UNRAVELLING THE HYDROGEN BONDING PATTERNS IN TELOMERIC G-QUADRUPLEXES: [1]FROM STRUCTURE TO FUNCTION [2]LIFE AT THE END OF CHROMOSOMES

Telomere Model of Aging

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THE BEST WAY TO PROLONG LIFE IS NOT TO SHORTEN IT. **SENECA**

GROWING OLD IS BORING, BUT IT IS THE ONLY WAY TO LIVE LONG. FAINA RANEVSKAYA

- **[Стареть скучно, но это единственный способ жить долго.**
- ***Фаина Раневская]***
- ***The discovery of the Hydrogen Bond could have won someone the Nobel Prize, but it didn't.***
  G.A. Jeffrey and W. Saenger. Hydrogen Bonding in Biological Structures. p.3
- **"The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X···H in which X is more electronegative than H, and an atom or a group of atoms in the same or different molecule, in which there is evidence of bond formation. A typical hydrogen bond may be depicted as X-H···Y-Z where the three dots denote the bond. X-H represents the hydrogen bond donor. The acceptor may be an atom or anion Y, or a fragment or a molecule Y-Z, where Y is bonded to Z."**
- IUPAC. Compendium of Chemical Terminology, Gold Book, Version 2.3.2, 2014-02-24.

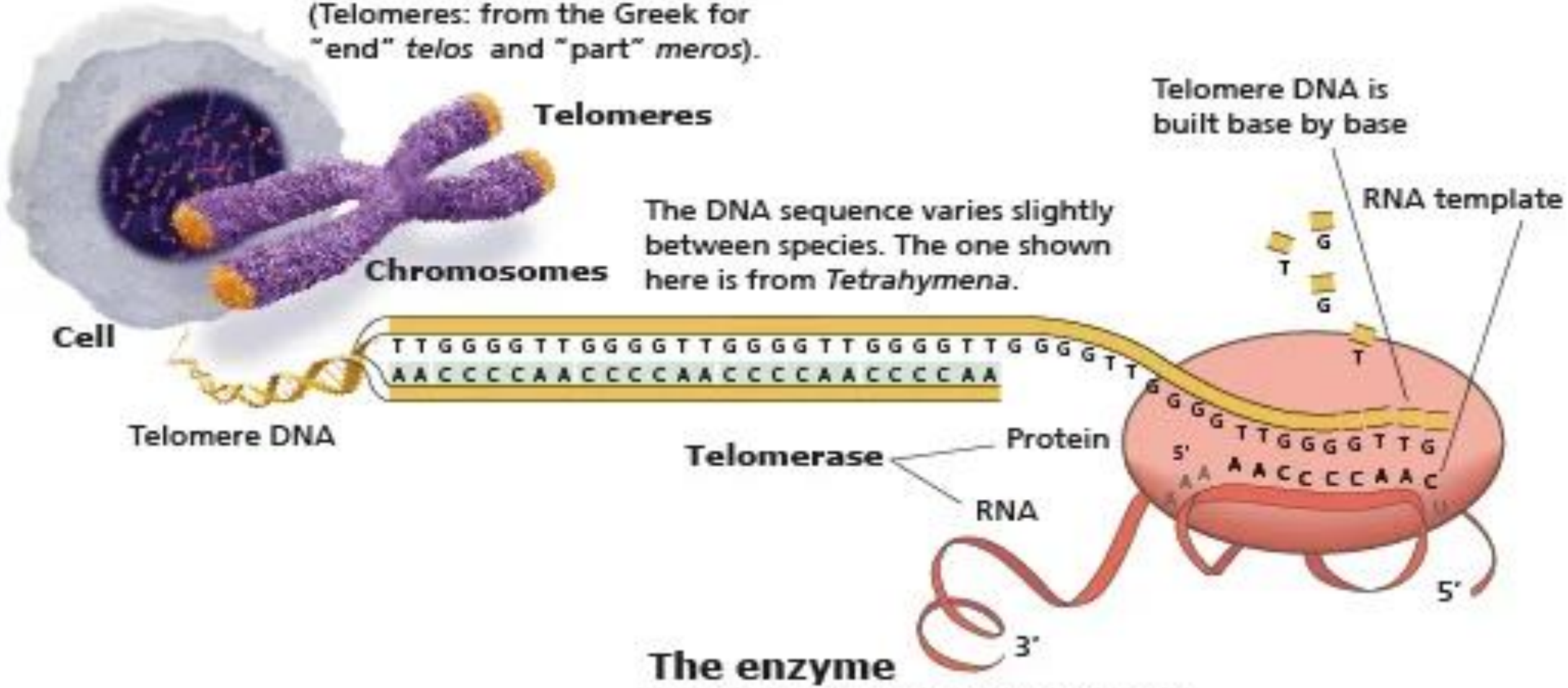
Age is a variable quantity, just a number.
The Paradigm of Aging? Why does a person age?

AGING is a naturally developing destructive biological process of limiting the adaptation of the organism, it is a process that increases the probability of death, reduces life expectancy, and contributes to the emergence of age-related pathology with a primary change in the hereditary apparatus.

V. V. Frolkis (1924-1999, 75 years;

Kiev's gerontologist)

The telomeres form caps at the ends of chromosomes. They contain a unique DNA sequence which is repeated several times. (Telomeres: from the Greek for "end" *telos* and "part" *meros*).



The enzyme

Telomerase operates at the end of the chromosome. It is an enzyme consisting of a protein and an RNA component. The RNA serves as a template for synthesizing telomere DNA.

Hypotheses about aging: no genetic program of aging:

genes cannot answer the question of why a person ages.

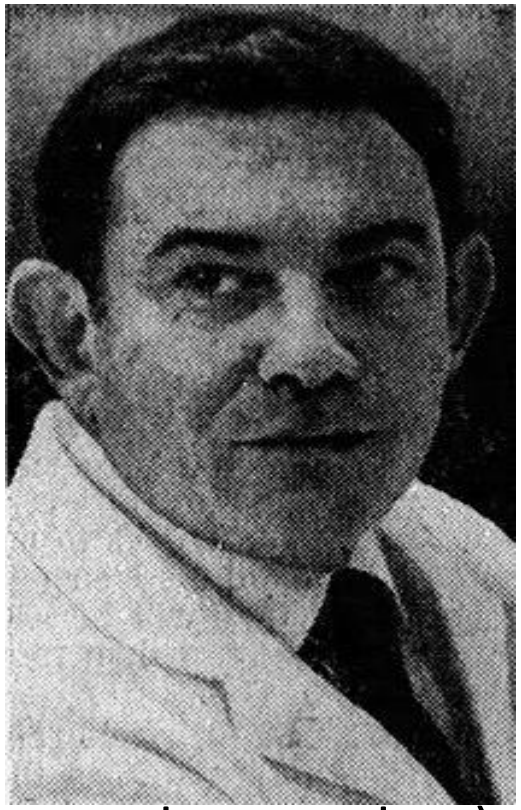
However, aging is under genetic control,
i.e. genes control the aging process by changing

its speed or genes can resist the aging process.

