7495.95	-7504.08	-7504.13	8.18	0.05	10.71	9.43	10.41	-0.30	0.98
11	-7531.20	-7539.32	-7539.12	7.92	-0.19	35.25	35.24	34.99	-0.26	-0.25
12	-7554.86	-7563.05	-7563.04	8.19	0.00	23.66	23.73	23.92	0.26	0.19
13	-7502.62	-7510.74	-7511.29	8.67	0.55	-52.24	-52.31	-51.76	0.48	0.55
14	-7451.75	-7459.53	-7460.11	8.36	0.58	-50.87	-51.21	-51.18	-0.31	0.03
15	-7585.20	-7592.50	-7593.38	8.18	0.88	133.45	132.97	133.27	-0.18	0.29
16	-7593.49	-7601.83	-7601.68	8.19	-0.14	8.30	9.33	8.31	0.01	-1.02
17	-7550.05	-7557.99	-7558.12	8.07	0.13	-43.44	-43.84	-43.56	-0.12	0.28
18	-7472.39	-7480.85	-7480.42	8.03	-0.43	-77.67	-77.14	-77.70	-0.04	-0.56
19	-7591.70	-7599.91	-7600.07	8.37	0.17	119.31	119.06	119.65	0.34	0.60
20	-7615.12	-7623.28	-7623.47	8.36	0.19	23.41	23.38	23.40	-0.01	0.02

Table 9S. **PM3** RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ).

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(M)	Δμ(L)	Δμ(Z)
1	0.0003	0.0001	0.0007	0.0004	255.84	255.82	255.76	0.08	0.21
2	0.0003	0.0001	0.0007	0.0003	262.30	262.26	262.22	0.08	0.11
3	0.0002	0.0001	0.0006	0.0003	253.04	252.95	252.94	0.11	0.15
4	0.0003	0.0001	0.0006	0.0003	226.69	226.61	226.61	0.08	0.06
5	0.0003	0.0001	0.0007	0.0004	263.04	263.07	262.98	0.07	0.13
6	0.0003	0.0001	0.0006	0.0003	214.02	213.98	213.95	0.08	0.09
7	0.0003	0.0001	0.0006	0.0003	211.04	210.90	210.93	0.13	0.07
8	0.0003	0.0001	0.0007	0.0003	249.21	249.26	249.12	0.10	0.14
9	0.0003	0.0001	0.0007	0.0004	279.95	279.91	279.83	0.13	0.10
10	0.0003	0.0001	0.0007	0.0003	228.82	228.78	228.72	0.11	0.11
11	0.0003	0.0001	0.0006	0.0003	238.54	238.63	238.46	0.09	0.19
12	0.0003	0.0001	0.0006	0.0003	205.68	205.70	205.59	0.09	0.16
13	0.0003	0.0001	0.0006	0.0003	197.22	197.16	197.11	0.11	0.11
14	0.0003	0.0001	0.0006	0.0003	158.83	158.82	158.77	0.06	0.11
15	0.0003	0.0001	0.0006	0.0003	146.82	146.86	146.75	0.07	0.14
16	0.0003	0.0001	0.0007	0.0003	152.50	152.48	152.41	0.09	0.12
17	0.0003	0.0001	0.0006	0.0003	177.26	177.32	177.19	0.08	0.13
18	0.0003	0.0001	0.0007	0.0003	162.29	162.35	162.20	0.10	0.20
19	0.0003	0.0001	0.0007	0.0003	200.52	200.50	200.44	0.08	0.07
20	0.0003	0.0001	0.0007	0.0003	139.86	139.93	139.79	0.08	0.15

Table 10S. **PM3** RMS errors for bond orders (B) and geometry gradients for non-hydrogen (%∇n) and hydrogen (%∇h) atoms.

Conf	B(L)	B(Z)	%∇n(L)	%∇h(L)	%∇n(Z)	%∇h(Z)
1	0.0001	0.0000	0.76	1.24	0.61	0.71
2	0.0001	0.0000	0.54	1.78	0.56	0.71
3	0.0001	0.0000	0.57	2.00	0.59	0.99
4	0.0001	0.0000	0.70	1.34	0.50	0.70
5	0.0001	0.0000	0.80	1.52	0.60	2.61
6	0.0001	0.0001	0.76	1.50	0.95	0.74
7	0.0001	0.0000	0.62	1.29	0.51	0.72
8	0.0001	0.0000	0.58	1.43	0.49	0.67
9	0.0001	0.0000	0.55	1.25	0.56	0.71
10	0.0001	0.0000	0.53	1.30	0.57	0.73
11	0.0001	0.0000	0.53	1.55	0.54	0.90
12	0.0001	0.0001	0.47	1.21	0.59	0.75
13	0.0001	0.0000	0.69	1.59	0.63	0.68
14	0.0001	0.0000	0.54	1.46	0.58	0.79
15	0.0001	0.0000	0.60	1.38	0.54	0.64
16	0.0001	0.0000	0.57	1.43	0.61	0.77
17	0.0001	0.0000	0.63	1.81	0.59	0.94
18	0.0001	0.0000	0.72	1.42	0.67	0.94
19	0.0001	0.0000	0.55	1.32	0.54	0.80
20	0.0001	0.0000	0.67	1.36	0.57	0.77

Table 11S. **PM5** total (Et) and conformational (Ec) energies, kcal/mol, obtained with default program settings LSCFR (L), MOZ12 (Z), and MOPAC (M), and differences between the linear scaling and MOPAC energies, for 20 insulin conformations (1247 atoms)..

Conf	Et(L)	Et(Z)	Et(M)	ΔEt(L)	ΔEt(Z)	Ec(L)	Ec(Z)	Ec(M)	ΔEc(L)	ΔEc(Z)
1	-7939.01	-7947.28	-7949.22	10.20	1.94					
2	-7920.20	-7928.30	-7930.14	9.94	1.84	-18.82	-18.98	-19.08	-0.26	-0.10
3	-7942.22	-7950.74	-7952.51	10.29	1.77	22.02	22.43	22.37	0.35	-0.06
4	-7914.83	-7923.54	-7925.08	10.25	1.53	-27.39	-27.19	-27.43	-0.04	-0.24
5	-7859.02	-7868.26	-7869.48	10.46	1.22	-55.81	-55.28	-55.60	0.21	-0.31
6	-7906.41	-7914.58	-7916.91	10.49	2.32	47.39	46.32	47.43	0.03	1.11
7	-7999.97	-8008.33	-8010.64	10.67	2.31	93.55	93.75	93.73	0.18	-0.02
8	-7944.78	-7953.60	-7955.26	10.48	1.66	-55.19	-54.73	-55.38	-0.20	-0.65
9	-7970.57	-7979.89	-7981.14	10.57	1.26	25.79	26.28	25.88	0.10	-0.40
10	-7951.43	-7960.11	-7961.93	10.50	1.82	-19.14	-19.77	-19.21	-0.07	0.56
11	-7958.94	-7967.83	-7969.25	10.32	1.42	7.51	7.72	7.32	-0.19	-0.40
12	-8010.03	-8019.18	-8020.80	10.77	1.62	51.10	51.35	51.55	0.45	0.20
13	-7950.54	-7958.92	-7961.33	10.80	2.41	-59.50	-60.26	-59.47	0.03	0.79
14	-7910.72	-7918.77	-7921.42	10.70	2.65	-39.82	-40.15	-39.91	-0.10	0.24
15	-8046.13	-8053.59	-8056.72	10.59	3.13	135.41	134.82	135.30	-0.11	0.49
16	-8030.17	-8038.53	-8040.65	10.48	2.12	-15.96	-15.06	-16.07	-0.11	-1.01
17	-7955.03	-7963.50	-7965.53	10.50	2.03	-75.15	-75.02	-75.12	0.02	-0.10
18	-7937.74	-7946.97	-7948.15	10.41	1.18	-17.29	-16.54	-17.38	-0.10	-0.85
19	-8028.40	-8037.21	-8039.23	10.83	2.02	90.66	90.24	91.09	0.43	0.84
20	-8075.20	-8083.87	-8085.94	10.73	2.07	46.81	46.66	46.71	-0.10	0.05

Table 12S. **PM5** RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ).

