

Supporting Information for

**Determination of Electrostatic Parameters for a
Polarizable Force Field Based on the Classical Drude
Oscillator**

Victor M. Anisimov¹, Guillaume Lamoureux², Igor V. Vorobyov¹, Niu Huang^{1†}, Benoît Roux³,

Alexander D. MacKerell, Jr.*¹

¹ Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD,
USA.,

² Département de physique, Université de Montréal, C.P. 6128, succ. centre-ville, Montréal, Québec,
Canada H3C 3J7

³ Department of Biochemistry, Weill Medical College of Cornell University, New York, NY, USA

*Corresponding author phone: (410)706-7442; fax: (410)706-5017; e-mail: amackere@rx.umaryland.edu.
Corresponding author address: 20 Penn Street, Baltimore, MD 21201.

†Current address: Department of Biopharmaceutical Sciences, UCSF, San Francisco, CA USA.

Appendix. Scaling and rounding strategy

The average ratios of calculated to experimental dipole moments at the B3LYP/aug-cc-pVDZ and B3LYP/cc-pVDZ levels for compounds listed in Table 1, excluding water, were 1.05 and 0.94, respectively. In principle, these factors could be used for the scaling of partial atomic charges after the electrostatic parameter fitting procedure. Moreover, the atomic charges may need to be scaled since polarizability scaling, as discussed in the main text, changes the molecular dipole thereby requiring adjustment of the final charges to reproduce the gas-phase dipole. It is also desirable to round off the obtained charges and molecular polarizabilities to, for example, three digits after the decimal points, as additional figures will not significantly impact the molecular properties. However, rounding off and charge scaling introduce an error in the formal molecular charge, where the sum of atomic charges is not equal to the total molecular charge. This error should be minimized and possibly equally distributed over all atoms. Because of rounding constraints it is not feasible to distribute the charge error in equal increments to all atoms. Instead by taking into account an equivalence constraint applied to selected atoms during fitting, the total charge error will be minimized, with the charge difference assigned to the first non-equivalent atom in the list.

The procedure for scaling and rounding off corrections is performed as follows. Atomic $q(A)$ and Drude $q_D(A)$ charges are obtained from the FITCHARGE procedure. Then the atomic polarizability is calculated from the Drude charges according to equation (1). Next, the polarizabilities are scaled by the factor $p = 0.724$ or 0.87 if the B3LYP/aug-cc-pVDZ or B3LYP/cc-pVDZ calculations, respectively, are used for obtaining QM ESP maps (see main text for more information). Then the scaled polarizabilities are rounded to three digits after the decimal point producing the final scaled atomic polarizabilities, which are the Drude model parameters:

$$\alpha'(A) = \text{round}(\alpha(A) \cdot p) \quad (1S)$$

The second part of the scaling and rounding procedure derives the final atomic charges. Here the Drude charges are calculated from the Drude polarizability $\alpha'(A)$:

$$q'_D(A) = \sqrt{k_D \cdot \alpha'(A)} \quad (2S)$$

Since the polarizability scaling changes the Drude charges initially produced by the FITCHARGE routine, we compensate for the introduced error by recalculation of atomic core charges $q_c(A)$ in order to retain the effective atomic charges $q(A)$:

$$q'_c(A) = q_c(A) + q_D(A) - q'_D(A) \quad (3S)$$

The obtained atomic core and Drude charges create a dipole moment μ_{emp} that slightly differs from the dipole obtained directly from the charge fitting to QM data. Since the final charges should reproduce the target gas-phase dipole moment μ_{target} , the effective atomic charges $q(A)$ need to be scaled by the following factor:

$$c = \frac{\mu_{target}}{\mu_{emp}} \quad (4S)$$

The final effective atomic charges $q'(A)$ are obtained through applying the charge scale factor, c , and rounded to three digits after the decimal point

$$q'(A) = round(q(A) \cdot c) \quad (5S)$$

Since we do not want the polarizability to be changed during this operation, we preserve the Drude charges, which are obtained from the polarizability scaling, and recalculate only the atomic core charges:

$$q'_c(A) = q'(A) - q'_D(A) \quad (6S)$$

The charges $q'_c(A)$ and $q'_d(A)$ are final results of the charge fitting procedure. As mentioned above, the total molecular charge is preserved by adding the small error accumulated after charge rounding to the first non-equivalent atom. The rounding error was 0.001e in the case of the cytosine base.

A number of points should be considered when performing charge scaling. Scaling cannot be applied to ions, such as dimethylphosphate anion (DMP^-), since the total molecular charge will not be conserved,

along with the dipole moment for ionic species being dependent on the molecular orientation.¹ The scaling factors presented in Table 1 are not fully systematic, which might argue against using a uniform scaling factor. Also, the scaling factor cannot be applied if experimental values of dipole moment are not available or of low accuracy. In the latter case very high-level QM calculations (e.g. CISD(T) with large basis sets) can be used for the derivation of the scaling factors for atomic charges. Charge scaling is also not recommended for molecular species with dipole moments less than 0.5 Debye (e.g. alkanes, see Table 1), since capabilities of charge fitting to identify unique atomic charges is essentially diminished for molecules with small dipole moments.

Table 1S. Comparison between QM polarizabilities and polarizabilities obtained using scaled and corrected ahp values.

