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2 AUTHORS:

Elizabeth A L Gillis
University of British Columbia - Vancouver
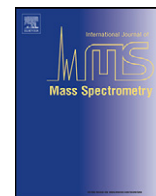**12** PUBLICATIONS **185** CITATIONS

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The hydrated Li⁺–adenine–thymine complex by IRMPD spectroscopy in the N–H/O–H stretching region

Elizabeth A.L. Gillis, Travis D. Fridgen *

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, A1B 3X7 Canada

ABSTRACT

The interaction of lithium ions with the nucleic acid bases which make up the A:T base pair, adenine and thymine, as well as the hydration of the complex by one water molecule has been studied in the gas phase. An IRMPD spectrum is reported for [A–T–Li⁺]–H_2O (A = adenine, T = thymine) over the N–H stretching region, 3200–3800 cm⁻¹. Calculations were performed using the B3LYP density functional and 6-31+G(d,p) basis set as well as MP2/6-311++G(2d,p) theory to model the thermochemistry and infrared spectra of potential structures. Theory and experimental results were used to determine possible structures of each complex. These structures, along with their corresponding thermochemical and spectroscopic data, are reported here. The lithium cation was found to bond most favorably to the O4 oxygen of thymine, and the water molecule was found to bind to the lithium cation. The adenine moiety of the complex is that of the A7 tautomer, leading to an A:T base pair which is not the canonical form. Based on the analysis, a number of low energy, intramolecular hydrogen-bonded structures are suggested as being present in the gas phase and thus responsible for generating the experimental infrared multi-photon dissociation (IRMPD) spectrum.

1. Introduction

The interaction of metal ions with DNA can have considerable consequences depending on the location of binding [1]. For example, a stabilizing effect is observed when a metal ion interacts with a phosphate group of the nucleic acid chain because of charge neutralization. On the other hand, binding of metal ions with nucleic acid bases can lead to competition for the hydrogen bonding system of Watson–Crick pairs, bringing about a disruption in the double helix [1–3]. The presence of ions, undoubtedly then, can have consequences on the structure of DNA. For instance, the coordination of divalent metal cations with purines has been shown to help stabilize a triplex DNA structure [4]. Using X-ray diffraction and NMR spectroscopy, Williams and co-workers [5] have identified monovalent metal cations in the minor groove of DNA with AT-tracts having been found to associate to significant amounts of cations. The 5′ A_pT 3′ steps are thought to bind hard monovalent cations with four oxygen atoms from DNA and two from water [6]. The presence of these solvated cations would obviously have effects on structure and function (e.g., recognition processes) of DNA. Thus, it is advantageous to investigate the interaction between nucleobases and metal ions to further understand the role of metal

ions in DNA processes. The two bases involved in this region (AT tract) are the pyrimidine base thymine (T) and the purine base adenine (A). Together, they form one of the major base pairs in the double helical structure of DNA [7]. The interactions of adenine and thymine with a wide range of metal ions including alkali metals, alkaline earth metals, and transition metals have been previously examined [4,8–25]. Of particular interest to this study, their interaction with the lithium cation has been extensively examined [2,8,9,11,13,15,17,20,23,25–29].

The tautomerization process is quite important when studying DNA as mispairing of bases in tautomeric form can lead to mutations within biological systems [1]. Tautomerism of thymine and adenine has been previously studied [30–41] and should be considered when examining the interaction between ions and nucleobases. While the canonical structure is the lowest energy structure when considering the base on its own, the interaction with metal cations can help stabilize higher energy tautomers so much that they become lower in energy than the canonical structure. This feature has been explored in a number of studies on tautomeric forms of thymine and adenine interacting with metal ions [17,18,20,22,23,25,32,42]. For example, in work by Rajabi et al. [18], the interaction of alkali metals with adenine revealed an exclusive preference for the A7 tautomer of adenine with alkali metal ions bound in a bidentate fashion at the N3 and N9 positions.

