Towards a chemical etiology of the structure of nucleic acids

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An etiology of life will have to be primarily a chemical etiology, and will probably be mainly concerned with the origin of the molecular structure which we encounter today in Nature's nucleic acids. An experimental approach to understanding the origin of biomolecular structures is the systematic study of the chemistry of structural alternatives, molecular structures which, according to chemical reasoning, could have, but have not, become (or survived as) biomolecules. Potential alternatives are chosen based on a chemical hypothesis about the self-assembly process that originally produced the biomolecule, using two criteria: first, whether the alternative can self-assemble, like the biomolecule itself, and, second, whether its chemical properties in principle allow it to fulfill the biological function of the biomolecule. By chemically synthesizing such an alternative structure and comparing its chemical properties with those of the actual biomolecule we may learn why the latter, and not the alternative, has been chosen by Nature. Such information will deepen our understanding of the structural basis of the biomolecule's function and, if we are lucky, we may also find candidates for intermediates (if there were any) on the evolutionary path towards the biomolecule we know today.

"Why pentose- and not hexose-nucleic acids?": this was the question that began a comprehensive study in our laboratory on alternative nucleic acid structures [1]. Our studies of the aldomerization chemistry of glycolaldehyde phosphate had shown that two sugars, one pentose, rac-ribose-2,4-diphosphate, and one hexose, rac-allose-2,4,6-triphosphate, were kinetically favored products, both forming with comparable ease and selectivity. We therefore synthesized hexopyranosyl-(6′ → 4′)-oligonucleotides derived from the hexopyranoses 2′,3′-dideoxy-D-glucose (the building block of 'homo-DNA'), D-allose, 2′-deoxy- and 3′-deoxy-D-allose, D-altrose and D-glucose [2] and compared their pairing properties with those of the corresponding natural DNA oligonucleotides. These studies presented us with a cascade of surprises and, consequently, insights: whereas hexopyranosyl-(6′ → 4′)-oligonucleotides in the model homo-DNA system show Watson–Crick purine–pyrimidine pairing that is uniformly stronger than the pairing in DNA and, in addition, display unprecedented purine–purine pairing to duplexes in the reverse-Hoogsteen mode [3,4], corresponding oligonucleotides derived from D-allose, D-altrose and D-glucose show pairing that is in some respects similar to, but in others drastically different from, the pairing in homo-DNA. The pairing is uniformly much weaker than that in homo-DNA, due to intrastrand steric hindrance. The natural $(CH_2O)_6$ hexopyranose sugars tested (and, foreseeably, also the four remaining diastereomers) are too bulky to be building blocks of efficient pairing systems. The short answer to the question "why pentose- and not hexose-nucleic acids?" simply turns out to be: "too many atoms!"

A comprehensive investigation of the chemical etiology of the structure of nucleic acids would require a systematic extension of these studies into hexo- and pentopyranosyl (as well as hexo- and pentofuranosyl) oligonucleotide systems which have their phosphodiester link in positions other than the (6′→4′)- or the (5′→3′)-link of the structures investigated so far. Qualitative conformational analysis of such pyranosyl systems predicts a variety of pairing systems and among them a pyranosyl isomer of RNA ('p-RNA') containing the phosphodiester linkage between positions C-2′ and C-4′ of neighboring ribopyranosyl units, which should show purine–pyrimidine and purine–purine (Watson–Crick) pairing comparable in strength to that observed in homo-DNA. In fact, Watson–Crick pairing in p-RNA is not only stronger than that in RNA and DNA, but p-RNA is also the most selective oligonucleotide pairing system known so far [5]. Thus, the homo-oligomers p-Ribo (A_n) and p-Ribo (G_n) (of n up to 10) show neither reverse-Hoogsteen nor Hoogsteen self-pairing, in sharp contrast to homo-DNA and, for guanine, also to DNA and RNA. These properties render this isomer of RNA of special interest in the context of the problem of RNA's origin.