Molecule		Polarizabilities (\AA^3)		
		QM	empirical	diff. (%)
ethane	C_2H_6	4.31	4.44	3.16
propane	C_3H_8	6.14	6.28	2.21
isobutane	C_4H_{10}	7.98	8.11	1.64
ethanol	$\text{C}_2\text{H}_6\text{O}$	5.04	5.08	0.79
methanol	CH_4O	3.19	3.25	1.76
dimethylether	$\text{C}_2\text{H}_6\text{O}$	5.09	5.08	-0.20
tetrahydrofuran	$\text{C}_4\text{H}_8\text{O}$	7.81	7.98	2.16
cyclohexane	C_6H_{12}	10.68	11.01	3.06
diethylether	$\text{C}_4\text{H}_{10}\text{O}$	8.87	8.75	-1.30
propanol	$\text{C}_3\text{H}_8\text{O}$	6.85	6.92	0.96
ribose	$\text{C}_5\text{H}_{10}\text{O}_5$	12.20	12.36	1.29
acetone	$\text{C}_3\text{H}_6\text{O}$	6.37	6.37	0.00
acetic acid	$\text{C}_2\text{H}_4\text{O}_2$	5.14	5.17	0.56
benzene	C_6H_6	10.35	10.43	0.81
toluene	C_7H_8	12.39	12.27	-0.96
dimethylamine	$\text{C}_2\text{H}_7\text{N}$	5.79	5.80	0.10
pyridine	$\text{C}_5\text{H}_5\text{N}$	9.55	9.73	1.88
adenine	$\text{C}_5\text{H}_5\text{N}_5$	14.44	15.05	4.22
guanine	$\text{C}_5\text{H}_5\text{N}_5\text{O}$	15.40	15.68	1.81
cytosine	$\text{C}_4\text{H}_5\text{N}_3\text{O}$	11.60	11.12	-4.12
thymine	$\text{C}_5\text{H}_6\text{N}_2\text{O}_2$	12.44	12.11	-2.67
trimethylphosphate	Me_3PO_4	11.23	11.21	-0.15

QM molecular polarizabilities were calculated at the B3LYP/aug-cc-pVDZ level using MP2/6-31G(d) optimized geometries. Empirical molecular polarizabilities were calculated using united-atom corrected Miller ahp values (see text).

Table 2S. Effect of the initial charge selection on the example of the cytosine base

(a) Fitted atomic charges

atom type	CHARMM27		NBO		Mulliken	
	initial	final	initial	final	initial	final
N1	-0.500	-0.350	-0.650	-0.500	-0.077	0.016
H1	0.370	0.202	0.423	0.233	0.095	0.132
C6	0.050	-0.044	0.097	0.030	0.164	0.040
H6	0.170	0.266	0.226	0.286	0.014	0.136
C2	0.520	0.600	0.851	0.874	0.174	0.244
O2	-0.490	-0.545	-0.641	-0.630	-0.275	-0.458
N3	-0.660	-0.602	-0.642	-0.687	-0.248	-0.344
C4	0.650	0.610	0.491	0.565	0.101	0.056
N4	-0.750	-0.708	-0.801	-0.625	-0.050	-0.158
H41	0.350	0.369	0.405	0.352	0.095	0.185
H42	0.350	0.369	0.405	0.352	0.095	0.185
C5	-0.130	-0.212	-0.399	-0.320	-0.058	-0.158
H5	0.070	0.045	0.235	0.070	-0.032	0.124

(b) Fitted atomic polarizabilities

atom type	initial	CHARMM27	NBO	Mulliken
N1	1.470	1.105	0.965	1.175
C6	1.731	1.227	1.281	1.328
C2	1.346	1.078	1.080	1.081
O2	0.566	0.444	0.478	0.349
N3	1.025	0.774	0.658	0.831
C4	1.346	0.870	0.866	0.873
N4	1.855	1.223	1.223	1.222
C5	1.731	1.143	1.128	1.145

(c) Interaction energies with the water molecule (kcal/mol)

Orientation	Interaction energies			
	QM LMP2	DRUDE calculations. Initial charges		
		CHARMM27	NBO	Mulliken
H1	-5.83	-5.32	-5.50	-5.06
O2_1	-7.01	-7.32	-7.69	-7.04
O2_2	-9.73	-9.17	-9.61	-8.46
N3	-8.20	-6.60	-6.73	-5.74
H41	-5.51	-4.44	-4.31	-3.14
H42	-5.43	-5.20	-5.15	-3.67
H5	-2.37	-2.14	-2.25	-2.62
H6	-2.83	-3.68	-3.86	-3.02

NBO and Mulliken charges were calculated at the B3LYP/aug-cc-pVDZ//MP2(fc)/6-31G(d) level. More details on the parameters of charge and polarizability fitting can be found in the footnote for Table 3S and in the main text. More details on the calculation of the cytosine-water interactions can be found in the footnote of Table 6S.

Table 3S. Effect of constraints on the fitted values of atomic charges and polarizabilities for selected model compounds