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(M)	Δμ(L)	Δμ(Z)
1	0.0003	0.0001	0.0007	0.0004	256.50	256.41	256.38	0.12	0.19
2	0.0002	0.0001	0.0007	0.0004	264.68	264.58	264.57	0.11	0.09
3	0.0002	0.0001	0.0007	0.0004	255.04	254.86	254.90	0.15	0.12
4	0.0003	0.0001	0.0006	0.0004	229.13	228.99	229.01	0.12	0.07
5	0.0002	0.0001	0.0007	0.0004	264.58	264.55	264.49	0.09	0.10
6	0.0002	0.0001	0.0007	0.0004	216.04	215.92	215.94	0.10	0.06
7	0.0002	0.0001	0.0006	0.0004	209.65	209.44	209.49	0.16	0.08
8	0.0002	0.0001	0.0007	0.0004	250.21	250.18	250.09	0.13	0.10
9	0.0002	0.0001	0.0007	0.0004	280.43	280.30	280.26	0.17	0.06
10	0.0002	0.0001	0.0007	0.0004	227.90	227.80	227.75	0.15	0.09
11	0.0002	0.0001	0.0006	0.0004	239.84	239.88	239.72	0.12	0.17
12	0.0002	0.0001	0.0006	0.0004	207.91	207.85	207.79	0.12	0.14
13	0.0002	0.0001	0.0007	0.0004	198.57	198.44	198.43	0.14	0.09
14	0.0002	0.0001	0.0007	0.0004	157.99	157.94	157.91	0.08	0.10
15	0.0002	0.0001	0.0006	0.0003	145.56	145.58	145.48	0.09	0.11
16	0.0002	0.0001	0.0007	0.0004	152.17	152.09	152.07	0.11	0.08
17	0.0002	0.0001	0.0006	0.0004	178.00	178.00	177.91	0.10	0.11
18	0.0003	0.0001	0.0007	0.0004	163.34	163.37	163.24	0.10	0.17
19	0.0003	0.0001	0.0007	0.0004	203.32	203.26	203.22	0.10	0.07
20	0.0002	0.0001	0.0007	0.0004	143.72	143.75	143.62	0.10	0.14

Table 13S. **PM5** RMS errors for bond orders (B) and geometry gradients for non-hydrogen (%∇n) and hydrogen (%∇h) atoms.

Conf	B(L)	B(Z)	%∇n(L)	%∇h(L)	%∇n(Z)	%∇h(Z)
1	0.0001	0.0001	0.87	1.24	0.93	0.98
2	0.0001	0.0000	0.71	1.49	0.86	0.89
3	0.0001	0.0001	1.19	1.24	1.01	0.99
4	0.0001	0.0001	0.70	1.16	0.70	0.87
5	0.0001	0.0001	0.64	1.30	0.87	1.15
6	0.0001	0.0001	1.04	1.24	1.00	0.88
7	0.0001	0.0001	0.72	1.15	0.81	0.99
8	0.0001	0.0001	0.68	1.12	0.98	0.92
9	0.0001	0.0001	0.81	1.12	0.94	1.04
10	0.0001	0.0001	0.67	1.69	1.10	1.41
11	0.0001	0.0001	0.88	1.27	0.79	0.98
12	0.0001	0.0001	0.59	1.13	0.81	0.98
13	0.0001	0.0001	0.97	1.21	1.56	1.00
14	0.0001	0.0001	0.70	1.20	0.93	1.15
15	0.0001	0.0001	0.71	1.34	0.88	0.96
16	0.0001	0.0001	0.81	1.24	1.01	1.12
17	0.0001	0.0001	0.69	1.50	1.10	1.10
18	0.0001	0.0001	0.77	1.41	1.01	1.17
19	0.0001	0.0001	1.00	1.40	1.15	1.35
20	0.0001	0.0001	1.35	1.22	2.33	1.12

Table 14S. Calculation time, seconds, of LSCFR and MOZ12 for 20 insulin conformations (1247 atoms).

	MNDO		AM1		PM3		PM5	
Conf	LSCFR	MOZ12	LSCFR	MOZ12	LSCFR	MOZ12	LSCFR	MOZ12
1	143	66	139	85	143	120	160	109
2	148	68	193	119	150	110	153	131
3	149	68	174	113	173	112	158	111
4	160	75	141	93	156	126	149	119
5	177	82	142	97	168	117	160	114
6	164	83	144	97	152	117	151	122
7	165	81	145	93	155	128	166	122
8	165	82	153	94	150	197	151	115
9	147	87	141	102	166	129	149	120
10	134	74	142	98	146	125	161	117
11	142	78	158	110	164	123	169	107
12	132	70	173	117	159	114	163	118
13	152	72	177	120	154	132	169	131
14	132	75	192	127	155	123	151	128
15	149	75	193	130	162	133	171	127
16	152	75	190	132	156	131	165	122
17	149	70	191	140	147	122	167	126
18	149	71	203	136	146	135	164	117
19	155	72	204	148	149	126	154	125
20	133	78	206	143	171	140	167	117

Table 15S. **AM1** total (Et) and conformational (Ec) energies, kcal/mol, obtained with fast program settings LSCFF (L), MOZ6 (Z), and MOPAC (M), and differences between the linear scaling and MOPAC energies, for 20 insulin conformations (1247 atoms).

Conf	Et(L)	Et(Z)	Et(M)	ΔEt(L)	ΔEt(Z)	Ec(L)	Ec(Z)	Ec(M)	ΔEc(L)	ΔEc(Z)
1	-7858.72	-7868.24	-7866.30	7.58	-1.94					
2	-7807.27	-7816.03	-7814.45	7.18	-1.58	-51.45	-52.22	-51.86	-0.40	0.36
3	-7883.12	-7892.84	-7890.54	7.42	-2.30	75.86	76.82	76.10	0.24	-0.72
4	-7838.22	-7847.21	-7845.51	7.28	-1.71	-44.90	-45.63	-45.04	-0.13	0.60
5	-7777.45	-7787.15	-7784.70	7.25	-2.45	-60.78	-60.07	-60.81	-0.03	-0.74
6	-7841.75	-7849.06	-7849.19	7.43	0.13	64.30	61.91	64.49	0.18	2.57
7	-7900.12	-7911.51	-7907.94	7.82	-3.57	58.37	62.45	58.75	0.38	-3.70
8	-7870.73	-7881.12	-7878.29	7.56	-2.83	-29.39	-30.39	-29.65	-0.26	0.74
9	-7863.99	-7873.82	-7871.67	7.68	-2.15	-6.74	-7.30	-6.62	0.12	0.68
10	-7889.25	-7899.59	-7896.69	7.44	-2.90	25.26	25.77	25.02	-0.24	-0.75
11	-7943.49	-7953.42	-7952.30	8.81	-1.12	54.25	53.84	55.62	1.37	1.78
12	-7877.88	-7887.45	-7885.26	7.37	-2.20	-65.61	-65.97	-67.05	-1.44	-1.08
13	-7893.93	-7903.88	-7902.03	8.11	-1.85	16.05	16.43	16.78	0.73	0.35
14	-7858.67	-7868.99	-7867.11	8.44	-1.89	-35.26	-34.89	-34.93	0.34	-0.04
15	-7981.62	-7991.51	-7989.38	7.76	-2.13	122.96	122.52	122.27	-0.69	-0.24
16	-7969.03	-7980.75	-7976.99	7.96	-3.76	-12.59	-10.76	-12.39	0.20	-1.63
17	-7902.57	-7913.43	-7910.33	7.76	-3.09	-66.46	-67.32	-66.66	-0.20	0.67
18	-7847.48	-7857.02	-7855.14	7.66	-1.88	-55.10	-56.41	-55.20	-0.10	1.22
19	-8004.53	-8015.57	-8012.40	7.87	-3.17	157.06	158.55	157.26	0.21	-1.29
20	-7959.25	-7969.18	-7967.33	8.08	-1.85	-45.28	-46.39	-45.07	0.21	1.32

Table 16S. **AM1** RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ).

