Electronic Supplementary Information

DNA-RNA hybrid duplexes with decreasing Pyrimidine content in the DNA strand Provide Structural Snapshots for the A- to B-form Conformational Transition of Nucleic Acids

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Supplementary Methods

Helical deformation analysis

The stiffness of translational and rotational deformations for different base pair steps can be explained by calculating the corresponding force constants in helical space. The inversion of helical covariance matrix ($C = < X_i X_j >$) gives stiffness matrix ($F = F[k_{ij}]$), and the diagonal elements give force constants corresponding to pure steps and off-diagonal elements represent force constant for cross terms.

$$F = k_B T C^{-1}$$

To further explain the stiffness at the translational, rotational and global levels, the respective force constants are calculated by using the equations.

$$k_{trans} = k_{shift}\, k_{rise}\, k_{slide}$$

$$k_{rotat} = k_{roll}\, k_{twist}\, k_{tilt}$$

$$k_{global} = k_{trans}\, k_{rotat}$$

Binding free energy calculations

The molecular mechanics with generalised born and surface area method (MM-GB/SA) is employed to calculate the free energies of the systems.[42] The free energy can be calculated as the sum of molecular mechanical energy, solvation free energy and mechanical entropy of the system. Mechanical entropic term is ignored in the present calculations. The binding free energy for DNA-RNA duplex can be estimated from the below equation.

$$\Delta G_{bind} = E_{vdw} + E_{ele} - G_{solv,hybrid} - G_{solv,DNA\ strand} - G_{solv,RNA\ strand}$$

The solvation free energy can be estimated using the following relation.

$$G_{solv} = G_{polar} + G_{non-polar}$$

GBMV method for polar solvation energy and the still equation $G_{non-polar} = 0.0072 * SASA$ for non-polar solvation energy were used. All the energies were computed without energy cutoff. In these calculations, we have compared the relative binding free energies of hybrids with respect to their corresponding to pure duplexes and the ratios of both relative binding free energies.

Supplementary Figures

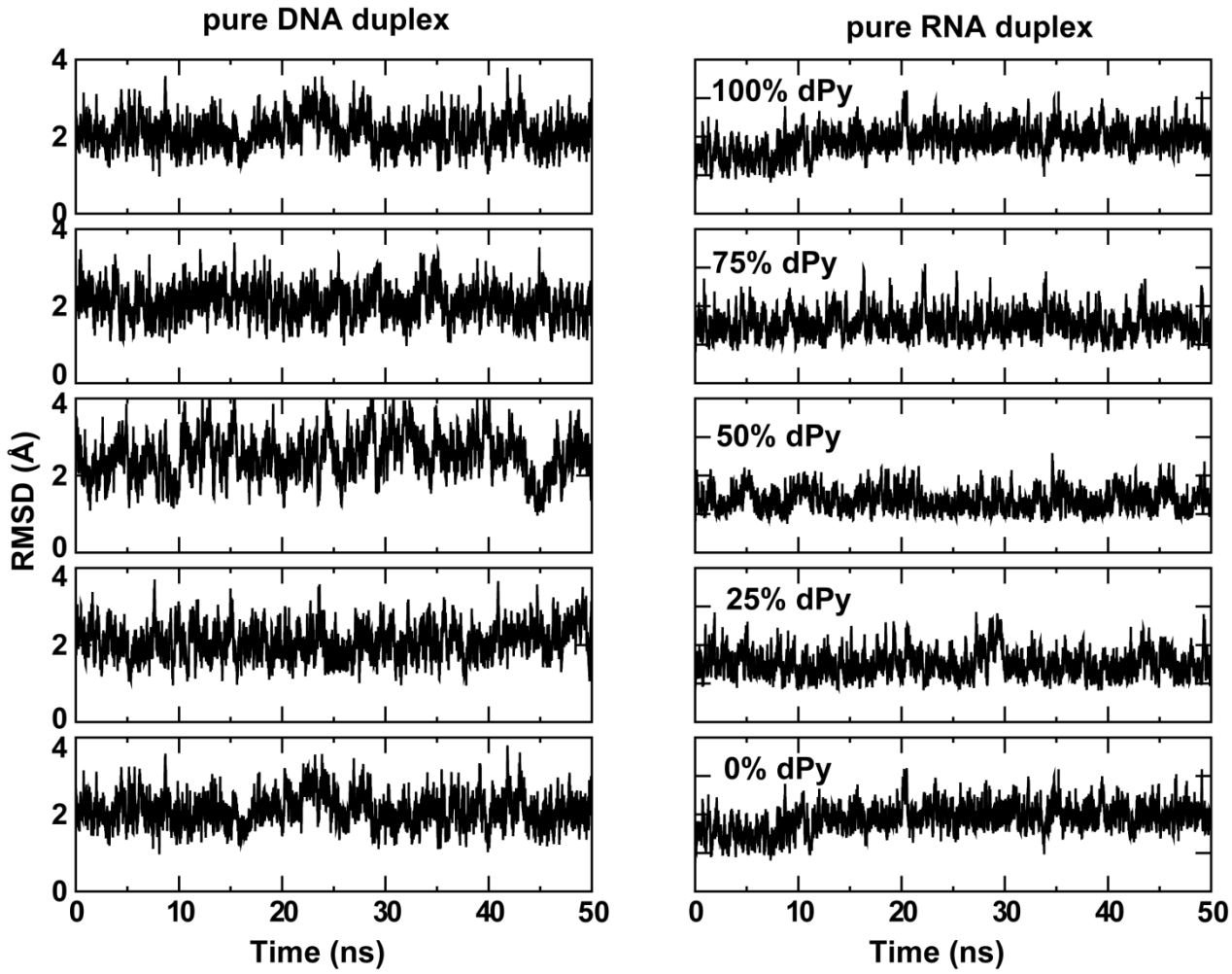

Figure S1: Time series of the root mean square deviations of pure DNA and RNA duplexes isosequential to the DNA-RNA hybrids.

