

Supporting Information

Structural and Functional consequences of Arsenate -Phosphate Substitutions in

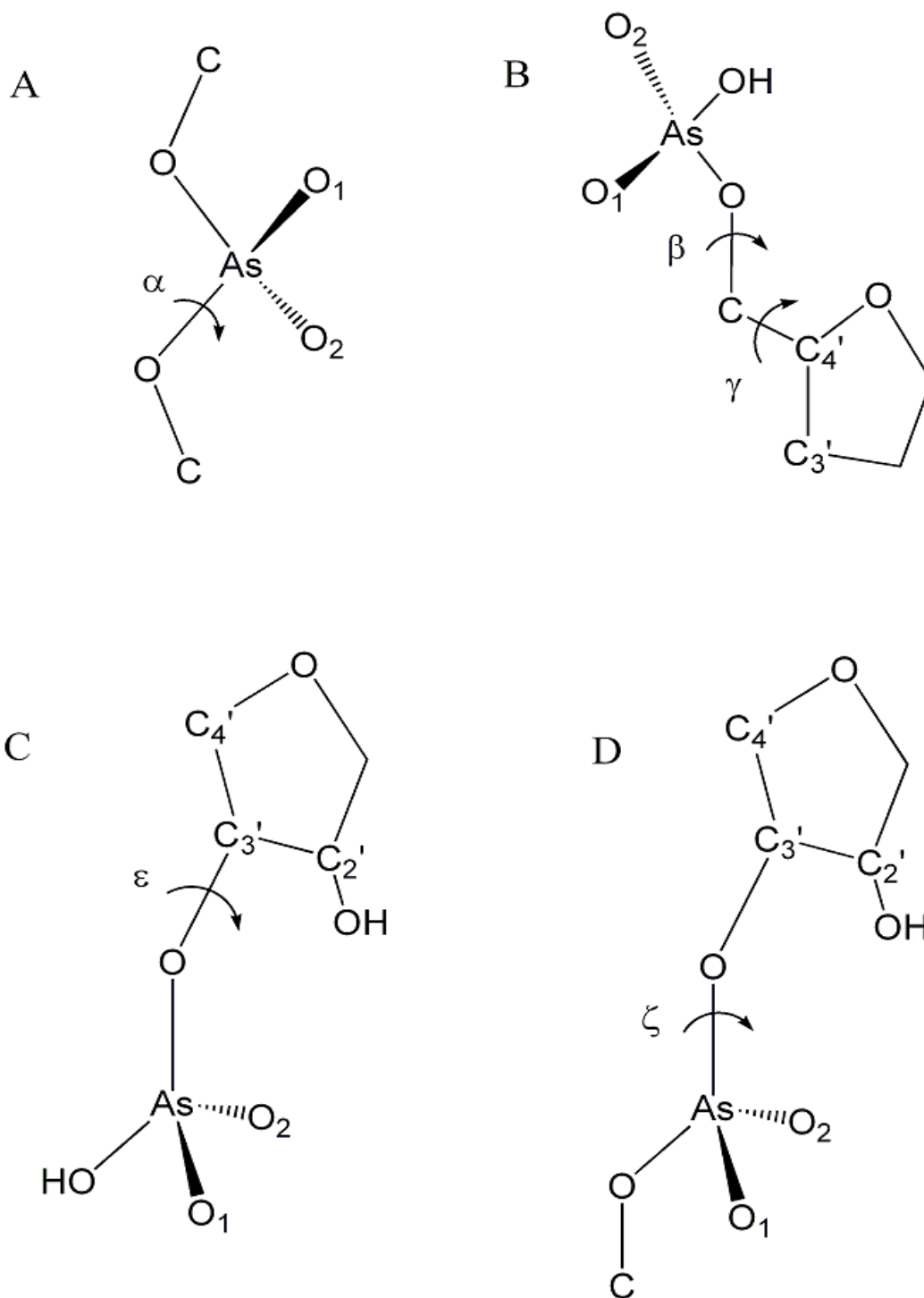
Selected Nucleotides: DNA, RNA, and ATP

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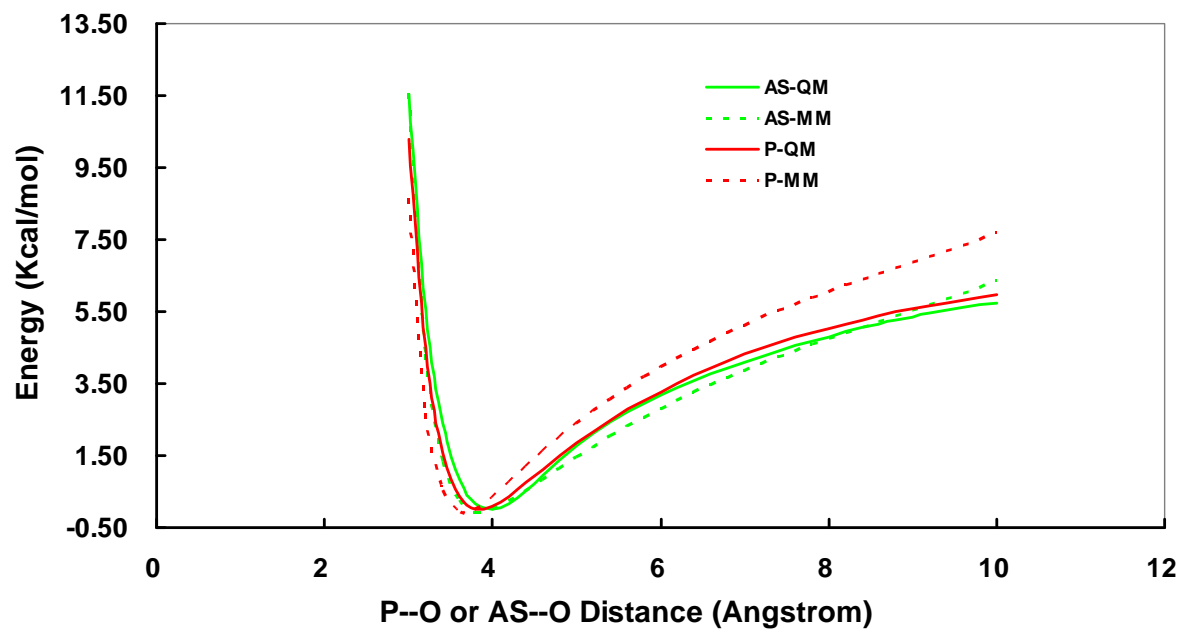