To be able to understand and predict the interactions of these bases in their natural environment (aqueous), one must understand their interactions with water and the role it plays in hydrogen bond-

* Corresponding author. Tel.: +1 709 737 8083.
  E-mail address: tfridgen@mun.ca (T.D. Fridgen).

ing and structure [43,44]. A number of studies have contributed to better understanding the behavior of nucelobases in the presence of water [35,37,39,43–65]. The spine of hydration, a network of water molecules in the AT minor groove, has been suggested to allow for the integration of sodium ions into the minor groove [66]. Thus, water molecules can play a crucial role in the structure and energetics of ion–base complexes. Microhydration, or the addition of water one unit at a time to a molecule of interest, allows one to investigate how these properties change during the solvation process [55]. For example, the interaction of water molecules with thymine–Li+ complexes has been reported [11], with the addition of one water molecule to a linear lithium bound thymine dimer leading to the formation of a hydrogen-bonded system similar to that seen in Watson–Crick pairing. Whether microhydrated or in a bulk environment, water has also been found to bring extra stabilization to tautomeric forms of bases such that the energy gap between these higher energy isomers and the canonical form is decreased [37,39,51]. Tautomerization is also often brought about by the presence of water as was the case in the work by Fogarasi where the tautomerization of cytosine has been studied as mediated by a single water molecule [47]. In the case of adenine and thymine, recent work has shown that a double proton transfer mechanism, aided by the presence of two water molecules, can lead to stable tautomers of the A:T base pair in the gas phase [67].

In this work, the interaction of the A:T base pair with a lithium cation and one water molecule is examined. While the [A–T–Li+] structure has been studied in the past, the studies were limited as the interaction was looked at strictly in terms of the Watson–Crick canonical form of the base pair [8,26]. Thus, tautomeric forms of the nucleobases (which can play an important role) were not examined. This has also been the case with the interaction of the A:T base pair with other metal ions [68]. Studies on base pairing in the absence of metal ions have also begun to show the importance of tautomeric forms. For example, in work by Plützer et al. [69], the IR–UV spectrum of A–T provided evidence of non-Watson–Crick pairing of adenine and thymine in the gas phase, which was later supported through anharmonic vibrational analysis [70]. As pairing of tautomeric forms of base pairs, or "abnormal pairing", is of interest in terms of mutations [1,35], it is clearly of importance in the biological field.

Over the past number of years, IRMPD spectroscopy has proven to be a valuable tool for obtaining structural insight into protonated and metal ion complexes of small biological molecules including amino acids, nucleobases, and peptides [71–73]. In this study, the technique is used in combination with computational methods to determine the structure of a lithium–A:T base pair complex as solvated by one water molecule.

2. Methods

2.1. Experimental

An ApexQe 70 Bruker Fourier Transform Ion Cyclotron Resonance (FT-ICR) coupled to a 10 Hz Nd:YAG pumped OPO (KTP, Euroscan) was used for this study. DNA bases and lithium chloride were purchased from Sigma–Aldrich and used without further purification. [A–T–Li+] complexes, m/z = 268, were electrosprayed from 1 mM concentration of aqueous adenine to which a few drops each of 2.5 mM thymine solution and 0.01 M LiCl were added. Solutions were prepared using 18 MΩ Millipore water. Hydration was performed in the accumulation/collision hexapole which was held at $\sim 10^{-2}$ mbar with water vapor as described previously by Rajabi et al. [74] [A–T–Li+]–H$_2$O, m/z 286, was then transferred to the ICR cell where it was isolated and irradiated for 3 s with the OPO laser.