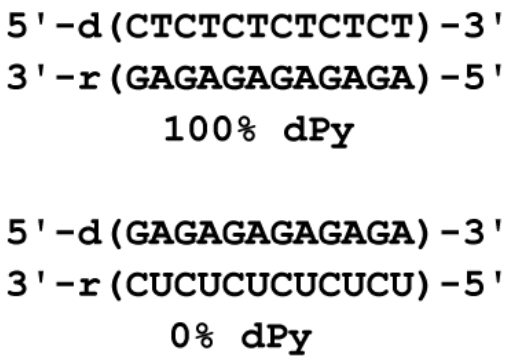

Figure S2: New sequences with alternate GA base pairs used to model the hybrid duplexes.

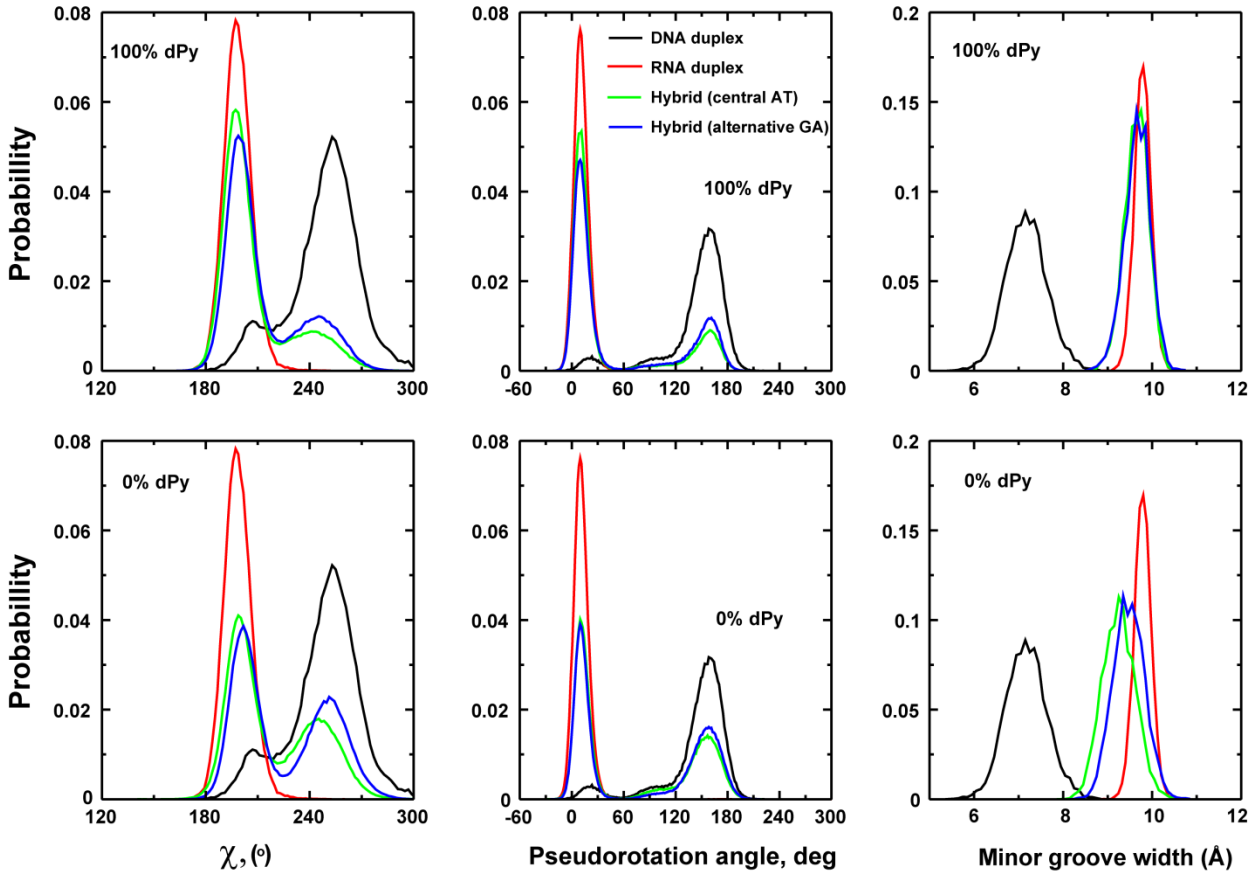

Figure S3: Probability distributions of sugar–base glycosidic bonds, pseudorotation angles, and minor groove width regions of the pure DNA, pure RNA, initial hybrids and hybrids with alternative AG base pairs.

