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Gas Phase Structure of Metal Mediated (Cytosine)₂Ag⁺ Mimics the Hemiprotonated (Cytosine)₂H⁺ Dimer in *i*-Motif Folding

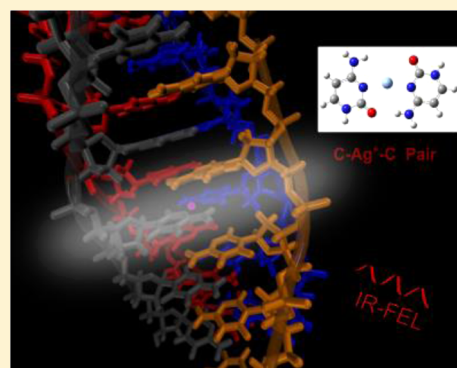
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S Supporting Information

ABSTRACT: The study of metal ion–DNA interaction aiming to understand the stabilization of artificial base pairing and a number of noncanonical motifs is of current interest, due to their potential exploitation in developing new technological devices and expanding the genetic code. A successful strategy has been the synthesis of metal-mediated base pairs, in which a coordinative bond to a central metal cation replaces a H-bond in a natural pair. In this work, we characterized, for the first time, the gas phase structure of the cytosine...Ag⁺...cytosine (C–Ag⁺–C) complex by means of InfraRed-MultiPhoton-Dissociation (IR-MPD) spectroscopy and theoretical calculation. The IR-spectrum was confidently assigned to one structure with the Ag⁺ acting as a bridge between the heteronitrogen atoms in each cytosine (both in the keto-amino form). This structure is biologically relevant since it mimics the structure of the hemiprotonated C–H⁺–C dimer responsible for the stabilization of the *i*-motif structure in DNA, with the replacement of the NH...N bond by a stronger N...Ag⁺...N bond. Moreover, since the structure of the C–Ag⁺–C complex is planar, it allows an optimum intercalation between pairs of the two antiparallel strand duplex in the DNA *i*-motif structure.



INTRODUCTION

DNA is one of the fundamental molecules in nature and plays a central role in life. It is composed of four building blocks that form two complementary pairs adenine–thymine (A–T) and guanine–cytosine (G–C). These four DNA bases constitute the alphabet of the genetic code, and their specific recognition through intermolecular hydrogen bonds (H-bonds) is a key for the correct transfer of the genetic information.¹

Many studies have been performed in the gas phase on the tautomeric and H-bonds structures and on the photochemistry/photostability of the DNA bases and their pairs, which have been recently reviewed.² Special attention has been paid to Watson–Crick (WC) pairs that constitute the monomeric structure of the well-known canonical double-helix of DNA. Although the double-helix is the most renowned form of DNA, it is also known that it can adopt other higher order structures whose stabilities are strongly dependent on the base sequence and environment, such as pH³ and presence and nature of ligands^{4–6} and cations.^{7,8}

In this sense, detailed study of the interaction of the DNA, or its four bases, with different species that can affect its structure, becomes highly desirable. Particularly interesting is the metal ion–nucleobase interactions, since it is recognized as fundamental for stabilizing a number of local motifs in the nucleic acid structure, and the readers are referred to a recent review on this topic for more details.⁹ This type of interaction

has been used for producing metal-mediated base pairs,⁹ and shown to be suitable for the development of new technological devices,^{10,11} artificial strands^{7,12} and even an adequate tool to expand the genetic code.⁹

The original idea was to replace the hydrogen atom within H-bonded base pairs by a metal ion as first reported by Lee et al., who were able to stabilize DNA duplexes by using some divalent metal ions such as Zn²⁺ to replace the H atoms involved in the intermolecular H-bonds.¹³

It is recognized in particular that the T–T and C–C mismatch pairs can be transformed into very stable T–Hg²⁺–T^{14–16} and C–Ag⁺–C^{17,18} metallo-mediated base pairs in the canonical form of the DNA, by incorporating Hg²⁺ or Ag⁺ cations, respectively. Metal–base interactions are highly specific in the two cases, and can be used for biorecognition. The specific C–Ag⁺–C interaction has led to the use of DNA strands rich in C as a template for highly fluorescent Ag_n clusters^{19–22} with the final goal of using them as biomarkers and fluorescent probes for microscopy and single molecule spectroscopy.