A typical dissociation enthalpy[1] of the [A–T–Li+]–H$_2$O complexes observed in this study has been calculated to be on the order of 81 kJ mol^{-1}, significantly higher than the energy of a single photon over the energy range studied ($\sim$38–46 kJ mol^{-1}). As such, the dissociation of the complex under study would have been the result of the absorption of energy from multiple infrared photons. The scan rate was 0.15 cm^{-1} s^{-1} corresponding to a step size of 0.45 cm^{-1} between points in the IRMPD spectrum which was collected over the 3200–3800 cm^{-1} N–H/O–H stretching region. IRMPD efficiency is defined as the negative of the natural logarithm of precursor ion intensity divided by the sum of the fragment and precursor ion intensities.

2.2. Computational

Calculations were performed using the Gaussian 03 suite of programs [75] with input created using Gaussview 3.0 [76]. Geometry optimizations and frequency calculations were performed using the B3LYP density functional and 6-31+G(d,p) basis function. Additional single point energy calculations were completed at the MP2 level of theory with the 6-311++G(2d,p) basis set on the B3LYP/6-31+G(d,p) optimized geometries. The reported thermochemical results are a combination of the MP2/6-311++G(2d,p) electronic energies using uncorrected thermal corrections and entropies from the B3LYP/6-31+G(d,p) calculations and are designated as MP2/6-311++G(2d,p)//B3LYP/6-31+G(d,p) thermochemistries. All calculated frequencies were scaled by a factor of 0.958 in accordance with that suggested for the level of theory and basis set [77]. The predicted spectra were convoluted with a Lorentzian profile with a FWHM of 10 cm^{-1}.

3. Results and discussion

The IRMPD spectrum was collected for the hydrated adenine–thymine–lithium cation complex [A–T–Li+]–H$_2$O, and is reported here. The observed dissociation pathway of the solvated complex was by the loss of water and can be expressed by:

$$[A–T–Li^+]–H_2O\,(m/z\,286) \rightarrow [A–T–Li^+]\,(m/z\,268) + H_2O \qquad (1)$$
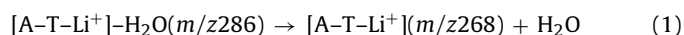
The calculated structures of [A–T–Li+] will be discussed prior to the hydrated form.

3.1. [A–T–Li+]

Calculated structures of the non-hydrated complex are presented in Fig. 1 and supplementary information Fig. S1. Corresponding energies are listed in Table 1. One challenging feature of adenine is the number of tautomers that can exist due to a lowering in energy through the interaction with metal ions. The two tautomers of adenine considered here (as interacting with the lithium cation) along with the canonical form are presented in Scheme 1 with numbering consistent with the literature [14]. While the stability of the lone adenine structures decreases A9 > A7 > A19r, our work shows that the interaction of adenine with lithium changes the order of stability such that A19r–Li+ is the lowest in ΔH over A7–Li+ and A9–Li+ by 8.0 and 34.7 kJ mol^{-1}, respectively. This is consistent with the work of Russo et al. where the A7–Li+ and A9–Li+ structures differed from A19r–Li+ by 9.03 and 41.7 kJ mol^{-1}, respectively [23]. Additionally, previous studies on adenine from our group have shown evidence of the A7 tautomer being present exclusively in systems involving the interaction with alkali metals