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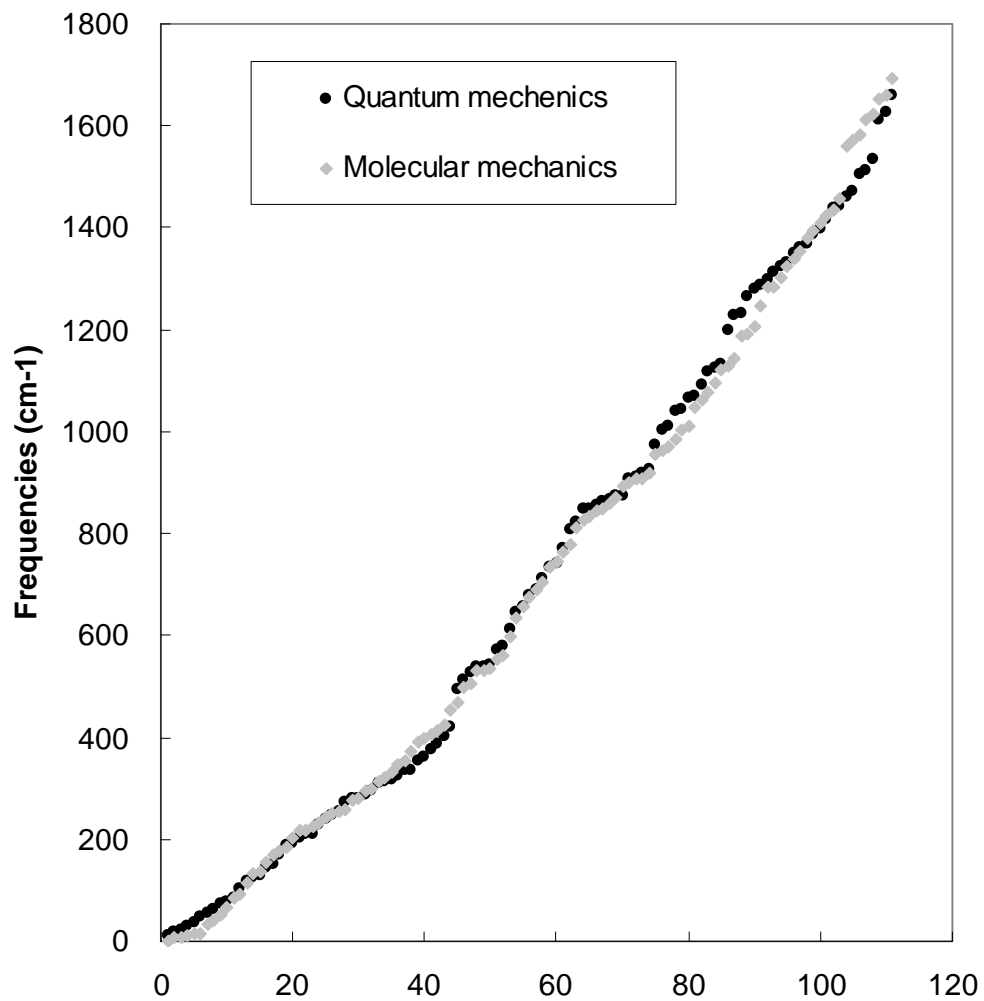
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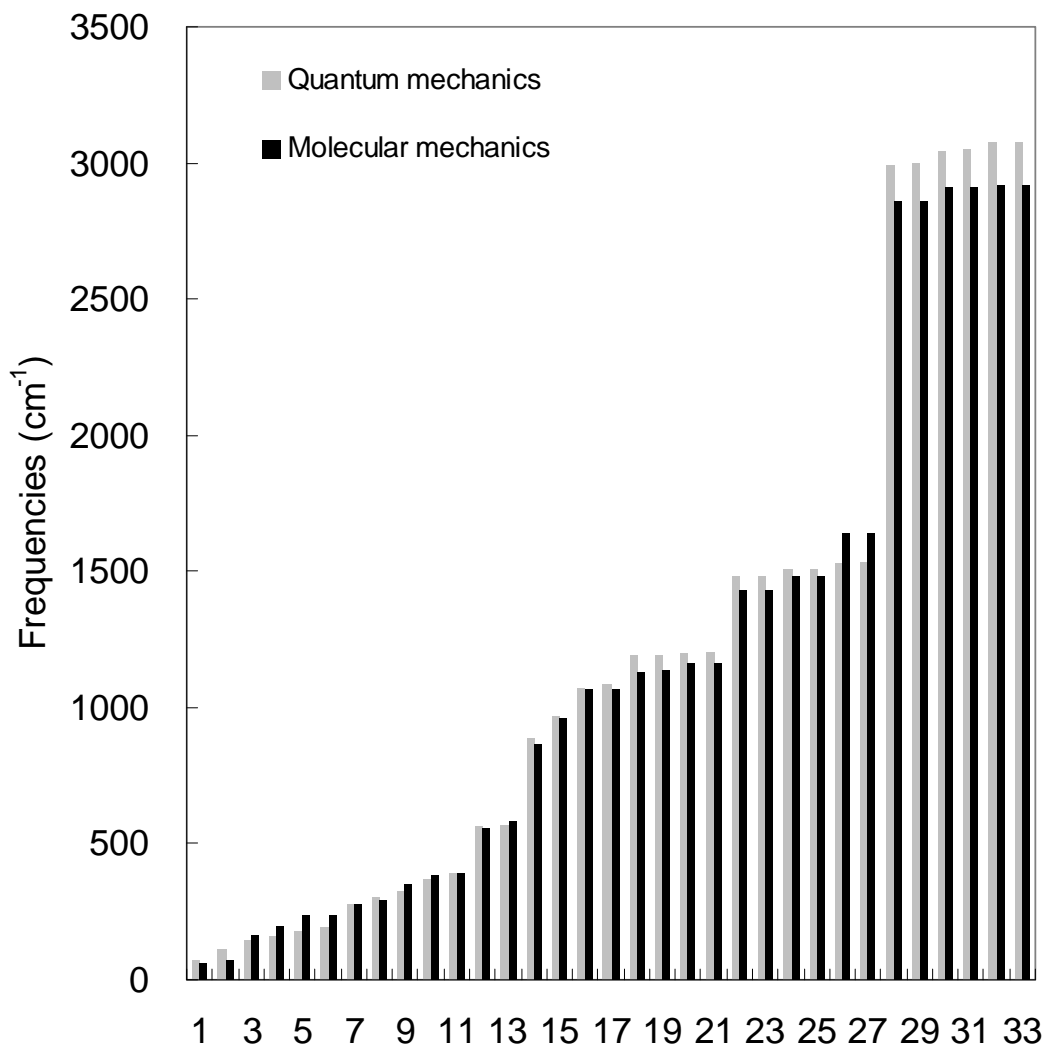
Sup-Figure 1. Model compounds and related dihedral angles are used to recalibrate the arsenate force field.



