JACS
EDITORIAL

Published on Web 03/25/2009

# Nucleic Acids: Expanding the Structural and Functional Horizons

The study of nucleic acids has been of interest to chemists and biochemists for several decades. The challenges associated with the preparation of the nucleoside building blocks of DNA and RNA, and their structural analogues, have attracted great attention due to the novel chemistry involved as well as the biochemical and biological activities associated with many of these compounds. The complexity of DNA and RNA oligonucleotide synthesis has included the need to define suitable protecting group strategies for the nucleobases and (deoxy)ribose moieties, efficient methods of establishing phosphate diester linkages, and pioneering methods for the purification of the elaborated DNAs and RNAs, which are polyanions and freely soluble only in water and other polar solvents. The analysis of nucleic acid primary, secondary, and tertiary structure, and of its interactions with ligands large and small, has likewise progressed dramatically in parallel based on the development of innovative biophysical and biochemical techniques.

The biochemical community has provided a steady stream of discoveries involving nucleic acids that have extended the initial horizons of workers in this field into new realms. The early findings that nucleic acids actively participated in the decoding, as well as storage, of genetic information proved central to our developing understanding of the mechanisms of DNA decoding, RNA splicing, and protein synthesis. The landmark discovery that RNA molecules could direct their own biosynthetic processing provided evidence for the existence of an early world in which RNAs were the primary catalysts and led promptly to techniques for identifying nucleic acids capable of highly selective substrate binding and catalysis. In recent years, the findings of regulation of gene expression by transposition of genes, RNA interference, microRNAs, and riboswitches have further enriched our understanding of the several ways in which nature uses nucleic acids and provided opportunities for more sophisticated intervention in natural systems.

As DNA is the repository of genetic information, its structural integrity is critical to maintenance of the identity of individual organisms and is central to the process of molecular evolution. Physical and chemical agents that alter DNA structure are mutagenic and have the potential to promote carcinogenesis. Accordingly, organisms have evolved elaborate systems to recognize and repair DNA damage. In the aggregate, these processes ensure continued viability of the organisms. In recent years, it has also become apparent that nucleic acids provide multiple opportunities for therapeutic intervention. Efforts in antitumor therapy have led to numerous clinically used agents that function at the level of nucleic acids in cancer cells. Ongoing efforts at selective control of gene expression with small molecules have progressed impressively in recent years and seem likely to afford new opportunities for selective therapy of a number of diseases in due course. New chemistries used for the synthesis of antigene and antisense oligonucleotides have afforded remarkable enhancements in the therapeutic potential of these agents, some of which are showing exceptional promise in clinical trials. The discovery of multiple natural mechanisms for the regulation of gene expression with naturally occurring oligonucleotides will undoubtedly extend the therapeutic reach of synthetic antisense drugs.

The 20 outstanding Articles and Communications in this *JACS* Select collection appeared in the Journal in 2008. They accurately reflect many of the continuing research activities summarized above and focus on issues critical to progress in the field. Four publications touch on important elements of structure determination of nucleic acids. RNAs can potentially adopt a number of secondary structures, and these can be critical to RNA function. **Graber**, **Moroder**, and **Micura** describe a new NMR technique that employs $^{19}$F-labeled RNAs to permit the analysis of coexisting RNA structures by one-dimensional $^{19}$F NMR spectroscopy.[1] Folding algorithms for RNA secondary and tertiary structure have traditionally been limited in their predictive value by the large number of possible structures of comparable energies. **Mathews, Turner**, and co-workers have demonstrated how readily obtained NMR data can be utilized in conjunction with a folding algorithm to limit the potential folding space of an RNA, and thereby

(1) Graber, D.; Moroder, H.; Micura, R. *J. Am. Chem. Soc.* **2008**, *130*, 17230–17231.

10.1021/ja9012485 CCC: $40.75  

increase the confidence in the modeling of RNA folding.[2] By systematic variation of a tetraloop structure or its receptor, **Chauhan** and **Woodson** were able to demonstrate that tertiary interactions are important to the accuracy of folding of a ribozyme derived from a self-splicing group I intron.[3] Finally, **Schlegel**, **Essen**, and **Meggers** utilized X-ray crystallography to define the structure of a minimal nucleic acid duplex, which is of great interest from the perspectives of both prebiotic nucleic acid duplexes and possible simplified antisense oligonucleotides.[4] Two additional Communications define the interactions of nucleic acids with small molecules. These include a molecular dynamics simulation of the 30S subunit of the bacterial ribosome by **Aleksandrov** and **Simonson**, which identified a preferred binding site for tetracycline,[5] and an X-ray crystallographic study of the binding of the acridine derivative BRACO-19 to a human telomeric G-quadruplex structure by **Neidle** and co-workers.[6]