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[1] MP2/6-311++G(2d,p)//B3LYP/6-31+G(d,p) thermochemistry on the lowest energy complex.
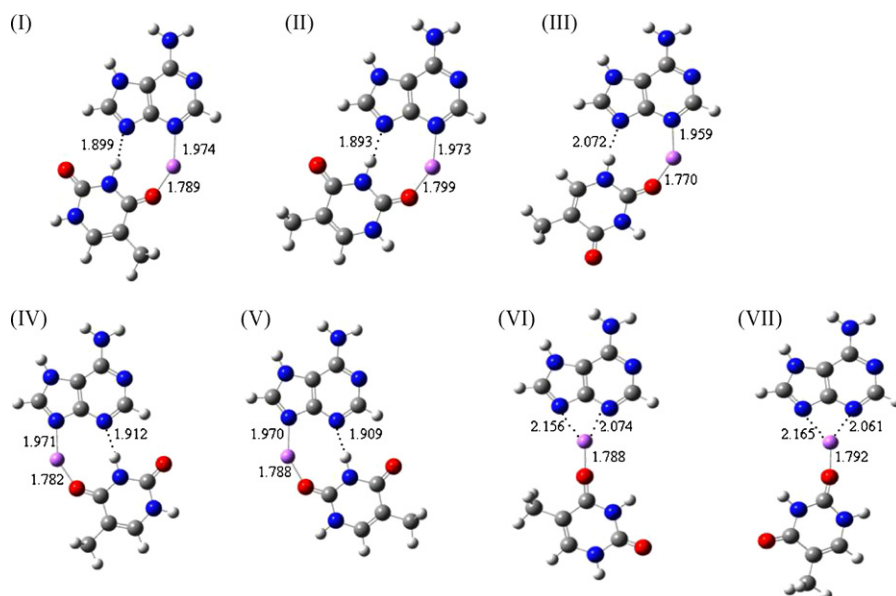
Fig. 1. Possible structures of the [A–T–Li]$^+$ complex. Bond lengths noted are in angstroms with thermochemical information listed in Table 2. Other higher energy structures can be seen in supplementary information Fig. S1.

Table 1
Relative enthalpies and free energies[a] for [A–T–Li$^+$] and [A–T–Li$^+$]–H$_2$O structure.

Structure	$\Delta\Delta H$	$\Delta\Delta G$	Structure	$\Delta\Delta H$	$\Delta\Delta G$
I	0.0	0.0	A	0.0	0.0
			B	11.8	16.4
			C	19.2	26.0
			D	37.2	40.8
			E	43.6	45.0
			F	43.9	48.2
II	2.6	3.0	G	3.5	0.7
III	17.5	15.6	H	16.1	12.0
IV	5.5	4.0	I	6.0	7.0
V	8.3	6.3	J	10.3	11.3
VI	15.5	2.6	K	10.7	5.5
VII	19.4	5.9	L	15.4	11.3

[a] In kJ mol^{-1}.

[18]. The interaction of each of these tautomeric forms of A–Li$^+$ has thus been considered when determining the structure of [A–T–Li$^+$]. The lowest energy structures were found to orient themselves such that both adenine and thymine interacted with the lithium cation, with those structures involving the A7 tautomer to be the lowest in energy. The structures of [A7–T–Li$^+$] will be discussed in greater detail and are hereon referred to as [A–T–Li$^+$]. The lowest energy structures of [A19r–T–Li$^+$] were 10–20 kJ mol^{-1} in excess free energy in comparison to [A–T–Li$^+$] and are thus less likely to be present during the solvation process. Those structures containing the A19r or A9 tautomer are available in the supplementary

Scheme 1. Tautomers of adenine considered in this study interacting with a lithium cation: (a) canonical form/A9 tautomer, (b) A7 tautomer, and (c) A19r tautomer. Structures (a) and (b) are also commonly referred to as the N$_9$H and N$_7$H tautomers, respectively.
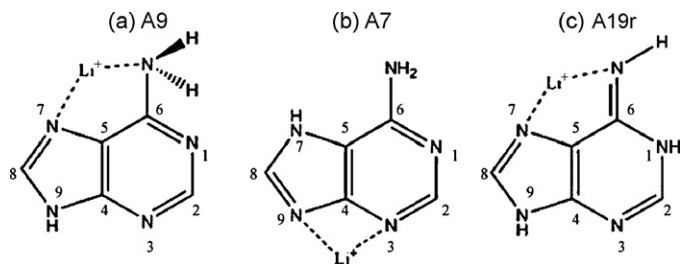
information Fig. S2. Previous studies on the interaction of thymine with the lithium cation have shown the diketo structure to be the major contributor in the gas phase [11,23,30]. As such, the canonical form is only considered here. In this form, thymine's two main binding sites [11,20,29] for the lithium cation are at the O4 and O2 oxygens. Results obtained by Rodgers and Armentrout [20] and del Bene [29] on thymine show the O4 site to be preferred over the O2 site by a stabilization energy of approximately 6 kJ mol^{-1}.

