Hydrogen Bond Disruption in DNA Base Pairs from ^{14}C Transmutation

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Recent *ab initio* molecular dynamics simulations have shown that radioactive carbon does not normally fragment DNA bases when it decays. Motivated by this finding, density functional theory and Bader analysis have been used to quantify the effect of C→N transmutation on hydrogen bonding in DNA base pairs. We find that ^{14}C decay has the potential to significantly alter hydrogen bonds in a variety of ways including direct proton shuttling (thymine and cytosine), thermally activated proton shuttling (guanine) and hydrogen bond breaking (cytosine). Transmutation substantially modifies both the absolute and relative strengths of the hydrogen bonding pattern, and in two instances (adenine and cytosine) the density at the critical point indicates development of mild covalent character. Since hydrogen bonding is an important component of Watson-Crick pairing, these ^{14}C-induced modifications, while infrequent, may trigger errors in DNA transcription and replication.

I. INTRODUCTION

Hydrogen bonds play a crucial role in molecular recognition for many chemical and biological systems.[1–5] This is particularly the case for Watson-Crick pairing of the canonical bases in DNA, where hydrogen bonding helps promote adenine-thymine (AT) and guanine-cytosine (GC) pairing.[6,7] Any modification to the donor-acceptor scheme that disrupts this pairing may in turn generate errors in the transcription and replication processes. One of the most widely studied modifications is tautomerization in which the less stable "enol" and "imino" forms can be sources of spontaneous mutation due to different pairing characteristics, such as AC*, A*C, G*T, and GT* (see Refs.[8–11] for a review). Wobble-type mispairs,[12] in particular created by protonation or deprotonation, are another pathway for genetic modification, where non-canonical pairings include A^+C and GT^-.[13] Recently we showed that transmutation of carbon into nitrogen by the decay of radioactive ^{14}C can also be a source of mutation.[14] These studies employed *ab initio* molecular dynamics to investigate ^{14}C-induced bond rupture in DNA base-pairs, and unexpectedly found that in most cases (∼90%), the shape and structure of the base is retained. Accordingly, ^{14}C decay offers a potential pathway for creating genetic damage.

In this work we quantify the effects of C→N transmutation on the hydrogen bonding pattern of AT and GC pairs using plane-wave density functional theory and Bader analysis.[15] The topological features of the electron density, $n(\vec{r})$, are given by the characteristics of the critical point of the bond, and the value of the electron density at the critical point, $n(\vec{r}_{CP})$, is used as a reference to evaluate changes in the strength of the electronic overlap along the hydrogen bonds between the complementary bases. The magnitude of $n(\vec{r}_{CP})$ gives valuable insight into the relative strength of each hydrogen bond, allowing a meaningful comparison of hydrogen bonds that involve different chemical species, such as N, O or C. From this analysis we deduce that ^{14}C decay has the potential to disrupt the hydrogen bonding pattern by altering bond strengths, shuttling protons and even breaking bonds.

II. METHODOLOGY

Density-functional-theory calculations were performed using the VASP package.[16,17] The PW91 exchange-correlation functional of Perdew and Wang[18] was applied along with spin-polarization and the Vosko–Wilk–Nusair (VWN) scheme.[19] The kinetic energy cutoff of the projector augmented wave[20] pseudopotentials was fixed at 520 eV. All calculations were carried out in the gas phase with a vacuum separation of 10 Å between the molecule and its periodic image. In all cases, the total energy was converged to 10^{-6} eV/cell and the force components were relaxed to 10^{-4} eV/Å.

To model C→N transmutation within a canonical base, a carbon atom was directly substituted by a nitrogen atom. For these calculations a supercell with a net charge of $+1e$ was used, reflecting the physics of beta-decay, whereby an electron is ejected far from the ^{14}N nucleus leaving behind a nitrogen cation.[21] Calculations of the DNA bases are performed in vacuum, an approach which has been shown to be an acceptable model of the analagous base pairs in the structure of DNA of the living cell surrounded by proteins.[22,23] The Critic code[24] was used to perform the topological analysis of the elec-

tron density to locate the critical points of the hydrogen bonds. Energy barriers for proton shuttling were calculated using linear interpolation of images between the two end-points and single point calculations were carried out for each image.