Prehistory. The first one is the hypothesis of the American biologist

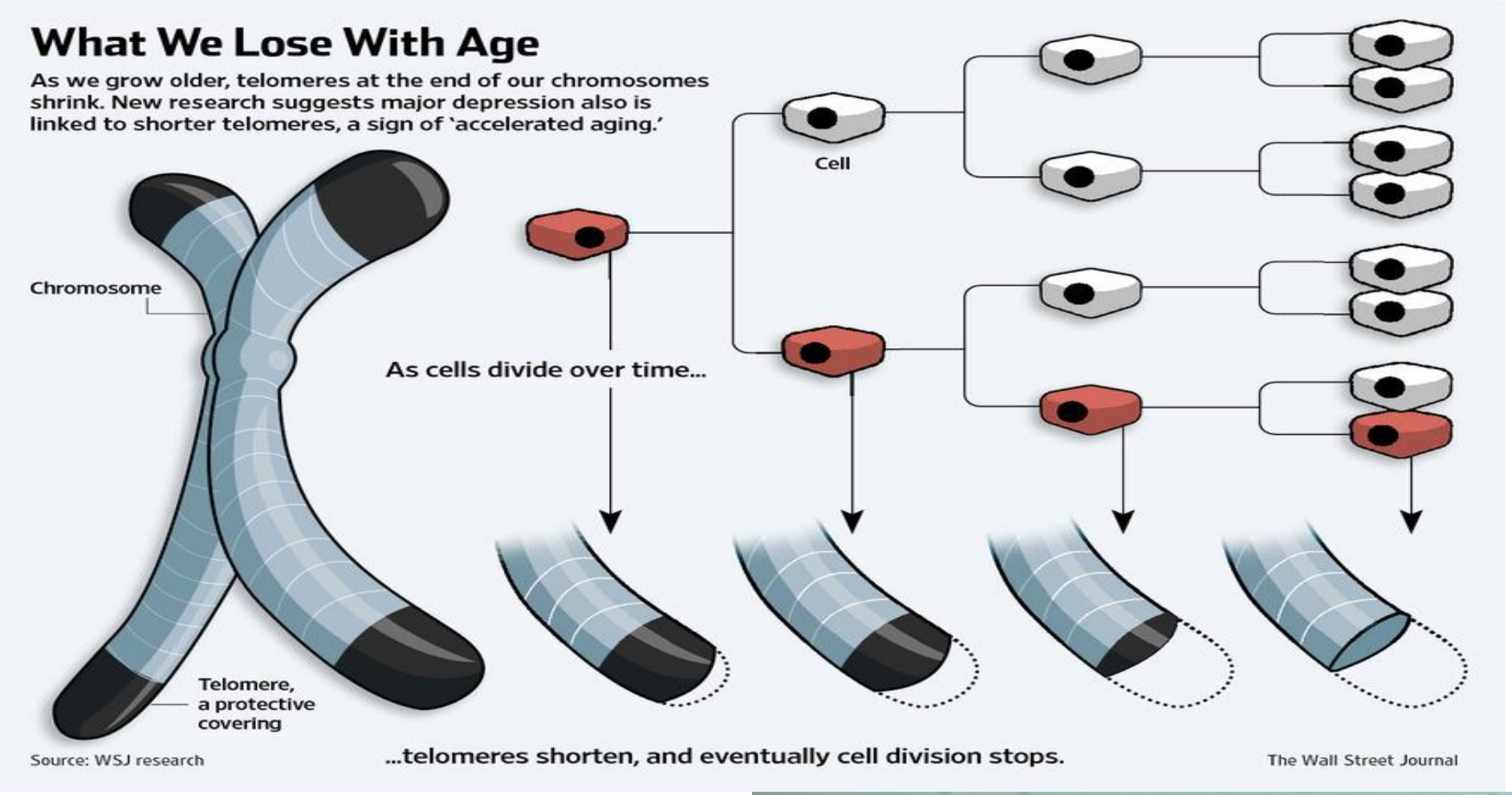
Leonard Hayflick (20.05.1928–01.08.2024) –

a so called Hayflick Limit.



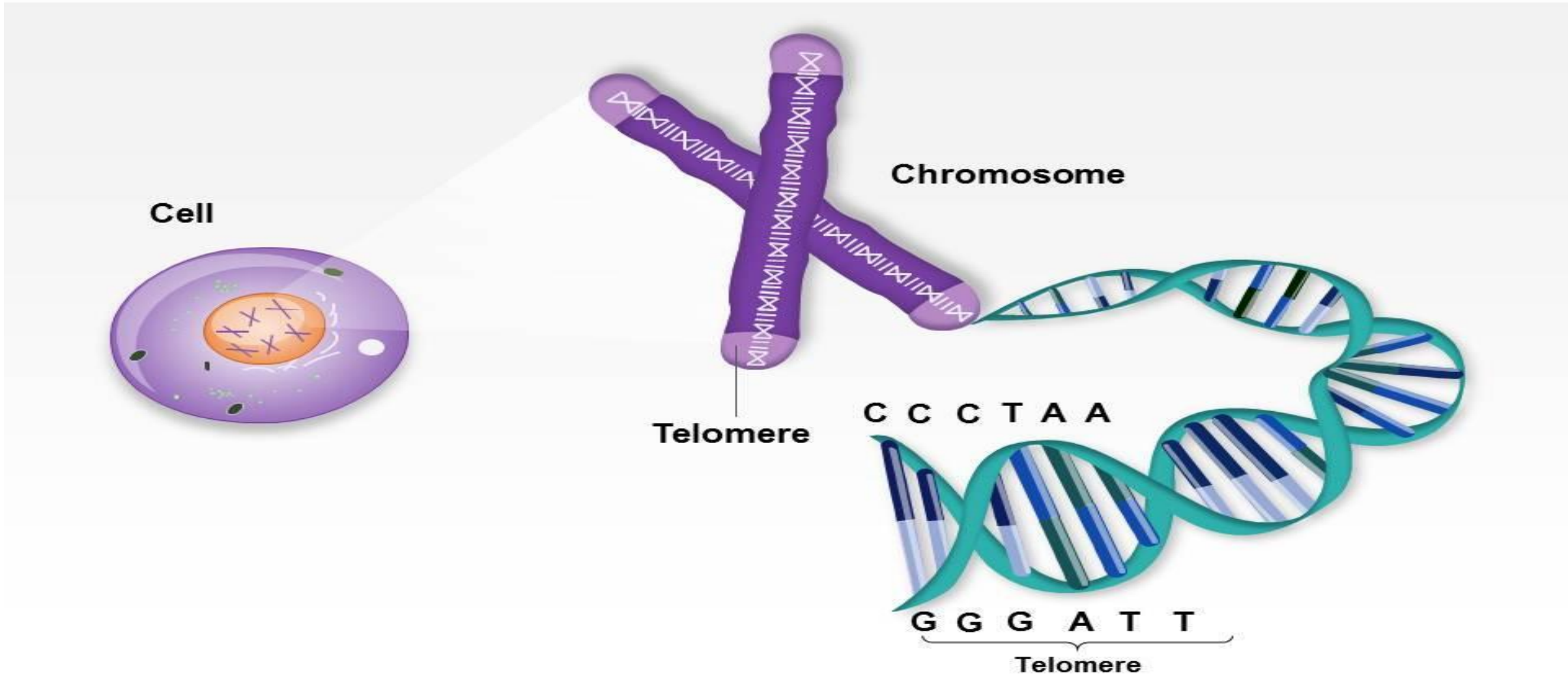
Theory of Marginotomy

(Marginotomy of DNA is the shortening of the replica with respect to the template)



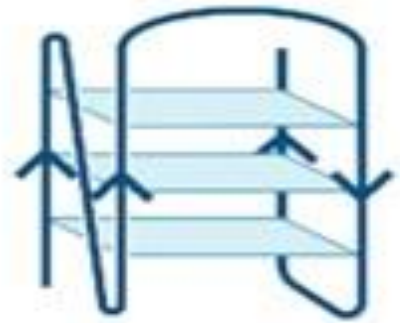
In 1961, Hayflick observed that human cells dividing in cell culture died after about 50 divisions and showed signs of senescence as they approached this limit.