There are three different binding motifs that are evident in the [A–T–Li$^+$] structures. The first and most dominant is for the lithium ion, which would have been bound between N3 and N9 of adenine, to shift to bind to only one nitrogen of adenine, allowing for hydrogen bonding between the thymine and adenine moieties. This can be seen in the low energy structures I–V of Fig. 1. The lowest energy structure in both free energy and enthalpy is that where the lithium ion binds to the O4 of thymine – as consistent with previous reports [11,20,29] – and N3 of adenine. There is hydrogen bonding between N3H$_T$ and N9$_A$. Other structures (II–V) with similar binding, for example, lithium bound to the N9 as opposed to N3 of adenine or to O2 of thymine rather than O4, range in relative enthalpies of 2.6–17.5 kJ mol^{-1}. A second type of binding that is observed is one in which the lithium ion remains bound between N9 and N3 of adenine, with thymine bound solely to lithium at the O4 or O2 positions (structures VI and VII, respectively). These two structures are slightly higher in free energy relative to structure I, 2.6 and 5.9 kJ mol^{-1}, respectively. However, the relative enthalpy was considerably higher at ∼16 and 19 kJ mol^{-1} as the hydrogen bonding between bases is absent. The third type of structure is that in which thymine does not bind to lithium, but rather, it binds to the adenine. These complexes were found to be much higher in energy and can be seen in the supplementary information Fig. S1.

Structure I, which is lowest in both relative enthalpy and free energy, was further examined as the precursor to the solvated structure, however, structures II, IV–VII are also possible contributors to the IRMPD spectrum inasmuch as they lie within 6 kJ mol^{-1} free energy of I. As such, all are considered in section 3.2.
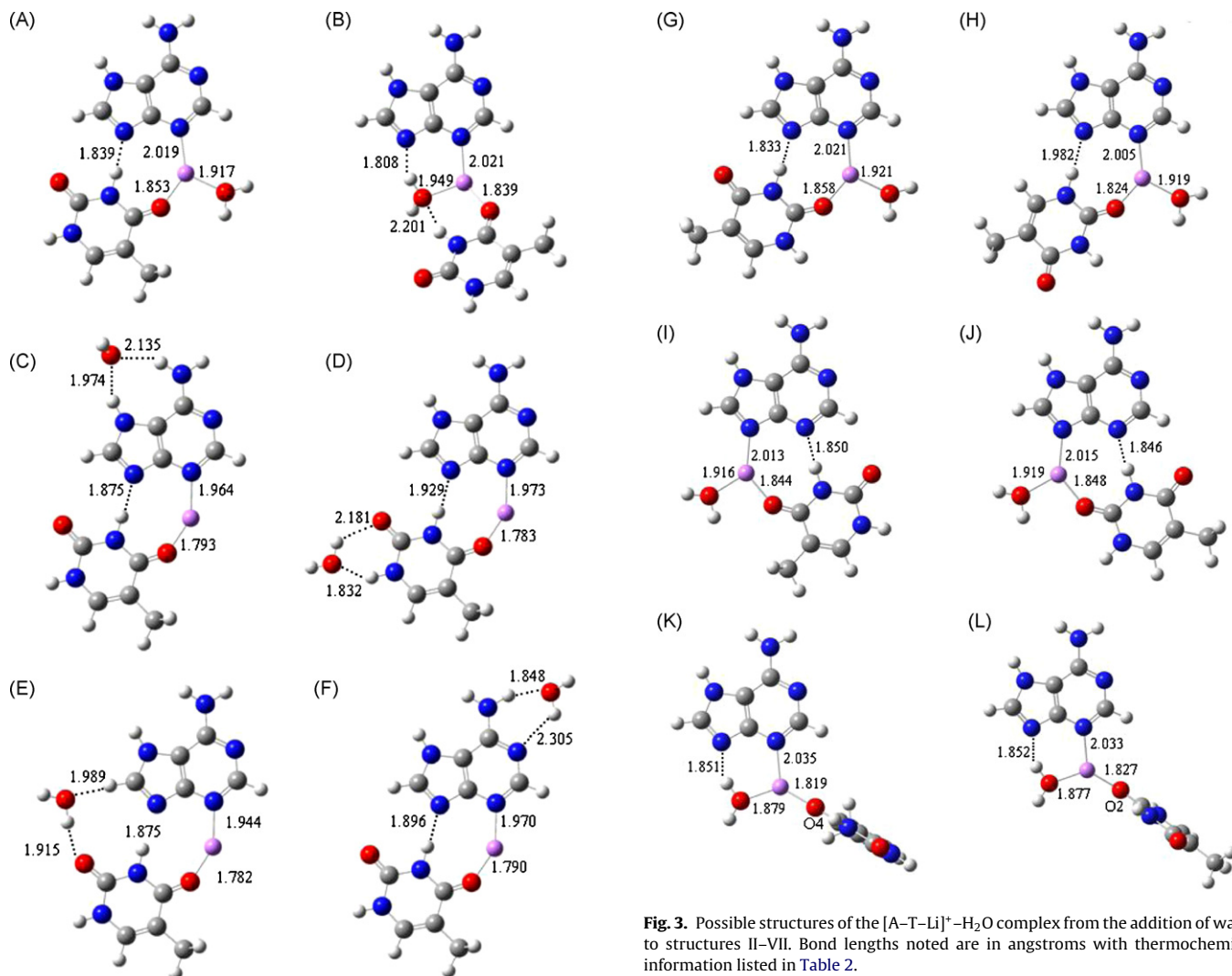
3.2. [A–T–Li$^+$]–H$_2$O

