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Review

Are the five natural DNA/RNA base monomers a good choice from natural selection? A photochemical perspective

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ABSTRACT

In order to prevent the damaging effects of sun radiation in the genetic material, its constituent chromophores, the five natural DNA/RNA nucleobases cytosine, thymine, uracil, adenine, and guanine, should be able to efficiently dissipate absorbed radiation, UV specifically, avoiding as much as possible photoreactions leading to lesions. It has been established experimentally and theoretically that efficient internal conversion channels, still open and relevant in the oligomer-stacked strands, exist in the monomers allowing an effective waste of the initial energy. Previous evidences cannot explain, however, why minor differences in the molecular structure modify drastically the photochemistry of the systems, leading for many derivatives to slower decays, sometimes to intense fluorescence, and also to reactivity. Using the accurate CASPT2//CASSCF quantum chemical method and the Photochemical Reaction Path Approach it is determined that the five natural nucleobases display barrierless paths from the allowed excited state toward accessible conical intersection seams with the ground state. Such features are known to be the funnels for efficient energy decay and fluorescence quenching. Modified nucleobases, except the methylated ones, are predicted less photostable because they display energy barriers along lowest-energy paths and hence restricted accessibility of the internal conversion channel. This specificity speaks in favor of the choice of the biological nucleobases by natural selection based on their resistance to photochemical damage. Whereas natural and methylated nucleobases, also frequent in the genetic code, are photostable and cannot be photochemically discarded, other non-natural nucleobases may have been eliminated at early stages of the natural selection process.

Contents

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Luis Serrano-Andrés was born in Baden, Switzerland, in 1966. In 1989 he graduated in chemistry by the University of Valencia, Spain, where he obtained in 1994 his Ph.D. degree by his studies on theoretical quantum-chemical organic photochemistry. His postdoctoral research was mainly developed from 1995 to 1998 in the University of Lund, Sweden, within the group of Björn Roos, working in particular in the development and application of quantum-chemical methods to the excited molecular state and their implementation in the MOLCAS software package. He has been invited researcher in the Universities of Lund, Sweden, Torun, Poland, and Sao Paulo, Brazil. In 1999 he joined the Quantum Chemistry of the Excited State (QCEXVAL) group in the University of Valencia as a researcher, obtaining in 2001 a "Ramón y Cajal" position. In 2002 he became Associate Professor of Physical Chemistry in the University of Valencia, where he co-leads with Manuela Merchán the QCEXVAL group. He was a recipient of the Spanish Royal Chemical Society Young Scientist Award in 2001 and Promising Scientist Nominee Prize of the International Society of Theoretical Physical Chemistry and the Centre de Mécanique Ondulatoire Appliquée of Paris in 2002.

Manuela Merchán was born in Castellón, Spain, in 1956. After graduating in 1980 in chemistry by the University of Valencia, Spain, she received in 1985 in this institution her Ph.D. degree for her studies in the quantum chemistry of metal–ligand compounds. After developing postdoctoral and research stays in the Universities of Toulouse, France, and Lund, Sweden, she became Associate Professor of Physical Chemistry in the University of Valencia in 1987, where she founded in 1993 the Quantum Chemistry of the Excited State (QCEXVAL) group. In 2004 she became Professor of Physical Chemistry in the University of Valencia. Her main research interest focuses on the development of computational strategies by using accurate quantum chemical *ab initio* methods and their application to the chemistry of the electronic excited states, in particular for relevant biomolecular systems. She was recipient of the National Prize in Physical Chemistry of the Spanish Royal Chemical Society in 2007.

1. Introduction

Are the five biologically relevant DNA and RNA base monomers cytosine (C), thymine (T), uracil (U), adenine (A), and guanine (G) the best molecules that natural selection could have chosen to build the genetic code among other close tautomers and derivatives? Although most part of the answer relates to structural considerations and its connection with the genetic function, it is possible also to focus on another aspect such as the stability of the genetic code upon external perturbations, for instance to the presence of UV radiation, especially frequent in the early stages of life on Earth [1,2]. We can get some insight into a complex problem if we encounter a manner to explain why analogous molecular structures are more prone to undergo productive photochemistry mainly leading to mutations. As it shall be discussed later, it is understandable that rapid non-radiative decay after UV-light absorption may have been highly advantageous during molecular evolution as a procedure to dissipate the energy before harmful photoproducts may be formed [3].