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(M)	Δμ(L)	Δμ(Z)
1	0.0003	0.0001	0.0016	0.0009	253.32	253.41	253.28	0.05	0.29
2	0.0006	0.0002	0.0016	0.0009	259.15	259.28	259.10	0.07	0.34
3	0.0005	0.0002	0.0016	0.0009	250.07	250.00	250.00	0.07	0.24
4	0.0005	0.0002	0.0016	0.0009	224.06	224.11	224.02	0.06	0.15
5	0.0005	0.0002	0.0017	0.0010	259.16	259.26	259.13	0.04	0.38
6	0.0005	0.0002	0.0015	0.0009	211.78	211.78	211.75	0.03	0.22
7	0.0005	0.0002	0.0016	0.0009	207.30	207.13	207.22	0.08	0.39
8	0.0005	0.0002	0.0017	0.0009	247.39	247.57	247.32	0.09	0.36
9	0.0005	0.0002	0.0017	0.0009	275.47	275.50	275.36	0.11	0.34
10	0.0005	0.0002	0.0016	0.0008	225.81	225.86	225.74	0.09	0.30
11	0.0005	0.0003	0.0015	0.0009	234.88	235.06	234.81	0.08	0.31
12	0.0005	0.0002	0.0015	0.0009	202.70	202.84	202.67	0.03	0.44
13	0.0005	0.0002	0.0017	0.0009	194.56	194.60	194.51	0.06	0.25
14	0.0005	0.0002	0.0016	0.0009	155.59	155.57	155.58	0.05	0.26
15	0.0005	0.0002	0.0016	0.0009	145.28	145.44	145.19	0.09	0.36
16	0.0006	0.0003	0.0017	0.0009	151.28	151.33	151.23	0.06	0.23
17	0.0004	0.0002	0.0016	0.0009	174.43	174.59	174.40	0.07	0.27
18	0.0005	0.0002	0.0018	0.0010	161.87	161.99	161.83	0.08	0.42
19	0.0005	0.0002	0.0016	0.0009	197.47	197.52	197.42	0.06	0.19
20	0.0005	0.0002	0.0016	0.0009	138.38	138.67	138.34	0.05	0.35

Table 17S. **AM1** RMS errors for bond orders (B) and geometry gradients for non-hydrogen (%∇n) and hydrogen (%∇h) atoms.

Conf	B(L)	B(Z)	%∇n(L)	%∇h(L)	%∇n(Z)	%∇h(Z)
1	0.0001	0.0001	3.45	5.58	1.67	2.37
2	0.0001	0.0001	4.61	7.74	1.51	2.23
3	0.0001	0.0001	4.12	7.17	1.75	2.31
4	0.0001	0.0001	3.67	7.77	1.56	2.77
5	0.0001	0.0001	3.43	6.43	1.68	2.73
6	0.0001	0.0001	3.46	5.71	1.67	2.33
7	0.0001	0.0001	4.16	8.46	1.65	2.84
8	0.0001	0.0001	3.80	6.30	1.84	2.40
9	0.0001	0.0001	3.26	5.18	1.72	2.46
10	0.0001	0.0001	3.95	6.41	1.52	2.31
11	0.0001	0.0001	4.37	6.01	1.54	2.51
12	0.0001	0.0001	3.15	8.04	1.46	3.62
13	0.0001	0.0001	3.37	7.11	1.34	2.31
14	0.0001	0.0001	3.70	6.82	2.13	2.49
15	0.0001	0.0001	3.66	6.27	1.45	2.25
16	0.0001	0.0001	3.65	9.73	1.79	2.96
17	0.0001	0.0001	3.46	6.21	1.48	2.51
18	0.0001	0.0001	4.15	6.12	1.71	2.70
19	0.0001	0.0001	4.01	7.35	1.61	2.48
20	0.0001	0.0001	2.49	5.12	1.51	2.82

Table 18S. **MNDO** total (Et) and conformational (Ec) energies, kcal/mol, obtained with fast program settings LSCFF (L), MOZ6 (Z), and MOPAC (M), and differences between the linear scaling and MOPAC energies, for 20 insulin conformations (1247 atoms).

Conf	Et(L)	Et(Z)	Et(M)	ΔEt(L)	ΔEt(Z)	Ec(L)	Ec(Z)	Ec(M)	ΔEc(L)	ΔEc(Z)
1	-5205.01	-5212.83	-5209.28	4.27	-3.56					
2	-5233.14	-5239.72	-5237.08	3.93	-2.65	28.13	26.89	27.80	-0.34	0.91
3	-5101.99	-5110.60	-5106.20	4.21	-4.40	-131.15	-129.12	-130.88	0.28	-1.75
4	-5171.15	-5179.13	-5175.02	3.88	-4.10	69.15	68.53	68.82	-0.33	0.29
5	-5028.23	-5036.71	-5032.20	3.97	-4.51	-142.92	-142.41	-142.83	0.09	-0.41
6	-5041.88	-5047.92	-5045.87	3.99	-2.05	13.65	11.21	13.67	0.02	2.46
7	-5229.05	-5238.54	-5233.45	4.40	-5.09	187.17	190.62	187.58	0.41	-3.04
8	-5210.55	-5219.32	-5214.91	4.36	-4.41	-18.50	-19.22	-18.54	-0.04	0.68
9	-5173.78	-5182.17	-5178.14	4.36	-4.02	-36.77	-37.15	-36.77	0.00	0.39
10	-5191.81	-5200.81	-5196.21	4.40	-4.60	18.03	18.64	18.07	0.04	-0.58
11	-5153.10	-5160.45	-5157.07	3.97	-3.38	-38.71	-40.36	-39.14	-0.42	1.22
12	-5153.74	-5161.52	-5158.35	4.62	-3.17	0.64	1.07	1.28	0.65	0.21
13	-5093.81	-5101.85	-5098.53	4.72	-3.32	-59.92	-59.67	-59.82	0.10	-0.15
14	-5131.80	-5140.82	-5137.07	5.27	-3.75	37.98	38.97	38.54	0.55	-0.43
15	-5262.65	-5270.66	-5267.15	4.51	-3.51	130.85	129.84	130.09	-0.77	0.25
16	-5164.68	-5175.71	-5169.45	4.77	-6.26	-97.97	-94.95	-97.70	0.26	-2.76
17	-5139.46	-5148.59	-5143.77	4.30	-4.82	-25.22	-27.12	-25.68	-0.47	1.44
18	-5169.59	-5177.23	-5173.82	4.23	-3.41	30.12	28.64	30.05	-0.08	1.41
19	-5212.40	-5221.88	-5216.79	4.39	-5.09	42.81	44.65	42.97	0.16	-1.68
20	-5206.70	-5216.36	-5211.68	4.99	-4.67	-5.70	-5.52	-5.10	0.60	0.42

Table 19S. **MNDO** RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ).