Calculated structures of the hydrated complex are presented in Figs. 2 and 3 with relative thermochemistries provided in Table 1.
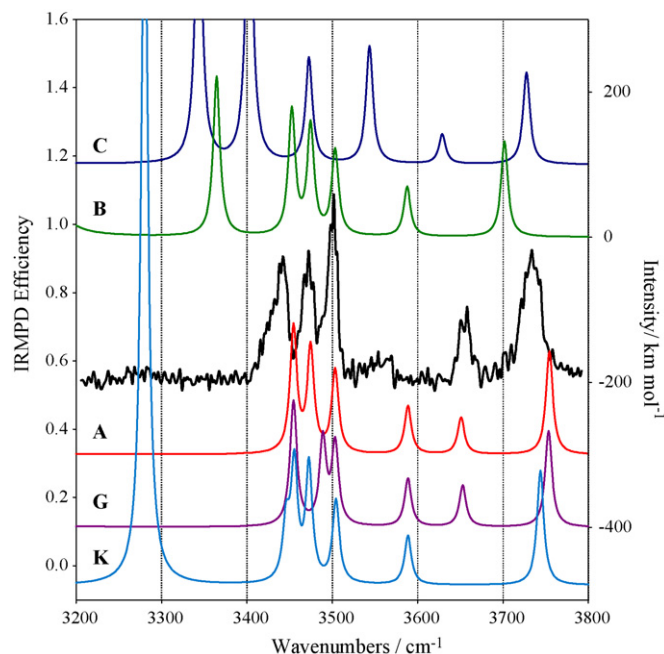
Fig. 2. Possible structures of the [A–T–Li]$^+$–H$_2$O complex from the addition of water to precursor complex I. Bond lengths noted are in angstroms with thermochemical information listed in Table 2.

Fig. 3. Possible structures of the [A–T–Li]$^+$–H$_2$O complex from the addition of water to structures II–VII. Bond lengths noted are in angstroms with thermochemical information listed in Table 2.