III. RESULTS AND DISCUSSION

Figure 1 shows the three types of hydrogen bonds, N–H···O, N–H···N and C–H···O, involved in AT and GC pairs. Each interatomic contact possesses a saddle critical point at which the electron density is a minimum along the bond and a maximum in the perpendicular plane. The positions of the critical points are indicated by small yellow spheres. Tables I and II summarize characteristics of the hydrogen bonds involved in the native and transmuted AT and GC base pairs. For each pair, the effect of C→N transmutation is determined for all carbon atoms, and the energy cost to shuttle a proton to the opposite side is calculated using linear interpolation. In native AT (Table I) the N···H–N bond has a moderately larger value of $n(\vec{r}_{CP})$ (0.0520 e$^-$/Å^3) than N–H···O1 (0.0350 e$^-$/Å^3), and a much larger value than that of C–H···O2 (0.0046 e$^-$/Å^3). This indicates that N···H–N is the strongest interaction, followed by N–H···O and C–H···O. According to the scheme of Jeffrey,[2] the N–H···N and N–H···O bonds mostly involve an electrostatic type of interaction. In contrast, the C–H···O contact is classified as weak and involves a mixture of electrostatic and dispersion interactions. The nature of this interaction has been debated in the literature, with some groups[26,27] arguing strongly against it being a true hydrogen bond

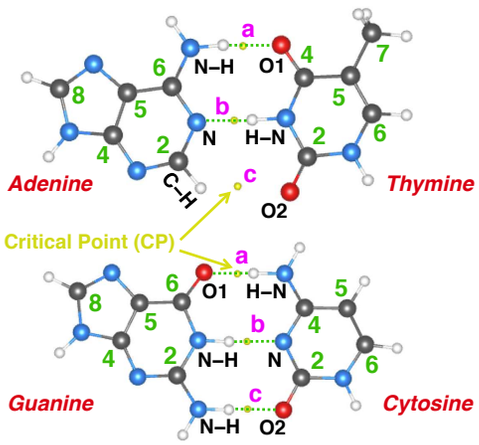

FIG. 1. Illustration of AT and GC base pairs in which the numbered carbon atoms (gray spheres) are transmuted to nitrogen. The enumeration scheme follows the standard labelling convention of Saenger,[25] with the addition of index 7 for the methyl group in thymine. The critical point of each hydrogen bond (green dashed line and labelled a, b or c) is indicated by a small yellow sphere.

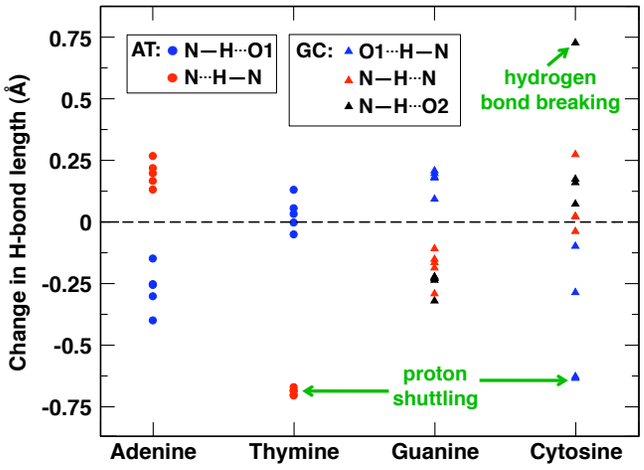

FIG. 2. Change in hydrogen bond lengths in AT and GC pairs upon C→N transmutation in each carbon of the four DNA bases. For the special cases of proton shuttling the reference distance for the final state is the newly formed covalent bond.

on the basis of orbital analysis and stretching frequencies, while others[3,5] contend that it does indeed satisfy the criteria of a hydrogen bond and plays a role in helping stabilise nucleobase pairs. Here we take a neutral position by simply reporting the critical density and noting that the interaction is very weak. The comparison of the relative strength between these three hydrogen bonds is schematically represented by $b > c \gg a$ in Table I. For native AT, this relative strength ordering is in agreement with recent theoretical calculations.[28]

Analysis of $n(\vec{r}_{CP})$ for the transmuted adenine shows a different trend in the relative strength of the hydrogen bonds as compared to the native pair. The N···H–N hydrogen bond is always weakened by transmutation, while the N–H···O1 hydrogen bond always becomes stronger. These effects are shown graphically in Figure 2, where for adenine transmutation simultaneously shortens the N–H···N hydrogen bond by 0.15–0.25 Å and lengthens the N–H···O bond by 0.15–0.40 Å. Thus, for all transmutations occurring in adenine, the relative strength of the a vs b bond inverts compared to native AT.