Besides the canonical double-helix structure of DNA, another important supramolecular tetrameric structure can be observed

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under moderated acid conditions in DNA with C-rich sequences.²³ This structure is called *i*-motif structure and is known to be important in the *fragile X mental retardation disease*.²⁴ The *i*-motif is produced by the interaction of hemiprotonated C–H⁺–C pairs of two parallel strands that form a duplex, and the interaction in a head to tail orientation of two of such duplexes, which are stabilized by intercalation of the hemiprotonated C–H⁺–C pairs of each one.³

There are only a very few examples of *i*-motif formation at physiological pH and special conditions.^{25–27} Very recently, it was shown that at this pH, Ag⁺ cations can induce *i*-motif folding in DNA, when replacing H⁺.²⁸

At present, there are only some examples of structural studies on metallo-DNAs, and in all the cases, they are referred to the canonical double-helix.^{17,8,29} In addition, H⁺ mediated *i*-motif DNAs have been structurally characterized in several systems.³ It should be stressed, however, that although there is strong evidence for the Ag⁺ mediated *i*-motif at neutral pH,²⁸ no direct structural characterization is available. Structural parameters remain too scarce to predict the stability or possible deformation of the DNA upon metal complexation. In this context, further experimental investigation in synergy with molecular modeling, on their structure is one of the main issues in the current research.

In a first approach to understand the interaction between metal cations and DNA bases, Dopfer and co-workers studied the structure of dimers of model bases stabilized by Ag⁺ (pyridine–Ag⁺–pyridine) in the gas phase, by means of IR-MPD spectroscopy combined with quantum-chemical calculations.³⁰ More recently, the gas phase structures of the 1:1 complexes between alkali metal cations–cytosine,³¹ Pb²⁺–uridine 5'-monophosphate,³² cisplatin–adenine/guanine,³³ and metal-mediated Hoogsteen-type³⁴ base pairs have been determined using the similar combination of experimental and quantum chemical approaches.

In a bottom-up strategy to disentangle the local structure of metal-mediated DNA base pairs, we report here a study on the IR-MPD spectroscopy of the mass selected C–Ag⁺–C complex in the gas phase together with quantum-chemical calculations that allow us to confidently assign its structure.

METHODS

1. IR-MPD Spectroscopy. The IR-MPD spectrum of the C–Ag⁺–C complex was obtained with the tunable IR-FEL at CLIO coupled to a modified quadrupole Paul ion trap (Bruker, Esquire 3000+) with an electrospray ionization (ESI) source. The coupling of the CLIO IR-FEL beam with the ion trap has already been described in detail elsewhere.³⁵

A solution of 25 μ M AgNO₃ and 50 μ M cytosine was prepared in a 1:1 mixture of water/methanol and introduced into the ESI source to generate the complexes under the following conditions: flow rates of 150 μ L/h, spray voltages of 4000 V, drying gas flow of 4 L s^{−1}, nebulizer pressures of 1.5 bar, and drying gas temperature of 150 °C. All the reactants were obtained from Sigma-Aldrich and used without further purification.

To obtain the IR-MPD spectrum, the C–Ag⁺–C parent ions were mass selected in the ion trap and subsequently irradiated for 150 ms by the attenuated IR-FEL. Before attenuation, the average FEL power in the spectral region of interest was around 925 mW, and it was attenuated by −6 dB. With the FEL tuned to a vibrational transition, multiple IR photons are absorbed by the ions in a stepwise and incoherent eventually leading to the

fragmentation. By monitoring the intensities of parent (I_{parent}) and resulting fragment ions (I_{fragment}) as a function of the laser frequency, the IR-MPD spectrum was obtained as the fragmentation efficiency $Y = -\ln(I_{\text{parent}}/[I_{\text{parent}} + \sum I_{\text{fragment}}])$.

