# How Does the Solvation Unveil AtO+ Reactivity?

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S *Supporting Information*

ABSTRACT: The AtO+ molecular ion, a potential precursor for the synthesis of radiotherapeutic agents in nuclear medicine, readily reacts in aqueous solution with organic and inorganic compounds, but at first glance, these reactions must be hindered by spin restriction quantum rules. Using relativistic quantum calculations, coupled to implicit solvation models, on the most stable $AtO^+(H_2O)_6$ clusters, we demonstrate that specific interactions with water molecules of the first solvation shell induce a spin change for the AtO+ ground state, from a spin state of triplet character in the gas phase to a Kramers-restricted closed-shell configuration in solution. This peculiarity allows rationalization of the AtO+ reactivity with closed-shell species in aqueous solution and may explain the differences in astatine reactivity observed in ^{211}At production protocols based on "wet" and "dry" processes.
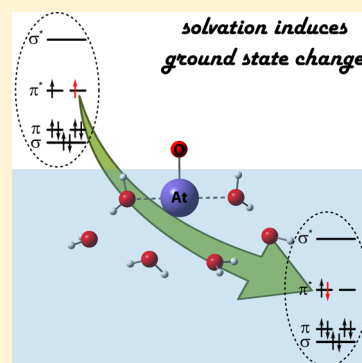
INTRODUCTION

Astatine (At) is the heaviest halogen (element 85), found below iodine in the periodic table of the elements. It is a rare radioelement; all of its isotopes are short-lived. ^{211}At is of considerable interest as it is a promising radiotherapeutic agent for targeted alpha therapy in nuclear medicine. It is a 100% α-particles emitter, with a half-life of 7.2 h. A carrier molecule must transport ^{211}At to the cancer cells, while α-particles emitted by the radionuclide allow destroying of the target. Two recent reviews summarize the use of At as a radiotherapeutic agent.[1,2] Binding At to cancer selective carrier molecules remains, however, a difficult task as the chemistry of this "invisible" element is simply not well understood. ^{211}At is produced in cyclotrons, and all investigations were consequently derived from radiochemical studies at ultratrace concentrations (typically smaller than 10^{-10} mol L^{-1}). Therefore, no spectroscopic tools can be used to assess At chemistry at the molecular level. This clearly limits the development of efficient labeling protocols. Molecular modeling is a valuable tool to gain an insight into At reactions.[3,4] We have recently identified one predominant form of At in water and oxidizing conditions, namely, AtO+.[4,5] The use of this cationic species for the binding of At to carrier molecules may be an efficient alternative.[1] Considering the experimental labeling conditions (pH-E_h), it might be currently used for the binding of At to boron cage compounds.[6] Several studies have shown the formation of complexes between AtO+ species and simple organic and inorganic ligands.[3,7−9] In fact, this behavior is quite surprising as AtO+ shares a priori the same spectrum, arising from the $(\pi^*)^2$ electronic configuration, of the chalcogen