Transmutations in thymine generally yield values of $n(\vec{r}_{CP})$ comparable to native AT. The relative bond strengths are similar too, with stronger N···H–N hydrogen bonds compared to N–H···O1, except for transmutation at carbon 2 where the strength of the two hydrogen bonds is similar. The most signficant effect involves the N···H–N hydrogen bonds which change their sense by shuttling the proton to the adenine side. This process, highlighted in bold in Table I, occurs for all five carbon positions and is exothermic and barrierless in each case. These reactions are easily identifiable in Figure 2, where the N–H···N hydrogen bond distance is reduced by about 0.65 Å compared to native AT. In contrast, the length of the N–H···O hydrogen bond is relatively unaffected, exhibiting a maximum deviation of 0.14 Å.

TABLE I. Hydrogen bond characteristics and proton transfer energy differences for the native and transmuted AT pair, with the labels a, b and c defined as in Figure 1. Bold type indicates proton shuttling, with the distance indicated referring to the newly formed hydrogen bond.

		Hydrogen bond	Distance (Å)	$n(\vec{r}_{CP})$ ($e^-/Å^3$)	Relative strength	Proton transfer (eV)
AT		N–H···O1	1.828	0.0350		1.67
		N···H–N	1.746	0.0520	$b > a \gg c$	0.61
		C–H···O2	2.812	0.0046		-
^{14}C transmutation in Adenine	2	N–H···O1	1.680	0.0508		0.71
		N···H–N	1.878	0.0362	$a > b \gg c$	2.02
		C–H···O2	2.964	0.0029		-
	4	N–H···O1	1.573	0.0661		0.47
		N···H–N	1.944	0.0316	$a > b \gg c$	1.76
		C–H···O2	3.297	0.0017		-
	5	N–H···O1	1.527	0.0742		0.35
		N···H–N	1.965	0.0300	$a > b \gg c$	1.92
		C–H···O2	3.411	0.0012		-
	6	N–H···O1	1.429	0.0954		0.12
		N···H–N	2.014	0.0265	$a > b \gg c$	2.08
		C–H···O2	3.487	≈0		-
	8	N–H···O1	1.576	0.0658		0.48
		N···H–N	1.913	0.0342	$a > b \gg c$	1.46
		C–H···O2	3.178	0.0022		-

		Hydrogen bond	Distance (Å)	$n(\vec{r}_{CP})$ ($e^-/Å^3$)	Relative strength	Proton transfer (eV)
^{14}C transmutation in Thymine	2	N–H···O1	1.778	0.0391		1.43
		N–H···N	**1.880**	**0.0365**	$b \approx a \gg c$	**1.39**
		C–H···O2	3.063	0.0027		-
	4	N–H···O1	1.959	0.0255		1.97
		N–H···N	**1.827**	**0.0411**	$b > a \gg c$	**1.24**
		C–H···O2	2.756	0.0051		-
	5	N–H···O1	1.861	0.0322		1.75
		N–H···N	**1.744**	**0.0511**	$b > a \gg c$	**0.81**
		C–H···O2	2.886	0.0039		-
	6	N–H···O1	1.826	0.0355		1.42
		N–H···N	**1.740**	**0.0518**	$b > a \gg c$	**0.72**
		C–H···O2	2.882	0.0039		-
	7	N–H···O1	1.884	0.0306		1.73
		N–H···N	**1.672**	**0.0612**	$b > a \gg c$	**0.51**
		C–H···O2	2.760	0.0051		-

We now consider transmutation in the GC base pair where three hydrogen bonds are present (Figure 1). The values of $n(\vec{r}_{CP})$ given in Table II show that for the native pair, the O1···H–N hydrogen bond is the strongest (0.0513 $e^-/Å^3$), while the N–H···O2 bond is the weakest (0.0331 $e^-/Å^3$). The N–H···N and N–H···O hydrogen bonds are classified as moderate in strength, similar to those involved in the AT base pair, and represent a mostly electrostatic-type interaction.