2. Computational Details. Spectral assignment was achieved by comparing experimental spectra and calculated absorption spectra. The potential energy surface of the [C₂Ag]⁺ complex was explored at the B3LYP level of theory using the 6-311G++(d,p) basis set for the C, H, N, and O atoms and the SDD effective core potential with their accompanying basis set for Ag³⁶ incorporated in Gaussian 09.³⁷ The IR linear absorption spectra of each minimum of energy were computed at the same level of theory. Despite the multiphotonic nature, the IR-MPD spectrum predominantly reflects the absorption of the first IR photon which justifies comparison with a calculated linear one-photon IR absorption spectrum.³⁰

For the sake of comparison, calculated bands were convoluted assuming a Gaussian profile with a 10 cm^{−1} full width at half-maximum (fwhm) in the C=O stretching region. The IR-MPD line width intrinsically depends on the finite laser bandwidth of 0.5% of the central wavelength (corresponding to $\Delta\nu = 5.0\text{--}10.5$ cm^{−1} for $\nu = 1000\text{--}2000$ cm^{−1}), the unresolved rotational structure and, to a lesser extent, on the spectral broadening arising from the multiphotonic character of the IR-MPD process.

Finally, the relative Gibbs free energies were computed at the same level of theory, at 300 K. This temperature is comparable with that of molecular ions thermalized through multiple collisions with the helium buffer gas in the Paul trap that has been determined to be of the order of 310 K.³⁸

All calculations were performed using the Gaussian 09 program package.³⁷

RESULTS AND DISCUSSION

A typical positive-ion ESI spectrum obtained when infusing a solution of AgNO₃ and cytosine in a 1:1 mixture of water/methanol using a quadrupole Paul ion trap is shown in Figure 1a. As expected, since the preferred coordination number of Ag⁺ ions in solution is 2, the most abundant C_{*m*}Ag_{*n*}⁺ complex correspond to *m*:*n* = 2:1. On the basis of the characteristic isotopic pattern of Ag (*m/z* 107/109), the cluster ions can be unambiguously identified. To obtain IR-MPD spectra of C–Ag⁺–C, the parent ions at *m/z* = 329 and 331 were isolated (Figure 1b) and subsequently irradiated by the IR radiation from the Free Electron Laser at Orsay (FEL at CLIO). The only fragmentation process observed upon IR-MPD with the FEL tuned at 1710 cm^{−1} corresponds to the loss of one neutral C molecule as depicted in Figure 1c.

The weak ions at *m/z* = 236 and 238 correspond to the C–Ag⁺–H₂O complex produced as a consequence of the collisions of the daughter fragment ion C–Ag⁺ with traces of H₂O present in the ion trap. Therefore, these ions were also considered to account for the total fragmentation efficiency *Y*.

The experimental IR-MPD spectrum of C–Ag⁺–C recorded between 1100 and 1800 cm^{−1} is depicted in Figure 2a. It clearly shows two pronounced features at 1645 and 1710 cm^{−1} and additional weaker bands appearing at 1210, 1435, 1490, and 1525 cm^{−1}.

To aid in the interpretation of the observed spectrum, DFT calculations were performed. A targeted exploration of the potential energy surface was carried out, and multiple trial structures with various bonding Ag⁺–cytosine motifs were considered for the geometry optimization. These starting