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(M)	Δμ(L)	Δμ(Z)
1	0.0004	0.0001	0.0015	0.0008	253.97	254.13	253.97	0.03	0.29
2	0.0006	0.0002	0.0014	0.0008	258.59	258.75	258.57	0.04	0.32
3	0.0005	0.0002	0.0014	0.0008	250.73	250.71	250.72	0.01	0.26
4	0.0005	0.0002	0.0014	0.0008	223.51	223.62	223.51	0.02	0.16
5	0.0004	0.0002	0.0014	0.0008	259.63	259.81	259.63	0.02	0.39
6	0.0005	0.0002	0.0013	0.0008	211.57	211.62	211.55	0.03	0.26
7	0.0005	0.0002	0.0014	0.0008	208.53	208.41	208.50	0.05	0.37
8	0.0005	0.0002	0.0015	0.0008	247.87	248.08	247.82	0.06	0.39
9	0.0006	0.0002	0.0014	0.0008	275.82	275.91	275.75	0.09	0.36
10	0.0005	0.0002	0.0014	0.0007	227.08	227.18	227.04	0.06	0.31
11	0.0004	0.0002	0.0013	0.0008	234.50	234.74	234.49	0.03	0.31
12	0.0005	0.0002	0.0013	0.0008	202.81	202.97	202.83	0.04	0.42
13	0.0005	0.0002	0.0015	0.0008	195.47	195.52	195.45	0.03	0.23
14	0.0005	0.0002	0.0014	0.0008	157.19	157.19	157.19	0.03	0.22
15	0.0005	0.0002	0.0014	0.0008	146.47	146.62	146.39	0.08	0.34
16	0.0006	0.0002	0.0015	0.0008	151.57	151.67	151.55	0.04	0.22
17	0.0004	0.0002	0.0014	0.0008	174.13	174.30	174.13	0.06	0.24
18	0.0005	0.0002	0.0016	0.0008	162.13	162.26	162.10	0.07	0.40
19	0.0005	0.0002	0.0014	0.0008	197.42	197.56	197.42	0.03	0.20
20	0.0005	0.0002	0.0014	0.0008	137.51	137.80	137.50	0.03	0.32

Table 20S. **MNDO** RMS errors for bond orders (B) and geometry gradients for non-hydrogen (%∇n) and hydrogen (%∇h) atoms.

Conf	B(L)	B(Z)	%∇n(L)	%∇h(L)	%∇n(Z)	%∇h(Z)
1	0.0001	0.0001	3.10	4.37	1.51	1.99
2	0.0001	0.0001	4.16	5.29	1.21	1.94
3	0.0001	0.0001	3.71	4.79	1.36	1.84
4	0.0001	0.0001	2.85	6.28	1.38	2.83
5	0.0001	0.0001	2.85	4.43	1.36	2.36
6	0.0001	0.0001	2.75	4.73	1.46	2.36
7	0.0001	0.0001	3.88	5.37	1.69	2.36
8	0.0001	0.0001	4.16	6.61	2.03	2.55
9	0.0002	0.0001	3.16	2.98	1.77	2.07
10	0.0002	0.0001	3.58	4.11	1.45	1.72
11	0.0001	0.0001	3.25	4.23	1.31	2.09
12	0.0002	0.0001	2.87	4.58	1.47	2.16
13	0.0001	0.0001	3.88	4.58	1.34	2.19
14	0.0002	0.0001	3.22	4.44	1.60	2.26
15	0.0001	0.0001	3.36	3.75	1.62	2.06
16	0.0001	0.0001	3.99	5.97	1.75	3.31
17	0.0002	0.0001	4.61	4.95	1.55	5.07
18	0.0002	0.0001	3.29	3.76	1.94	2.38
19	0.0001	0.0001	3.81	5.60	1.50	2.00
20	0.0002	0.0001	2.35	3.61	1.57	2.57

Table 21S. **PM3** total (Et) and conformational (Ec) energies, kcal/mol, obtained with fast program settings LSCFF (L), MOZ6 (Z), and MOPAC (M), and differences between the linear scaling and MOPAC energies, for 20 insulin conformations (1247 atoms).

Conf	Et(L)	Et(Z)	Et(M)	ΔEt(L)	ΔEt(Z)	Ec(L)	Ec(Z)	Ec(M)	ΔEc(L)	ΔEc(Z)
1	-7458.93	-7466.66	-7467.04	8.11	0.38					
2	-7407.76	-7415.21	-7415.62	7.86	0.42	-51.17	-51.45	-51.42	-0.25	0.03
3	-7499.80	-7507.81	-7508.36	8.57	0.56	92.04	92.60	92.74	0.70	0.14
4	-7414.70	-7422.11	-7422.88	8.17	0.77	-85.09	-85.70	-85.49	-0.39	0.21
5	-7431.88	-7439.42	-7440.02	8.14	0.59	17.17	17.31	17.14	-0.04	-0.17
6	-7489.11	-7494.25	-7497.33	8.22	3.08	57.23	54.83	57.32	0.08	2.49
7	-7506.55	-7515.31	-7515.13	8.58	-0.18	17.44	21.06	17.80	0.36	-3.26
8	-7446.42	-7454.23	-7454.59	8.17	0.36	-60.13	-61.08	-60.55	-0.41	0.54
9	-7485.16	-7492.76	-7493.72	8.56	0.96	38.74	38.54	39.13	0.39	0.60
10	-7496.05	-7504.25	-7504.13	8.08	-0.12	10.89	11.49	10.41	-0.48	-1.08
11	-7531.34	-7537.44	-7539.12	7.79	1.68	35.29	33.19	34.99	-0.30	1.80
12	-7555.03	-7561.61	-7563.04	8.01	1.44	23.70	24.16	23.92	0.22	-0.24
13	-7502.53	-7510.24	-7511.29	8.75	1.05	-52.50	-51.37	-51.76	0.74	-0.39
14	-7451.56	-7458.76	-7460.11	8.55	1.35	-50.97	-51.47	-51.18	-0.20	0.30
15	-7585.16	-7592.80	-7593.38	8.22	0.58	133.60	134.04	133.27	-0.34	-0.77
16	-7593.50	-7602.62	-7601.68	8.19	-0.94	8.34	9.82	8.31	-0.03	-1.52
17	-7550.27	-7557.68	-7558.12	7.85	0.44	-43.23	-44.95	-43.56	-0.33	1.38
18	-7472.31	-7479.76	-7480.42	8.11	0.66	-77.96	-77.92	-77.70	0.26	0.22
19	-7591.73	-7599.44	-7600.07	8.34	0.63	119.43	119.68	119.65	0.23	-0.03
20	-7614.83	-7621.55	-7623.47	8.64	1.92	23.10	22.11	23.40	0.30	1.29

Table 22S. **PM3** RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ).

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(M)	Δμ(L)	Δμ(Z)
1	0.0005	0.0001	0.0021	0.0009	255.83	255.88	255.76	0.08	0.27
2	0.0006	0.0002	0.0020	0.0009	262.29	262.32	262.22	0.08	0.22
3	0.0005	0.0002	0.0021	0.0010	253.03	252.95	252.94	0.09	0.25
4	0.0005	0.0002	0.0021	0.0009	226.69	226.68	226.61	0.09	0.12
5	0.0006	0.0002	0.0021	0.0010	263.05	263.05	262.98	0.08	0.28
6	0.0006	0.0002	0.0019	0.0010	214.00	214.00	213.95	0.06	0.16
7	0.0006	0.0002	0.0020	0.0009	211.03	210.85	210.93	0.11	0.24
8	0.0005	0.0001	0.0021	0.0009	249.23	249.35	249.12	0.11	0.28
9	0.0006	0.0002	0.0021	0.0010	279.94	279.96	279.83	0.13	0.31
10	0.0005	0.0002	0.0020	0.0009	228.82	228.82	228.72	0.11	0.25
11	0.0005	0.0002	0.0019	0.0009	238.52	238.66	238.46	0.07	0.29
12	0.0006	0.0002	0.0019	0.0009	205.66	205.76	205.59	0.07	0.38
13	0.0006	0.0002	0.0020	0.0009	197.22	197.21	197.11	0.11	0.20
14	0.0006	0.0002	0.0021	0.0009	158.82	158.79	158.77	0.06	0.18
15	0.0006	0.0002	0.0019	0.0009	146.83	146.97	146.75	0.08	0.28
16	0.0006	0.0002	0.0021	0.0009	152.47	152.51	152.41	0.08	0.17
17	0.0006	0.0002	0.0019	0.0009	177.24	177.37	177.19	0.07	0.24
18	0.0005	0.0002	0.0023	0.0010	162.29	162.36	162.20	0.10	0.38
19	0.0005	0.0002	0.0020	0.0009	200.51	200.53	200.44	0.07	0.17
20	0.0005	0.0002	0.0020	0.0010	139.86	140.12	139.79	0.08	0.34

Table 23S. **PM3** RMS errors for bond orders (B) and geometry gradients for non-hydrogen (%∇n) and hydrogen (%∇h) atoms.