Transmutation in cytosine affects the hydrogen bond interactions in two important ways. Firstly, transmutation of carbons 4 and 5 in cytosine drives proton shuttling along the O1···H–N hydrogen bond. As highlighted in bold in Table 2, this creates a new type of hydrogen bond, O1–H···N, not initially present in native GC. Secondly, transmutation of carbon 2 essentially breaks the N–H···O2 hydrogen bond, while strengthening the O1···H–N hydrogen bond. This remarkable hydrogen bond weakening is due to the more electronegative nitrogen atom substituting for the carbon, resulting in a strong reduction of the covalent N=O bond dipole in cytosine, as compared to the original C=O bond. The values of $n(\vec{r}_{CP})$ shown in Table II indicate that the weakened N–H···O2 hydrogen bond (0.0057 $e^-/Å^3$) is similar in strength to the C–H···O2 hydrogen bond (0.0046 $e^-/Å^3$) in the AT pair, and that it contains a mix of electrostatic and dispersion interactions. In contrast, the strongest N–H···O2 interaction (0.1051 $e^-/Å^3$) has covalent character, and similar strengthening occurs for transmutation at carbon 6 in adenine. Both of these key effects, proton shuttling and hydrogen bond breaking, are highlighted by green arrows in Figure 2.

Transmutation in guanine alters the relative strength of the hydrogen bonds, with the strongest O1···H–N bond becoming the weakest interaction in all five cases. The weak N–H···O2 hydrogen bond is always strengthened significantly, as is the central N–H···N bond. As seen in Figure 2, these modifications are associated with changes in the hydrogen bond length, where the O1···H–N bonds increase by up to 0.2 Å, while the other two hydrogen bonds reduce by 0.10–0.30 Å. Even more significantly, transmutation at carbons 2 and 6 enables thermally activated proton shuttling with high probability. As shown in Figure 3, transmutation at carbon 2 of guanine substantially modifies the shape of the energy surface for proton transfer along the central N–H···N bond. While there is a large energy difference of 1.04 eV for the

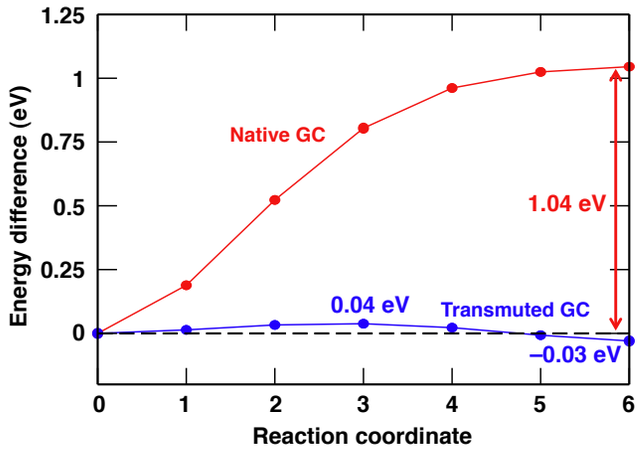

FIG. 3. Energy barrier for a proton transfer reaction along the N–H···N bond of native GC (red line) and a GC pair with a C→N transmutation at carbon 2 in guanine (blue line).

TABLE II. Same as Table 1 but for a GC pair. The asterisks for transmutation in guanine denote proton shuttling which is exothermic with small barriers as discussed in the text.

		Hydrogen bond	Distance (Å)	$n(\vec{r}_{CP})$ (e$^-$/Å^3)	Relative strength	Proton transfer (eV)
GC		O1···H–N	1.674	0.0513		0.88
		N–H···N	1.848	0.0405	$a > b > c$	1.04
		N–H···O2	1.853	0.0331		1.75
^{14}C transmutation in Cytosine	2	O1···H–N	1.388	0.1051		0.08
		N–H···N	2.122	0.0206	$a \gg b \gg c$	2.15
		N–H···O2	2.580	0.0057		3.26
	4	**O1–H···N**	**1.716**	**0.0521**		**0.67**
		N–H···N	1.870	0.0375	$a > b > c$	1.20
		N–H···O2	1.926	0.0271		1.99
	5	**O1–H···N**	**1.595**	**0.0712**		**0.46**
		N–H···N	1.810	0.0436	$a > b > c$	1.05
		N–H···O2	2.013	0.0224		2.25
	6	O1···H–N	1.576	0.0647		0.30
		N–H···N	1.871	0.0376	$a > b > c$	0.91
		N–H···O2	2.027	0.0213		1.76