dimers. Both free AtO+ and O_2 molecules adopt a triplet spin multiplicity for their electronic ground states, $X^3\Sigma^-$ and $X^3\Sigma_g^-$ respectively (see Figure 1). This fact has severe consequences for O_2; the molecule is nonreactive with most compounds, both in the gas phase and in solution.[10,11] The latter being usually closed-shell species, the reaction with triplet molecular oxygen
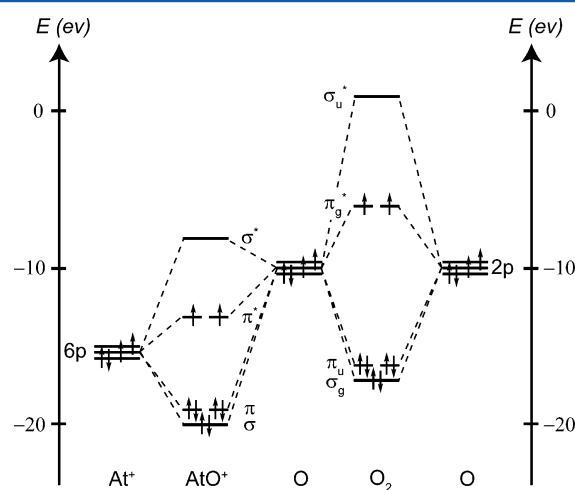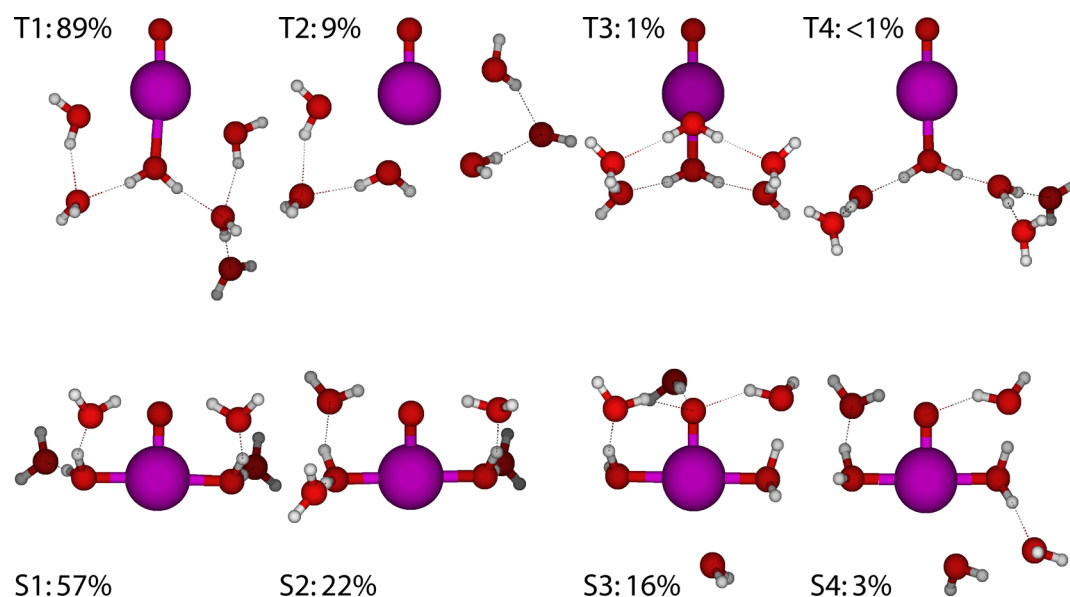

Figure 1. Schematic energy diagrams obtained from M06-2X/mAVDZ calculations on free AtO+ ($X^3\Sigma^-$) and O_2 ($X^3\Sigma_g^-$) species.

Figure 2. Molecular structures and Boltzmann populations of the four most stable $AtO^+(H_2O)_6$ clusters computed at the M06-2X/mAVDZ level of theory for the triplet (top, T index) and singlet (bottom, S index) spin multiplicities. Color code: magenta for At, red for O, and gray for H.

is spin-forbidden. It has recently been shown in the series of chalcogen diatomics that the ordering between the triplet ground state and the first singlet excited state could not be inverted by relativistic effects even for the heavier chalcogens.[12] In this article, we address the question of why the AtO^+ species is highly reactive in aqueous solution.