Conf	B(L)	B(Z)	%∇n(L)	%∇h(L)	%∇n(Z)	%∇h(Z)
1	0.0001	0.0001	4.02	4.46	1.61	1.89
2	0.0001	0.0001	4.90	5.40	1.60	1.93
3	0.0001	0.0001	4.71	4.84	1.42	2.44
4	0.0001	0.0001	3.69	3.67	1.60	1.95
5	0.0001	0.0001	4.30	5.37	2.09	6.91
6	0.0001	0.0001	3.67	4.34	1.91	2.19
7	0.0001	0.0001	4.29	4.39	1.51	2.06
8	0.0001	0.0001	4.70	4.42	1.64	2.00
9	0.0001	0.0001	2.98	3.66	1.49	1.94
10	0.0001	0.0001	4.06	4.32	1.38	1.99
11	0.0001	0.0001	3.53	4.09	1.35	2.14
12	0.0001	0.0001	2.90	3.82	1.39	2.18
13	0.0001	0.0001	5.54	5.31	1.57	2.36
14	0.0001	0.0001	4.25	4.05	1.55	2.18
15	0.0001	0.0001	3.85	3.99	1.43	1.95
16	0.0001	0.0001	4.48	4.77	1.70	2.14
17	0.0001	0.0001	3.77	5.09	1.50	2.66
18	0.0001	0.0001	2.71	4.03	1.91	2.86
19	0.0001	0.0001	3.79	4.37	1.42	1.93
20	0.0001	0.0001	3.24	3.63	1.60	2.51

Table 24S. **PM5** total (Et) and conformational (Ec) energies, kcal/mol, obtained with fast program settings LSCFF (L), MOZ6 (Z), and MOPAC (M), and differences between the linear scaling and MOPAC energies, for 20 insulin conformations (1247 atoms).

Conf	Et(L)	Et(Z)	Et(M)	ΔEt(L)	ΔEt(Z)	Ec(L)	Ec(Z)	Ec(M)	ΔEc(L)	ΔEc(Z)
1	-7930.40	-7927.18	-7949.22	18.82	22.03					
2	-7911.37	-7907.71	-7930.14	18.76	22.43	-19.03	-19.48	-19.08	-0.05	0.40
3	-7933.92	-7928.17	-7952.51	18.58	24.34	22.55	20.46	22.37	-0.18	1.91
4	-7906.48	-7900.47	-7925.08	18.59	24.61	-27.44	-27.70	-27.43	0.01	0.27
5	-7849.01	-7846.77	-7869.48	20.47	22.71	-57.47	-53.70	-55.60	1.87	-1.90
6	-7899.33	-7890.73	-7916.91	17.58	26.17	50.32	43.96	47.43	-2.89	3.47
7	-7992.72	-7988.60	-8010.64	17.92	22.04	93.38	97.87	93.73	0.35	-4.14
8	-7937.19	-7932.52	-7955.26	18.07	22.73	-55.52	-56.08	-55.38	0.14	0.70
9	-7961.90	-7956.82	-7981.14	19.24	24.32	24.71	24.30	25.88	1.17	1.59
10	-7941.92	-7939.04	-7961.93	20.01	22.89	-19.98	-17.78	-19.21	0.77	-1.43
11	-7951.72	-7945.13	-7969.25	17.53	24.13	9.80	6.09	7.32	-2.48	1.23
12	-8002.88	-7996.63	-8020.80	17.92	24.17	51.16	51.50	51.55	0.39	0.04
13	-7944.52	-7937.02	-7961.33	16.81	24.31	-58.36	-59.61	-59.47	-1.11	0.15
14	-7903.47	-7896.39	-7921.42	17.95	25.03	-41.05	-40.63	-39.91	1.14	0.71
15	-8039.57	-8032.58	-8056.72	17.15	24.14	136.10	136.19	135.30	-0.80	-0.89
16	-8025.02	-8018.60	-8040.65	15.63	22.05	-14.56	-13.98	-16.07	-1.52	-2.09
17	-7947.03	-7942.34	-7965.53	18.50	23.19	-77.98	-76.26	-75.12	2.86	1.14
18	-7929.37	-7924.90	-7948.15	18.78	23.25	-17.66	-17.44	-17.38	0.28	0.05
19	-8021.03	-8016.05	-8039.23	18.21	23.18	91.66	91.15	91.09	-0.57	-0.07
20	-8066.06	-8060.04	-8085.94	19.88	25.90	45.04	43.99	46.71	1.67	2.72

Table 25S. **PM5** RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ).

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(M)	Δμ(L)	Δμ(Z)
1	0.0017	0.0006	0.0020	0.0010	256.29	256.38	256.38	0.14	0.27
2	0.0019	0.0007	0.0021	0.0009	264.59	264.65	264.57	0.05	0.16
3	0.0020	0.0006	0.0021	0.0010	254.96	254.81	254.90	0.12	0.14
4	0.0017	0.0006	0.0021	0.0010	229.10	229.03	229.01	0.14	0.04
5	0.0022	0.0007	0.0022	0.0010	264.67	264.50	264.49	0.23	0.24
6	0.0017	0.0006	0.0020	0.0010	216.00	215.90	215.94	0.12	0.08
7	0.0020	0.0007	0.0020	0.0010	209.55	209.34	209.49	0.08	0.30
8	0.0021	0.0007	0.0022	0.0010	250.20	250.28	250.09	0.14	0.24
9	0.0019	0.0006	0.0022	0.0010	280.37	280.27	280.26	0.11	0.20
10	0.0016	0.0006	0.0021	0.0009	227.95	227.80	227.75	0.20	0.18
11	0.0015	0.0006	0.0020	0.0009	239.76	239.88	239.72	0.13	0.21
12	0.0020	0.0008	0.0019	0.0009	207.84	207.88	207.79	0.20	0.23
13	0.0019	0.0007	0.0023	0.0009	198.63	198.42	198.43	0.29	0.09
14	0.0019	0.0007	0.0021	0.0010	157.97	157.85	157.91	0.09	0.22
15	0.0020	0.0007	0.0021	0.0009	145.55	145.70	145.48	0.08	0.26
16	0.0017	0.0006	0.0022	0.0009	152.14	152.11	152.07	0.12	0.11
17	0.0022	0.0007	0.0021	0.0009	178.06	178.02	177.91	0.16	0.17
18	0.0022	0.0008	0.0024	0.0010	163.41	163.31	163.24	0.18	0.31
19	0.0019	0.0006	0.0020	0.0009	203.35	203.19	203.22	0.16	0.15
20	0.0018	0.0007	0.0020	0.0010	143.81	143.87	143.62	0.19	0.29

Table 26S. **PM5** RMS errors for bond orders (B) and geometry gradients for non-hydrogen (%∇n) and hydrogen (%∇h) atoms.

Conf	B(L)	B(Z)	%∇n(L)	%∇h(L)	%∇n(Z)	%∇h(Z)
1	0.0001	0.0001	5.75	7.71	2.71	3.19
2	0.0001	0.0001	8.30	11.71	2.25	3.69
3	0.0001	0.0001	9.17	9.33	3.50	3.07
4	0.0001	0.0001	6.80	8.30	2.65	3.23
5	0.0001	0.0001	5.73	8.71	2.47	3.33
6	0.0001	0.0001	6.97	8.59	3.93	3.52
7	0.0001	0.0001	7.44	9.16	2.87	3.33
8	0.0001	0.0001	6.33	7.96	2.74	2.88
9	0.0001	0.0001	5.58	6.41	2.67	2.90
10	0.0001	0.0001	7.21	10.06	2.96	4.77
11	0.0001	0.0001	6.93	8.08	2.78	2.91
12	0.0001	0.0001	6.83	9.93	3.10	2.97
13	0.0001	0.0001	15.04	8.95	3.79	3.19
14	0.0001	0.0001	8.07	8.12	2.78	3.15
15	0.0001	0.0001	7.19	8.83	2.51	2.96
16	0.0001	0.0001	8.06	9.08	2.83	3.18
17	0.0001	0.0001	6.67	9.36	2.77	3.46
18	0.0001	0.0001	6.59	10.39	2.77	3.82
19	0.0001	0.0001	8.69	11.14	3.12	3.38
20	0.0001	0.0001	6.14	7.12	5.17	3.71

Table 27S. Calculation time, seconds, of LSCFF and MOZ6 for 20 insulin conformations (1247 atoms).