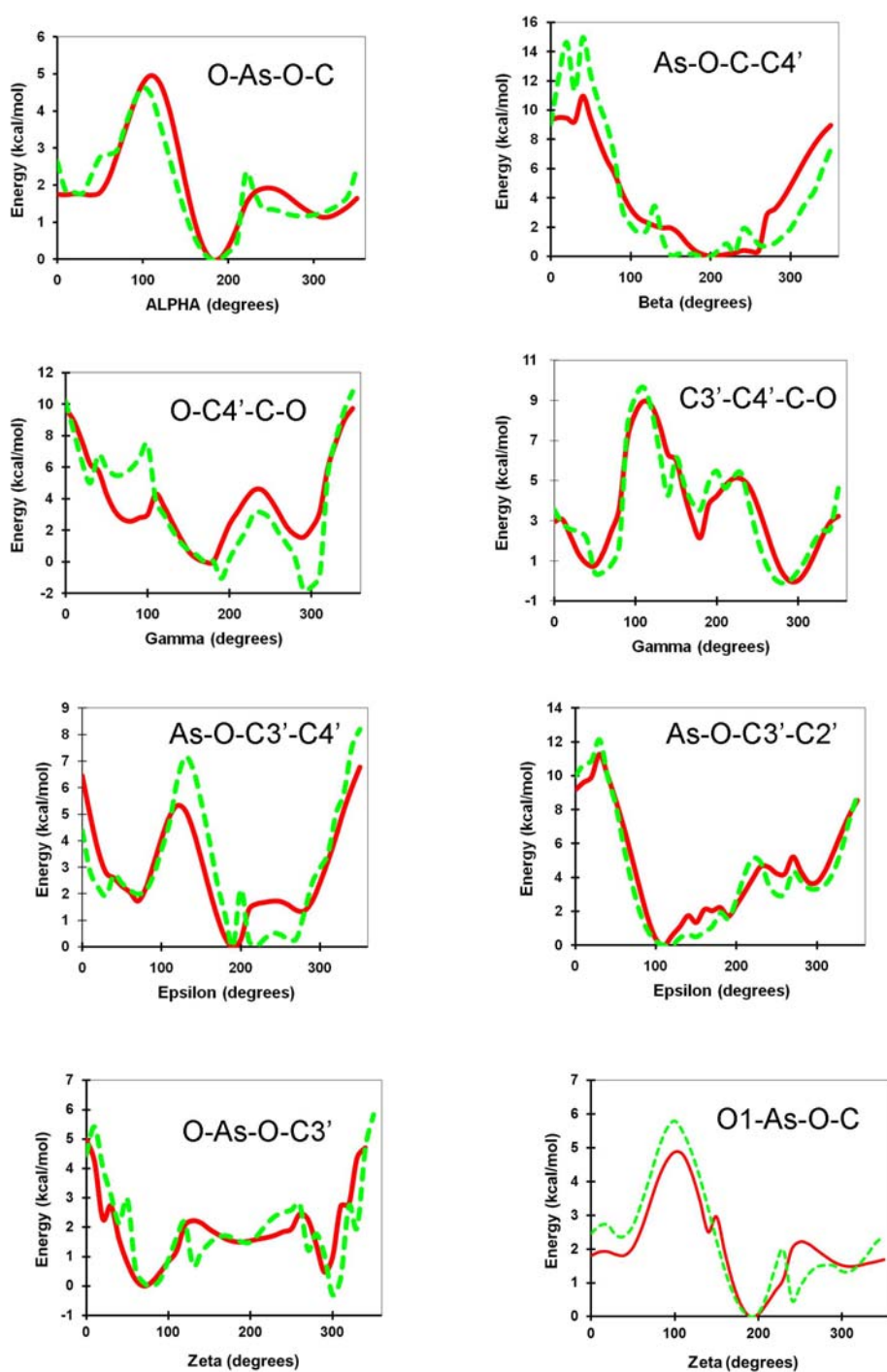
Sup-Figure 2. Fitting of the potential energy curve of $\text{H}_2\text{O}\cdots(\text{CH}_3)_2\text{AsO}_4^-$ interactions obtained at the B3LYP/6-31G* level.