Tetrahydrofuran (THF)			Dimethylphosphate (DMP)			Ethanol (ETOH)					
	initial	free fit restrained		initial	free fit restrained		initial	free fit restrained			
Charges											
O4'	-0.500	-0.568	-0.394	P1	1.500	0.978	1.326	C1	0.050	0.494	0.100
C4'	0.070	0.455	0.117	O3	-0.780	-0.740	-0.938	O1	-0.660	-0.573	-0.490
C3'	-0.180	0.021	-0.144	O4	-0.780	-0.740	-0.938	HO1	0.430	0.304	0.325
C2'	-0.180	0.021	-0.144	O1	-0.570	-0.422	-0.500	H11	0.090	-0.065	0.054
C1'	0.070	0.455	0.117	O2	-0.570	-0.422	-0.500	H12	0.090	-0.065	0.054
H11'	0.090	-0.068	0.037	C1	-0.170	-0.100	-0.136	C2	-0.270	-0.278	-0.250
H12'	0.090	-0.068	0.037	H11	0.090	0.091	0.137	H21	0.090	0.061	0.069
H21'	0.090	-0.028	0.075	H12	0.090	0.091	0.137	H22	0.090	0.061	0.069
H22'	0.090	-0.028	0.075	H13	0.090	0.091	0.137	H23	0.090	0.061	0.069
H31'	0.090	-0.028	0.075	C2	-0.170	-0.100	-0.136				
H32'	0.090	-0.028	0.075	H21	0.090	0.091	0.137				
H41'	0.090	-0.068	0.037	H22	0.090	0.091	0.137				
H42'	0.090	-0.068	0.037	H23	0.090	0.091	0.137				
Polarizabilities											
O4'	0.637	0.018	0.575	P1	2.063	0.000	2.277	C1	1.835	3.874	1.895
C4'	1.835	2.537	1.904	O3	0.858	2.113	0.973	O1	1.024	0.261	0.904
C3'	1.835	1.695	1.995	O4	0.858	2.113	0.973	C2	2.222	0.315	2.000
C2'	1.835	1.695	1.995	O1	0.637	2.480	0.742				
C1'	1.835	2.537	1.904	O2	0.637	2.480	0.742				
				C1	2.222	0.800	1.893				
				C2	2.222	0.800	1.893				
RMSE	7.9E-04	9.2E-04	RMSE		8.0E-04	1.6E-03		1.0E-03	1.4E-03		

All atom names correspond to those used in the CHARMM27 topology files (downloadable from <http://www.pharmacy.umaryland.edu/faculty/amackere/>). The initial charges are CHARMM27 charges, the initial polarizabilities are Miller's ahp values² summed to heavy atoms (see text). The fitting was performed to the B3LYP/aug-cc-pVDZ response electrostatic potential maps using MP2/6-31+G(d) for the DMP⁻ or MP2/6-31G(d) geometries for the THF and ETOH. The scheme for the placement of the ESP grid points and perturbation ions is described in the text. The gg and tg conformers of the DMP⁻ and trans and gauche(+) conformers of the ETOH were used for fitting. Fitting to the same charge and polarizability values was imposed for chemically equivalent atoms. No other restraints were used for the free fitting. The parabolic RESP restraints with the weighting factor of 10⁻⁵ Å⁻² were imposed to all charges and polarizabilities in the restrained fitting. Additionally, the flat well potential with the half-width 0.1e was used for atomic charges and polarizabilities. The fitted atomic charges and polarizabilities values were not scaled. The root mean square errors (RMSE) are in the potential units (e/Å).

Table 4S. Initial and final (fitted and scaled) values of atomic charges and polarizabilities for the model compounds:

(a) Nucleic bases

Cytosine (CYT)		Thymine (THY)		Adenine (ADE)		Guanine (GUA)		
	initial	final		initial	final		initial	final
charges								
N1	-0.500	-0.350	N1	-0.800	-0.660	C5	0.280	0.145
H1	0.370	0.202	H1	0.460	0.347	N7	-0.710	-0.531
C6	0.050	-0.044	C6	0.170	0.259	C8	0.340	0.259
H6	0.170	0.266	H6	0.170	0.191	H8	0.120	0.120
C2	0.520	0.600	C2	0.510	0.597	N9	-0.370	-0.381
O2	-0.490	-0.545	O2	-0.410	-0.505	H9	0.320	0.273
N3	-0.660	-0.602	N3	-0.460	-0.342	N1	-0.740	-0.546
C4	0.650	0.610	H3	0.360	0.211	C2	0.500	0.320
N4	-0.750	-0.708	C4	0.500	0.449	H2	0.130	0.060
H41	0.370	0.369	O4	-0.450	-0.404	N3	-0.750	-0.615
H42	0.330	0.369	C5	-0.150	-0.152	C4	0.430	0.435
C5	-0.130	-0.212	C5M	-0.110	-0.204	C6	0.460	0.357
H5	0.070	0.045	H51	0.070	0.071	N6	-0.770	-0.542
			H52	0.070	0.071	H61	0.380	0.323
			H53	0.070	0.071	H62	0.380	0.323
							C8	0.250
							H8	0.160
								0.133
polarizabilities								
N1	1.470	1.105	N1	1.470	0.963	C5	1.566	1.025
C6	1.731	1.227	C6	1.731	1.240	N7	1.025	0.833
C2	1.346	1.078	C2	1.346	0.921	C8	1.731	1.143
O2	0.566	0.444	O2	0.566	0.347	N9	1.345	1.077
N3	1.025	0.774	N3	1.470	0.966	N1	1.025	0.657
C4	1.346	0.870	C4	1.346	1.080	C2	1.731	1.373
N4	1.855	1.223	O4	0.566	0.477	N3	1.025	0.756
C5	1.731	1.143	C5	1.346	0.878	C4	1.566	1.176
			C5M	2.212	1.459	C6	1.346	0.872
						N6	1.855	1.214
							C5	1.566
							N7	1.025
							C8	1.731
								1.143

Table 4S, continued.

(b) Phosphodiester backbone model compounds

Tetrahydrofuran (THF)		Dimethylphosphate (DMP)				Ethanol (ETOH)	
		initial	final	initial	final	initial	final
Charges				Charges			
O4'	-0.500	-0.350	P1	1.500	1.326	C1	0.050
C4'	0.070	0.105	O3	-0.780	-0.938	O1	-0.660
C3'	-0.180	-0.130	O4	-0.780	-0.938	HO1	0.430
C2'	-0.180	-0.130	O1	-0.570	-0.500	H11	0.090
C1'	0.070	0.105	O2	-0.570	-0.500	H12	0.090
H11'	0.090	0.033	C1	-0.170	-0.136	C2	-0.270
H12'	0.090	0.033	H11	0.090	0.137	H21	0.090
H21'	0.090	0.067	H12	0.090	0.137	H22	0.090
H22'	0.090	0.067	H13	0.090	0.137	H23	0.090
H31'	0.090	0.067	C2	-0.170	-0.136		
H32'	0.090	0.067	H21	0.090	0.137		
H41'	0.090	0.033	H22	0.090	0.137		
H42'	0.090	0.033	H23	0.090	0.137		
Polarizabilities				Polarizabilities			
O4'	0.637	0.417	P1	2.063	1.648	C1	1.835
C4'	1.835	1.379	O3	0.858	0.705	O1	1.024
C3'	1.835	1.444	O4	0.858	0.705	C2	2.222
C2'	1.835	1.444	O1	0.637	0.537		
C1'	1.835	1.379	O2	0.637	0.537		
			C1	2.222	1.370		
			C2	2.222	1.370		