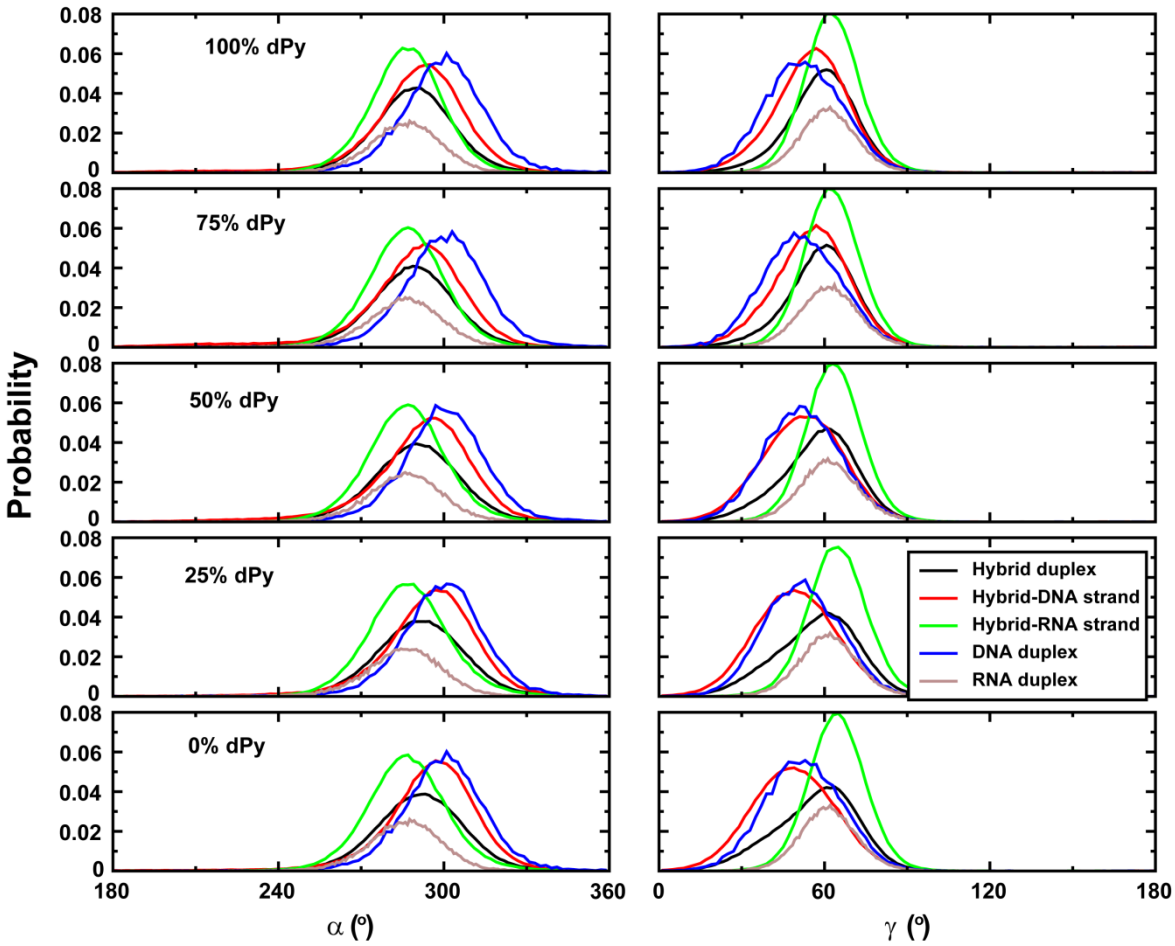

Figure S4: Probability distributions of the backbone dihedral angles α and γ of DNA-RNA hybrid duplexes in comparison to the respective pure DNA and RNA duplexes.

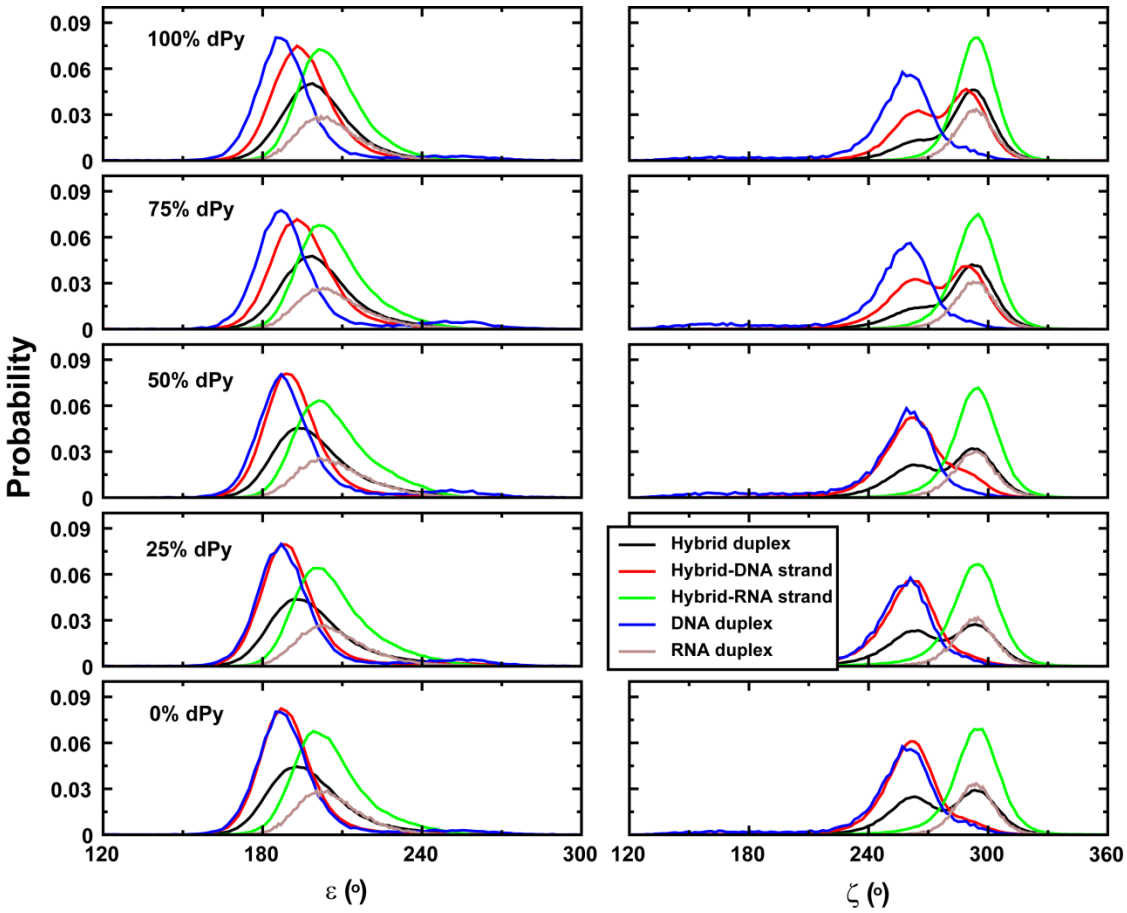

Figure S5: Probability distributions of the backbone dihedral angles ε and ξ of DNA-RNA hybrid duplexes in comparison to the respective pure DNA and RNA duplexes.