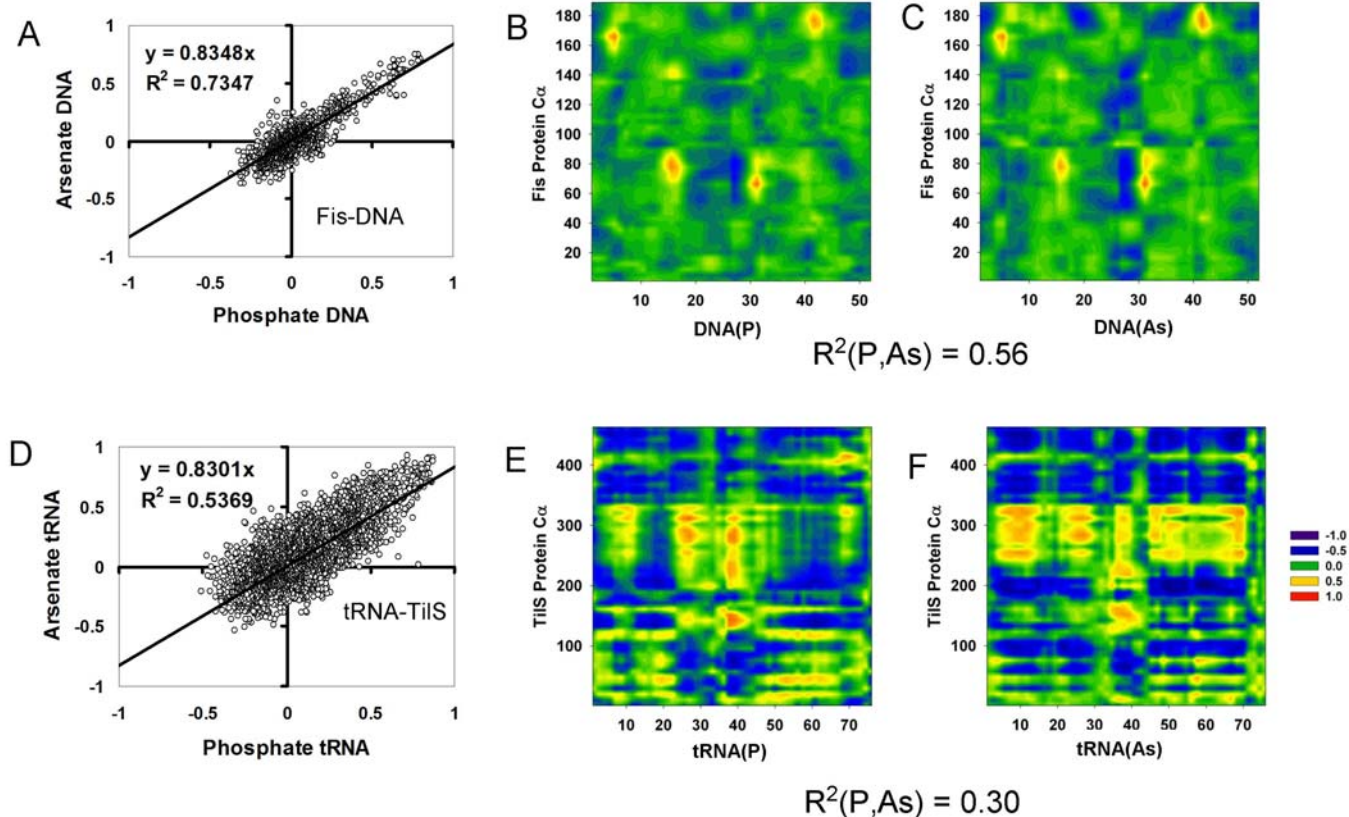
Sup-Figure 3. The calculated first 111 frequencies for compound ATAs from quantum mechanics calculations at the B3LYP/6-31+G* level of theory, and molecular mechanics calculations.