In order to tackle the title question, we have focused our attention on clusters of AtO^+ with six water molecules. At first glance, this approach may appear modest because we are limiting the number of explicit water molecules. Our intention is not to simulate the full solvation process but rather to use an appropriate model to provide insight into the specific localized AtO^+-solvent interactions. We have furthermore carried out implicit solvation calculations to account for long-range bulk effects on the solute. The $AtO^+(H_2O)_6$ clusters have been studied at both triplet and singlet spin multiplicities. Consideration of relativistic effects is essential to the theoretical description of molecules that contain heavy elements such as At. Previous theoretical investigations have notably shown that the reactivity of the cationic forms of At is highly sensitive to spin-orbit coupling (SOC).[3] The most accurate approach to incorporate relativity would be to perform four-component (4c) calculations based on the many-electron Dirac–Coulomb–Breit equation. However, their use is still limited to small molecules, and several alternative two-component (2c) approaches have been proposed. Due to the computational expediency and the implicit inclusion of electron correlation effects, the spin-orbit DFT (SODFT) method available in the NWChem programs package[13] appears particularly attractive. The inclusion of spin-dependent terms into the variational treatment of the one-electron operator ensures that scalar-relativistic and spin-orbit effects are treated on an equal footing. The SODFT method has been successfully used to investigate relativistic effects on molecules containing At.[3–5,14–16] In order to highlight the SOC effects on the AtO^+ solvation, scalar-relativistic results are discussed first, while quasirelativistic calculations that take into account spin-orbit effects are investigated in a second step.

■ COMPUTATIONAL DETAILS

The energies, structures, and vibrational properties of the most stable stationary points of the triplet and singlet potential energy surfaces have been first determined through DFT calculations. Due to its efficiency for accurately predicting (i) singlet–triplet transition energies and (ii) nonbonding interactions including hydrogen bonding, we have selected the recently introduced M06-2X meta hybrid functional.[17,18] We have used the small-core ECP60MDF pseudopotential (PP) in conjunction with a modified aug-cc-pVDZ-PP (mAVDZ) basis set for the At atom[3,19] and the aug-cc-pVDZ basis set for H and O atoms.[20,21] On the optimized structures, single-point ab initio energy calculations have been carried out using MP2 and CCSD(T) methods. The aug-cc-pVTZ-PP-2c (AVTZ-2c) basis set[22] was used for the At atom in conjunction with the aug-cc-pVTZ basis set[20,21] for H and O atoms. For the sake of simplicity, Gibbs free energies calculated using (i) either MP2 or CCSD(T) energies and (ii) M06-2X structural and vibrational properties will be referred, respectively, to as MP2//M06-2X and CCSD(T)//M06-2X throughout the text. Note that all scalar-relativistic calculations have been carried out using the Gaussian program package.[23]

Starting from the previous wave functions and structures localized on the triplet and singlet potential energy surfaces, 2c-M06-2X/mAVDZ geometry optimizations have been performed following the SODFT framework.[13] The reader can find detailed coverage of the spin-orbit DFT methods in refs 24 and 25. Harmonic vibrational frequencies were evaluated by two-sided finite differences of analytical gradients. On the previous 2c-M06-2X/mAVDZ optimized structures, single-point energy calculations have been carried out using (i) the above-mentioned PP and triple-ζ basis sets and (ii) the 2c-MP2 method[22] and the resolution of the identity technique as implemented in the TURBOMOLE program package.[26] Note that the core electrons were frozen for all post-HF calculations (notably the 5s, 5p, and 5d inner cores of At). For the sake of simplicity, free energies calculated using (i) 2c-MP2/AVTZ-2c energies and (ii) 2c-M06-2X/mAVDZ structural and vibra-

tional properties will be referred to as 2c-(MP2//M06-2X) throughout the text.

Free energies of the clusters in solution were derived by means of a thermodynamic cycle applied to systems in the gas phase, with corrections for solvation energies (see Scheme S1 in the Supporting Information). Gibbs free energies of aqueous solvation were computed using the CPCM continuum model.[23,27] This implicit solvation model used in conjunction with HF calculations and the UAHF cavity model[28] yields accurate solvation free energies at a very low computational cost.[29] For the At atom, we have retained the basic radius (R_0) and charge factor (γ_q) recently introduced in agreement with the other UAHF parameters.[3,5] Note that for the comparison of the free energies of the various $AtO^+(H_2O)_6$ clusters in water, we have retained only the electrostatic term in the CPCM calculations (the dispersion and repulsion terms are notably unavailable for At). It is well-known for charged species that the contribution of nonelectrostatic terms is especially weak.[30] The solvation free energies were estimated through single-point HF energy calculations using the above-mentioned PP and double-ζ basis sets. For each cluster, both geometries optimized at M06-2X and 2c-M06-2X levels have been considered.

