

**Why Does TNA Cross-Pair More Strongly with RNA than with DNA? — An Answer from X-ray Analysis.** Pradeep S. Pallan<sup>†</sup>, Albert Eschenmoser<sup>‡</sup>, Christopher J. Wilds,<sup>‡</sup> Zdzislaw Wawrzak<sup>§</sup>, Ramanarayanan Krishnamurthy<sup>¶</sup>, Martin Egli<sup>\*†</sup>, <sup>†</sup>Dept. of Biochemistry, Vanderbilt Univ., Nashville, TN, USA, <sup>‡</sup>Dept. of Chemistry and Biochemistry, Concordia Univ., Montreal, Canada; <sup>§</sup>DND-CAT, Advanced Photon Source, Argonne, IL, USA; <sup>¶</sup>The Skaggs Inst. for Chemical Biology, The Scripps Research Inst., La Jolla, CA, USA, Lab. für Organische Chemie, Eidgenössische Technische Hochschule, Zürich, Switzerland.

As part of research directed toward a chemical etiology of nucleic acid structure, (*L*)- $\alpha$ -threofuranosyl (3'→2') nucleic acid (TNA) has recently been established as an efficient Watson-Crick base-pairing system, capable of informational cross-pairing with both RNA and DNA. TNA and RNA sequences can act as templates for the ligation of TNA fragments. Moreover, certain DNA polymerases are able to copy a TNA template sequence, and a DNA polymerase has been identified that is capable of significant TNA synthesis. We have determined X-ray crystal structures of B-form and A-form DNA duplexes with incorporated TNA nucleotides to atomic resolution. The structural observations provide a qualitative rationalization of the earlier experimental observations that (i) TNA hybridizes more stably with RNA than with DNA and that (ii) RNA constitutes a better template for ligating TNA fragments than DNA. The close and specific resemblance between TNA and RNA with respect to a structural parameter (inter-nucleotide P...P distance) that is among the determinants of the capabilities by oligonucleotide systems for cross-pairing and for serving as cross-templates, together with TNA's relative generational simplicity and higher stability toward hydrolytic cleavage, lend support to the notion of a possible etiological relationship between RNA and TNA.