JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Impact of Arsenic/Phosphorus Substitution on the Intrinsic Conformational Properties of the Phosphodiester Backbone of DNA Investigated Using ab Initio Quantum Mechanical Calculations

Elizabeth J. Denning and Alexander D. MacKerell, Jr.*

Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, 20 Penn Street, Baltimore, Maryland 21201, United States

Supporting Information

ABSTRACT: Deoxyribonucleic acid (DNA) is composed of five major elements carbon, hydrogen, nitrogen, oxygen, and phosphorus. The substitution of any of these elements in DNA would be anticipated to have major biological implications. However, recent studies have suggested that the substitution of arsenic into DNA (As-DNA) in bacteria may be possible. To help evaluate this possibility, ab initio quantum mechanical calculations are used to show that arsenodiester and phosphodiester linkages have similar geometric and conformational properties. Based on these results, it is suggested that the As-DNA will have similar conformational properties to phosphorus-based DNA, including the maintenance of base stacking.

DNA is composed of five elements: carbon, hydrogen, nitrogen, oxygen, and phosphorus.[1] Recently, a study was undertaken suggesting the possibility of sustaining life if one of these essential elements has been substituted.[2] In the study, Wolfe-Simon et al. using the GFAJ-1 strain from the Halomonadaceae family of Gammaproteobacteria obtained results suggesting that arsenate (AsO_4^{3-}) may be incorporated into the main biological macromolecules of the organism such as DNA, where it substitutes for phosphate (PO_4^{3-}), and may maintain cellular life.[2]

For arsenic (As) to be able to substitute for phosphorus (P) in biological molecules it is necessary that it have similar chemical properties. Consistent with As being on the same column of the periodic table as P, a number of physical properties of As and P, as well as of AsO_4^{3-} and PO_4^{3-}, have been shown to be similar, as overviewed by Wolfe-Simon et al.,[2] although the increased reactivity of an "arsenodiester" linkage may be inconsistent with the required stability of DNA to support life.[3] While questions exist it might still, theoretically, be possible for an organism to substitute As for P in oligonucleotides. However, for this to occur upon substitution of As for P in the phosphodiester backbone of DNA, the resulting arsenodiester linkage in As-DNA must have similar intrinsic conformational properties as the normal phosphodiester linkage in P-DNA in order for DNA to maintain its helical character. In the present communication it is shown using ab initio quantum mechanical (QM) calculations that an arsenodiester linkage does have similar conformational properties to that of a phosphodiester linkage, such that it may be predicted that As-DNA will have conformational properties similar to that of P-DNA.

Oligonucleotide conformational properties result from a combination of intrinsic conformational properties and environmental contributions. In a combined QM/Bioinformatics study we have shown that the conformational properties of a model compound, T3PS (Figure 1), representative of the phosphodiester linkage in DNA, are consistent with those of DNA in crystallographic structures, thereby indicating the contribution of the intrinsic conformational properties of the phosphodiester linkage to the conformation of DNA.[4] These contributions include the relative populations of the A, B_I, and B_{II} forms of DNA and the regions of backbone dihedrals being populated in DNA. Building upon that study, in the present work we perform ab initio calculations on the As analog of the compound T3PS (Figure 1) from which the conformational properties (i.e., the change in relative energy as a function of selected dihedral angles in the arsenodiester linkage) were determined and compared to those of the P containing model compound.

The model compounds P-T3PS and As-T3PS, (Figure 1), designed to represent the phospho- or an arsenodiester backbone of DNA, include the five rotatable torsions in the backbone (α, β, γ, ε, and ζ) along with capping furanose moieties; omission of the nitrogenous bases avoids confounding effects of these entities on the intrinsic conformational properties of the backbone as well as keeping the size of the compound computationally tractable. Potential energy surfaces were obtained via QM optimization at the MP2/6-31+G(d) level using the Gaussian03 package[5] with all degrees of freedom allowed to relax except for those that define the A, B_I, and B_{II} conformations, as previously presented.[4] The dihedral constraints were selected to sample energy surfaces of the target dihedrals consistent with the A, B_I, and B_{II} forms of DNA an approach validated previously in our laboratory (Table S1, Supporting Information).[6] Changes in potential energy as a function of the α, β, γ, ε, and ζ dihedral angles are presented in Figure 2 for As-T3PS along with those for the P analog from our previous study.[4]