	MNDO		AM1		PM3		PM5	
Conf	LSCFF	MOZ6	LSCFF	MOZ6	LSCFF	MOZ6	LSCFF	MOZ6
1	97	47	79	56	101	65	103	67
2	102	47	100	56	100	69	103	72
3	107	47	105	54	119	64	108	63
4	98	46	101	60	105	72	104	65
5	105	47	100	61	114	68	112	66
6	108	50	102	61	110	68	114	74
7	105	49	103	59	110	70	119	72
8	104	49	111	55	109	93	105	69
9	93	48	102	59	123	66	106	68
10	92	50	90	60	107	66	107	67
11	99	56	93	54	126	72	116	66
12	92	51	115	59	128	106	114	70
13	112	53	117	66	116	77	119	71
14	95	50	112	71	109	70	109	64
15	109	51	113	69	112	104	116	68
16	109	45	110	59	99	74	110	62
17	101	51	106	62	105	73	116	70
18	104	48	103	64	101	79	114	66
19	112	48	108	62	108	66	109	69
20	95	53	106	58	119	72	120	67

Table 28S. **AM1** total (Et) and conformational (Ec) energies, kcal/mol, obtained with fast LSCFF (L), MOZ6 (Z) program settings and with LSCFR (R) conformational energies serving as target data, for 20 snapshots of insulin in water box (20058 atoms).

Conf	Et(L)	Et(Z)	Et(R)	Ec(L)	Ec(Z)	Ec(R)
1	-404467.42	-405305.17	-405151.41			
2	-404495.48	-405268.76	-405179.05	28.06	-36.42	27.64
3	-404546.25	-405335.70	-405234.02	50.78	66.94	54.97
4	-404824.53	-405602.16	-405500.66	278.28	266.46	266.63
5	-404448.30	-405247.27	-405136.15	-376.23	-354.89	-364.51
6	-404704.01	-405498.67	-405388.00	255.71	251.40	251.85
7	-404510.31	-405325.58	-405196.61	-193.70	-173.09	-191.39
8	-404738.91	-405515.10	-405423.65	228.60	189.52	227.05
9	-404848.71	-405600.25	-405530.38	109.80	85.15	106.72
10	-404800.34	-405592.55	-405488.73	-48.37	-7.70	-41.65
11	-404406.30	-405177.89	-405089.47	-394.04	-414.65	-399.26
12	-404655.40	-405394.91	-405338.04	249.09	217.02	248.57
13	-404283.66	-405046.53	-404969.93	-371.74	-348.38	-368.11
14	-404549.21	-405337.83	-405231.54	265.55	291.30	261.61
15	-404765.87	-405553.32	-405450.85	216.66	215.49	219.31
16	-404473.75	-405290.24	-405166.39	-292.12	-263.08	-284.46
17	-404709.18	-405487.69	-405395.24	235.43	197.45	228.85
18	-404333.07	-405105.24	-405020.05	-376.11	-382.45	-375.20
19	-404869.51	-405654.74	-405557.60	536.43	549.51	537.55
20	-404477.87	-405281.90	-405161.19	-391.64	-372.84	-396.41

Table 29S. **AM1** LSCFF (L), MOZ6 (Z) RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ) for 20 snapshots of insulin in water box (20058 atoms) with LSCFR (R) target data.

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(R)	Δμ(L)	Δμ(Z)
1	0.0016	0.0011	0.0010	0.0007	416.95	420.34	418.18	1.24	2.40
2	0.0016	0.0011	0.0010	0.0008	207.93	209.22	208.24	0.58	3.00
3	0.0016	0.0011	0.0010	0.0008	338.43	342.46	339.16	0.92	4.15
4	0.0016	0.0011	0.0010	0.0008	443.33	448.84	444.67	1.50	5.04
5	0.0016	0.0011	0.0010	0.0007	423.80	426.51	424.58	0.92	2.97
6	0.0016	0.0011	0.0010	0.0008	610.23	617.58	612.08	1.96	6.34
7	0.0016	0.0011	0.0010	0.0008	542.52	550.17	544.33	1.98	7.22
8	0.0016	0.0011	0.0010	0.0008	272.02	276.81	273.18	1.27	5.19
9	0.0016	0.0011	0.0010	0.0008	463.81	467.26	464.77	0.99	2.89
10	0.0016	0.0011	0.0010	0.0008	201.60	202.44	201.98	0.65	2.49
11	0.0016	0.0011	0.0010	0.0008	457.67	462.56	458.93	1.29	3.96
12	0.0016	0.0011	0.0010	0.0008	308.24	312.06	309.34	1.15	3.56
13	0.0016	0.0011	0.0010	0.0008	136.85	138.99	137.32	0.75	2.90
14	0.0016	0.0011	0.0010	0.0007	391.50	395.05	392.38	1.00	3.32
15	0.0016	0.0011	0.0010	0.0008	303.86	307.79	304.72	0.94	3.86
16	0.0017	0.0011	0.0009	0.0007	260.90	266.22	262.20	1.38	4.89
17	0.0016	0.0011	0.0010	0.0007	126.49	126.67	126.48	0.38	2.18
18	0.0016	0.0011	0.0010	0.0007	310.16	312.47	310.75	0.60	1.83
19	0.0016	0.0011	0.0010	0.0007	461.71	467.51	463.15	1.48	4.76
20	0.0016	0.0011	0.0010	0.0007	619.76	628.26	621.57	1.82	6.84

Table 30S. **AM1** calculation time, (T) seconds, and consumed memory, (M) MB, of LSCFF (L) MOZ6 (Z) and reference LSCFR (R) computations for 20 snapshots of insulin in water box (20058 atoms).

Conf	T(L)	T(Z)	T(R)	M(L)	M(Z)	M(R)
1	3914	11967	19502	238	816	188
2	3688	13577	20011	244	815	191
3	3487	12416	17985	249	816	194
4	3487	10044	18305	249	815	194
5	3537	9852	19263	253	816	196
6	3595	10076	17926	254	816	201
7	3594	11846	19733	257	816	198
8	4102	13581	19244	257	816	197
9	3992	12725	21447	256	815	198
10	4750	9954	19910	258	816	199
11	4758	11599	20857	258	816	199
12	4385	9739	19493	259	816	199
13	4151	12961	19054	260	816	199
14	4059	14027	18401	259	815	199
15	3748	12930	18774	261	816	200
16	3953	9321	20044	261	816	204
17	4193	12437	19490	262	816	200
18	4156	8999	18870	261	816	204
19	4661	12386	19789	262	816	205
20	4150	13193	18934	261	816	204

Table 31S. **MNDO** total (Et) and conformational (Ec) energies, kcal/mol, obtained with fast LSCFF (L), MOZ6 (Z) program settings and with LSCFR (R) conformational energies serving as target data, for 20 snapshots of insulin in water box (20058 atoms).