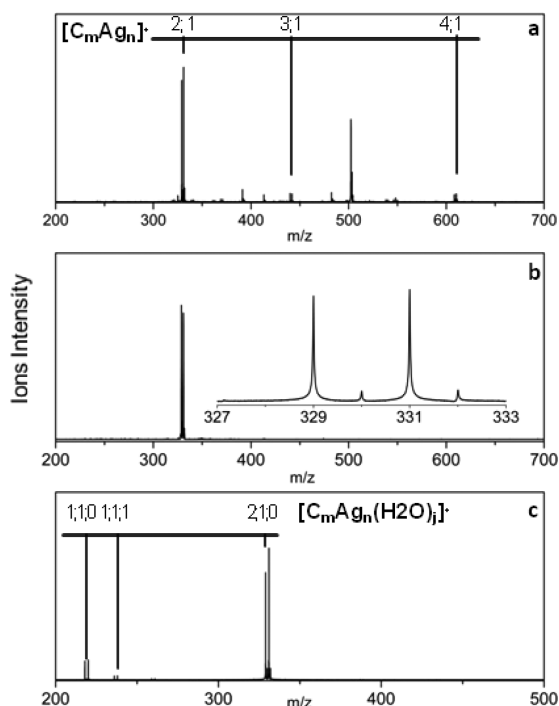


Figure 1. Positive-ions ESI spectra obtained when infusing a solution of AgNO_3 and cytosine in a mixture 1:1 of water/methanol. (a) Mass spectrum before isolation (MS); (b) mass spectrum obtained after isolation of the $m = 2$, $n = 1$ complex (MS^2); (c) mass spectrum obtained after irradiation of the isolated $m = 2$, $n = 1$ complex with 1710 cm^{-1} (MS^2).

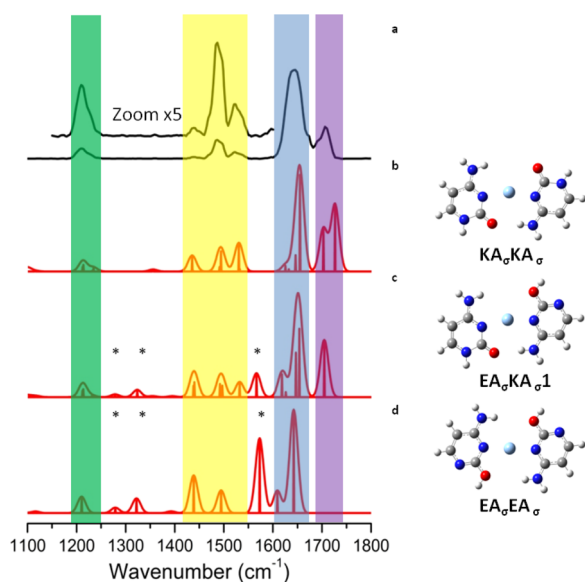


Figure 2. (a) Experimental IR-MPD spectrum of the $\text{C-Ag}^+-\text{C}$ complex, between 1100 and 1800 cm^{-1} . Panels b, c and d correspond to the simulated IR spectra of the $\text{KA}_\sigma\text{KA}_\sigma$, $\text{EA}_\sigma\text{KA}_\sigma1$ and $\text{EA}_\sigma\text{EA}_\sigma$ structures, respectively (see Table 1). Calculated vibrational frequencies were scaled using a factor value of 0.98 .³⁹

structures were based on different tautomers of cytosine (keto (K), enol (E), amino (A), imino (I)) and different coordination modes to Ag^+ (σ - or π -type). Eight structures were optimized and they are shown in the Supporting Information. Overall, σ -type structures are favored, and the lowest π -type containing

structure is 96.5 kJ/mol higher than the lowest energy structure (see Supporting Information).

The three lowest energy structures found for the $\text{C-Ag}^+-\text{C}$ complex are displayed in Table 1. The global energy minimum corresponds to a planar structure in which both C molecules are found in the Keto-Amino (KA) tautomeric form with Ag^+ interacting with the lone electron pairs of both heterocyclic N(3) [see inset in Table 1 for atoms' labeling] atoms ($d_{\text{Ag-N}^+} = 2.1\text{ \AA}$) in σ -type bonds ($\sigma\sigma$), hereafter called $\text{KA}_\sigma\text{KA}_\sigma$. In this complex, the N(1)H and N(1')H bonds, expected to be involved in the glycosidic bonds of the nucleotides, are found in a *transoid* orientation.⁴⁰ Many of the trial structures converged to the $\text{KA}_\sigma\text{KA}_\sigma$ structure.

This structure is asymmetric with respect to the intermolecular $\text{O}(7)\cdots\text{N}(8')$ (3.3 \AA) and $\text{O}(7')\cdots\text{N}(8)$ (5.3 \AA) distances as shown in Figure 3. The optimization of the symmetric structure was possible under symmetry constraints and the vibrational frequency analysis shows that it is a transition state for the switch between forming one or the other $\text{NH}_2\cdots\text{O}=\text{C}$ H-bond. The relatively small imaginary frequency $i17\text{ cm}^{-1}$ value associated with this motion indicates that the PES is quite flat along this coordinate.