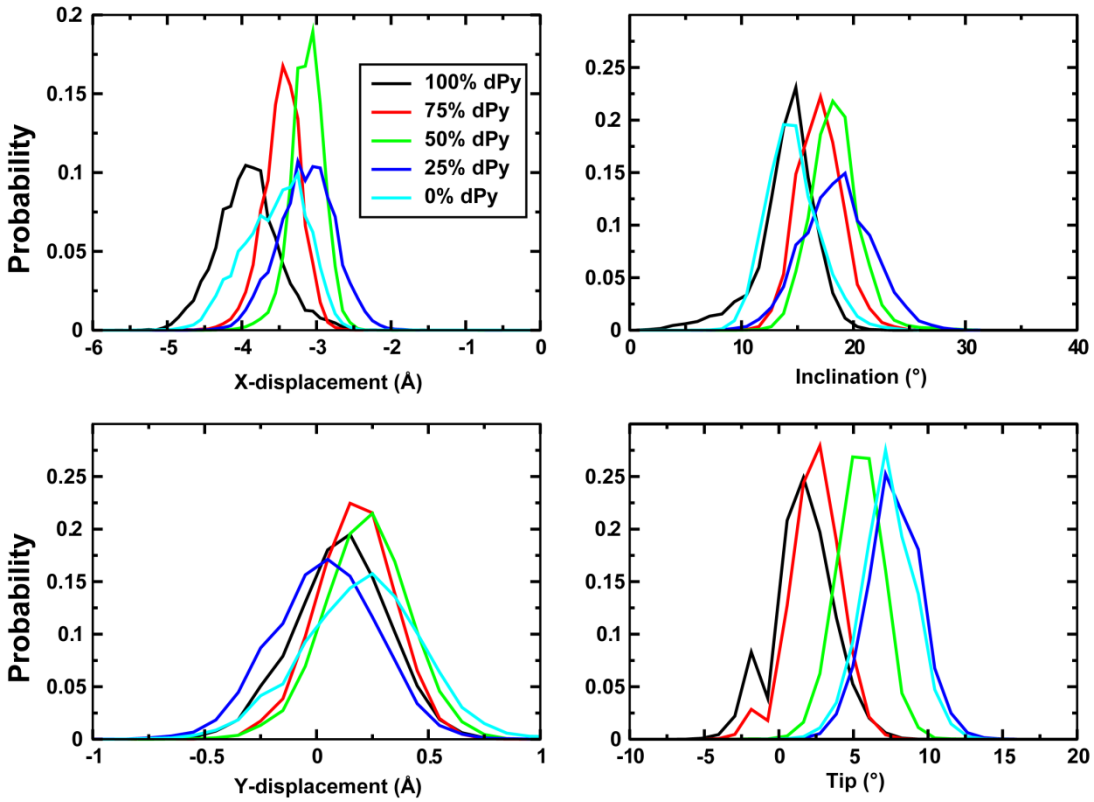

Figure S6: Probability distributions of base pair axis parameters of all the DNA-RNA hybrid duplexes studied.

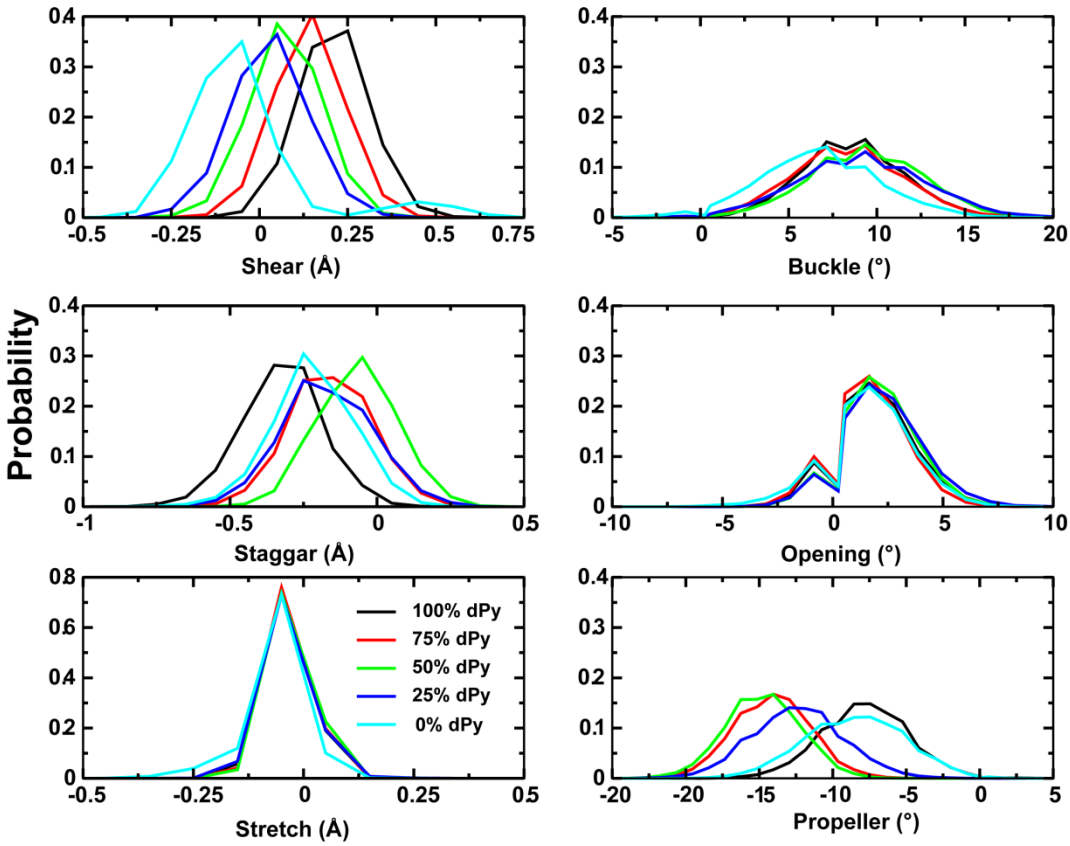

Figure S7: Probability distributions of base pair parameters of all the DNA-RNA hybrid duplexes studied.