All atom names correspond to those used in the CHARMM27 topology files, which can be obtained from http://www.pharmacy.umaryland.edu/faculty/amackere/force_fields.htm. The initial charges are CHARMM27 charges, the initial polarizabilities are “united atom” corrected Miller’s ahp values² (see text). The fitting was performed to the B3LYP/aug-cc-pVDZ perturbed electrostatic potentials using MP2/6-31+G(d) for the DMP⁻ or MP2/6-31G(d) geometries for the THF and ETOH. The scheme for the placement of the ESP grid points and perturbation ions is described in the text. The gg and tg conformers of the DMP⁻ and trans and gauche(+) conformers of the ETOH were used for fitting. Fitting to the same charge and polarizability values was imposed for chemically equivalent atoms. No other restraints were used for the free fitting. The parabolic RESP restraints with the weighting factor of 10⁻⁵ Å⁻² were imposed to all charges and polarizabilities in the restrained fitting. Additionally, the flat well potential with the half-width 0.1e was used for atomic charges and polarizabilities. Final values of polarizabilities were scaled by 0.724 (see text) following which the charges were scaled for all compounds but DMP to reproduce the experimental or B3LYP/aug-cc-pVDZ gas-phase dipole moment.

Table 5S. Base pairing interaction energies (kcal/mol).

Orientation	QM¹	DRUDE²	DRUDE–QM³	CH27⁴	CH27–QM⁵
ATRH	-11.75	-11.35	0.40	-12.66	-0.91
ATRWC	-11.77	-10.33	1.44	-12.07	-0.30
ATH	-8.86	-11.45	-2.60	-12.93	-4.08
ATWC	-8.22	-10.48	-2.27	-12.35	-4.13
AC1	-11.18	-11.20	-0.02	-12.87	-1.69
AC2	-10.49	-11.47	-0.99	-12.63	-2.14
GA1	-12.50	-12.83	-0.33	-13.93	-1.43
GA2	-9.42	-9.15	0.27	-11.11	-1.69
GA3	-10.60	-12.25	-1.65	-12.59	-1.99
GA4	-10.27	-10.45	-0.18	-11.79	-1.52
GT1	-8.95	-12.67	-3.72	-12.96	-4.01
GT2	-9.56	-12.30	-2.75	-12.48	-2.92
GCWC	-18.47	-22.59	-4.12	-24.36	-5.89
GC1	-10.18	-12.28	-2.10	-15.01	-4.82
TC1	-9.26	-8.04	1.22	-9.86	-0.60
TC2	-9.17	-8.25	0.93	-10.31	-1.13
GG1	-16.74	-21.54	-4.79	-21.33	-4.59
GG3	-10.16	-15.93	-5.77	-18.22	-8.07
GG4	-9.09	-10.32	-1.23	-11.81	-2.72
AA1	-11.72	-9.37	2.35	-11.31	0.41
AA2	-10.35	-8.86	1.48	-10.64	-0.29
AA3	-9.01	-7.96	1.04	-9.88	-0.87
TT1	-6.13	-9.32	-3.19	-9.62	-3.50
TT2	-5.93	-9.57	-3.64	-10.03	-4.10
TT3	-6.68	-9.06	-2.38	-9.22	-2.54
CC	-12.35	-15.38	-3.03	-17.31	-4.96
AAD⁶		2.07		2.74	
RMSE		2.14		1.97	

¹LMP2/cc-pVQZ energy calculation based on MP2/6-31G(d) all-atom optimized geometries of the base pairs ³;

²Interaction energy calculation based on fully optimized geometry of base pairs by classical Drude oscillator polarizable force field;

³DRUDE – LMP2 difference in interaction energy of the DNA bases;

⁴CHARMM27 interaction energy based on CHARMM27 fully optimized geometry of the base pairs;

⁵CHARMM27 – LMP2 difference in interaction energy of the DNA bases.

⁶AAD – average absolute difference.

Table 6S. Base - water interactions.¹

Orientation	R _{min} (Å)			Energy (kcal/mol)		
	QM ²	Drude ³	CH27 ⁴	QM ⁵	Drude	CH27
Cyt-H1	1.91	1.78	1.84	-5.83	-5.32	-6.43
Cyt-O2'	2.02	1.84	1.79	-7.01	-7.32	-8.45
Cyt-O2"	1.84	1.76	1.72	-9.73	-9.17	-10.37
Cyt-N3	1.98	2.02	1.88	-8.20	-6.60	-9.71
Cyt-H41	1.93	2.00	1.86	-5.51	-4.44	-5.81
Cyt-H42	2.02	2.02	1.92	-5.43	-5.20	-6.00
Cyt-H5	2.37	2.50	2.45	-2.37	-2.14	-2.84
Cyt-H6	2.27	2.34	2.35	-2.83	-3.68	-4.11
AD⁶	0.01	0.07		-0.38	0.85	
AAD	0.09	0.11		0.67	0.85	
RMSE	0.10	0.10		0.71	0.45	
Gua-H1	1.94	1.94	1.89	-8.62	-5.73	-7.21
Gua-O6'	1.88	1.88	1.74	-7.43	-7.97	-9.94
Gua-O6"	2.05	2.00	1.80	-3.58	-5.07	-5.47
Gua-N7	2.04	2.04	1.95	-9.79	-6.50	-5.05
Gua-H8	2.27	2.20	2.36	-4.43	-1.97	-2.81
Gua-H9	1.91	1.84	1.84	-8.40	-5.37	-6.85
Gua-N3	2.06	1.88	1.92	-7.31	-5.11	-4.72
Gua-H21	2.01	2.02	1.89	-8.38	-6.19	-8.25
Gua-H22	1.95	2.00	1.87	-7.33	-4.57	-6.24
AD	0.03	0.09		-1.87	-0.97	
AAD	0.05	0.11		2.32	1.95	
RMSE	0.06	0.09		1.59	2.08	