		Hydrogen bond	Distance (Å)	$n(\vec{r}_{CP})$ (e$^-$/Å^3)	Relative strength	Proton transfer (eV)
^{14}C transmutation in Guanine	2	O1···H–N	1.767	0.0398		1.54
		N–H···N	1.557	0.0823	$b > c > a$	−0.03 (∗)
		N–H···O2	1.533	0.0737		0.42
	4	O1···H–N	1.857	0.0321		1.96
		N–H···N	1.697	0.0585	$b \approx c > a$	0.26
		N–H···O2	1.624	0.0577		0.80
	5	O1···H–N	1.882	0.0299		2.15
		N–H···N	1.684	0.0603	$b \approx c > a$	0.25
		N–H···O2	1.627	0.0572		0.82
	6	O1···H–N	1.871	0.0299		2.38
		N–H···N	1.662	0.0640	$b > c > a$	−0.01 (∗)
		N–H···O2	1.671	0.0583		0.88
	8	O1···H–N	1.853	0.0325		1.90
		N–H···N	1.740	0.0528	$c \approx b > a$	0.42
		N–H···O2	1.631	0.0569		0.81

native case, there is a small barrier of just 0.04 eV for the transmuted pair, and the final configuration, a deprotonated guanine base, is more stable by 0.03 eV. Similar behavior occurs at carbon 6 of guanine, where the final configuration is more favorable by 0.01 eV and the barrier is 0.12 eV. Both of these barriers can be surmounted thermally, and hence proton oscillation between the two bases can occur, with a slight preference for the deprotonated guanine according to the Boltzmann factor.

Proton transfer energies for all possible cases are listed in Tables 1 and 2. In most cases the reaction is strongly endothermic, and the barrier is the same as the energy difference since the final state is not a local minima. For adenine there is no possibility for proton transfer, except perhaps for carbon 6 where the N···H–O1 configuration is just 0.12 eV higher in energy. For thymine, where transmutation causes shuttling of the proton between the two nitrogens, the transfer energy shown is for the reverse process in which the proton returns to the thymine. In all five cases there is a large penalty (0.5–1.4 eV) for this reaction, and hence the protonated adenine is strongly favored. A similar situation exists for proton shuttling in cytosine where the reverse reaction to restore the original O1···H–N bond is unfavorable by around half an eV.

Inspection of Tables I and II shows there is an inverse relationship between $n(\vec{r}_{CP})$ and bond length. We quantify this behavior in Figure 4 by plotting all of the data for each type of hydrogen bond. Similar to the work of Abramov[29] and Espinosa *et al.*,[30] the critical density depends exponentially on the hydrogen bond length. The solid lines in Figure 4 are exponential fits to each bond family, and the relationship holds over a wide range, as seen in the inset where the data is plotted on a logarithmic scale. Espinosa *et al.* report exponents b between 2.7 and 3.6 Å^{-1}, while for our data b=2.5 Å^{-1} for N–H···N and N–H···O and 2.7 Å^{-1} for C–H···O. Special cases (1) and (2) do not lie on the exponential curve, as they correspond to proton shuttling in cytosine which creates an O1–H···N bond. Since the new bond is chemically distinct from its parent, the points labelled (1) and (2) do not fall on the blue line. In contrast, the data points for proton shuttling in thymine remain on the universal curve (red line) as the initial and final structures are both N–H···N bonds, albeit with a different sense. Special case (3) highlights the situation where the N–H···O2 hydrogen bond in GC is essentially disabled, and has a much weaker strength, comparable to that of C–H···O.

The spread of the critical densities in Figure 4 highlights the extent to which transmutation alters the hydrogen bond strength. Whereas the native N–H···N and N–H···O bonds are mostly clustered in the range 0.033–0.052 e$^-$/Å^3 (see solid horizontal bars in the figure), transmutation results in a far larger distribution. The two strongest bonds have critical densities nearly twice the highest native case and the magnitude of the

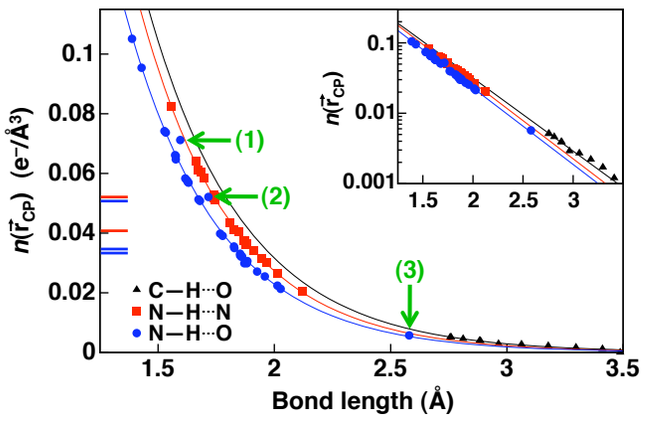

FIG. 4. Calculated $n(\vec{r}_{CP})$ as a function of hydrogen bond length for the different types of hydrogen bonds present in AT and GC base pairs. The inset highlights the exponential relationship, and the green arrows denote special cases of proton shuttling and bond breaking as discussed in the text.