Conf	Et(L)	Et(Z)	Et(R)	Ec(L)	Ec(Z)	Ec(R)
1	-284378.38	-284824.45	-284863.95			
2	-285225.69	-285590.28	-285711.08	847.31	765.83	847.13
3	-284622.53	-285001.18	-285110.87	-603.16	-589.10	-600.21
4	-286157.56	-286529.40	-286637.44	1535.04	1528.22	1526.57
5	-284170.31	-284567.35	-284659.25	-1987.26	-1962.05	-1978.19
6	-285370.65	-285760.47	-285856.41	1200.34	1193.12	1197.15
7	-284700.44	-285112.82	-285187.73	-670.21	-647.64	-668.68
8	-284814.26	-285173.72	-285300.45	113.82	60.90	112.72
9	-286633.42	-286966.82	-287117.31	1819.16	1793.09	1816.86
10	-285115.44	-285501.07	-285604.31	-1517.98	-1465.74	-1513.00
11	-284914.97	-285278.78	-285399.79	-200.47	-222.29	-204.52
12	-285520.87	-285840.32	-286005.13	605.90	561.54	605.34
13	-284062.63	-284414.35	-284549.53	-1458.24	-1425.97	-1455.60
14	-285625.66	-286010.87	-286109.71	1563.03	1596.52	1560.18
15	-285683.52	-286061.01	-286170.02	57.86	50.14	60.31
16	-284243.76	-284653.15	-284735.79	-1439.76	-1407.86	-1434.24
17	-284553.93	-284923.19	-285040.89	310.17	270.03	305.11
18	-284129.09	-284488.70	-284616.82	-424.84	-434.48	-424.07
19	-285069.77	-285440.80	-285558.02	940.68	952.09	941.19
20	-284806.65	-285201.55	-285291.33	-263.12	-239.25	-266.68

Table 32S. **MNDO** LSCFF (L), MOZ6 (Z) RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ) for 20 snapshots of insulin in water box (20058 atoms) with LSCFR (R) target data.

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(R)	Δμ(L)	Δμ(Z)
1	0.0013	0.0009	0.0010	0.0008	409.09	412.41	410.02	0.94	2.61
2	0.0013	0.0009	0.0010	0.0008	204.52	205.81	204.76	0.48	3.14
3	0.0013	0.0009	0.0010	0.0008	330.86	334.88	331.40	0.68	4.40
4	0.0013	0.0009	0.0010	0.0008	435.24	440.64	436.27	1.16	5.27
5	0.0013	0.0009	0.0010	0.0008	419.62	422.43	420.22	0.70	3.23
6	0.0013	0.0009	0.0010	0.0008	595.67	602.99	597.07	1.50	6.74
7	0.0013	0.0009	0.0011	0.0008	525.41	532.92	526.77	1.50	7.50
8	0.0013	0.0009	0.0010	0.0008	259.93	264.51	260.81	0.96	5.30
9	0.0013	0.0009	0.0010	0.0008	454.77	458.13	455.50	0.77	3.07
10	0.0013	0.0009	0.0010	0.0008	204.06	204.94	204.31	0.47	2.56
11	0.0013	0.0009	0.0010	0.0008	448.76	453.63	449.71	0.97	4.22
12	0.0013	0.0009	0.0010	0.0008	302.91	306.62	303.71	0.85	3.78
13	0.0013	0.0009	0.0010	0.0008	140.35	142.35	140.67	0.57	2.95
14	0.0013	0.0009	0.0010	0.0008	383.47	387.08	384.16	0.81	3.61
15	0.0013	0.0009	0.0011	0.0008	299.26	303.24	299.91	0.74	4.12
16	0.0013	0.0009	0.0010	0.0008	250.84	256.08	251.86	1.11	5.13
17	0.0013	0.0009	0.0010	0.0008	126.94	127.09	126.90	0.29	2.24
18	0.0013	0.0009	0.0010	0.0008	303.74	306.05	304.15	0.43	2.03
19	0.0013	0.0009	0.0010	0.0008	445.47	451.28	446.63	1.21	5.08
20	0.0013	0.0009	0.0010	0.0008	599.35	607.80	600.74	1.41	7.19

Table 33S. **MNDO** calculation time, (T) seconds, and consumed memory, (M) MB, of LSCFF (L) MOZ6 (Z) and reference LSCFR (R) computations for 20 snapshots of insulin in water box (20058 atoms).

Conf	T(L)	T(Z)	T(R)	M(L)	M(Z)	M(R)
1	3720	13486	19402	224	816	174
2	3585	9631	19023	229	815	176
3	3539	10341	18246	234	816	179
4	3644	9468	18864	234	815	178
5	3785	8651	18906	237	816	180
6	3634	9330	19439	239	816	181
7	3721	9758	18625	241	816	182
8	3542	9564	18014	242	816	182
9	3946	9364	18931	241	815	181
10	4151	10118	18276	243	816	182
11	3615	12581	18369	242	816	181
12	3760	10429	18700	243	816	183
13	3676	8915	18425	244	816	183
14	3857	10313	18299	243	815	182
15	3965	11404	18858	246	816	183
16	3808	9566	18479	245	816	183
17	3868	9397	19163	246	816	184
18	3506	8859	18222	245	816	183
19	3063	9590	18452	247	816	184
20	3748	10013	19157	246	816	183

Table 34S. **PM3** total (Et) and conformational (Ec) energies, kcal/mol, obtained with fast LSCFF (L), MOZ6 (Z) program settings and with LSCFR (R) conformational energies serving as target data, for 20 snapshots of insulin in water box (20058 atoms).

Conf	Et(L)	Et(Z)	Et(R)	Ec(L)	Ec(Z)	Ec(R)
1	-367019.46	-367182.95	-367052.98			
2	-367133.62	-367237.06	-367165.19	114.17	54.10	112.21
3	-367393.69	-367509.15	-367424.93	260.07	272.09	259.74
4	-367026.39	-367139.23	-367055.84	-367.30	-369.92	-369.09
5	-367083.89	-367208.87	-367116.01	57.50	69.65	60.17
6	-367192.53	-367315.56	-367224.05	108.65	106.69	108.04
7	-367070.02	-367213.05	-367103.27	-122.51	-102.52	-120.79
8	-367058.99	-367165.46	-367089.78	-11.04	-47.59	-13.49
9	-367049.57	-367138.03	-367080.97	-9.42	-27.42	-8.81
10	-367058.30	-367175.99	-367090.64	8.73	37.96	9.67
11	-367181.16	-367288.30	-367213.71	122.87	112.31	123.07
12	-367039.54	-367112.78	-367070.15	-141.63	-175.52	-143.56
13	-366791.49	-366886.29	-366824.47	-248.05	-226.49	-245.69
14	-367121.65	-367239.85	-367153.16	330.15	353.56	328.70
15	-367046.57	-367161.67	-367078.33	-75.08	-78.18	-74.83
16	-367372.60	-367515.13	-367407.67	326.03	353.46	329.34
17	-367266.81	-367370.78	-367297.74	-105.79	-144.34	-109.92
18	-367255.30	-367356.19	-367288.04	-11.52	-14.59	-9.71
19	-367158.51	-367268.25	-367189.63	-96.79	-87.94	-98.40
20	-367057.87	-367190.73	-367090.21	-100.64	-77.51	-99.42

Table 35S. **PM3** LSCFF (L), MOZ6 (Z) RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ) for 20 snapshots of insulin in water box (20058 atoms) with LSCFR (R) target data.