Table 6S, continued.

Orientation	R_{min} (Å)			Energy (kcal/mol)		
	QM	Drude	CH27	QM	Drude	CH27
Thy-H1	1.90	1.80	1.82	-6.60	-7.04	-7.51
Thy-O2'	1.90	1.92	1.77	-6.99	-7.11	-8.33
Thy-O2"	1.92	1.96	1.78	-5.62	-4.52	-6.35
Thy-H3	1.88	1.72	1.83	-5.90	-5.79	-6.54
Thy-O4'	1.91	1.92	1.76	-7.64	-4.86	-6.73
Thy-O4"	1.98	2.00	1.79	-7.97	-5.00	-6.29
Thy-H6	2.25	2.32	2.34	-3.30	-4.03	-4.30
AD	0.01	0.09		-0.81	0.29	
AAD	0.06	0.12		1.18	1.03	
RMSE	0.08	0.09		1.41	1.04	
Ade-N1	2.02	1.70	1.89	-7.23	-7.29	-6.97
Ade-H2	2.38	2.50	2.45	-1.47	-0.44	-1.55
Ade-N3	2.05	1.70	1.90	-7.15	-7.75	-7.07
Ade-H9	1.90	1.74	1.89	-7.21	-5.83	-7.16
Ade-H8	2.25	2.38	2.37	-2.79	-2.29	-3.27
Ade-N7	2.00	2.00	1.84	-6.94	-5.51	-7.25
Ade-H61	1.96	2.00	1.89	-5.21	-3.07	-4.54
Ade-H62	1.90	2.00	1.85	-5.50	-4.58	-5.35
AD	0.05	0.05		-0.84	-0.04	
AAD	0.15	0.10		1.01	0.26	
RMSE	0.18	0.10		0.82	0.33	

¹Base – water interaction calculations were performed on fixed MP2/6-31G(d) optimized geometry of the DNA bases and fixed gas-phase geometry of water molecule. Only base – water intermolecular distance and water orientation angle with base oxygen atom were optimized.

²MP2/6-31G(d) partial optimization of water – base interaction.

³Classical Drude oscillator polarizable force field partial optimization of water-base interaction. SWM4-DP polarizable water model was used in these calculations.

⁴CHARMM27 partial optimization of water-base interaction on CHARMM27 optimized geometry of DNA bases and TIP3P water molecule.

⁵LMP2/cc-pVQZ base-water interaction energy calculation on MP2/6-31G(d) partially optimized geometry of the complex.³

⁶AD – average difference.

Table 7S. Interactions of the dimethylphosphate anion (DMP) and tetrahydrofuran (THF) with water

Orientation	R _{min} (Å)			Energy (kcal/mol)		
	QM ¹	DRUDE ³	CH27 ²	QM ¹	DRUDE	CH27
DMP gg P1IN	3.32	3.53	3.29	-15.1	-15.3	-16.7
DMP gg P1OUT	3.61	3.85	3.60	-8.5	-9.6	-11.1
DMP gg O3ANI	1.83	1.90	1.66	-12.4	-12.5	-13.3
DMP gg O4ANI	1.83	1.90	1.66	-12.4	-12.5	-13.3
DMP gg O1EST	1.90	1.78	1.86	-9.3	-9.2	-9.5
DMP gg O2EST	1.90	1.78	1.86	-9.3	-9.2	-9.5
DMP gg AAD	0.14		0.08	0.3		
DMP gg RMSE	0.14		0.07	0.4		
DMP gt P1IN	3.33	3.54	3.29	-15.5	-16.3	-16.8
DMP gt P1OUT	3.63	3.89	3.60	-8.7	-9.3	-11.0
DMP gt O3ANI	1.83	1.88	1.66	-12.6	-13.3	-13.3
DMP gt O4ANI	1.82	1.88	1.66	-12.4	-13.3	-13.6
DMP gt O1EST	1.92	1.79	1.87	-8.9	-8.4	-9.1
DMP gt O2EST	1.87	1.79	2.50	-9.9	-8.4	-4.4
DMP gt AAD	0.13		0.18	0.8		
DMP gt RMSE	0.14		0.27	0.9		
THF O4'IN	1.97	1.84	1.85	-5.1	-4.5	-5.9
THF O4'OUT	1.95	1.83	1.85	-5.4	-4.6	-6.1

¹QM calculations were performed at the LMP2/cc-pVQZ//MP2/6-31G(d) level³ for THF, LMP2/aug-cc-pVTZ//MP2/6-31+G(d) level for DMP;

^{2,3}Fully optimized monomer geometries were used for the CHARMM27 (CH27) and classical Drude polarizable (DRUDE) empirical force field calculations. TIP3P water was used for CHARMM27, whereas SWM4-DP water model was used for Drude polarizable calculations.