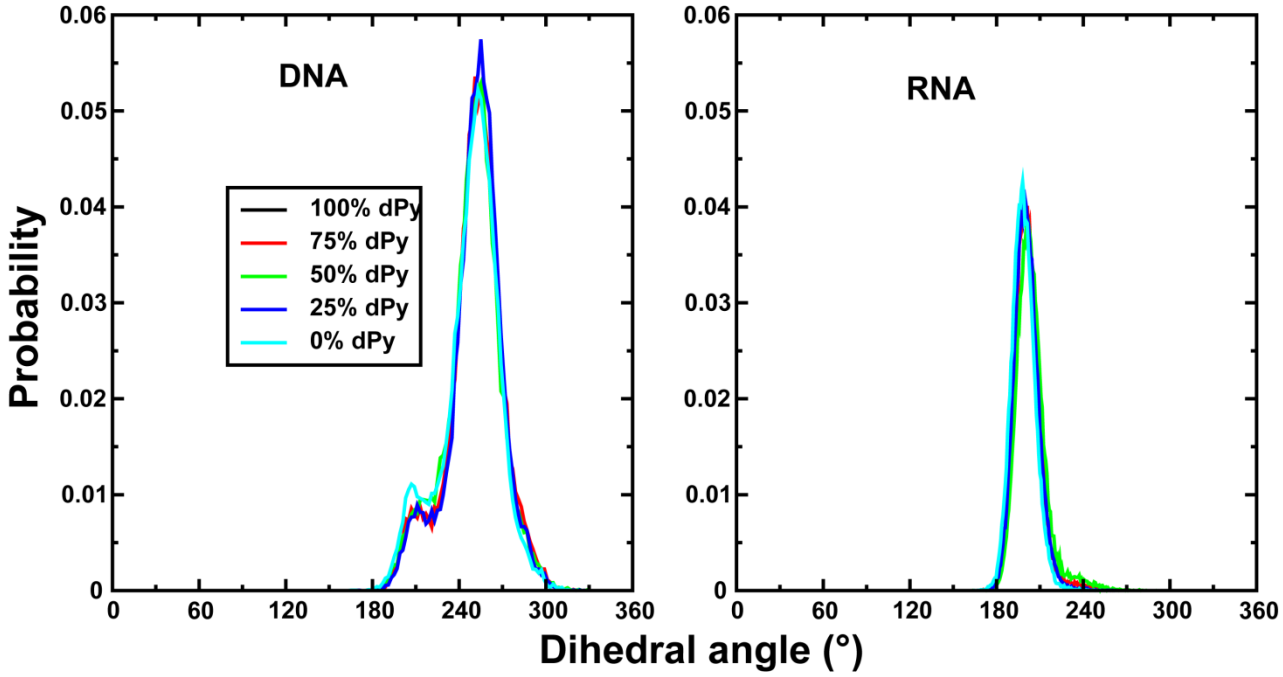

Figure S8: Probability distributions of sugar–base glycosidic bonds corresponding to the pure DNA and pure RNA duplexes.