In all the surfaces, the low energy regions correspond to torsion angle distributions obtained from surveys of DNA crystal structures, as previously discussed (Figure S1, Supporting Information).[4] Notably, the energy surfaces are remarkably similar for As-T3PS and P-T3PS (Figure 2). The largest differences occur in the high-energy regions of the surfaces (e.g., ~60° for the α surface), which are typically not sampled in the canonical forms of DNA. In the low energy regions, the largest differences occur with the B_{II} form of DNA, although these differences are small.

Received: February 8, 2011
Published: March 28, 2011

dx.doi.org/10.1021/ja201213b | J. Am. Chem. Soc. 2011, 133, 5770–5772

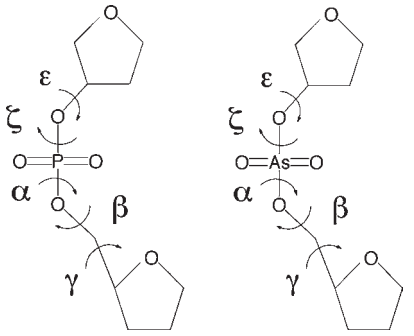

Figure 1. Model compounds P-T3PS, left, and As-T3PS, right, that are used to represent the DNA diester backbone. The α, β, γ, ε, and ζ dihedrals for which potential energy surfaces were calculated are shown.

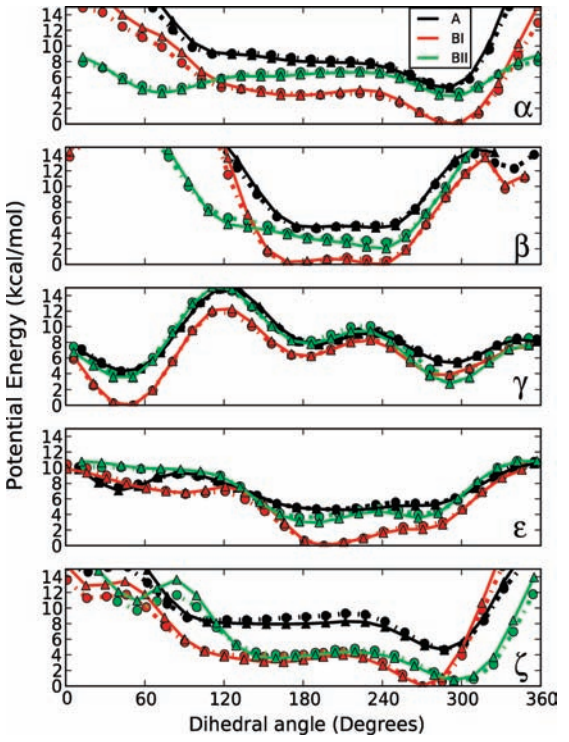

Figure 2. Potential energy surfaces for the α, β, γ, ε, and ζ dihedrals for the model compounds shown in Figure 1. Surfaces were obtained via MP2/6-31+G* optimizations with the remaining phospho- or arseno-diester dihedrals and selected furanose dihedrals constrained to values mimicking the A, B_I, and B_{II} of DNA (details in Table S1, Supporting Information). [Triangle, solid line: P-T3PS; Circle, dashed line: As-T3PS].

Single-point energy calculations[7] at the RIMP2/cc-pVTZ level (Table S2, Supporting Information) on the P-DNA energy minima yield relative energies similar to those shown in Figure 2. These results indicate that substitution of As for P in DNA will lead to As-DNA exhibiting conformational properties similar to P-DNA. However, even small differences in potential energies may lead to changes in the global conformational properties of duplex DNA as they are dictated by the free energy of the macromolecule and its environment.