Table 8S. Comparison of the average N1···N3 base pairing distance from the 1 ns CHARMM27 and Drude polarizable GAGTACTC duplex DNA molecular dynamics simulation.¹

Interacting bases		N1···N3 distance (Å)				
Strand 1	Strand 2	CHARMM27		DRUDE		
G1	C8	3.68	± 0.87	3.20	± 0.26	
A2	T7	4.97	± 0.70	4.29	± 0.58	
G3	C6	3.85	± 0.73	3.61	± 0.63	
T4	A5	2.94	± 0.12	3.24	± 0.71	
A5	T4	2.96	± 0.12	3.06	± 0.43	
C6	G3	3.01	± 0.12	3.18	± 0.23	
T7	A2	2.98	± 0.12	2.98	± 0.30	
C8	G1	3.02	± 0.14	3.19	± 0.21	

¹The N1···N3 base pairing distance was averaged over the 1000 ps simulation. Errors represent RMS fluctuations.

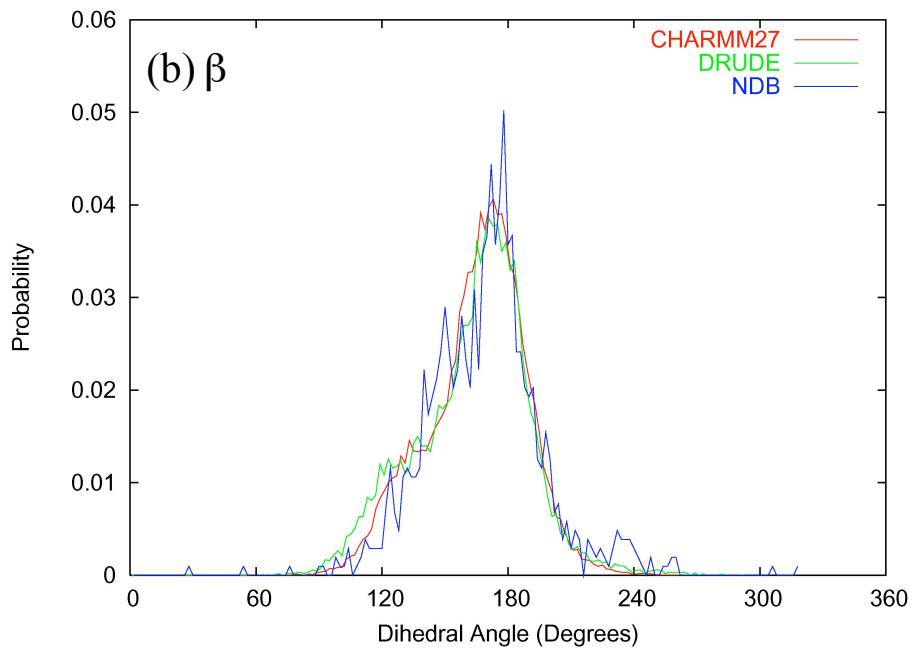
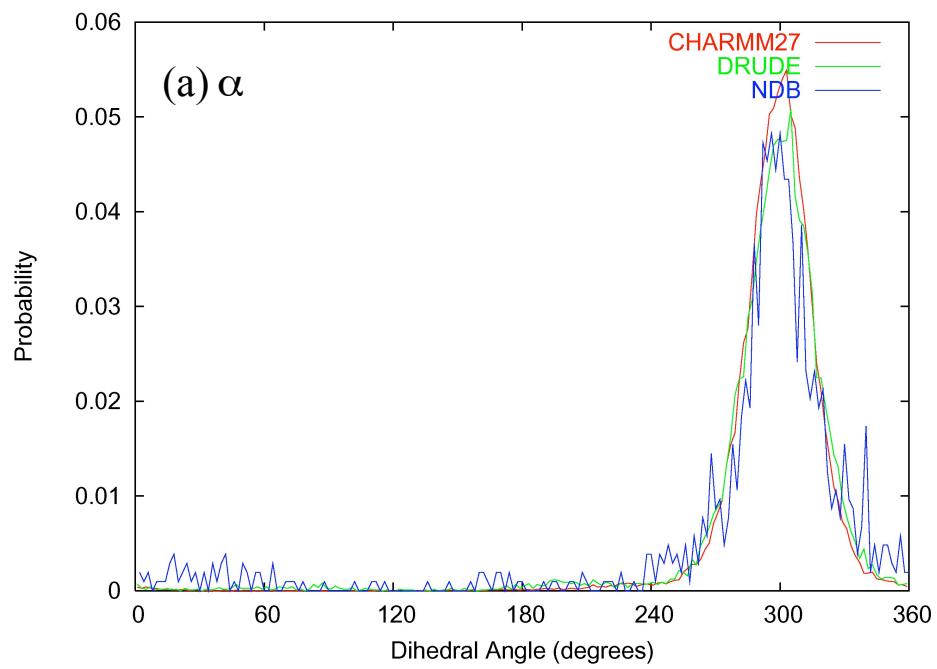


Figure 1S. Probability distribution from the solution molecular dynamics simulations of the GAGTACTC duplex DNA using additive CHARMM27⁴ and Drude polarizable CHARMM (DRUDE) force fields and from a survey of B DNA crystal structures in the nucleic acid databank (NDB)⁵ as a function of dihedral

angles $\alpha, \beta, \gamma, \delta, \varepsilon, \chi, \zeta$.