Six publications in the collection deal with DNA modifications and their effects on DNA structure and function. These include a report by **Ober** and **Lippard** on the effects of intrastrand GpG cross-links formed by cisplatin. The assembly of nucleosomes using site-specifically platinated synthetic DNAs and core histones from HeLa cells was found to result in an altered rotational setting of the DNA on the histone octamer core.[7] The effect of methylation on a DNA structure was investigated by **Chaires** and co-workers.[8] They studied the thermal stability of G-quadruplex DNA containing one $O^6$-methylguanosine moiety and found that the presence of $O^6$-methylguanosine lowered the thermal stability of the G-quadruplex. By the use of CD spectra and molecular dynamics calculations, it was found that the basic quadruplex structure was retained, albeit with some modification. Many reagents that modify DNA result in the loss of one or more nucleobases, and the resulting abasic lesion is known to be electrophilic. **Sczepanski**, **Jacobs**, and **Greenberg** have documented the ability of a 4′-OH apurinic acid to form DNA interstrand cross-links and analyzed the nature of the formed cross-links.[9] 8-Oxoguanosine is another common DNA lesion resulting from oxidative stress. **Burrows** and co-workers have characterized an interesting tricyclic adduct resulting from 8-oxoguanosine and tyrosine under conditions of oxidative DNA stress.[10] DNA-mediated charge transport has been a topic of great interest in recent years. **Elias**, **Shao**, and **Barton** report a comparison of charge transport involving both oxidatively and reductively transformed DNA,[11] the latter of which has been studied less extensively to date. The two processes were found to share similar characteristics, including a dependence on base stacking but a shallow distance dependence. Finally, **Taylor** and co-workers have characterized an interesting interstrand-type *cis-anti* cyclobutane thymine dimer produced in high yield by UVB irradiation at low pH.[12] In addition to these studies, **Luo** and **Schramm** have studied an *E. coli* enzyme that modifies a homologous tRNA and characterized the transition state structure for adenosine deamination by that enzyme.[13]

As noted above, there are numerous mechanisms for control of gene expression and consequent cellular metabolism. One well studied process in certain bacteria is the stringent response, whereby the guanosine nucleotides ppGpp and pppGpp regulate bacterial response to nutrient deprivation. **Hong** and co-workers describe the synthesis of a fluorescent chemosensor for these nucleoside phosphates that should greatly facilitate the study of the compounds in cellular systems.[14] Several metabolites can regulate their own synthesis by direct binding to specific regions of mRNA (riboswitches). **Thore**, **Frick**, and **Ban** characterized the eukaryotic thiamine pyrophosphate riboswitch in complex with two TPP analogues.[15] The X-ray crystallographic structures provide high-resolution information concerning the nature of the formed complexes. Hairpin pyrrole−imidazole polyamides are programmable minor groove DNA binders that have strong affinities for their DNA substrates and can selectively inhibit gene expression in intact cells through modulation of transcription factor−DNA interaction. **Dervan** and co-workers report the preparation and characterization of a new type of hairpin


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(6) Campbell, N. H.; Parkinson, G. N.; Reszka, A. P.; Neidle, S. *J. Am. Chem. Soc.* **2008**, *130*, 6722–6724.
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(8) Mekmaysy, C. S.; Petraccone, L.; Garbett, N. C.; Ragazzon, P. A.; Gray, R.; Trent, J. O.; Chaires, J. B. *J. Am. Chem. Soc.* **2008**, *130*, 6710–6711.
(9) Sczepanski, J. T.; Jacobs, A. C.; Greenberg, M. M. *J. Am. Chem. Soc.* **2008**, *130*, 9646–9647.
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(15) Thore, S.; Frick, C.; Ban, N. *J. Am. Chem. Soc.* **2008**, *130*, 8116–8117.

polyamide containing (*R*)-3,4-diaminobutyric acid.[16] Hairpins containing this motif were found to inhibit androgen receptor-mediated gene expression in cell culture, implying cell permeability. Finally, **Romesberg** and co-workers described the discovery, characterization, and optimization of a new unnatural base pair that has potential for expansion of the genetic alphabet in experimental systems.[17]

In recent years, DNA has been shown to be capable of acting as a template for chemical reactions other than DNA replication and RNA transcription. Thus, **Snyder**, **Tse**, and **Liu** have studied the effects of DNA sequence and secondary structure on the facility of DNA-templated synthesis.[18] They found that sequences that were predicted to contain either very extensive or no secondary structure in the reagent binding site exhibited impaired reactivity, while those having modest secondary structure displayed good reactivity. **Datta** and **Schuster** prepared a new class of materials via DNA-directed synthesis through the linking of aniline-containing oligomers that were attached to the DNA nucleobases.[19] In a third study involving DNA-based catalysis, **Feringa**, **Roelfes**, and co-workers studied an enantioselective Diels−Alder reaction, the rate and enantioselectivity of which were dependent on the DNA sequence.[20]

In the aggregate, these studies illustrate the continuing conceptual and practical advances being made in several aspects of nucleic acids studies and the role of the Journal in bringing the work to the attention of the scientific community. We hope that this *JACS* Select will provide the readership with a better understanding of the present scope of activities in the area and key issues being addressed at the present time.

*Sidney M. Hecht, Associate Editor*

JA9012485

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