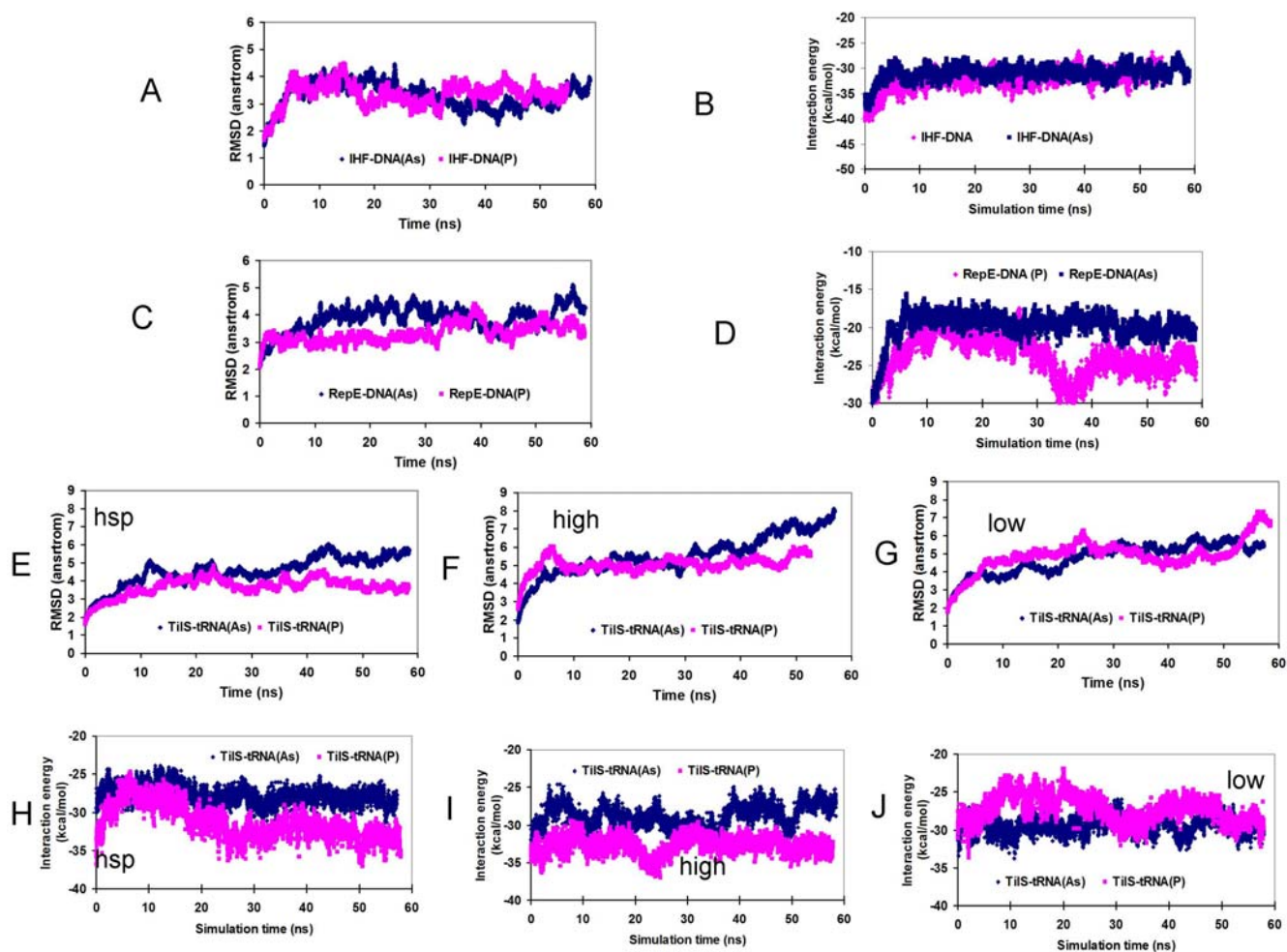
Sup-Figure 4. Comparison of harmonic vibrational frequencies obtained from quantum mechanics and molecular mechanics calculations.



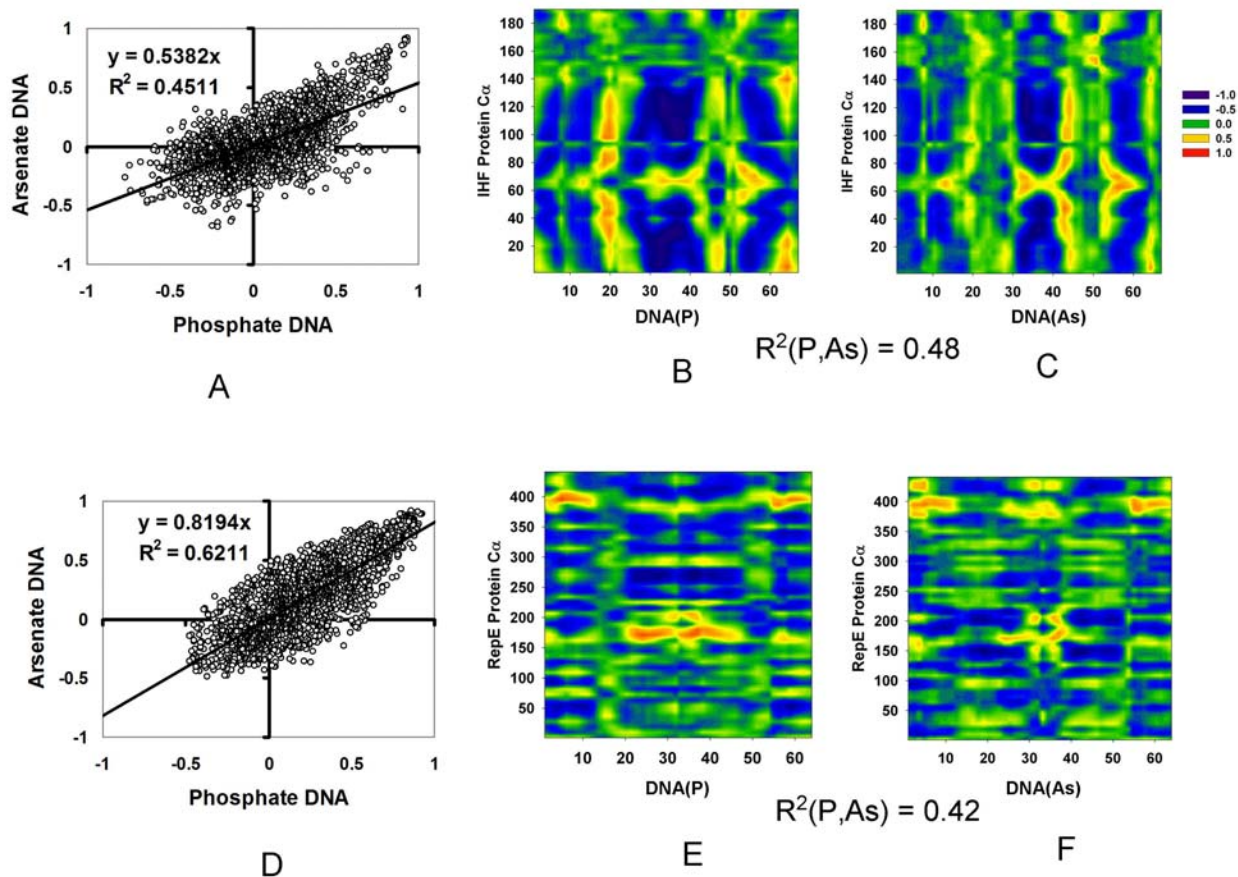
Sup-Figure 5. The potential energy surfaces for the indicated torsions of compounds A, B, C, and D (See Sup-Figure 1). The solid red lines are the results from quantum mechanics calculations at the B3LYP/6-31+G* level of theory, and the dotted green lines from molecular mechanics calculations.