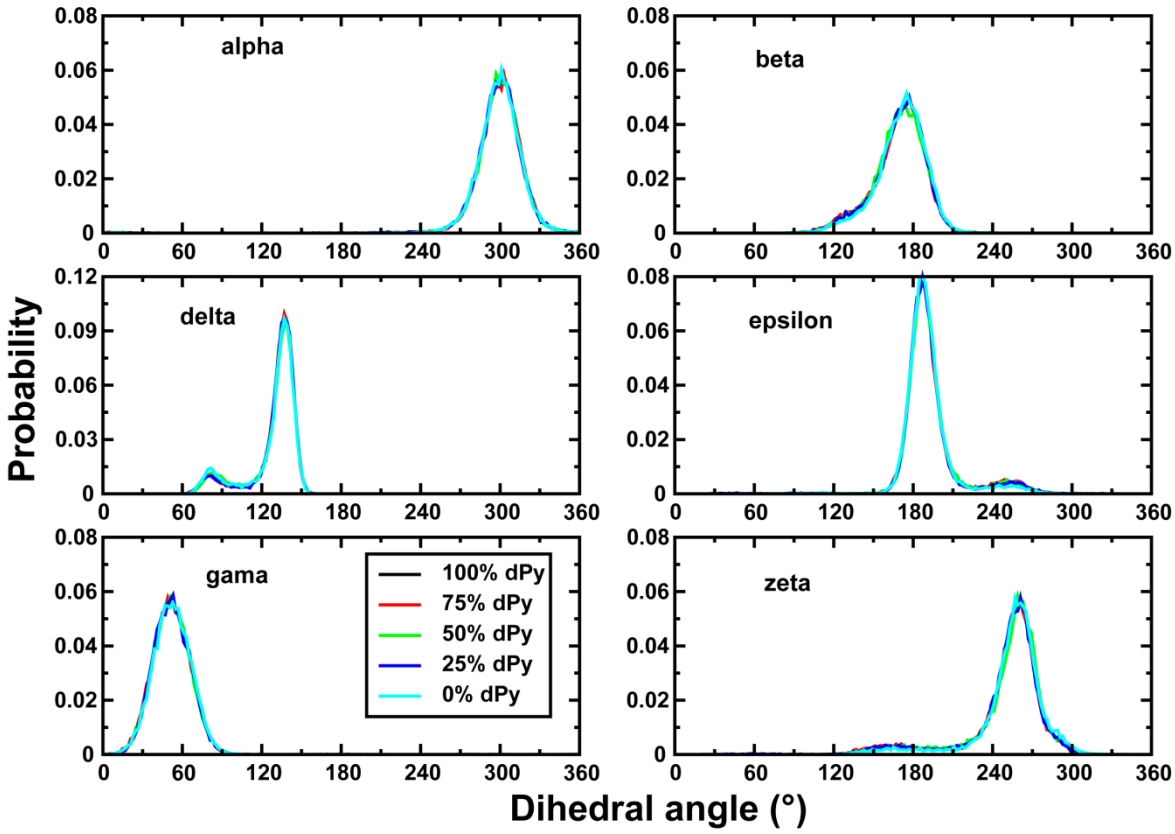

Figure S9: Probability distributions of all the backbone dihedral angles present in pure DNA duplexes.

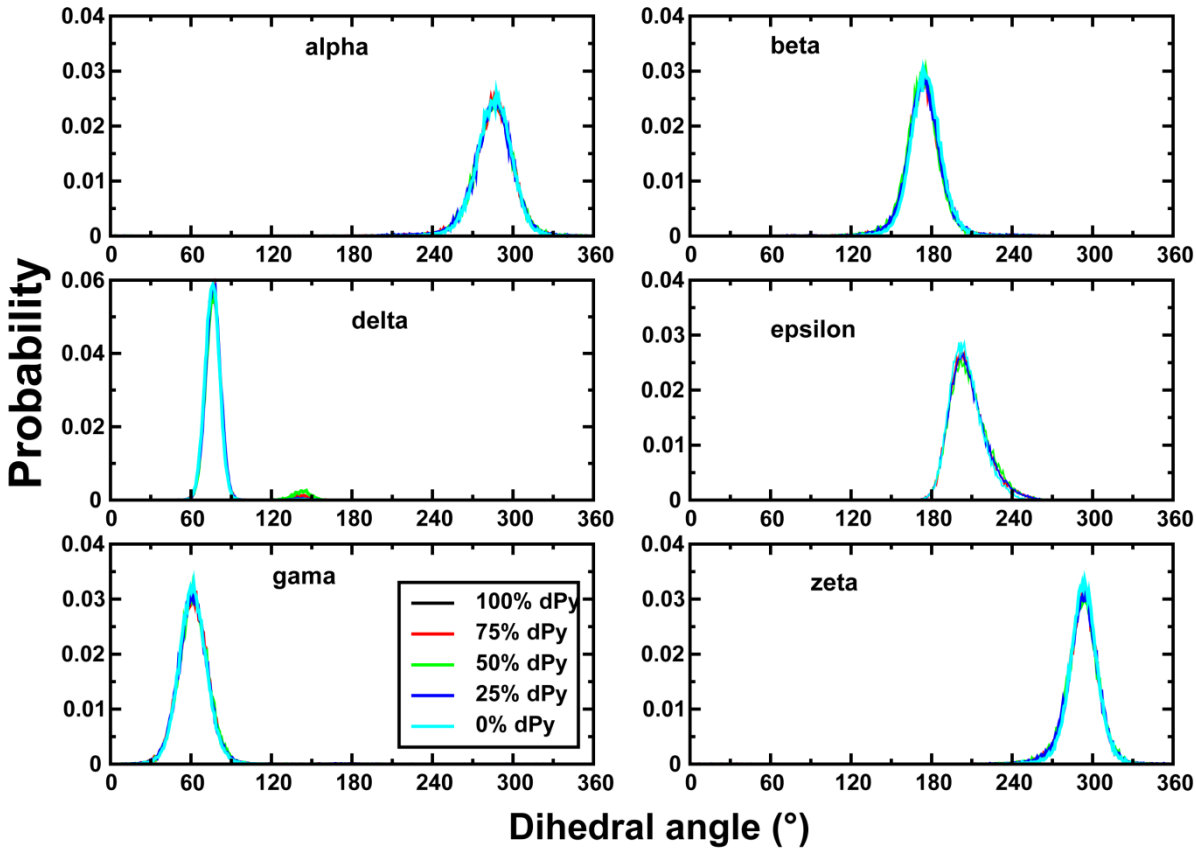

Figure S10: Probability distributions of all the backbone dihedral angles present in pure RNA duplexes.