References

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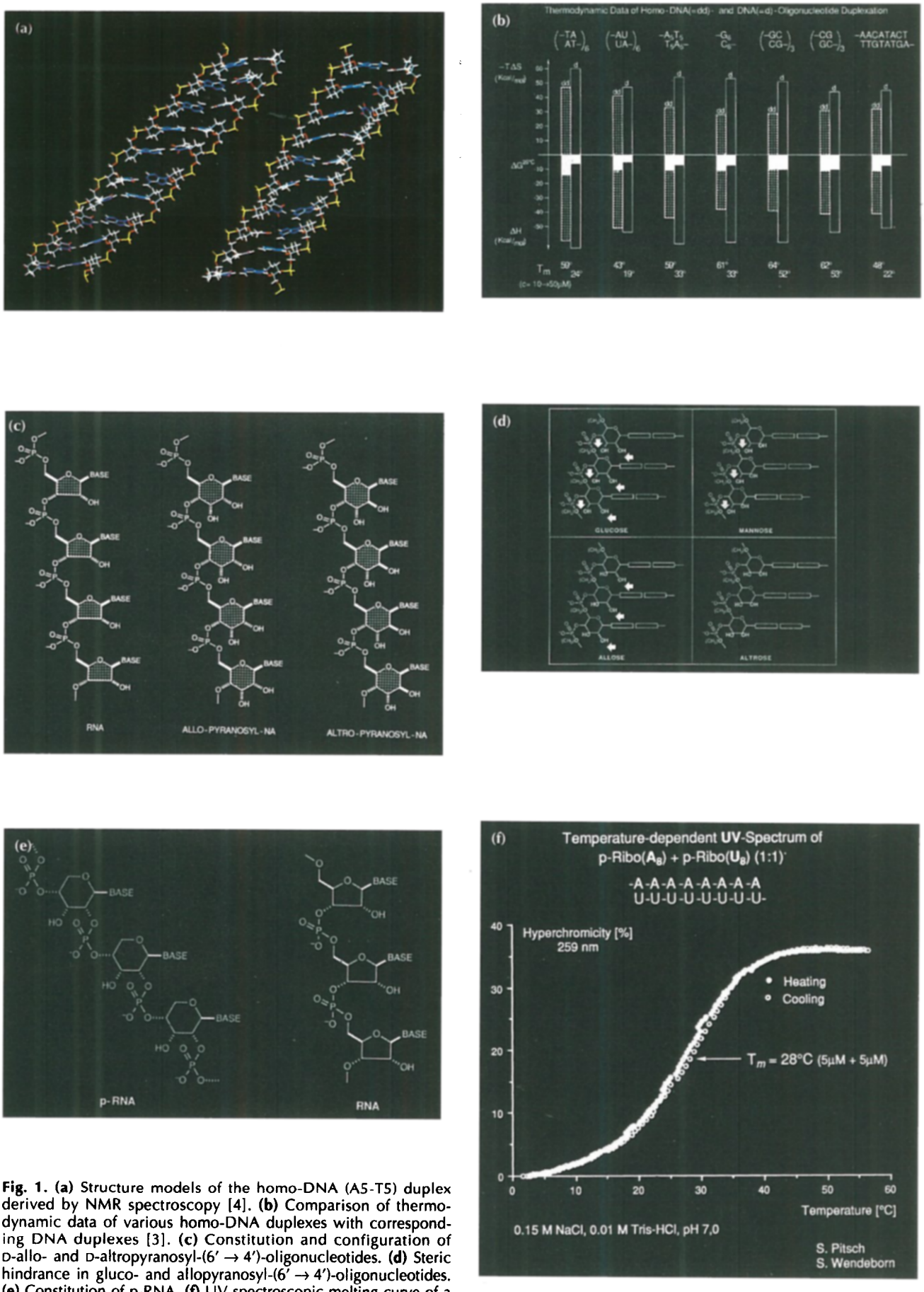

Fig. 1. **(a)** Structure models of the homo-DNA (A5-T5) duplex derived by NMR spectroscopy [4]. **(b)** Comparison of thermodynamic data of various homo-DNA duplexes with corresponding DNA duplexes [3]. **(c)** Constitution and configuration of D-allo- and D-altropyranosyl-(6′ → 4′)-oligonucleotides. **(d)** Steric hindrance in gluco- and allopyranosyl-(6′ → 4′)-oligonucleotides. **(e)** Constitution of p-RNA. **(f)** UV spectroscopic melting curve of a p-RNA duplex [5].