RESULTS AND DISCUSSION

Scalar-Relativistic Calculations. Among the 18 $AtO^+(H_2O)_6$ clusters localized at the M06-2X/mAVDZ level of theory, the predicted most stable for each spin multiplicity are displayed in Figure 2. The structures of the triplet species exhibit extremely different patterns from those of the singlet ones. The water molecules are essentially connected within a network of hydrogen bonds, which is organized around one water molecule. The latter seems to be linked to At through halogen bonding, as witnessed by the linearity of the interaction (close to 180°) between the water oxygen atom (donor) and the AtO^+ fragment. In the case of the most stable singlet species, two water molecules bind to At such that At adopts a T-shape structure. The remaining water molecules are mainly engaged in hydrogen bonds with the two previous ones and some of them with the oxygen atom of AtO^+. We have calculated the gas-phase free-energy difference between the most stable clusters of each spin multiplicity (T1 ($^1A'$) and S1 (^3A) species in Figure 2. Unexpectedly, we found the singlet species to be more stable than the triplet one. Its greater stability was as large as 39.5 kJ mol^{-1}. We have evaluated how the basis set superposition error (BSSE) affects this value. Using the counterpoise methodology with monomer relaxation, we found a small decrease of 3.5 kJ mol^{-1}, and BSSE was neglected in what follows.

We have then estimated the free energy of (i) the full population of the triplet clusters and (ii) the full population of the singlet clusters according to the following relation

$$G^{\circ}_{\{A\}} = -RT \ln \sum_{i \in \{A\}} e^{-G^{\circ}_i / RT}$$

where {A} emphasizes calculation over the population of all A clusters (A being a triplet or singlet). The results show that the singlet clusters are 40.4 kJ mol^{-1} more stable than the triplet ones (see Table 1). Hence, we are confident that missing one or more clusters during the scan of the potential energy surfaces could not alter significantly the trend, that is, the singlet state is more stable than the triplet one. If we consider the bulk electrostatic contribution provided by CPCM-UAHF

Table 1. Gibbs Free-Energy Difference (kJ mol^{-1}) between the Singlet and Triplet $AtO^+(H_2O)_6$ Clusters Computed at Various Levels of Theory

theory	$\Delta G^{\circ}_{\text{sing-trip}}$ (g)	$\Delta G^{*}_{\text{sing-trip}}$ (aq)
M06-2X/mAVDZ	−40.4	
+ CPCM-UAHF		−49.7
MP2/AVTZ-2c	−138.3	
+ CPCM-UAHF		−138.7
CCSD(T)/AVTZ-2c	−90.1	
+ CPCM-UAHF		−100.3
2c-M06-2X/mAVDZ	−10.1	
+ CPCM-UAHF		−28.2
2c-MP2/AVTZ-2c	−122.0	
+ CPCM-UAHF		−135.3

solvation calculations, the singlet clusters become even more stable, by 49.7 kJ mol^{-1}. Therefore, the combined contributions of specific interactions (hydrogen bonding, charge transfer to the At atom) with water molecules of the first solvation shell and long-range bulk effects of the solvent are able to change the ground state of the AtO^+ molecular ion. This behavior contrasts with the case of molecular oxygen, where solvation effects could not lift off the spin restriction rule; the ground state remains triplet and inhibits the O_2 reactivity.[31] A priori, this fact is a decisive element for understanding AtO^+ reactivity; as it adopts a stable closed-shell form in water, it can readily react with most compounds that are singlet spin multiplicity.