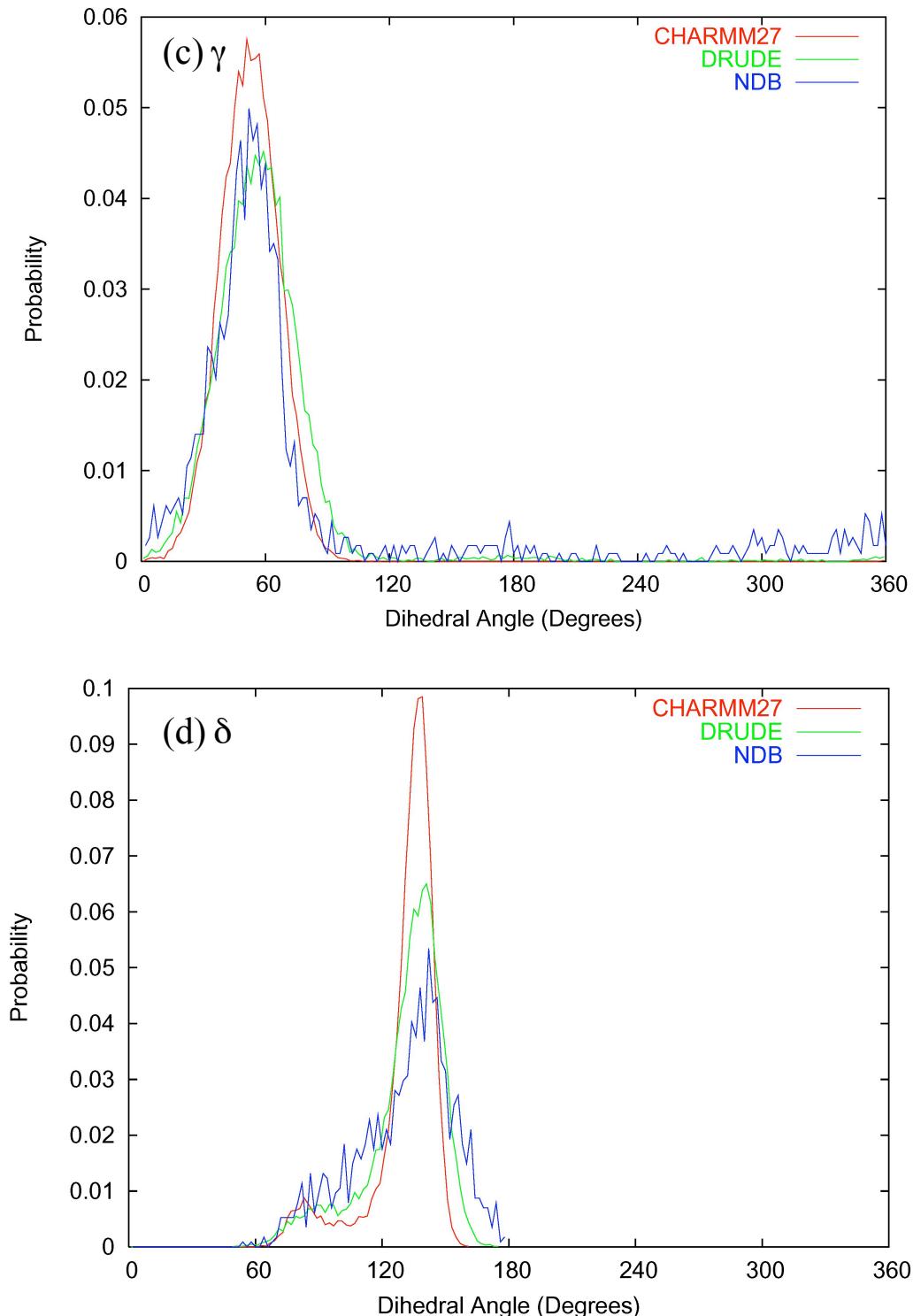


Figure 1S continued

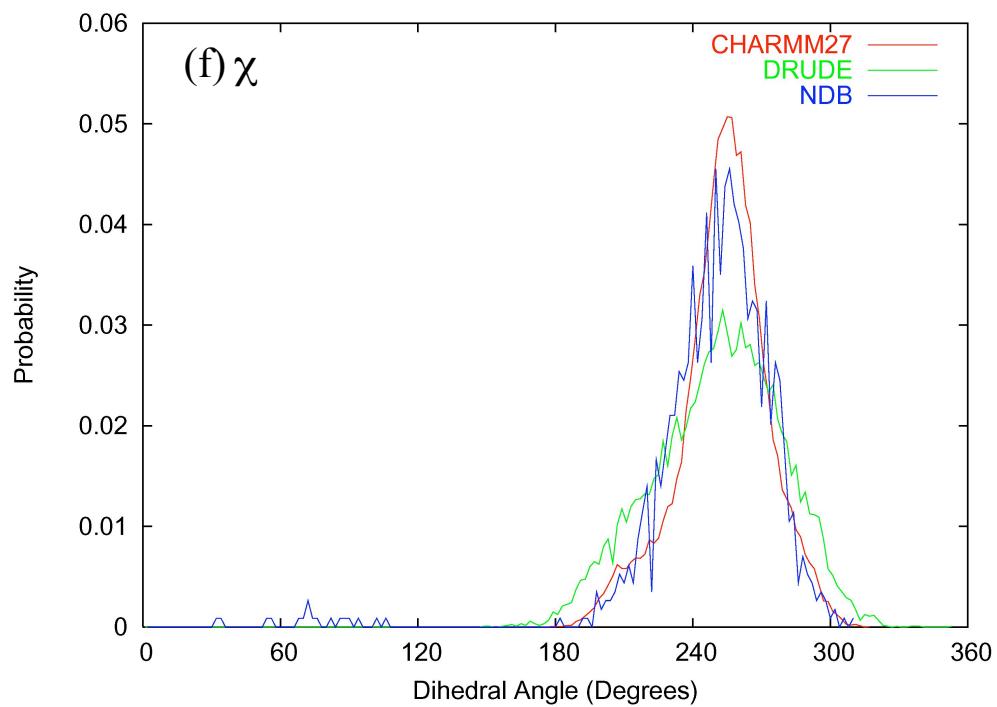
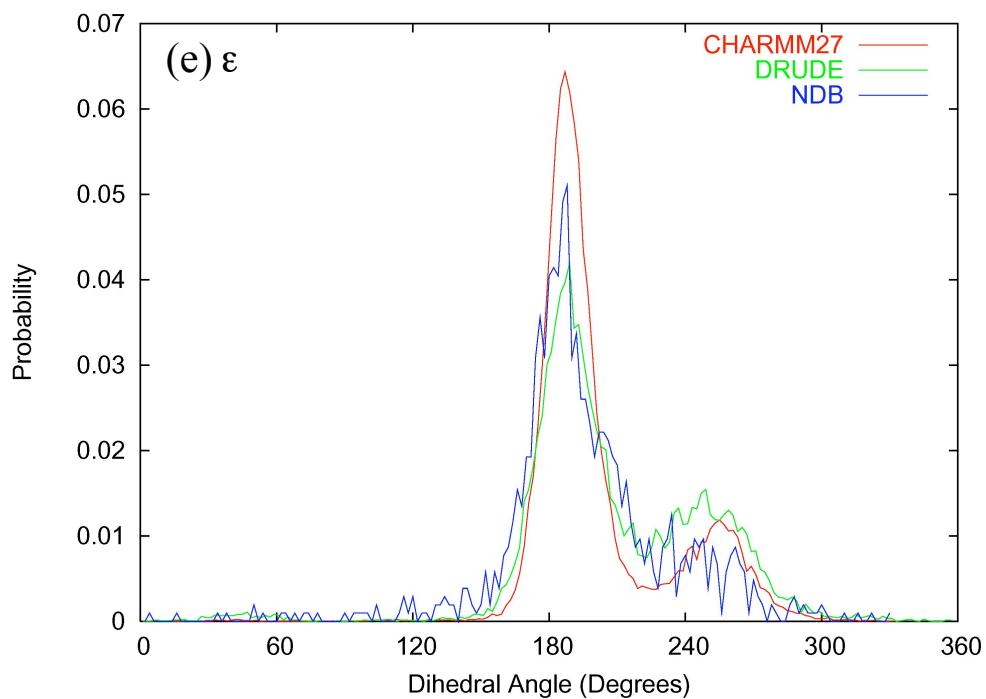


Figure 1S. continued.

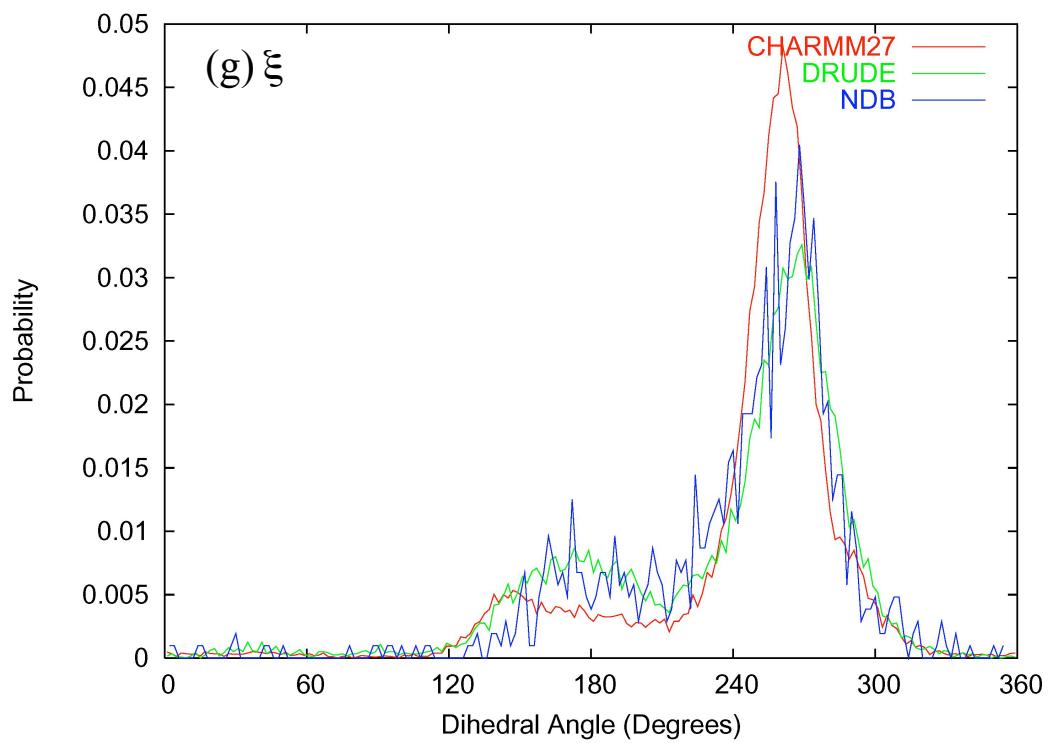


Figure 1S continued.

References

- (1) Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*; Gaussian, Inc: Pittsburgh, PA, 1996.
- (2) Miller, K. J. *J. Am. Chem. Soc.* **1990**, *112*, 8533.
- (3) Huang, N.; MacKerell, A. D., Jr. *J. Phys. Chem. B* **2002**, *106*, 7820.
- (4) Foloppe, N.; MacKerell, A. D., Jr. *J. Comp. Chem.* **2000**, *21*, 86.
- (5) Berman, H. M.; Olson, W. K.; Beveridge, D. L.; Westbrook, J.; Gelbin, A.; Demeny, T.; Hsieh, S.-H.; Srinivasan, A. R.; Schneider, B. *Biophys. J.* **1992**, *63*, 751.