

*A Summary  
(including Table of Contents)  
on the Monograph  
on*

# **Stereoelectronic Effects in Nucleosides and Nucleotides and their Structural Implications**

Christophe Thibaudeau, Parag Acharya and Jyoti Chattopadhyaya\*

*\* To whom correspondence should be addressed. E-mail: [jyoti@boc.uu.se](mailto:jyoti@boc.uu.se)*

Department of Bioorganic Chemistry  
Box 581, Biomedical Center, Uppsala University, Sweden  
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Bioorganic Chemistry, Box 581, Uppsala University, S-75123 Uppsala, Sweden, version 140303. [jyoti@boc.uu.se](mailto:jyoti@boc.uu.se)

Christophe Thibaudeau, Parag Acharya and Jyoti Chattopadhyaya\*  
Dept of Bioorganic Chemistry  
Uppsala University  
Biomedical Center, Box 581  
S-751 23 Uppsala

*\*To whom correspondence should be addressed.*

E-mail: [jyoti@boc.uu.se](mailto:jyoti@boc.uu.se)

F +4618554495

T +46184714577

Web: [www.boc.uu.se](http://www.boc.uu.se)

Dr C. Thibaudeau has completed his Ph.D  
in Feb, 1999 at the Dept of Bioorganic Chemistry  
under the supervision of Prof J. Chattopadhyaya

Mr P. Acharya is currently a Ph.D student  
at the Dept of Bioorganic Chemistry under  
the supervision of Prof J. Chattopadhyaya

Dr J. Chattopadhyaya is professor of Bioorganic Chemistry  
at the Uppsala University.

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## PREFACE

The three essential components of DNA and RNA are the aglycone, the pentofuranose sugar in  $\beta$ -D stereochemistry and the phosphodiester. The phosphates at the backbone makes DNA/RNA to behave as polyelectrolyte, the pentose sugar gives the flexibility, and the aglycones help in the self-assembly process. The stability of the folded structure of nucleic acids is usually attributed to the interplay of various forces such as hydrogen bonding, stacking, electrostatics, hydrophobics and hydration.

Are the physico-chemical roles of the aglycone, sugar and phosphate correlated and interdependent? How do they respond to the local change of the environment, and affect the recognition process that culminate into function?

It has long been qualitatively known that they are not isolated structural elements. The electronic nature of the aglycone dictates certain preferred sugar torsions, which are again correlated with certain phosphate torsions. X-ray crystallographic and NMR studies have demonstrated how the sugar and phosphate moieties can adopt different conformations in DNA and RNA. It has been shown that the rotations about C-O and P-O ester bonds are restricted, and certain sugar-phosphate torsions are preferred over the others.

Prior to the work summarized here from the Uppsala group, very little was known about the dynamic interdependency of the conformational changes between the three essential components of DNA and RNA or the energetics involved in this process. Through our solution NMR studies, we have attempted to show the dynamic character of the interdependency of the electronic nature of the aglycone and the sugar conformation, dictating the phosphate backbone torsions. The important aspect of this dynamic interdependency of the aglycone-sugar-phosphate orientation is that it can be modulated by the change of the environment with a certain energy penalty. The mechanism of this modulation is stereoelectronic in character, and the concerted conformational change is unidirectional, originating from the aglycone to the sugar and further to the phosphate. In this book, we have explored the nature of the stereoelectronic forces arising from the gauche and anomeric interactions, that are partly responsible for the self-organization of nucleosides and nucleotides. Most importantly, we have experimentally measured the strength and the interplay of these interactions, for the first time, and shown the significance of their effects in dictating the overall dynamics and the structure of nucleos(t)ides and their analogs. This process has enabled engineering of specific conformations in a predictable manner in nucleos(t)ides by having appropriate substituent(s) in the sugar moiety.

Hexopyranoses are much less flexible than pentoses. The intrinsic flexibility of pentoses in natural nucleosides and nucleotides, owing to their lower energy barrier for interconversions compared to the hexopyranoses, is dictated by the energetics of stereoelectronic effects, which simply can be tuned and modulated by choice of substituents and their ionization state as well as by their complexation with potential ligands present in the medium. Stereoelectronic effects operate by appropriate orbital overlap between the donor and acceptor through-bond and through-space. The strength of the stereoelectronic effects induced stabilization is proportional to the square of the overlap of the donor and acceptor orbitals, and is inversely proportional to their energy difference.

We believe this book is of considerable value to those medicinal and pharmaceutical chemists in the academia or in the industry, who wish to understand fundamental mechanism involved in the design of structure of modified nucleos(t)ides, and use this knowledge to rationally develop antisense, RNAi or triplexing agents or specific enzyme inhibitors.

Finally, a new section has been added covering the latest in the field (Appendix: Chapter 10), which makes this monograph current till the end of 2002.

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