Telomere

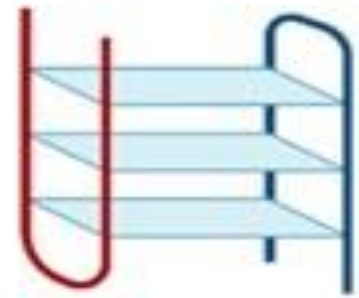


anti-parallel

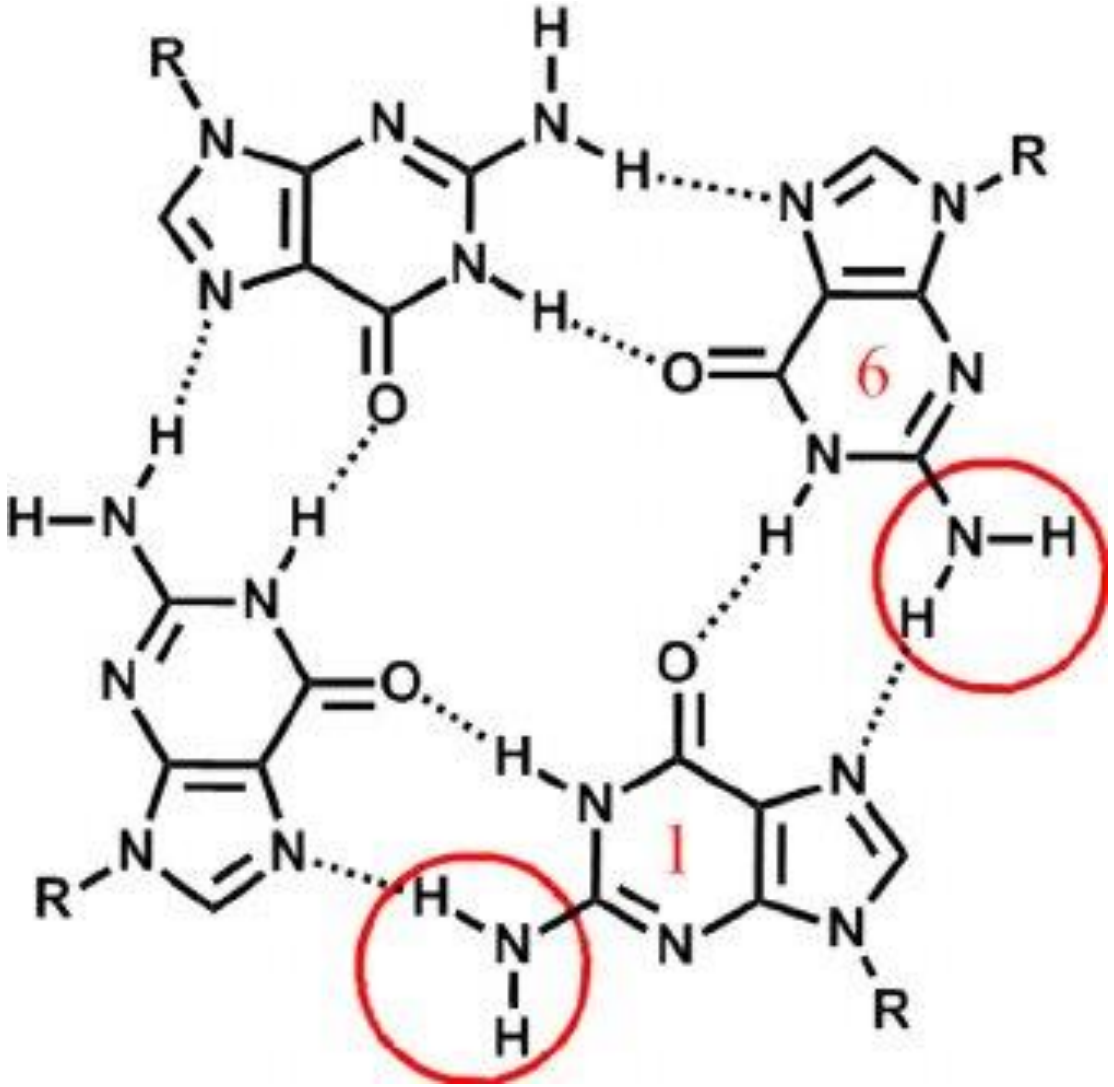
parallel

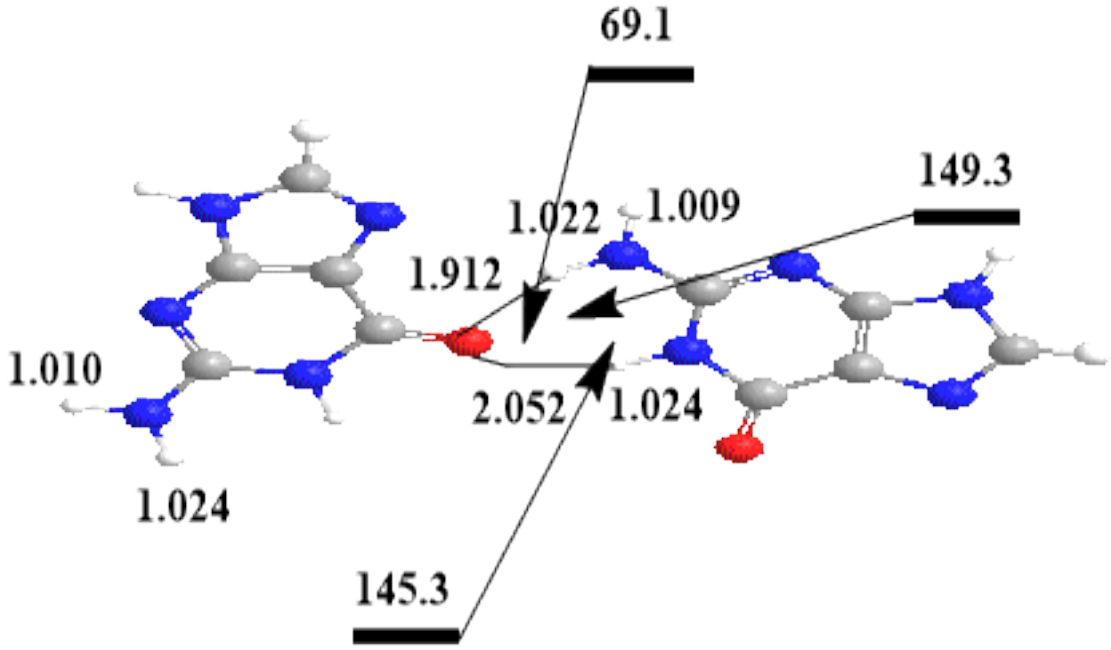


hybrid



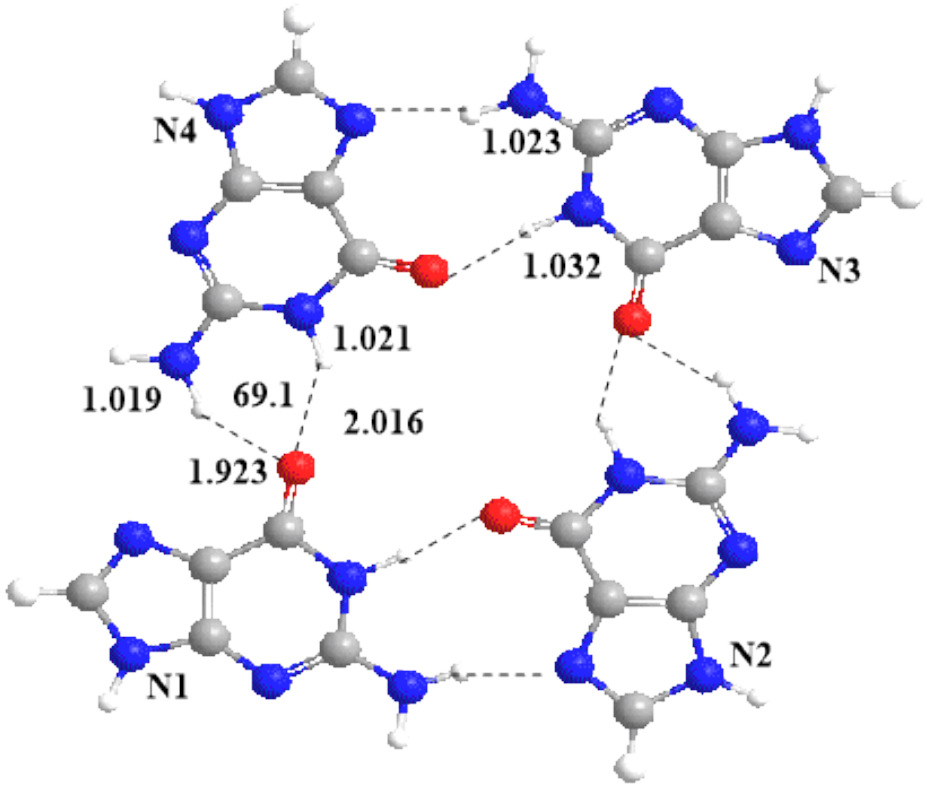
intermolecular

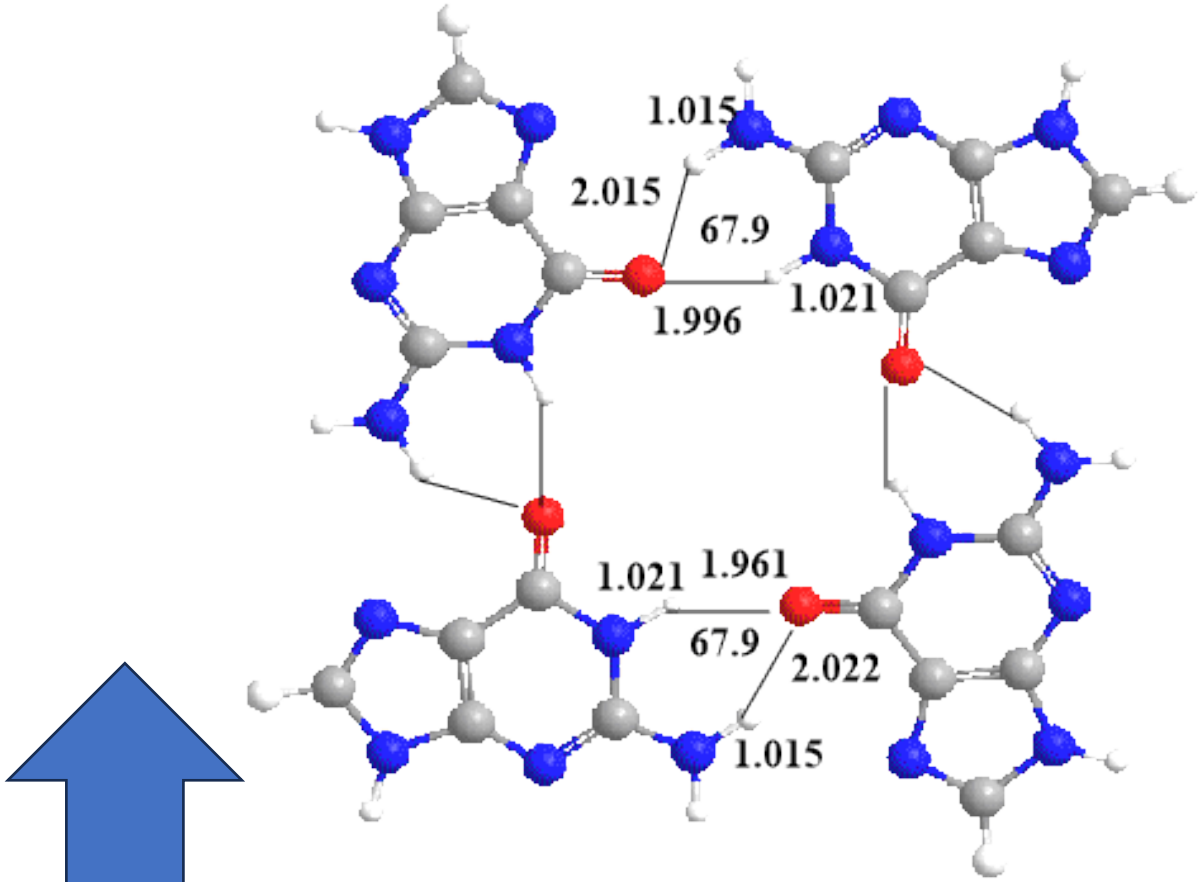