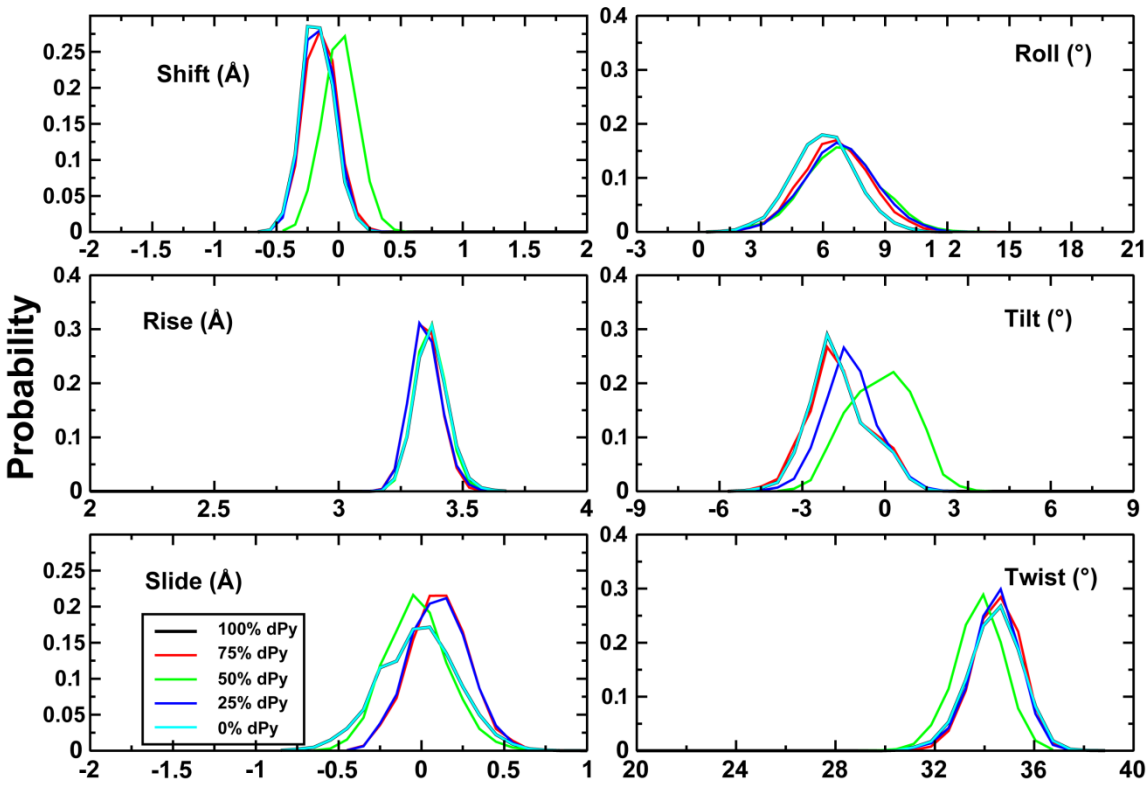

Figure S11: Probability distributions of base pair step parameters of the pure DNA duplexes.

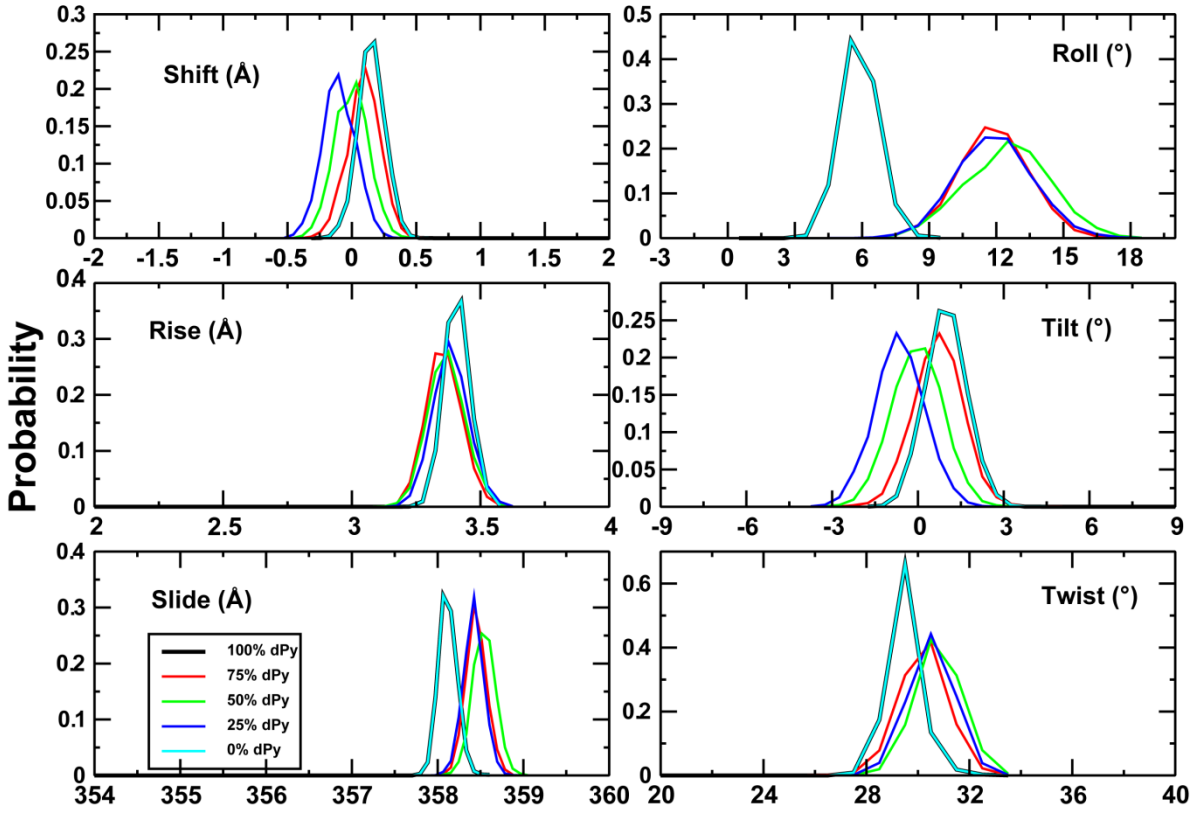

Figure S12: Probability distributions of base pair step parameters of the pure RNA duplexes

Supplementary Tables

Table S1: Elastic force constants along translational and rotational deformation modes of DNA-RNA hybrid duplexes. (Units: roll, twist, tilt - cal/mol/deg^2; shift, rise, slide - cal/mol/Å^2; translational – (kcal/mol/Å^2)^3; rotational- (kcal/mol/deg^2)^3)

Region	100% dPy	75% dPy	50% dPy	25% dPy	0%dPy
Roll	0.5979	1.7811	1.8633	0.4736	2.3605
Twist	1.4004	2.7096	4.2355	1.0938	1.5848
Tilt	2.6329	2.6115	2.6218	2.1156	2.7974
Shift	0.1373	0.1613	0.1486	0.1046	0.1416
Rise	0.3814	0.5879	0.6492	0.2363	0.5269
Slide	0.0735	0.0913	0.1263	0.0432	0.1059
Translational	0.0384	0.0865	0.1219	0.0107	0.0790
Rotational	2.2046	12.6031	20.6909	1.0958	10.4649
Global	0.0846	1.0901	2.5222	0.0117	0.8267

Table S2: Solvent accessible surface area (SASA) values ($Å^2$) for different regions of DNA-RNA hybrid duplexes.