Wave function theory (WFT) calculations support and reinforce the DFT results (see Table 1). The free-energy difference between the singlet and triplet clusters, calculated using either MP2//M06-2X or CCSD(T)//M06-2X single-point energies, is even greater. The singlet clusters are more stable by 138.7 and 100.3 kJ mol^{-1}, respectively, if the solvation free energies obtained from CPCM-UAHF calculations are added to the computed gas-phase free energies. Note that MP2/AVTZ-2c and CCSD(T)/AVTZ-2c calculations are not performed on the geometries optimized at these levels of theory, which may partly explain the difference between the later values and the one obtained at the M06-2X/mAVDZ level of theory. The influence of the selected continuum model on the description of the long-range bulk effects was also investigated. Using the alternative SMD solvation model,[32] we found no significant differences on the calculated free-energy difference between the singlet and triplet clusters (see Table S1 in the Supporting Information).

Quasirelativistic Calculations. The 2c wave functions are variationally optimized from the singlet and triplet wave functions obtained by scalar-relativistic calculations. Despite the fact that the expectation value of the total spin, $\langle S^2 \rangle$, or the number of unpaired electrons, N_S, is no longer an observable, their values are reported in the Supporting Information (see the Table S2) as they have at least a certain practical meaning for the characterization of the electronic state. The SOC effects on the AtO^+ solvation are evidenced through the comparison of scalar-relativistic and quasirelativistic results. Figure 3 displays the obtained structures at the 2c-M06-2X/mAVDZ level of theory for the most stable $AtO^+(H_2O)_6$ clusters. The explicit inclusion of SOC in the calculations induces smaller geometrical relaxations for the species issued from a singlet electronic state than those for the ones issued from a triplet electronic state. The relative stabilities of various clusters are also modified (see Figure 2 and Figure S1 in the Supporting
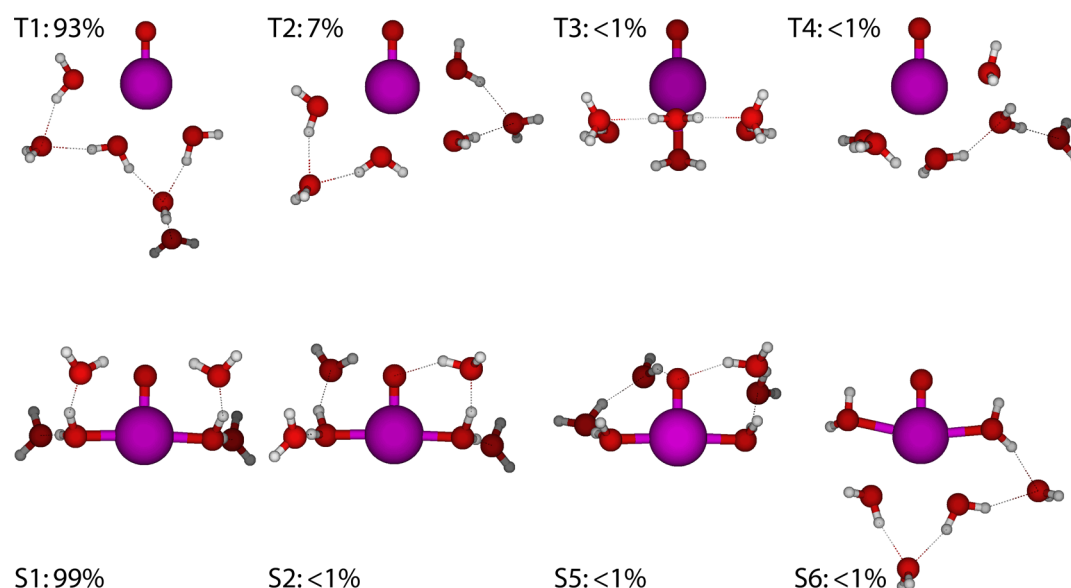
Figure 3. Most stable $AtO^+(H_2O)_6$ clusters obtained at the 2c-M06-2X/mAVDZ level of theory from the triplet (top, T index) and singlet (bottom, S index) electronic states. Boltzmann populations are corrected from the solvent effects contribution (CPCM-UAHF computations). Color code: magenta for At, red for O, and gray for H.