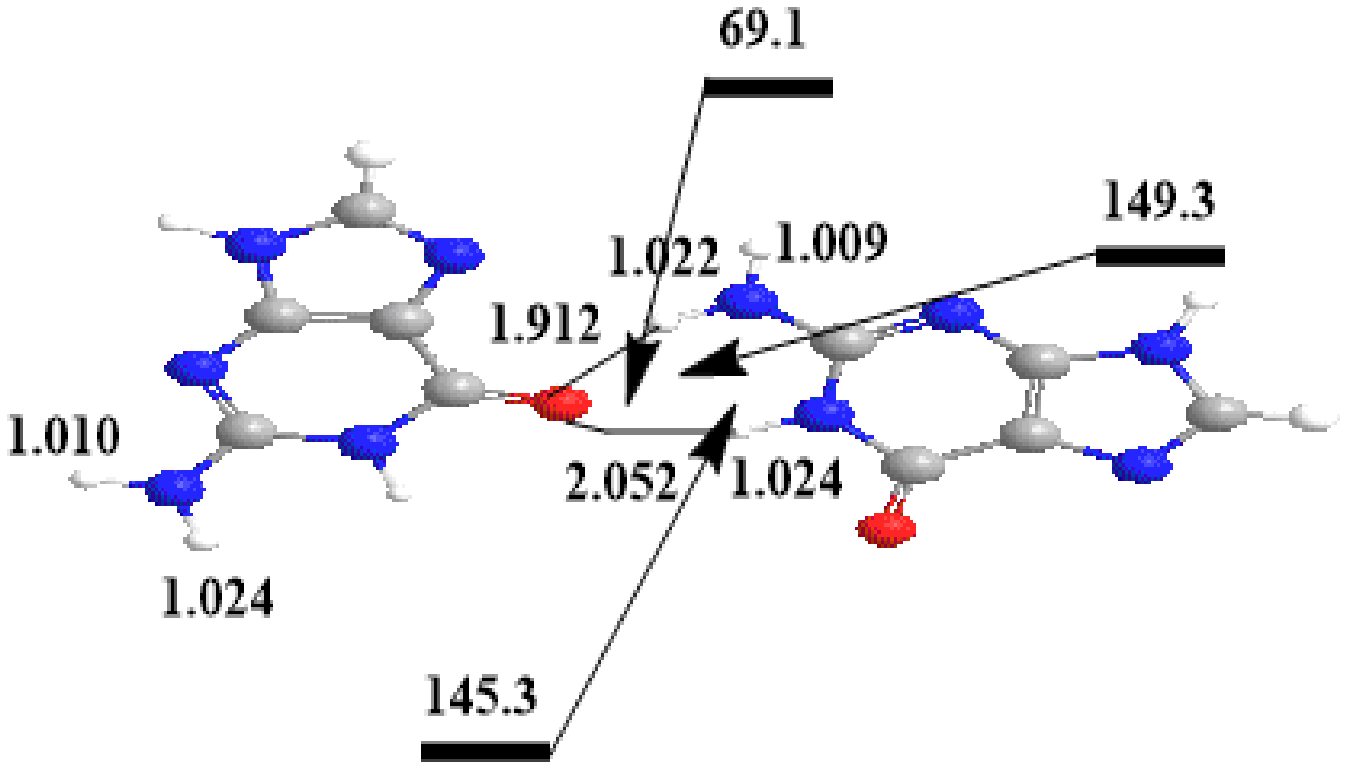
These are so called ‘over-coordinated oxygen (OCO)’ bifurcated hydrogen bonds, OCO BHB.

Potential Energy Surface of G-tetrad and Infrared Spectra





0.22 kcal/mol



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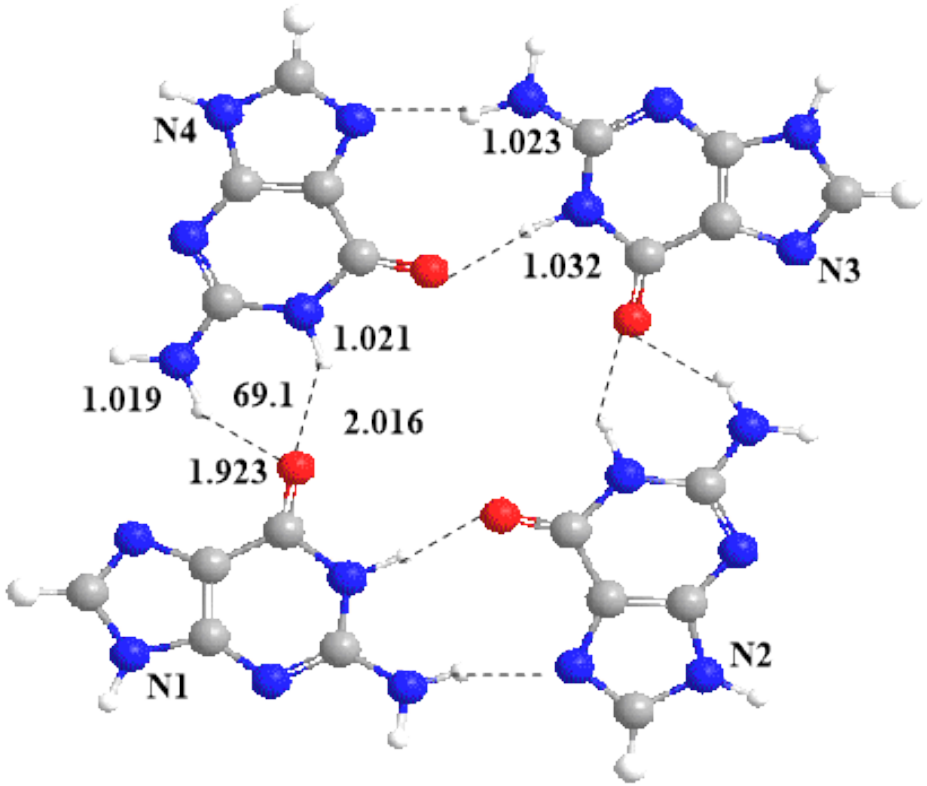