The second higher energy isomer is named $\text{EA}_\sigma\text{KA}_\sigma1$ (many $\text{EA}_\sigma\text{KA}_\sigma$ structures were found and number 1 refers to the most stable one (see Supporting Information)), in which Ag^+ is bound to one Enol-Amino (EA) and one Keto-Amino (KA) isomer through their heterocyclic N(3) and N(3') atoms. The 0 K enthalpy for $\text{EA}_\sigma\text{KA}_\sigma1$ was found to lie 32.1 kJ/mol above the $\text{KA}_\sigma\text{KA}_\sigma$ isomer. Finally, in the third type of stable structure ($\text{EA}_\sigma\text{EA}_\sigma$), both C molecules are present as the EA tautomer and Ag^+ also interacts with the lone electron pairs of both heterocyclic N(3) atoms in σ -type $\text{Ag}^+-\text{N}(3)$ bonds. This isomer is predicted to lie 70.9 kJ/mol above the most stable structure.

The 0 K enthalpies, corrected for basis set superposition errors using the counterpoise correction method and the ΔG at 300 K , relative to the $\text{KA}_\sigma\text{KA}_\sigma$ isomer are given in Table 1. It should be stressed that prior to IR irradiation, mass-selected ions are thermalized to a temperature which can be estimated to be room temperature.³⁸ The corresponding expected relative Boltzmann populations are also given in Table 1, from which it is clearly observed that the populations of the $\text{EA}_\sigma\text{KA}_\sigma1$ and $\text{EA}_\sigma\text{EA}_\sigma$ isomers are predicted to be negligible as compared with the population of the $\text{KA}_\sigma\text{KA}_\sigma$ isomer under the present experimental conditions.

Structural assignment is based on the comparison of the experimental spectrum Figure 2a with the predicted IR linear absorption spectrum of the three lowest energy isomers which are given in Figure 2b–d. Nevertheless, the structural assignment is more convincing if it is based on the observation (or nonobservation) of isomer specific IR bands. The strong band observed at 1710 cm^{-1} with a shoulder at 1690 cm^{-1} for example, can be assigned to two carbonyl $\text{C}=\text{O}$ stretches, which suggest the presence of KAs containing isomers. Conversely, $\text{EA}_\sigma\text{KA}_\sigma1$ and $\text{EA}_\sigma\text{EA}_\sigma$ (Figure 2, panels c and d, respectively) isomers containing one or two enol tautomers, are expected to present spectral features predicted at 1280 and at 1325 cm^{-1} , highlighted in Figure 2 with an asterisk (*). The band predicted at 1575 cm^{-1} associated with the in-plane ring deformation mode bound to a π -donor such as the OH group is also a fingerprint of EA tautomers and it does not appear in the experimental spectrum (Figure 2a). Besides, the $\text{EA}_\sigma\text{EA}_\sigma$ isomer does not present any feature at 1710 cm^{-1} where one of the

Table 1. Structure^a and Thermochemical Properties^b of the Three Most Stable Conformers

	KA _σ KA _σ	EA _σ KA _σ 1	EA _σ EA _σ
ΔH (0 K)	0	32.1	70.9
ΔG (300 K)	0	32.2	62.2
Relative Population	1	2.4x10 ⁻⁶	1.4x10 ⁻¹¹

^aThe potential energy surface of the [C₂Ag]⁺ complex was explored at the B3LYP level of theory using the 6-311G++(d,p) basis set for the C, H, N, and O atoms and the SDD effective core potential for Ag³⁶ with their accompanying basis set incorporated in Gaussian 09.³⁷ ^bThermochemical properties have been computed at 300 K taking in to account the zero point correction and the counterpoise correction. Units: kJ/mol. ^cAtom labeling of cytosine.