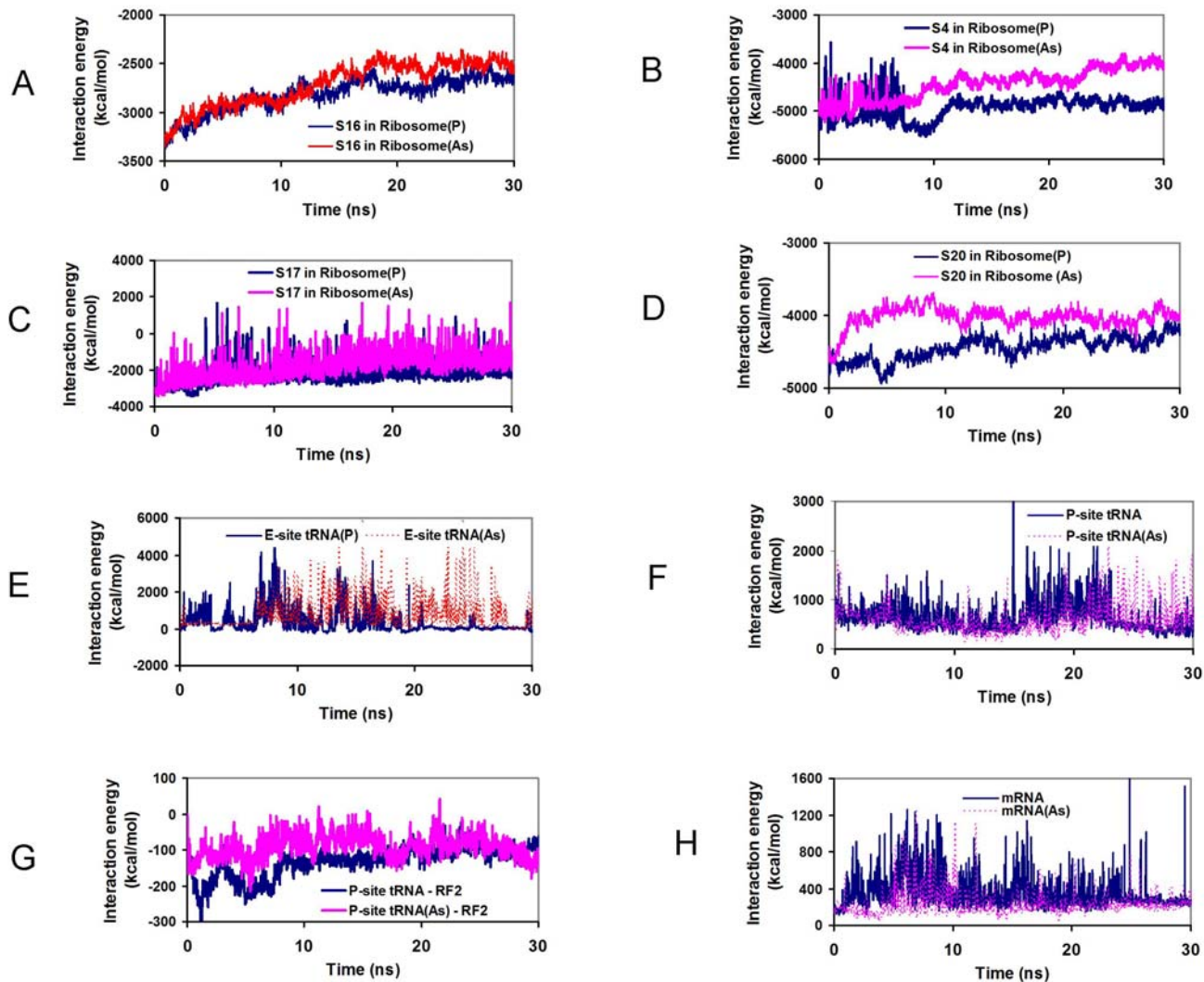
Sup-Figure 6. Arsenate-Phosphate replacement results in larger energetic and dynamic changes in the tRNA-protein complex than in the DNA-protein complex. (A) Correlations of covariance matrix elements of the Fis-DNA(P) and Fis-DNA(As) complexes indicate that DNA(P) and DNA(As) have similar dynamics in the Fis-DNA complex. The covariance matrix of the phosphate DNA-Fis interaction (B) is similar to that of arsenate DNA-Fis (C), with a correlation coefficient $R^2 = 0.56$. (D) The correlations of covariance matrix elements of tRNA(P) and tRNA(As) in tRNA-TiIS indicate that the dynamics of tRNA(P) and tRNA(As) are relatively similar. However, the covariance matrix of tRNA(P)-TiIS (E) presents a weaker correlation with the arsenate tRNA(As)-TiIS interaction (F), with a correlation coefficient of $R^2 = 0.3$. In Figures C, D, E, and F, red color indicates that two atoms move in same direction, blue a movement in opposite directions, and green color that the atoms move randomly with respect to each other.