While the relative energy surfaces are similar, geometric properties about the As atom as well as of the overall model compound need to be considered. The As−O bonds are longer than the P−O bond lengths by 0.12 to 0.15 Å, but the angles are similar. While local differences in the geometry about the As vs P atom are present, the overall geometry of the model compound, as judged by the average C1′−C1′ distance between the furanose rings, are nearly identical (Table 1). The C1′−C1′ behavior for As-T3PS and P-T3PS also mirror each other as a function of the diester torsions with distances ranging from 3 to 4 Å in the low-energy regions and 8 to 10 Å in the high-energy regions (Figure S2, Supporting Information). These similarities are important as it indicates that As substitution would theoretically preserve the distance between adjacent nitrogenous bases, thereby maintaining base stacking, one of the major classes of interactions influencing the structure and stability of DNA.[8,9]

Table 1. Selected Geometric Values for the As vs P T3PS Model Compounds[a]

Geometric Property	X = As	X = P
X−O5′ (Bond)	1.80 ± 0.01 Å	1.68 ± 0.03 Å
X−O3′ (Bond)	1.81 ± 0.01 Å	1.69 ± 0.01 Å
X−O2P (Bond)	1.65 ± 0.01 Å	1.50 ± 0.01 Å
X−O1P (Bond)	1.65 ± 0.01 Å	1.51 ± 0.01 Å
O5′−X−O3′ (Angle)	127° ± 4°	125° ± 2°
O1P−X−OP2 (Angle)	96° ± 4°	98° ± 3°
C1′−C1′ (Distance)	4.73 ± 1.67 Å	4.76 ± 1.61 Å

[a] Mean values and standard deviations are based on the lowest-energy conformation from each of the backbone dihedral surfaces.

Overall, the presented ab initio QM calculations show that both As-T3PS and P-T3PS exhibit similar conformational properties along the diester backbone. In addition, the internal geometry associated with As substitution will not significantly impact the geometry of DNA backbone with respect to sugar−sugar distances such that base stacking is predicted to be maintained. These results suggest that As-DNA will assume conformations similar to that of traditional DNA, allowing other biological molecules, including proteins, to interact with As-DNA.

■ ASSOCIATED CONTENT

Supporting Information. Tables of the constraints used in the QM calculations and relative energies of selection conformers, figures showing the MP2/6-31G* energy surfaces/crystal survey probability distributions and the C1′−C1′ distances as a function of backbone torsions, and full citations for refs 5 and 7 are included. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
alex@outerbanks.umaryland.edu

■ ACKNOWLEDGMENT

Financial support is acknowledged from the NIH (GM051501), and we thank Profs. Peter Swaan and C.S. Raman for helpful discussions.

■ REFERENCES

(1) Berg, J.; Tymoczko, J.; Stryer, L. *Biochemistry*, 6th ed.; WH Freeman & Co: New York, 2007.

(2) Wolfe-Simon, F.; Blum, J. S.; Kulp, T. R.; Gordon, G. W.; Hoeft, S. E.; Pett-Ridge, J.; Stolz, J. F.; Webb, S. M.; Weber, P. K.; Davies, P. C. W.; Anbar, A. D.; Oremland, R. S. *Science* **2010**, Article ASAP, DOI: 10.1126/science.1197258.
(3) Fekry, M. I.; Tipton, P. A.; Gates, K. S. *ACS Chem. Biol.* **2011**, Article ASAP, DOI: 10.1021/cb2000023.
(4) MacKerell, A. D., Jr. *J. Phys. Chem. B* **2009**, *113*, 3235–3244.
(5) Frisch, M. J. et al. *Gaussian03*; Gaussian, Inc: Wallingford CT, 2004.
(6) Foloppe, N.; Nilsson, L.; MacKerell, A. D., Jr. *Biopolymers (Nucleic Acid Sciences)* **2002**, *61*, 61–76.
(7) Shao, Y.; et al. *J. Phys. Chem. Chem.* **2006**, *8*, 3172–3191.
(8) Calladine, C. R. *J. Mol. Biol.* **1982**, *161*, 343–352.
(9) Marky, L. A.; Breslauer, K. J. *Biopolymers* **1982**, *21*, 2185–2194.