Region	100% dPy	75% dPy	50% dPy	25% dPy	0%dPy
Full	4765.1 ± 3.0	4745.9 ± 2.7	4802.7 ± 1.5	4805.0 ± 0.9	4808.9 ± 1.7
Bkb	3791.3 ± 1.1	3800.8 ± 1.0	3833.0 ± 0.6	3848.9 ± 0.5	3840.2 ± 1.5
Bases	973.9 ± 2.6	944.9 ± 1.8	969.7 ± 1.0	956.1 ± 1.2	968.7 ± 2.6
DNA strand	2328.1 ±2.6	2370.7 ± 2.4	2438.1 ± 1.3	2440.1 ± 0.5	2482.2 ± 0.9
DNA-bkb	1849.3 ± 0.9	1862.7 ± 0.9	1903.2 ± 0.5	1928.3 ± 0.3	1932.6 ± 0.6
DNA-bases	478.8 ± 1.8	508.1 ± 1.5	534.9 ± 0.9	511.9 ± 0.5	549.5 ± 1.1
RNA strand	2437.2 ± 0.9	2375.0 ± 0.4	2364.6 ± 0.3	2364.8 ± 0.8	2326.7 ± 0.9
RNA-bkb	1942.0 ± 0.4	1938.2 ± 0.2	1929.8 ± 0.2	1920.6 ± 0.3	1907.5 ± 1.1
RNA-bases	495.2 ± 1.2	436.8 ± 0.5	434.7 ± 0.3	444.2 ± 0.9	419.1 ± 1.7
Major groove	253.6 ± 1.0	197.3 ± 0.4	188.5 ± 0.3	229.0 ± 0.5	278.4 ± 1.0
Minor groove	127.7 ± 0.7	141.0 ± 0.3	149.4 ± 0.3	147.1 ± 0.4	135.5 ± 1.7

*Full: all the non-hydrogen atoms of the duplex.

Bkb: the phosphate groups and furanose sugar atom without hydrogen atoms.

Bases: the non-hydrogen atoms of nitrogenous bases.

Table S3: Solvent accessible surface area (SASA) values (Å^2) for different regions of pure DNA and RNA duplexes.

Region	100% dPy	75% dPy	50% dPy	25% dPy	0%dPy
			DNA		
Full	4821.5 ± 1.4	4814.8 ± 1.2	4858.4 ± 1.4	4816.2 ± 1.0	4821.5 ± 1.4
Bkb	3774.5 ± 1.1	3776.7 ± 0.7	3777.5 ± 1.2	3776.4 ± 0.8	3774.5 ± 1.1
Bases	1047.1 ± 1.6	1038.1 ± 1.2	1080.9 ± 1.2	1039.8 ± 1.2	1047.1 ± 1.6
Major groove	224.5 ± 0.8	196.2 ± 0.4	177.0 ± 0.5	195.8 ± 0.6	224.5 ± 0.8
Minor groove	126.0 ± 0.8	130.1 ± 0.4	137.9 ± 0.7	132.1 ± 0.6	126.0 ± 0.8
			RNA		
Full	4780.8 ± 0.9	4755.0 ± 1.7	4739.0 ± 3.8	4745.4 ± 2.5	4780.8 ± 0.9
Bkb	3837.0 ± 0.4	3851.6 ± 1.2	3840.0 ± 2.7	3845.8 ± 2.7	3837.0 ± 0.4
Bases	943.7 ± 1.2	903.3 ± 2.1	899.0 ± 2.4	899.6 ± 1.1	943.7 ± 1.2
Major groove	305.3 ± 0.4	227.7 ± 1.0	223.8 ± 1.8	231.3 ± 0.7	305.3 ± 0.4
Minor groove	111.1 ± 0.2	139.9 ± 0.7	145.5 ± 1.2	141.4 ± 0.6	111.1 ± 0.2

Table S4: Average number of water molecules present around the different regions of DNA-RNA hybrid duplexes.

Region	100% dPy	75% dPy	50% dPy	25% dPy	0%dPy
Full	364.0 ± 5.6	375.2 ± 5.3	406.2 ± 5.1	334.0 ± 6.3	385.6 ± 5.2
Bkb	281.1 ± 4.4	295.4 ± 4.3	320.1 ± 4.1	265.2 ± 4.8	302.3 ± 4.1
Bases	158.3 ± 3.0	154.5 ± 2.7	165.7 ± 2.7	132.3 ± 3.5	162.2 ± 2.8
DNA strand	187.8 ± 3.2	194.1 ± 3.1	218.7 ± 3.0	183.3 ± 3.8	216.2 ± 3.1
DNA str + bkb	137.2 ± 2.2	144.2 ± 2.2	157.5 ± 2.1	133.3 ± 2.4	150.9 ± 2.1
DNA str + bases	89.1 ± 1.9	87.5 ± 1.8	100.3 ± 1.8	80.0 ± 2.2	101.9 ± 1.9
RNA strand	202.3 ± 3.8	205.9 ± 3.3	218.3 ± 3.1	173.1 ± 3.5	199.5 ± 3.1
RNA str + bkb	144.7 ± 2.6	151.8 ± 2.4	163.0 ± 2.3	132.7 ± 2.5	151.8 ± 2.2
RNA str + bases	92.8 ± 2.1	89.8 ± 1.7	94.1 ± 1.8	72.5 ± 2.1	88.0 ± 1.7
Major groove	60.1 ± 1.3	59.2 ± 1.2	63.6 ± 1.2	51.0 ± 1.5	63.0 ± 1.2
Minor groove	76.6 ± 1.5	73.6 ± 1.3	79.2 ± 1.3	63.9 ± 1.8	77.5 ± 1.3