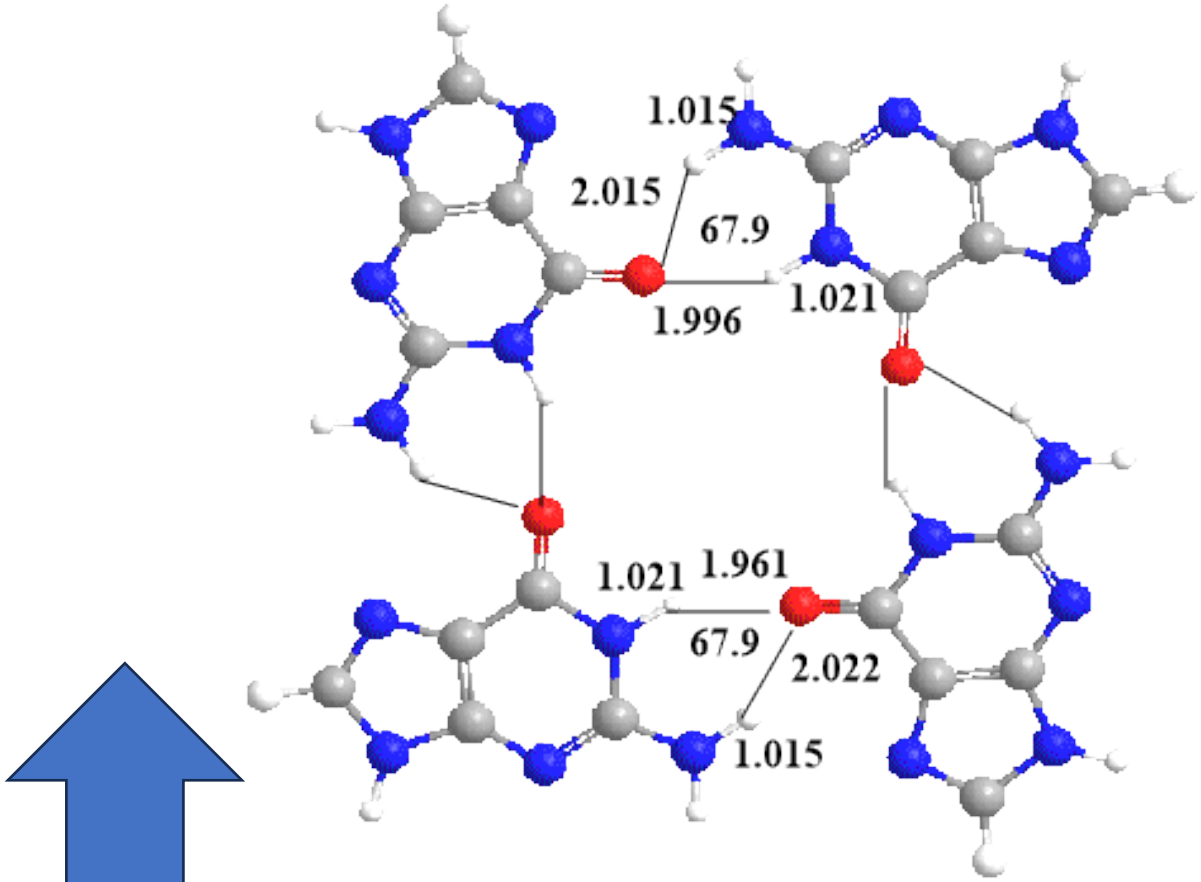

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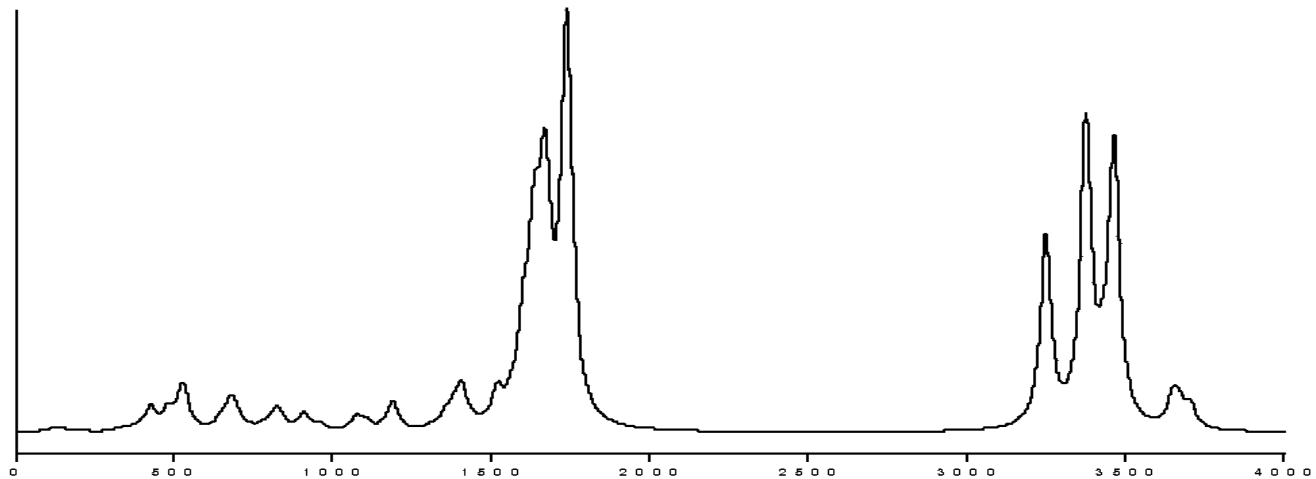
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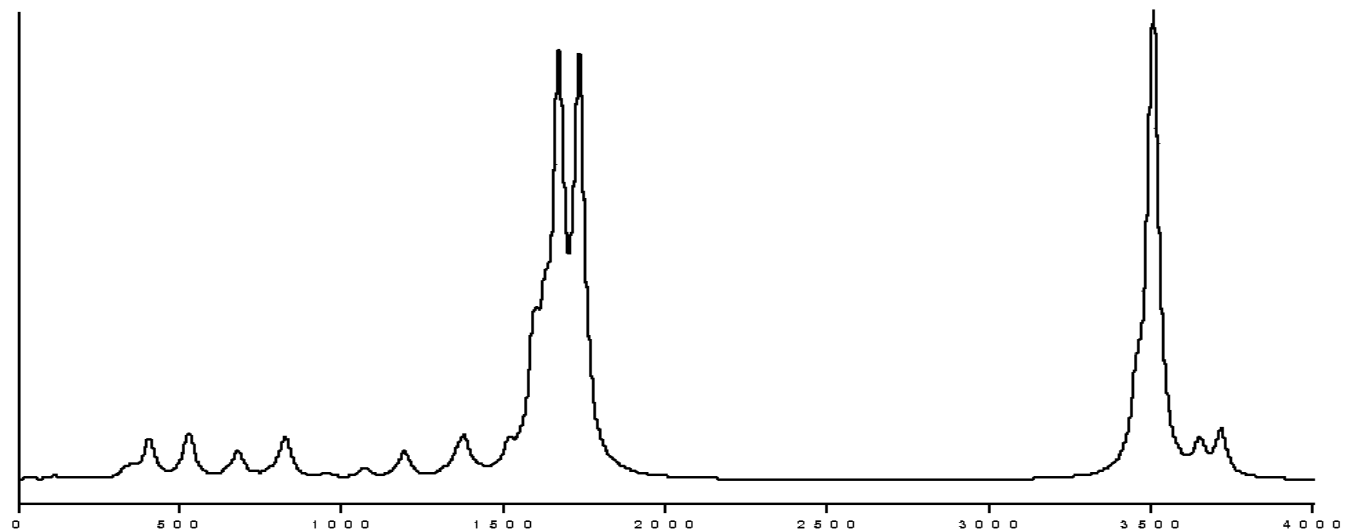