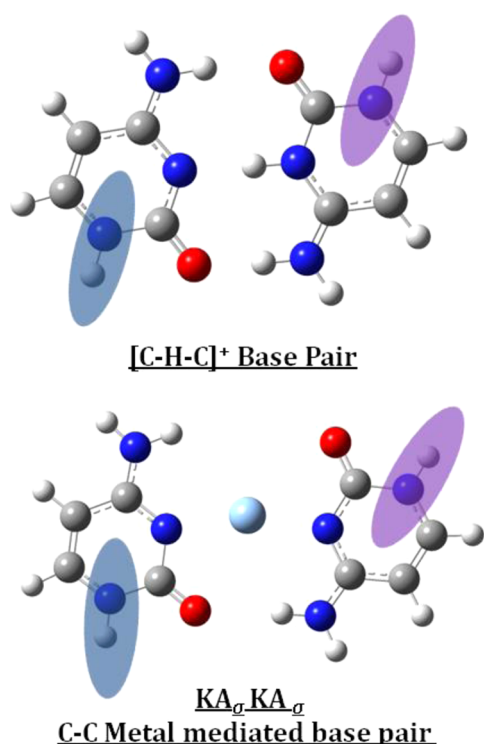


Figure 3. Comparison between the hemiprotonated [C₂H]⁺ dimer in the *i*-motif DNA structure and the KA_σKA_σ metal mediated [C₂Ag]⁺ complex. Highlighted are the positions where the glycosidic bonds take place.

most intense band peaks in the experimental spectrum (Figure 2d). On the other hand, the EA_σKA_σ1 isomer does show an absorption band at 1710 cm⁻¹ corresponding to the keto tautomer, but the three characteristic bands of the enol tautomer are not present in the experimental spectrum (Figure 2.c).

Among the three isomers, the KA_σKA_σ has the IR spectrum that best matches with the experimental spectrum. The simulated IR linear absorption spectrum of this isomer (Figure 2b) has two characteristic band around 1720 and 1702 cm⁻¹, assigned to two C=O stretching modes arising from two carbonyl groups that are found at different distances from the NH₂ group of the other cytosine molecule, and another intense band at 1650 cm⁻¹ assigned to the H-bonded NH₂ bending. Additionally, the three bands group in the spectral region

1450–1550 cm⁻¹ is also predicted by the calculated IR spectrum of this isomer. As discussed above, the symmetrized structure was also optimized and found to be a transition state. The corresponding IR absorption spectrum is given in Figure S1 for comparison (see Supporting Information). As expected, it shows a single band at 1723 cm⁻¹ corresponding to two equivalent C=O stretching modes with almost the same intensity as the band at 1650 cm⁻¹. The observation of the doublet at 1710 and 1690 cm⁻¹ is thus a clear IR signature of the asymmetric structure formed under the experimental conditions, and confirms that this asymmetry is not an artifact of the calculations.

Although the presence of the less stable EA_σKA_σ1 and EA_σEA_σ isomers cannot be completely ruled out, the theoretical results (ΔG and relative population), in addition to the prominent fitting between the simulated IR spectra of the most stable KA_σKA_σ isomer and the experimental one, allow us to neglect the contribution of the former isomers and to confidently assign the experimental spectrum to the most stable asymmetric KA_σKA_σ isomer.

In the context of searching for artificial creation of metal mediated base pairing, our structural finding is interesting for two reasons. First, similar structures were reported for proton-bound cytosine (C–H⁺–C)⁴¹ and XC substituted-cytosine (XC–H⁺–XC)^{42,43} dimers. As can be seen in Figure 3, the KA_σKA_σ isomer can be considered as formally deriving from the commonly accepted hemiprotonated C–H⁺–C dimer that stabilizes the noncanonical *i*-motif structure of DNA, with two antiparallel glycosidic bonds (*transoid* orientation). These results are in line with the recent findings of *i*-motif formation at neutral pH in the presence of Ag⁺ cations.²⁸ Such results are counterintuitive since H⁺ and Ag⁺ are quite different in size, which makes H⁺ and Ag⁺ behaves as a hard and soft acid, respectively. The second point to be considered is the fact that the KA_σKA_σ isomer keeps the planar structure required for an optimum intercalation between pairs of the two antiparallel duplex in the DNA *i*-motif structure.