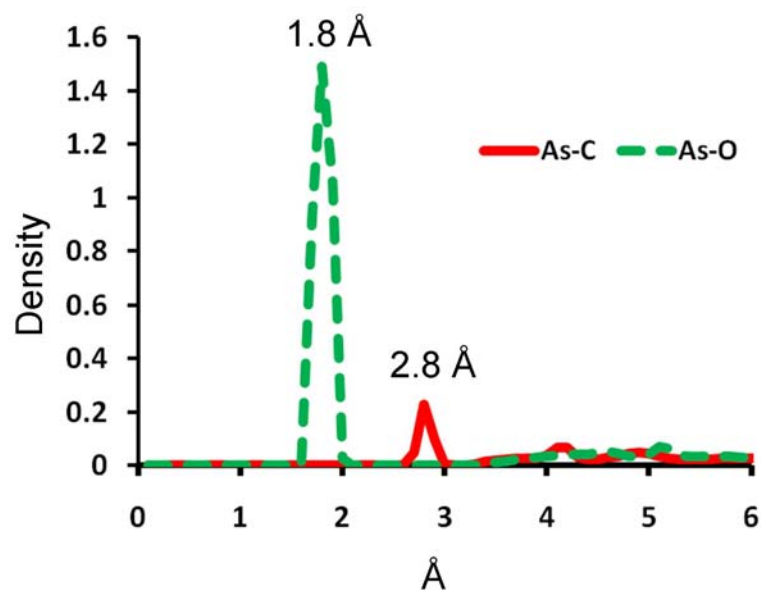
Sup-Figure 7. RMSDs and interaction energies of snapshots along the trajectories of DNA-protein and tRNA-protein complexes relative to their starting crystal structures from MD simulations indicate that arsenate-phosphate replacement introduces larger conformational changes in the tRNA-protein complex than in the DNA-protein complexes. (A) and (B) RMSDs and interaction energies of Phosphate and Arsenate DNA-IHF protein complexes. (C) and (D) RMSDs and interaction energies of Phosphate and arsenate DNA- RepE protein complexes. (E) to (J) Phosphate and arsenate tRNA-TiIS protein complexes at three different ionic conditions: ‘Hsp’ is for protonated TiIS histidines, ‘low’ for low ion concentration, and ‘high’ for high ionic concentration. Consistent with the TiIS functional domain movements, the TiIS-tRNA complex undergoes large conformational fluctuations during the simulations. At both low and high ionic concentrations, the TiIS-tRNA complex has larger conformational changes than the tRNA. However, with protonated histidines, the complex is able to follow the dynamics of the tRNA. At low ionic concentration, the arsenate substituted tRNA complex has lower fluctuations than the phosphate tRNA; at high ionic concentration, both phosphate and arsenate TiIS-tRNA have large RMSDs.



Sup-Figure 8. In the IHF-DNA and RepE-DNA complexes, arsenate-phosphate replacements cause changes in the conformational dynamics of the DNA and in DNA-protein interactions. However, correlation analysis of their covariance matrices indicates that the structural and dynamical properties of arsenate DNA and phosphate DNA do not present marked differences. The DNA in the IHF-DNA complex has a highly bent U-shape, and the IHF-DNA complex represents the extreme case of sensitivity due to arsenate-phosphate replacement. The covariance matrices of the two DNAs have a correlation coefficient of $R^2 = 0.45$ (A), lower than the Fis-DNA complexes. For the DNA-IHF protein interaction, the covariance matrix of phosphate DNA – IHF interaction (B) and that of arsenate DNA – IHF interaction (C) have a similar correlation coefficient of $R^2 = 0.48$. The DNA in the RepE-DNA complex is curved, but is less bent than the U-shaped DNA in the IHF-DNA complex. Thus, the correlation between the covariance matrices of phosphate and arsenate DNA is $R^2 = 0.62$ (D), which is less than that of Fis-DNA, but larger than of IHF-DNA. The covariance matrix of DNA(P)-RepE interaction (E) and that of DNA(As)-RepE complex (F) have a correlation coefficient of $R^2 = 0.4$, which is better than the tRNA-protein interaction ($R^2 = 0.3$) in Sup-Figure 6. In Figures C, D, E, and F, red color indicates that the two atoms move in same direction, blue color indicates that the two atoms move in opposite directions, and green color that the atoms move randomly with respect to each other.