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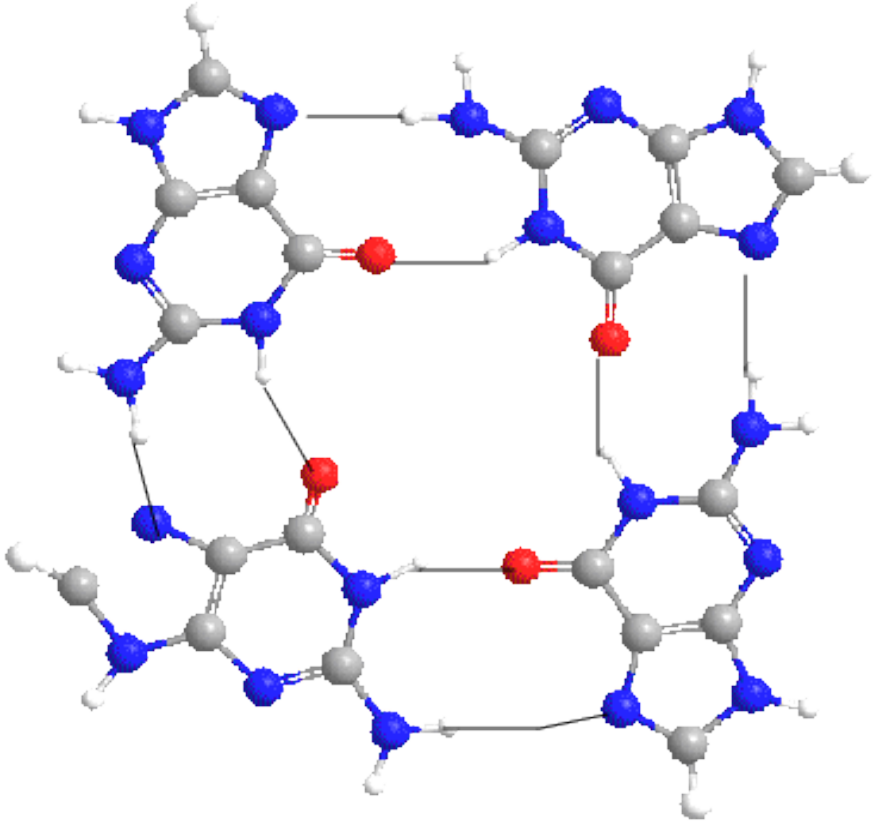
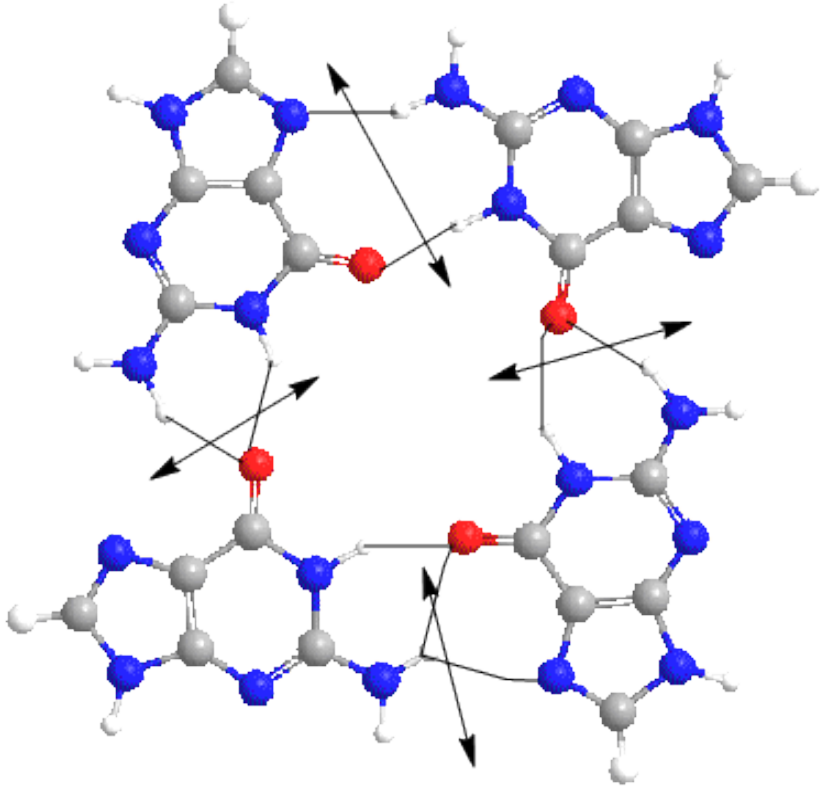
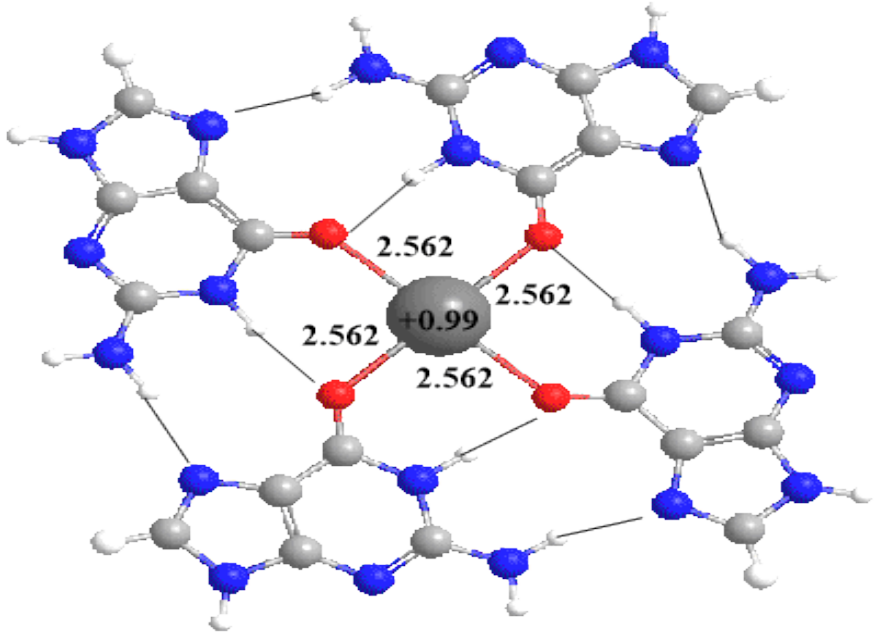
The B3LYP/A transition structures G4-tetrad^{tr1} and G4-tetrad^{tr2}.