It is worth noting that despite the efforts it was not possible to locate a minimum energy structure with a *cisoid* orientation of the N(1)H and N(1')H bonds expected for the C–C mismatching in the canonical double-helix structure of the DNA. This is in agreement with previous results for which the authors reported that this structure, when optimized under symmetry constraints, is a transition state for the internal rotation leading to the *transoid* isomer, due mainly to the steric

and electrostatic repulsion between the NH_2 groups of both C molecules.⁴⁰ In addition, the *cisoid* structure does not allow the formation of intermolecular H-bond, and as a consequence, it lies 32 kJ/mol above the $\text{KA}_\sigma\text{KA}_\sigma$ isomer with *transoid* orientation.⁴⁰

The $\text{C}-\text{Ag}^+\cdots\text{C}$ interaction energy was calculated to be 214 kJ/mol for the $\text{KA}_\sigma\text{KA}_\sigma$ isomer. This energy is considerably higher than the interaction energy of the protonated analogous $\text{C}-\text{H}^+\cdots\text{C}$, for which it was recently determined to be 169.9 and 168.9 kJ/mol, by means of threshold collision induced dissociation and theoretical calculations, respectively.⁴²

The high interaction energy in the $\text{KA}_\sigma\text{KA}_\sigma$ is mostly due to the strong bonding between Ag^+ cation and N(3) of the C molecules, but it also has an important contribution from the $\text{NH}_2\cdots\text{O}=\text{C}$ intermolecular H-bond, as in the case of the $\text{C}-\text{H}^+-\text{C}$ dimer. In the $\text{KA}_\sigma\text{KA}_\sigma$ complex, the $d_{\text{Ag}-\text{N}^+} = 2.1$ Å leads to a $d_{\text{N}(3)-\text{N}(3')} = 4.2$ Å, and therefore, the observed symmetry distortion is required to allow for the formation of a H-bond between the NH_2 group of one C and the $\text{C}=\text{O}$ group of the other one, and this is the driving force that stabilizes the asymmetric structure as compared with the symmetric one. The H-bond contribution is expected to be close to the energy difference (32 kJ/mol) between the *cisoid*, where H-bonds are not possible, and the *transoid* structures.

Recently, it was reported that in the presence of Ag^+ cations, a duplex with a mismatching $\text{C}-\text{C}$ in *cisoid* orientation shows a melting temperature ($T_m = 309.6$ K) lower than the corresponding T_m for the same duplex containing the mismatching $\text{m}^5\text{iC}-\text{C}$ in *transoid* orientation (m^5iC stands for 5-methylisocytosine) for which it is 318.6 K.¹⁸ The authors suggested that the enhanced T_m for the latter could be related to a synergetic effect of Ag^+ coordination and possible H-bonding.¹⁸ We show here that this hypothesis is likely to be true and the synergetic effect is only possible upon symmetry breaking of the $\text{KA}_\sigma\text{KA}_\sigma$ isomer in the *transoid* orientation.

CONCLUSIONS

By combining mass selected IR-MPD spectroscopy with theoretical calculations, we could confidently determine the structure of the nonconventional metal mediated base pair $\text{C}-\text{Ag}^+-\text{C}$. The structure found is relevant since it mimics the structure of the hemiprotonated $\text{C}-\text{H}^+-\text{C}$ dimer responsible for the stabilization of the *i*-motif structure of DNA, with the formal replacement of one $\text{NH}\cdots\text{N}$ intermolecular bond by a stronger $\text{N}\cdots\text{Ag}^+\cdots\text{N}$ bond. The high stability of this structure is suggested to be due to a synergetic effect between the strong interaction $\text{N}\cdots\text{Ag}^+$ and intermolecular H-bond. This work is consistent with recent results in bulk¹⁸ and it could be exploited to evaluate the competition between Ag^+ and H^+ substitution in *i*-motif structure, for developing pH and silver concentration dependent molecular switches.

ASSOCIATED CONTENT

Supporting Information

Structure and thermochemical properties of the eight most stable conformers; simulated IR spectrum of the symmetric $\text{KA}_\sigma\text{KA}_\sigma$ isomer. 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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