Information). The computed gas-phase free energies augmented by solvation free energies obtained from CPCM-UAHF calculations (see Table 1) show that the species issued from a singlet electronic state are 28.2 kJ mol^{-1} more stable than the ones issued from a triplet electronic state. Therefore, DFT and SODFT calculations agree to predict a closed-shell ground state for AtO^+ in aqueous solution. The finding was also confirmed by quasirelativistic WFT calculations; the free energies calculated using 2c-(MP2//M06-2X) single-point energies and the bulk electrostatic contribution provided by the CPCM-UAHF solvation model yield a difference of 135.3 kJ mol^{-1} in favor of the species issued from a singlet electronic state. Nevertheless, we presume that the latter result is somewhat overestimated on the basis of scalar-relativistic results (see Table 1). Previous CCSD(T) calculations have shown a decrease of about 40 kJ mol^{-1} on the energy difference between singlet and triplet clusters with respect to the MP2 values. This may result from the partial multiconfigurational character of the wave function of some triplet clusters (witnessed by the T1 diagnostic values reported in the Supporting Information, Table S2), which is not well accounted for by the MP2 method. The basis set dependence of the free-energy difference calculated at the quasirelativistic level of theory was also investigated. As expected, a quantifiable dependence was found for 2c-MP2 calculations (but this does not alter the trends drawn above), while rather small effects were noticed for 2c-M06-2X calculations (see Table S1 in the Supporting Information). At last we noticed that SOC in both WFT and DFT calculations stabilizes more the species issued from a triplet electronic state and therefore reduces the free-energy gap with the species dominated by a Kramers-restricted closed-shell configuration.

CONCLUSIONS

Using scalar and quasirelativistic quantum calculations, we have determined the stability of $AtO^+(H_2O)_6$ clusters for the lower states arising from the triplet and singlet spin multiplicities. The bulk solvent effects were included at all stages by means of

implicit models. The fact that AtO^+ reacts with closed-shell species may be explained by the mixing of pure triplet and singlet electronic states, which partially suppresses the spin restriction rule. However, we show that there is no need to invoke relativistic effects such as the SOC to understand the AtO^+ behavior in aqueous solution. It mainly originates from strong short-range interactions with the water molecules in the first solvation shell. These specific interactions allow the gas-phase ground state, of triplet spin multiplicity ($X^3\Sigma^-$ denoted $X_1 0^+$ with SOC), to become dominated in solution by a Kramers-restricted closed-shell configuration resembling a scalar-relativistic singlet. Obviously, just introducing the AtO^+ molecule into an implicit solvation model could not reproduce this phenomenon. To the best of our knowledge, this ground-state change for a molecular species between the gas and aqueous phases seems to be unique and exclusive to AtO^+. This original information brings to light a very recent turnaround regarding the process for extracting At from the irradiated target in a cyclotron. While working for 2 decades on the ^{211}At-labeling of compounds for potential uses in therapy on humans, Wilbur and co-worker moved in 2011 from the classic distillation procedure (also known as "dry extraction"; At is first obtained in gas phase) to the "wet extraction" (At is first obtained in an acidic aqueous solution) to gain usable ^{211}At for their in vivo evaluations.[33] We believe that there may exist a correlation with the predicted difference of reactivity between gas and aqueous phases for the chemical form of At. We hope that this finding may help to rationalize the currently developed labeling protocols for nuclear medicine.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Supplementary figure of molecular structures, a scheme showing the thermodynamic cycle applied to the calculation of the Gibbs free-energy difference, and tables of the Gibbs free-energy differences and computed expectation values, in addition to the geometries of the 18 clusters optimized at the 2c-M06-2X/mAVDZ level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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5211

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