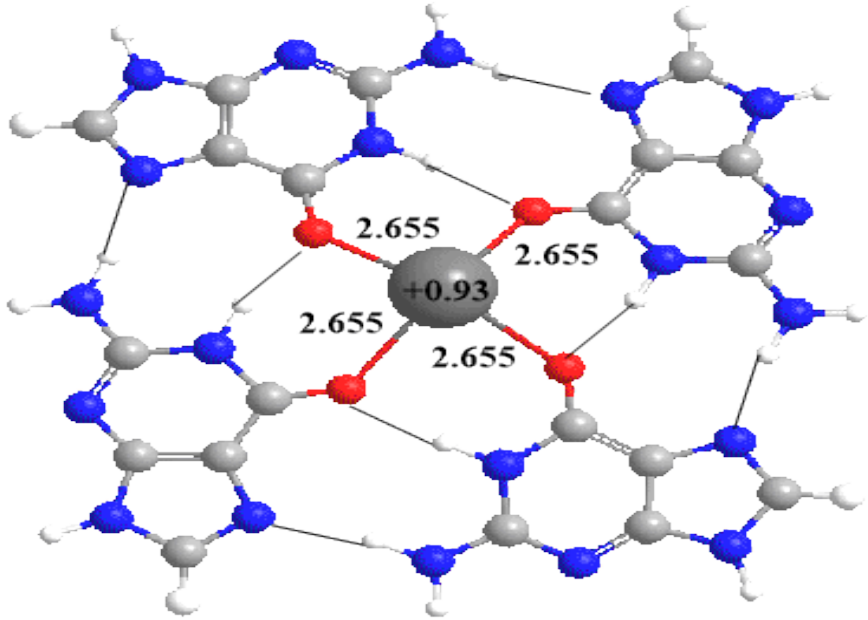




K^+ - G-tetrad Complex

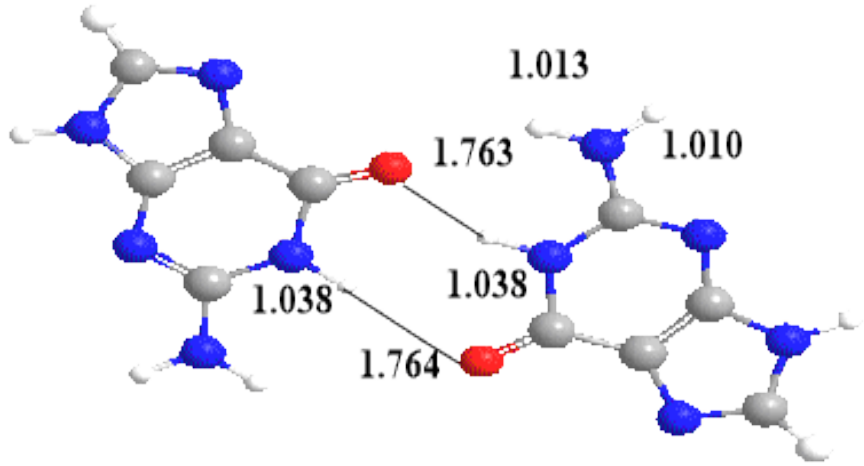
The planar transition (l.h.s) and the energy-minimum (r.h.s.) states of K^+ - G-tetrad complex