density is approaching that of a covalent bond, which is typically $\sim$0.2 $e^-/Å^3$. Both of these cases belong to the N–H$\cdots$O family and occur in adenine and thymine; the large associated reduction in bond length can be easily seen in Figure 2

Taking a broader view of the present findings, it is apparent that radiocarbon decay is a potential source of point mutations in DNA. Proton shuttling is of particular significance, since it creates the possibility of wobble-type mispairs which are mutagenic. For example, transmutation in thymine creates an A^+T^- pair where the adenine is protonated and the thymine is deprotonated. This pairing will produce errors in both transcription and replication, since protonated adenine (A^+) can pair with cytosine and deprotonated thymine (T^-) pairs with guanine.[13] In subsequent replication steps the native bases will pair with their canonical counterparts, and hence the dominant effect of the ^{14}C decay is an AT→GC substitution, albeit with the A^+ and T^- bases persisting. As shown above, the A^+T^- pair is just one of many non-canonical pairings which may be mutagenic. For example, transmutation in cytosine at carbons 4 and 5 creates G^+C^- pairs, while transmutation at carbon 2 breaks the N–H$\cdots$O2 bond and creates a modified cytosine which has only a single acceptor and donor and may no longer prefer to pair with guanine. Transmution in guanine leads to even more possibilities in the form of G^-C^+ pairs created by thermally activated proton shuttling. The recent review by Jissy and Datta[31] summarizes some of the many possibilities and applications for mispairs due to protonation/deprotonation.

While proton shuttling in conventional hydrogen bonds is well-known,[23,32,33] proton shuttling driven by transmutation is a distinctly different phenomenon as the process is strongly energetically favored, being driven by the presence of the cationic nitrogen. Accordingly, the transfer of a proton from one base to the other can occur under standard physiological conditions. In contrast, recent laboratory verification of mutation via protonation/deprotonation[34] and tautomers[35] required careful experimental design and special chemical environments; high pH in the case of the former, and a mutagenic Mn^{2+} cation in the polymerase active site for the latter. The case of double proton transfer as a source of Löwdin-type tautomers[36–38] is worthy of special mention, as this mutation pathway has received enormous attention over the years, but it is now well established that under normal conditions the lifetime of the tautomeric state is too short to create mutations to any appreciable degree.[11,39] Against this backdrop, radiocarbon provides an intriguing counterpoint, as each decay event creates a modified base and genetic alteration can easily follow without any further conditions. Transcription errors from transmutation will impact at the cellular level, since mispairing will alter proteins if the codon sequence is modified such that a different amino acid is expressed or a start/stop codon is interferred with. Here the most vulnerable points are the first two bases, as there is considerable redundancy in the final base in the codon triplet. Consequences are magnified for replication errors as mispairs lead to permanent genetic change that propagates through subsequent cell division with corresponding mutagenic implications. Replication fidelities of 10^{-8} are typical for DNA,[40] but as we have discussed previously,[14] it is uncertain what the significance of radiocarbon is relative to other sources of DNA damage, as the key question is whether the DNA cell repair mechanism is sensitive to the presence of a transmuted carbon. Accordingly, while around 1 in every thousand cells will experience a ^{14}C transmutation over a human lifetime, it is difficult to predict the biological effects of such events.

IV. CONCLUSIONS

In summary, we have shown that radiocarbon transmutation in DNA modifies hydrogen bonds between basepairs in a variety of significant ways. The presence of a nitrogen in place of carbon can break bonds, alter the strength of the bond substantially and shuttle protons. For the latter, a variety of processes can occur, including thermally activated shuttling in N–H$\cdots$N bonds in guanine and two types of direct proton shuttling (a symmetric process in thymine N$\cdots$H–N bonds and an asymmetric process in cytosine O$\cdots$H–N bonds). All of these processes are plausible sources of mispairing in DNA replication and transcription, and stimulate further study of the potential of radiocarbon to be an important source of genetic damage.

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[1] Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N.-L. Patterns in hydrogen bonding: Functionality and graph set analysis in Crystals. *Angew. Chem. Int. Ed.* **1995**, *34*, 1555–1573.

[2] Jeffrey, G. A. *An introduction to hydrogen bonding*; Oxford University Press: Oxford, 1997.