Fig. 2 shows structures A–F which correspond to the solvation of precursor structure I by a single water molecule. Structure A was found to be lowest in energy and showed the most favorable site for binding of water to be at the lithium cation. This is consistent with other work involving the solvation of DNA bases bound to lithium [11,18]. Structure B also has the water molecule bound to lithium, however, it is also bound via hydrogen bonding between the two bases. This configuration leads to an increase in enthalpy and free energy of 12 and 16 kJ mol^{-1}, respectively. Structures C–F have the water molecule bound to either or both base moieties without interaction with Li$^+$.

The predicted infrared spectrum for the lowest energy structure of [A–T–Li$^+$]–H$_2$O is presented and compared to the experimental IRMPD spectrum in Fig. 4 (red trace, A). The experimental spectrum consists of three strong features in the 3400–3500 cm^{-1} region, a weaker absorbance at ~3550 cm^{-1} and two bands at 3650 and 3750 cm^{-1} (For interpretation of the references to color in text, the reader is referred to the web version of the article). The experimental and predicted band positions agree quite well in all cases, as outlined in Table 2. There are some differences in the positions of the NH$_2$ symmetric and asymmetric stretching as the predicted spectrum shows a shift in peak positions towards higher wavenumbers. The difference between the experimental

Fig. 4. IRMPD spectrum of the [A–T–Li$^+$]–H$_2$O complex (black trace) compared to theoretical spectra for a number of possible structures.

Table 2
Experimental IRMPD band positions and assignments for $[A–T–Li^+]–H_2O$ in comparison to corrected theoretical values.

Assignment[a]	Observed/cm^{-1}	A[b]	B	G	H	I	J	K	L
NH_2 sym. stretch	3442	3455	3454	3455	3454	3453	3452	3456	3455
$N1H_T$ stretch	3472	3475	3475	3490	3164	3475	3492	3473	3487
$N7H_A$ stretch	3502	3504	3503	3504	3503	3504	3504	3505	3505
NH_2 asym. stretch	3554	3589	3588	3589	3588	3587	3585	3590	3589
OH_2 sym. stretch	3658	3651		3653	3650	3647	3651		
OH_2 asym. stretch	3734	3755		3754	3750	3756	3755		
$N3H_T$ stretch			3365		3450			3447	3448
OH stretch			3702					3744	3743
OH stretch (h-bond)			3155					3281	3278

[a] Subscripts T and A refer to thymine and adenine moieties, respectively.
[b] B3LYP/6-31+G(d,p) scaled by 0.958. Band assignment based on lowest energy structure.

and computed NH_2 symmetric and asymmetric stretches has been previously discussed in detail [78]. This discrepancy is not seen with N–H stretching modes which agree with scaled theoretical values. Recent anharmonic calculations on adenine have predicted values for the NH_2 stretching which are more consistent with the experimental results without affecting the agreement with N–H stretching vibrations [79].

The IRMPD spectrum of $[A–T–Li^+]–H_2O$ is also compared to theoretical spectra of the two structures (B and C) originating from precursor complex I which are closest in relative energy to A. From examination of both structure and spectrum, there are some important features that suggest B is not contributing to the IRMPD spectrum. The first is that the water molecule is bound between the bases, leading to a significant red shift of the O–H stretch involved in bonding. This is not evident in the experimental spectrum as bands are observed at 3658 and 3734 cm^{-1}; frequencies characteristic of symmetric and asymmetric OH stretching of water, respectively. The predicted spectrum for B does not contain a band about ~3658 cm^{-1}. It should be noted that in this higher frequency range, no other vibrational modes of the complex except free OH stretching could be responsible for the strong IRMPD efficiency observed. Structure B is further eliminated spectroscopically due to the absence of the band predicted to occur at 3365 cm^{-1} which corresponds to the $N3H_T$ stretching of thymine. The predicted spectrum of structure C is also compared with the IRMPD spectrum in Fig. 4. Structure C, which has water bound to adenine only at the oxygen of water, has predicted OH stretching which is consistent with that observed in the experimental spectrum. However, as is evident in comparing spectra, there are significant differences in positions of N–H stretching, in particular, those involved in binding with water on adenine (e.g., $N7H_A$). It should be clear then that structures B and C can be ruled out spectroscopically as well as on energetic grounds as they are higher in free energy than the lowest energy structures by some 16–26 $kJ\,mol^{-1}$. Structures D–F can also be ruled out energetically as they are over 40 $kJ\,mol^{-1}$ higher in energy than A. Furthermore, examination of their structures show the symmetric O–H stretch does not exist since water is asymmetric, containing one weakly hydrogen-bound O–H and one free O–H. This is not consistent with what is observed experimentally.