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(R)	Δμ(L)	Δμ(Z)
1	0.0003	0.0002	0.0012	0.0008	412.47	414.47	412.76	0.33	2.12
2	0.0003	0.0002	0.0012	0.0008	210.53	210.56	210.56	0.09	3.27
3	0.0003	0.0002	0.0012	0.0008	336.24	339.59	336.39	0.18	4.75
4	0.0003	0.0002	0.0012	0.0008	439.19	443.30	439.49	0.32	5.08
5	0.0003	0.0002	0.0012	0.0008	421.28	422.68	421.51	0.26	2.71
6	0.0003	0.0002	0.0011	0.0008	600.48	606.41	600.80	0.35	7.03
7	0.0003	0.0002	0.0012	0.0008	534.63	541.36	534.98	0.39	8.25
8	0.0003	0.0002	0.0011	0.0008	266.81	270.92	266.95	0.19	6.40
9	0.0003	0.0002	0.0012	0.0008	459.43	461.37	459.55	0.19	2.73
10	0.0003	0.0002	0.0012	0.0008	198.59	198.59	198.72	0.20	3.20
11	0.0003	0.0002	0.0011	0.0008	451.07	454.79	451.31	0.24	4.33
12	0.0003	0.0002	0.0012	0.0008	305.58	308.54	305.82	0.26	4.11
13	0.0003	0.0002	0.0012	0.0008	130.30	132.19	130.42	0.13	3.34
14	0.0003	0.0002	0.0011	0.0008	391.31	393.78	391.50	0.19	2.90
15	0.0003	0.0002	0.0012	0.0008	302.65	305.39	302.83	0.20	3.63
16	0.0003	0.0002	0.0011	0.0008	259.39	263.30	259.70	0.34	4.91
17	0.0003	0.0002	0.0012	0.0008	121.58	121.96	121.59	0.05	2.74
18	0.0003	0.0002	0.0011	0.0008	305.76	307.48	305.82	0.09	1.82
19	0.0003	0.0002	0.0012	0.0008	461.71	465.87	461.96	0.26	4.55
20	0.0003	0.0002	0.0011	0.0008	611.24	618.17	611.48	0.25	6.78

Table 36S. **PM3** calculation time, (T) seconds, and consumed memory, (M) MB, of LSCFF (L) MOZ6 (Z) and reference LSCFR (R) computations for 20 snapshots of insulin in water box (20058 atoms).

Conf	T(L)	T(Z)	T(R)	M(L)	M(Z)	M(R)
1	4841	18499	21179	263	816	214
2	5087	21513	21170	269	815	218
3	5372	24194	21422	275	816	225
4	5366	19558	20222	276	815	225
5	6002	21619	20842	280	816	228
6	6673	19692	20259	281	816	232
7	6505	18132	21353	284	816	234
8	5644	17263	20432	284	816	234
9	5953	19956	23467	283	815	233
10	6360	18895	20898	286	816	235
11	5321	15159	20604	285	816	235
12	5536	17015	21882	286	816	235
13	5408	19031	18558	287	816	240
14	5799	15412	22806	286	815	235
15	5873	19846	22039	288	816	240
16	5768	18640	18917	289	816	240
17	5837	16232	21867	290	816	237
18	6189	18975	22044	289	816	244
19	6736	22998	20380	290	816	245
20	6208	18069	20680	289	816	244

Table 37S. **PM5** total (Et) and conformational (Ec) energies, kcal/mol, obtained with fast LSCFF (L), MOZ6 (Z) program settings and with LSCFR (R) conformational energies serving as target data, for 20 snapshots of insulin in water box (20058 atoms).

Conf	Et(L)	Et(Z)	Et(R)	Ec(L)	Ec(Z)	Ec(R)
1	-345557.48	-354503.51	-355406.56			
2	-345811.55	-354653.33	-355593.02	254.07	149.83	186.46
3	-345840.60	-354748.49	-355680.79	29.05	95.16	87.77
4	-345946.36	-354761.01	-355683.11	105.77	12.52	2.32
5	-345340.39	-354239.53	-355165.90	-605.97	-521.48	-517.21
6	-345795.29	-354680.43	-355605.41	454.89	440.90	439.51
7	-345675.22	-354608.49	-355525.89	-120.07	-71.94	-79.52
8	-345603.06	-354511.10	-355445.40	-72.16	-97.39	-80.49
9	-346007.91	-354813.07	-355758.04	404.85	301.98	312.65
10	-345652.19	-354557.18	-355489.02	-355.72	-255.90	-269.03
11	-345595.11	-354442.55	-355380.81	-57.08	-114.62	-108.21
12	-345728.82	-354568.14	-355526.26	133.70	125.59	145.45
13	-345193.43	-354081.20	-355034.76	-535.39	-486.95	-491.50
14	-345801.74	-354675.88	-355601.62	608.31	594.68	566.86
15	-345881.01	-354776.55	-355704.53	79.28	100.67	102.91
16	-345604.73	-354547.17	-355461.60	-276.29	-229.38	-242.93
17	-345646.20	-354561.45	-355505.72	41.47	14.28	44.12
18	-345453.01	-354326.81	-355269.13	-193.19	-234.63	-236.58
19	-345867.56	-354773.57	-355710.20	414.55	446.76	441.07
20	-345508.17	-354420.91	-355333.68	-359.39	-352.66	-376.52

Table 38S. **PM5** LSCFF (L), MOZ6 (Z) RMS errors for partial atomic charges on non-hydrogen (Qn) and hydrogen (Qh) atoms, in electron units, total dipole moments (μ), in units of Debye, and dipole RMS errors (Δμ) for 20 snapshots of insulin in water box (20058 atoms) with LSCFR (R) target data.

Conf	Qn(L)	Qh(L)	Qn(Z)	Qh(Z)	μ(L)	μ(Z)	μ(R)	Δμ(L)	Δμ(Z)
1	0.0158	0.0109	0.0013	0.0009	432.23	442.40	441.85	9.63	1.05
2	0.0157	0.0109	0.0013	0.0009	223.76	229.65	229.58	8.01	2.10
3	0.0158	0.0109	0.0013	0.0009	353.23	363.14	361.07	9.29	2.89
4	0.0156	0.0108	0.0013	0.0009	459.75	472.11	469.63	11.16	3.20
5	0.0157	0.0109	0.0013	0.0009	437.40	444.72	444.12	8.31	1.81
6	0.0157	0.0109	0.0013	0.0009	639.22	656.99	653.86	15.49	4.09
7	0.0158	0.0109	0.0013	0.0009	570.93	588.34	584.53	15.81	5.14
8	0.0158	0.0109	0.0013	0.0009	292.14	306.26	303.92	12.63	4.05
9	0.0156	0.0108	0.0013	0.0009	485.24	496.69	495.77	10.83	1.59
10	0.0158	0.0109	0.0013	0.0009	197.81	200.05	200.10	3.59	2.30
11	0.0157	0.0109	0.0013	0.0009	473.31	485.78	483.95	10.84	2.45
12	0.0157	0.0109	0.0013	0.0009	317.33	325.75	324.07	7.33	2.64
13	0.0158	0.0109	0.0013	0.0009	131.82	135.46	134.08	5.12	2.26
14	0.0157	0.0109	0.0012	0.0009	408.90	418.05	416.86	10.06	1.59
15	0.0157	0.0109	0.0013	0.0009	316.05	325.98	324.37	9.59	2.28
16	0.0158	0.0109	0.0012	0.0009	280.92	295.60	293.50	13.50	2.97
17	0.0158	0.0109	0.0013	0.0009	121.21	121.14	120.71	3.77	1.77
18	0.0157	0.0109	0.0012	0.0009	323.27	329.80	328.92	6.49	1.20
19	0.0158	0.0109	0.0013	0.0009	497.25	514.51	512.38	16.08	2.48
20	0.0157	0.0109	0.0012	0.0009	659.61	682.68	678.64	19.56	4.13

Table 39S. **PM5** calculation time, (T) seconds, and consumed memory, (M) MB, of LSCFF (L) MOZ6 (Z) and reference LSCFR (R) computations for 20 snapshots of insulin in water box (20058 atoms).

Conf	T(L)	T(Z)	T(R)	M(L)	M(Z)	M(R)
1	5529	13703	25658	248	816	199
2	4570	13556	21395	254	815	202
3	5899	15054	22030	259	816	205
4	6075	14432	19822	260	815	205
5	5301	14714	24280	264	816	218
6	5438	15048	24348	265	816	210
7	5022	21585	21637	268	816	224
8	5636	14558	24849	271	816	228
9	5837	10552	23032	267	815	223
10	5113	16175	21445	269	816	224
11	4892	11379	24370	276	816	232
12	4955	14127	22394	273	816	229
13	6231	13936	23858	271	816	225
14	6481	14667	20595	273	815	233
15	5919	11701	23647	275	816	229
16	6018	14238	25055	283	816	238
17	6163	14229	23518	280	816	234
18	5364	15678	25070	283	816	238
19	5362	15938	19794	288	816	242
20	5405	12495	23498	275	816	230