Experimentally it was earlier established that nucleic acid base monomers in aqueous phase largely quench their fluorescence [4–6]. Evidences of extremely efficient non-radiative decays to non-emitting states [6,7] were also put forward. Recently the presence of ultrafast internal conversion (IC) events transferring the energy from the excited to the ground state in nucleic acids has been directly detected by subpicosecond techniques as an intrinsic feature of nucleotides, nucleosides, and nucleic acid base monomers (see Fig. 1), in isolated conditions and condensed phases [8–13]. Photostability of nucleobases has been therefore an issue of a lively debate in recent years. Is DNA/RNA really so resistant to near-UV radiation? Additional long-lived excited states components have been determined in polynucleotide chains and double-stranded DNA [14–18], particularly related to the stacked-bases structure and the existence of excited state excimers [14,16,18]. Also quite recently, the mechanism of formation of mutated cyclobutane dimers between DNA pyrimidine bases after UV irradiation has been established [19–23]. As a matter of fact, the production of such lesions, considering that has as a prior step the formation of longer-lived singlet excited excimer states, is a strong proof of a more general hypothesis: that the increase in the lifetime of an excited state enhances the probability for a photoreaction, as it occurs for triplet states, even if the correlation of these magnitudes is not necessarily simple. One may then wonder if the photostability of the individual nucleobases can be after all extended to the DNA strand. It has been clearly established that the paths for ultrafast deactivation found in nucleobases are still open in the oligonucleotide strand. A large part of the initially absorbed energy will decay in an ultrafast manner by the same channels as those of the monomers, in particular from those conformations that remain basically unstacked or slightly stacked, but even – with slightly larger lifetimes – from bound excimer states [3,14–18,24,25]. In summary, the ultrafast decay processes may well predominate and most of the energy absorbed by the system will be rapidly dissipated in those systems in which the monomeric nucleobases provide efficient funnels for internal conversion to the ground state.

Independent of the degree of photostability of the biological compound, a striking evidence is put forward by experiment. The photochemical properties of many nucleobases tautomers and derivatives are radically different from those of the natural chromophores. Upon tautomerization or substitution on the nucleobase the ultrafast energy decay channels are severely affected [8,10,26,27]. In some cases, like for 7-substituted adenine derivatives, the femtosecond channel vanishes [8,10,28]; in other situations the picosecond lifetime increases in one or two orders of magnitude [8,26,27,29,30]. There are even more obvious cases, like 2-aminopurine, a close constitutional isomer of adenine (6-aminopurine) [31]. Whereas the latter efficiently quenches its fluorescence leading to very small quantum yields in water ($\phi_F \approx 10^{-4}$) [6,8], 2-aminopurine displays a strong emission ($\phi_F \approx 0.66$) [29,30], in such a way that the compound is commonly used to substitute adenine in DNA as a fluorescent probe to detect protein-induced local conformational changes [32–36]. Similar scenarios are obtained for protonated, oxidized, and reduced nucleobases [8], whereas substitution by methyl does not seem to strongly affect the photochemical outcome [8,10,11,26–28]. Even if it cannot be claimed that such type of behavior is universal for all possible modified nucleobases – and specific systems have been found to decay rapidly in solvation [37]-, it is common enough to be understood as a pattern to have consequences in the biological context.

As mentioned above, a question to be raised is, therefore, why natural nucleobases display such characteristic photochemical feature, so convenient for a safe genetic behavior, and why this property can be perturbed by minor structural modifications. First we have to establish the mechanism for rapid energy dissipation in natural nucleobases. Former proposals to explain low quantum yields of fluorescence and excited-singlet-state deactivation in nucleobases by means of excited-state photoreactions or phototautomerisms were ruled out because of the absence of photoproducts and deuterium isotope effects in different solvents [8]. Modern theoretical photochemistry associates the efficiency of radiationless decay between different electronic states taking place in IC processes to the presence of crossings of different potential energy hypersurfaces (PEH) along an hyperline or seam of molecular structures, i.e., a N-2 dimensional subspace on the N-dimensional surfaces [38–42]. The points belonging to these subspaces, named conical intersections (CI) and representing energy degeneracies between two or more states, behave as energy funnels in whose proximity the probability for non-adiabatic, non-radiative, jumps is