In Fig. 3, structures corresponding to the solvation of different precursor ions (Structures II–VII) are presented. Thermochemistries of structures G–L are presented in Table 1 to the right of the structures II–VII. Theoretical spectra of structures I, J, and L are nearly identical to those of A, G, and K, respectively. Only the latter are presented here (Fig. 4), however, any differences in peak positions for the other three spectra are listed in Table 2. As previously discussed, the predicted spectrum for A (therefore also I) and the experimental are consistent with each other. It is also clear from Fig. 4 that the predicted spectrum for structure G (and J) is in fairly good agreement with the IRMPD spectrum, although the N–H stretching region of A is a better match. It is therefore impossible to assign a single structure based solely on a comparison

of theoretical and experimental spectra over this range. Thermochemically speaking, G is essentially equivalent to A in free energy at +0.7 $kJ\,mol^{-1}$. As structures A and G originate from the electrosprayed ions I and II, respectively, which are nearly identical in free energy, it is possible that a mixture of both ions are solvated and thus being observed by IRMPD. Structures I and J are higher in free energy over A by 7.0 and 11.3 $kJ\,mol^{-1}$, respectively. Therefore, it is likely that there is an equilibrium of structures existing in the gas phase, dominated by A and G. Structure K, which differs from A in enthalpy and free energy by 10.7 and 5.5 $kJ\,mol^{-1}$ respectively, can be ruled out spectroscopically due to differences in the observed OH stretching of water. As previously discussed, the experimental spectrum of $[A–T–Li^+]–H_2O$ has two bands at 3658 and 3734 cm^{-1}, which are consistent with symmetric and asymmetric stretching of water. With structure K having one hydrogen of water bound to N9 of adenine, the symmetric νOH, which is observed experimentally, is not predicted. Additionally, there is an intense peak predicted for the h-bonded νOH in structure K at 3281 cm^{-1} which is absent in the IRMPD spectrum.

4. Summary

The structure of hydrated adenine–thymine–lithium cation was examined through IRMPD spectroscopy and theoretical studies at the B3LYP/6-31+G(d,p) and MP2/6-311++G(2d,p)//B3LYP/6-31+G(d,p) level of theory and basis sets. Experimental and theoretical spectra are reported along with structures and thermochemical data of possible complexes. The lowest energy structure (A), whereby adenine and thymine are bound through both the interaction with lithium and hydrogen bonding, was found to have a predicted spectrum which is consistent with the experimental IRMPD spectrum. The water molecule was found to bind most favorably to the lithium cation. Other similar structures (e.g., G), however, could not be completely ruled out either energetically or spectroscopically, at least over the wavenumber region examined. It is most likely that a number of low energy structures co-exist in the gas phase and are responsible for the experimental spectrum. It is interesting to note that the adenine moiety of the complexes was not the canonical form but rather the A7 tautomer. This is a result of the binding with the metal ion which allows a lowering in energy. Subsequently, the A:T base pair is not in the canonical form.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijms.2010.04.005.

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