[3] Yurenko, Y. P.; Zhurakivsky, R. O.; Samijlenko, S. P.; Hovorun, D. M. Intramolecular CH···O hydrogen bonds in the AI and BI DNA-like conformers of canonical nucleosides

and their Watson-Crick pairs. Quantum chemical and AIM analysis. *J. Biomol. Struct. Dyn.* **2011**, *29*, 51–65.

[4] Martin-Pintado, N.; Deleavey, G. F.; Portella, G.; Campos-Olivas, R.; Orozco, M.; Damha, M. J.; Gonzalez, C. Backbone FC-H···O hydrogen bonds in 2'F-substituted nucleic acids. *Angew. Chem. Int. Ed.* **2013**, *52*, 12065–12068.

[5] Brovarets', O. O.; Yurenko, Y. P.; Hovorun, D. M. Intermolecular CH···N H-bonds in the biologically important pairs of natural nucleobases: a thorough quantum-chemical study. *J. Biomol. Struct. Dyn.* **2014**, *32*, 993–1022.

[6] Fonseca-Guerra, C.; Bickelhaupt, F. M.; Snijders, J. G.; Baerends, E. J. Hydrogen bonding in DNA base Pairs: Reconciliation of theory and experiment. *J. Am. Chem. Soc.* **2000**, *122*, 4117–4128.

[7] Kool, E. T. Hydrogen bonding, base stacking, and steric effects in dna replication. *Annu. Rev. Biophys. Biomol. Struct.* **2001**, *30*, 1–22.

[8] Brovarets', O. O.; Hovorun, D. M. The physicochemical essence of the purine·pyrimidine transition mismatches with Watson-Crick geometry in DNA: A·C* versa A*·C. A QM and QTAIM atomistic understanding. *J. Biomol. Struct. Dyn., in press.* DOI: 10.1080/07391102.2013.852133. Published Online: Nov 21, 2013.

[9] Brovarets', O. O.; Hovorun, D. M. Why the tautomerization of the G·C Watson-Crick base pair via the DPT does not cause point mutations during DNA replication? QM and QTAIM comprehensive analysis. *J. Biomol. Struct. Dyn.* **2014**, *32*, 1474–1499.

[10] Brovarets', O. O.; Hovorun, D. M. The nature of the transition mismatches with Watson-Crick architecture: the G*·T or G·T* DNA base mispair or both? A QM/QTAIM perspective for the biological problem. *J. Biomol. Struct. Dyn., in press.* DOI: 10.1080/07391102.2014.924879. Published Online: Jun 23, 2014.

[11] Brovarets', O. O.; Hovorun, D. M. Can tautomerization of the A·T Watson-Crick base pair via double proton transfer provoke point mutations during DNA replication? A comprehensive QM and QTAIM analysis. *J. Biomol. Struct. Dyn.* **2014**, *32*, 127–154.

[12] Brovarets', O. O.; Zhurakivsky, R. O.; Hovorun, D. M. DPT tautomerisation of the wobble guanine·thymine DNA base mispair is not mutagenic: QM and QTAIM arguments. *J. Biomol. Struct. Dyn., in press.* DOI: 10.1080/07391102.2014.897259. Published Online: Mar 21, 2014.

[13] Sinden, R. R. *DNA Structure and Function*; Academic Press, Inc.: San Diego, 1994.

[14] Sassi, M.; Carter, D. J.; Uberuaga, B. P.; Staneck, C. R.; Marks, N. A. Carbon-14 decay as a source of non-canonical bases in DNA. *Biochim. Biophys. Acta-Gen. Subj.* **2014**, *1840*, 526–534.

[15] Bader, R. F. W. *Atoms in molecules: A quantum theory*; The International Series of Monographs on Chemistry, Clarendon Press: Oxford, 1990.

[16] Kresse, G.; Furthmüller, J. Efficient iterative schemes for ab initio total-energy calculations using a plane-wave basis set. *Phys. Rev. B* **1996**, *54*, 11169–11186.

[17] Kresse, G.; Furthmüller, J. Efficiency of ab-initio total energy calculations for metals and semiconductors using a plane-wave basis set. *Comput. Mater. Sci.* **1996**, *6*, 15–50.

[18] Wang, Y.; Perdew, J. P. Correlation hole of the spin-polarized electron gas, with exact small-wave-vector and high-density scaling. *Phys. Rev. B* **1991**, *44*, 13298–13307.

[19] Vosko, S. H.; Wilk, L.; Nusair, M. Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.* **1980**, *58*, 1200–1211.