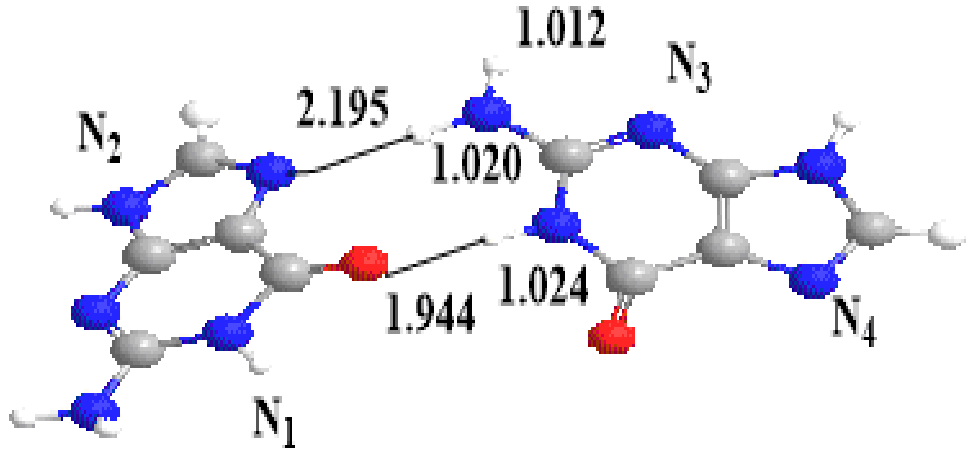




Structural Decomposition of G-tetrad

Dimers of guanine: left - G-2_1; right - G-2_2. The latter dimer is bent with the dihedral angle $\angle N_1N_2N_3N_4 = 44.6^o$. It lies above G-$2_1$ by 11.68 kcal·mol^{-1}. The dipole moments of G-2_1 and G-2_2 are equal to 6.80 and 11.74 D, correspondingly. The binding energy of G-2_1 amounts to -23.39 kcal·mol^{-1}, that exceeds the experimentally well-known energy of formation of the A·T and G·C pairs of DNA, respectively equal to -13.0 and -21.0 kcal·mol^{-1} . Interestingly, it implies a higher thermodynamic stability of G-dimer and G-tetrad.





Afterword: Our Thoughts

The discovered complexity (say, instability) of the G-tetrads may cast doubt on the effectiveness of the telomere model, which, on the other hand, is expected and seems natural since it is difficult to believe in the existence of a single-cell mode of ageing rather than to the multi-cellular ones.

- **This is actually one message we wish to convey. Another is rather opposite, in the light of the new concept very recently (16 May) published in Frontiers of Ageing, whose the author, Prof. John Tower of the University of Southern California interpreted as a new law of biology. He suggests that the selectively advantageous instability (SAI), which states that certain variations in biological components, such as proteins and genetic material, give cells an advantage. In his view, "SAI is the basis of life". Even the simplest cells contain proteases and nucleases that regularly destroy and replace proteins and RNA, indicating the importance of SAI for life. We may suggest that a topological richness of the PES of G-tetrad at the level of hydrogen bonding, interpreted above by us as instability and chaos, may allow the structures to crawl on that PES and, crawling, to act from mechanical to chemical actuation, and this way to create a G-quadruplex that generates a cap to the chromosomes.**
- **However, life goes on! And week ago, Chinese scientists say they have identified a "longevity gene." It can potentially increase human life expectancy, Tengri Life reports, citing Xinhua.**

Acknowledgments … Et cetera

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Unravelling the hydrogen bonding patterns in telomeric G-quadruplexes: From structure to function - What can quantum chemistry contribute to understanding the telomere hypothesis of aging? It unveils hydrogen-bonding patterns and structure-function insights.

1. At the 2002 annual meeting of the Gerontological Society of America, a symposium was held with the provocative title

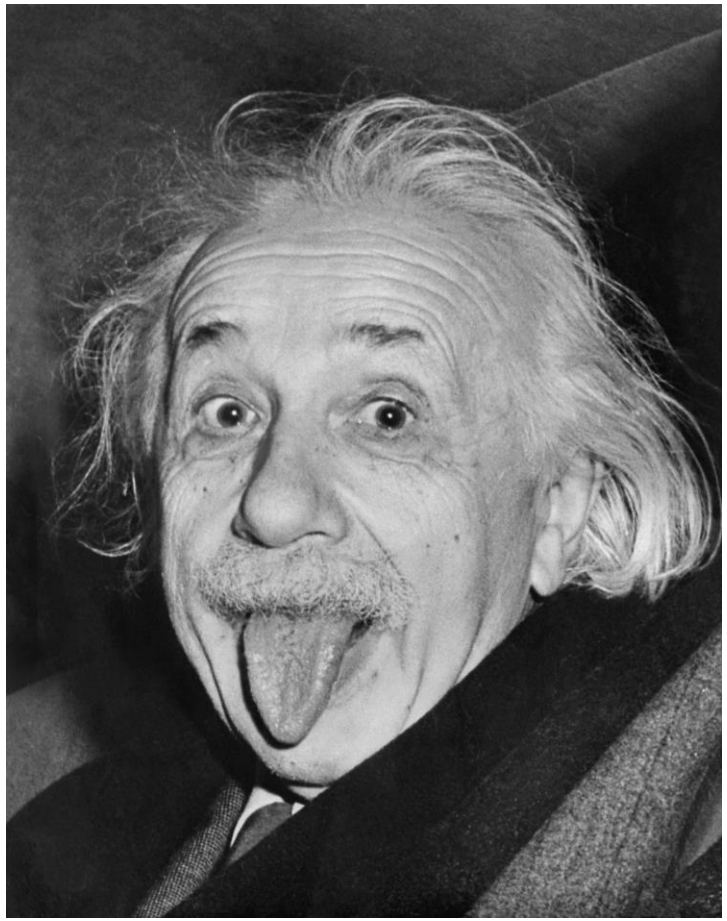
“Has Anyone Ever Died of Old Age?”

(title of Hayflick’s book)

Sponsored by the International Longevity Center-USA, it drew participants from a variety of disciplines into a lively discussion relating to our need to understand the underlying biology of aging that predisposes us to death.

2. “Aging is the product of Evolution”.

For this I want to take my leave.



A. Einstein (March 14, 1879 – April 18, 1955; ~76 years)