Sup-Figure 9. Interaction energies for selected molecules in the 70S ribosome indicate that arsenate-phosphate replacement may hinder the assembly and proper function of 70S. Surface areas are not considered for the interaction energies in this figure. Four selected proteins [S16(A) , S4 (B), S17 (C), and S20 (D)] are important for 30S subunit assembly, yet their interactions with arsenate rRNA are systematically weaker than with phosphate rRNA. (E) Interaction energies of the E-site tRNA with other ribosome units are more repulsive for arsenate system. However, the interaction energies for arsenate P-site tRNA(As) with the RF2 protein (G) and other nearby molecules (E) are similar to that of phosphate P-site tRNA. It is interesting to note that arsenate mRNA is less repulsive to other molecules than phosphate mRNA (H), which could be due to the smaller size of mRNA compared with tRNA. If the repulsive interaction of mRNA is related to mRNA translation efficiency, arsenate mRNA could be less efficient than phosphate mRNA.



Sup-Figure 10. Radial distributions of As-O and As-C distances in the simulated 70S arsenate ribosome. The As-C nonbonding distances have been characterized to be 2.35Å and 2.92Å, while the radial distribution from the arsenate 70S ribosome is 2.8Å and there is no density around 2.35Å.

Supporting information, force field parameterization Table 1

The main CHARMM force field parameters of bond lengths (BL) and bond angles (BA) for arsenic and phosphorus^a in DNA and RNA.

As	Force constant	BL or BA	P	Force constant	BL or BA
As-O	190.0	1.82	P-O	270.0	1.60
As=O	420.0	1.65	P=O	580.0	1.48
As2 ^b -O	220.0	1.83	P2 ^b -O	300.0	1.68
As2=O	420.0	1.68	P2=O	480.0	1.53
O-As-O	50.0	100.0	O-P-O	80.0	104.3
O=As=O	80.0	127.0	O=P=O	120.0	120.0
O=As-O	70.0	108.6	O=P-O	98.9	111.6
As-O-As2	30.0	140.0	P-O-P2	15.0	140.0
		(40.0, 3.80) ^c			(-40.0, 2.80) ^c
As2-O-As2	30.0	140.0	P2-O-P2	15.0	140.0
		(-40.0, 2.90) ^c			(-40.0, 2.80) ^c
O-As2-O	60.0	104.3	O-P2-O	80.0	104.3
O=As2=O	40.0	120.0	O=P2=O	104.0	120.0
O=As2-O	68.9	111.6	O=P2-O	88.9	111.6

^a From reference (Foloppe, N.; MacKerell, J. A. D. *Journal of Computational Chemistry* **2000**, *21*, 86.)

^b As2 and P2 indicate pyroarsenate arsenic and pyrophosphate phosphorus, respectively.

^c The Urey-Bradley parameters for the corresponding bond angles.

^d the vdw radius of As atom is 2.25 and epsilon is -0.585.

Supporting information, Thermodynamics of hydrolysis of adenosine triphosphate and adenosine triarsenate obtained by quantum mechanical calculation at B3LYP/6-311++G** level of theory. ATP: adenosine triphosphate, ADP: adenosine diphosphate, ADP-AS: adenosine diphosphate arsenate, ATAs: Adenosine triarsenate, ADAs: adenosine diarsenate, AMP: adenosine monophosphate, AMAs, adenosine monoarsenate.

	ATP(Hartree)	ADP(Hartree)	AMP(Hartree)	Pi(Hartree)	PPI(Hartree)	H2O(Hartree)	Reaction 1 (Kcal/mol)	Reaction 4 (Kcal/mol)
Energies without zpve	-2665.51639	-2098.13188	-1530.74537	-643.85645	-1211.25604	-76.46648	-3.43	-11.63
Energies after zpve	-2665.23831	-2097.86749	-1530.49473	-643.81985	-1211.20429	-76.44528	-2.35	-9.68
thermal Energies (298.15k)	-2665.20855	-2097.84202	-1530.47358	-643.81427	-1211.19564	-76.44244	-3.32	-11.43
thermal Enthalpies (298.15k)	-2665.20761	-2097.84108	-1530.47264	-643.81332	-1211.19470	-76.44150	-3.32	-11.44
thermal Free Energies (298.15k)	-2665.30282	-2097.92560	-1530.54671	-643.84790	-1211.23741	-76.46293	-4.86	-11.52
	ATAS	ADAS	AMAS	ASi	PASI	H2O	Reaction 3	Reaction 5
Energies without zpve	-8348.72416	-5886.93615	-3425.14599	-2538.25761	-5000.06037	-76.46648	-1.96	-9.87
Energies after zpve	-8348.45719	-5886.67881	-3424.89893	-2538.22481	-5000.01571	-76.44528	-0.72	-7.64
thermal Energies (298.15k)	-8348.42402	-5886.65124	-3424.87668	-2538.21817	-5000.00524	-76.44244	-1.85	-9.70
thermal Enthalpies (298.15k)	-8348.42307	-5886.65029	-3424.87573	-2538.21723	-5000.00430	-76.44150	-1.85	-9.70
thermal Free Energies	-8348.52921	-5886.74105	-3424.95349	-2538.25463	-5000.05162	-76.46293	-2.23	-8.14

(298.15k)								
	APPAS						Reaction 2	
Energies without zpve	-4559.91972						-2.07	
Energies after zpve	-4559.64539						-1.02	
thermal Energies (298.15k)	-4559.61446						-2.06	
thermal Enthalpies (298.15k)	-4559.61352						-2.06	
thermal Free Energies (298.15k)	-4559.7125						-3.01	