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Preface

Fluorescent nucleoside analogs: synthesis, properties, and applications

Researchers have long relied on fluorescence-based techniques to decipher the fundamental structural, folding, and recognition features of biomolecules. Many proteins contain fluorescent aromatic amino acid residues (e.g., tryptophan, tyrosine, and phenylalanine), or interact with fluorescent cofactors (e.g., NADH), thus providing researchers with inherently emissive, 'built-in', probes. Nucleic acids, in contrast, present a challenge.

In a monograph published in 1967 on 'Fluorescence and Phosphorescence of Proteins and Nucleic Acids', the author, Konev, dedicated a seven-page chapter to the photophysical properties of the latter. This minimal part describes early observations from the 1930s and 1940s, where intense visible emission was observed from nucleobases and nucleic acids. Intriguingly, repeated purification steps of the nucleic acids or their building blocks resulted in continuously diminishing emission, which ultimately led to the conclusion that emissive impurities were responsible for the observed photoluminescence. Somewhat more refined studies then resulted in the conclusion that the purines and pyrimidines commonly found in nucleic acids are non-emissive in neutral aqueous conditions. This view still prevails today, although more accurate techniques reveal finite, albeit very small, fluorescence quantum yields for the natural nucleobases (0.5×10^{-4}–3×10^{-4}). This exceedingly weak emission is associated with very short excited state life times (of the order of picoseconds). Not surprisingly, Mother Nature has selected the building blocks for her genetic material to have favorable photophysical properties, thus minimizing photochemically induced transformations. Since natural nucleobases are practically non-emissive, fluorescence-based biophysical studies have to rely on exogenous fluorescent tags or synthetically modified nucleobases with more desirable emissive characteristics.

Organic chemists have long been attracted to the heterocyclic structures found in nucleic acids and have generated numerous modified nucleosides and nucleotides. Early work, pertinent to the topic of this issue, was inspired by examples of naturally occurring emissive heterocycles, especially the wyeosine bases, a family of tricyclic guanine derivatives (e.g., yW, Yt, etc.). The pioneering work of Nelson Leonard, where an etheno bridge was constructed across the H-bonding face of the purines and pyrimidines has led to a series of emissive nucleobase analogs. Ethenoadenosine (εA), in particular, was employed in some of the earliest bioorganic studies with modified nucleotide triphosphates. In addition, organic and medicinal chemists have prepared numerous modified nucleosides over the years, mostly as potential antiviral and chemotherapeutic agents. Quite a few are fluorescent, although most were not originally examined for their photophysical properties and were not employed as fluorescent probes. This is understandable, in retrospect, as many of these studies preceded the development of solid-phase oligonucleotide synthesis as well as many of the fundamental discoveries deciphering nucleic acid recognition. Our contemporary landscape is vastly different as the market for modified nucleosides and nucleotides in biological chemistry, biotechnology, and biophysics is rich.

This issue, one of *Tetrahedron's Symposia-in-Print*, brings together contributions from many of the leading research groups in this multidisciplinary research area. Diverse themes are covered, illustrating the breadth of this growing field. Specific topics include: the synthesis and incorporation of emissive nucleosides and nucleoside surrogates, the photophysical analysis of useful fluorescent nucleobases, and the application of established emissive nucleosides (e.g., 2-aminopurine and pteridines) for the fabrication of biophysical assays. In addition, the interested reader will find contributions describing the design and implementation of environmentally and sequence sensitive fluorescent nucleoside analogs as well as the application of multi-color and novel base pair probes for nucleic acid detection. The creative and elegant approaches presented here address significant problems in nucleic acid structure, function and recognition, and illustrate the utility of judiciously implemented fluorescence probes. It is highly likely that we will continue to see growth in this attractive research area parallel to further development in diagnostics and sensor design.

Putting such *Symposia-in-Print* together, as any guest editor knows, takes longer than anticipated and requires the productive interaction of many scientists. I would like to acknowledge all my colleagues who have agreed to contribute and to review the articles included in this issue. I would also like to thank my assistant, Ms. Robyn Swanland, for

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her help in assembling this issue. Finally, I would like to dedicate this collection of articles to the memory of the late Professor Nelson Leonard, who passed away very recently. His pioneering work in the bioorganic chemistry of modified nucleosides and nucleotides has inspired many of the researchers in this flourishing and colorful field.

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