[20] Blöchl, P. E. Projector augmented-wave method. *Phys. Rev. B* **1994**, *50*, 17953–17979.

[21] Halpern, A.; Stöcklin, G. Chemical and biological consequences of β-decay. Part I. *Rad. and Environm. Biophys.* **1977**, *14*, 167–183.

[22] Zoete, V.; Meuwly, M. Double proton transfer in the isolated and DNA-embedded guanine-cytosine base pair. *J. Chem. Phys.* **2004**, *121*, 4377–4388.

[23] Brovarets', O. O.; Hovorun, D. M. Does the G·G*syn DNA mismatch containing canonical and rare tautomers of the guanine tautomerise through the DPT? A QM/QTAIM microstructural study. *Mol. Phys., in press.* DOI: 10.1080/00268976.2014.927079. Published Online: Jun 27, 2014.

[24] Otero-de-la Roza, A.; Blanco, M. A.; Martín Pendàs, A.; Luaña, V. Critic: a new program for the topological analysis of solid-state electron densities. *Comput. Phys. Commun.* **2009**, *180*, 157–166.

[25] Saenger, W. *Principles of nucleic acid structure*; Springer advanced texts in chemistry; Springer-Verlag, 1984.

[26] Fonseca-Guerra, C.; Bickelhaupt, F. M.; Snijders, J. G.; Baerends, E. J. The nature of the hydrogen bond in DNA base pairs: The role of charge transfer and resonance assistance. *Chem.–Eur. J.* **1999**, *5*, 3581–3594.

[27] Shishkin, O. V.; Šponer, J.; Hobza, P. Intramolecular flexibility of DNA bases in adenine-thymine and guanine-cytosine Watson-Crick base pairs. *J. Mol. Struct.* **1999**, *477*, 15–21.

[28] Szatyłowicz, H.; Sadlej-Sosnowska, N. Characterizing the strength of individual hydrogen bonds in DNA base pairs. *J. Chem. Inf. Model.* **2010**, *50*, 2151–2161.

[29] Abramov, Y. A. On the possibility of kinetic energy density evaluation from the experimental electron density distribution. *Acta. Cryst. A* **1997**, *53*, 264–272.

[30] Espinosa, E.; Molins, E.; Lecomte, C. Hydrogen bond strengths revealed by topological analyses of experimentally observed electron densities. *Chem. Phys. Lett.* **1998**, *285*, 170–173.

[31] Jissy, A. K.; Datta, A. Design and applications of non-canonical DNA base pairs. *J. Phys. Chem. Lett.* **2014**, *5*, 154–166.

[32] Steiner, T. The hydrogen bond in the solid state. *Angew. Chem. Int. Ed.* **2002**, *41*, 48–76.

[33] Brovarets', O. O.; Hovorun, D. M. How does the long G·G* Watson-Crick DNA base mispair comprising keto and enol tautomers of the guanine tautomerise? The results of a QM/QTAIM investigation. *Phys. Chem. Chem. Phys.* **2014**, *16*, 15886–15899.

[34] Bebenek, K.; Pedersen, L. C.; Kunkel, T. A. Replication infidelity via a mismatch with Watson-Crick geometry. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 1862–1867.

[35] Wang, W.; Hellinga, H. W.; Beese, L. S. Structural evidence for the rare tautomer hypothesis of spontaneous mutagenesis. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 17644–17648.

[36] Löwdin, P.-O. Proton tunneling in DNA and its biological implications. *Rev. Mod. Phys.* **1963**, *35*, 724–732.

[37] Löwdin, P.-O. Effect of proton tunneling in DNA on genetic information and problems of mutations, aging, and

tumors. *Biopolymers Symp.* **1964**, *1*, 161–181.
[38] Löwdin, P.-O. Quantum genetics and the aperiodic solid: Some aspects on the biological problems of heredity, mutations, aging, and tumors in view of the quantum theory of the DNA molecule. *Adv. Quantum Chem.* **1965**, *2*, 213–360.
[39] Perez, A.; Tuckerman, M. E.; Hjalmarson, H. P.; von Lilienfeld, O. A. Enol tautomers of Watson-Crick base pair models are metastable because of nuclear quantum effects. *J. Am. Chem. Soc.* **2010**, *132*, 11510–11515.
[40] Kunkel, T. A. DNA Replication Fidelity. *J. Biol. Chem.* **2004**, *279*, 16895–16898.

V. GRAPHICAL TOC ENTRY