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Hexose nucleic acids

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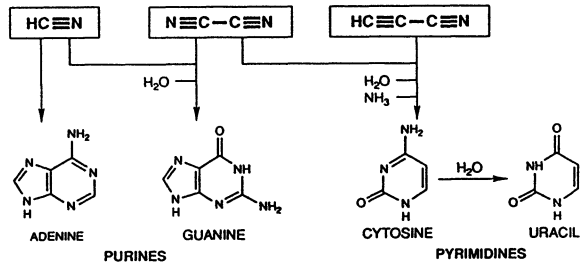
Abstract - This manuscript is, in fact, an extended abstract, supplemented by self-explanatory figures (slides) presented at the lecture.

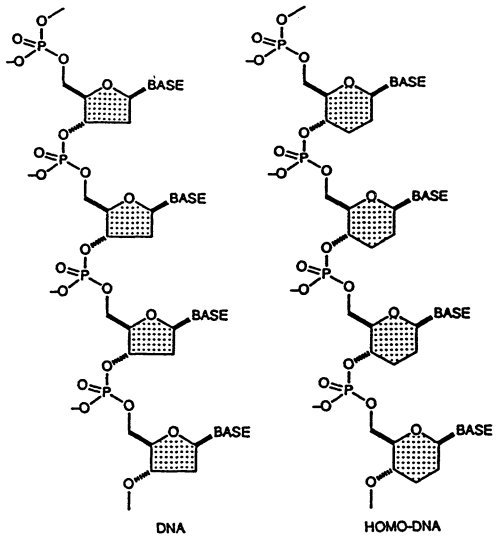
Why did Nature choose pentoses and not hexoses as sugar building blocks in her nucleic acids? Since the potential for constitutional self-assembly for hexoses is comparable to that of pentoses, Nature's choice of pentoses must have had functional reasons. The question can be dealt with experimentally by synthesizing hexose analogues of natural nucleic acids, studying their chemical properties and systematically comparing these properties with those of their natural counterparts. Differences in such properties can be expected to reflect reasons why pentose nucleic acids are - as is implicit in the fact of their existence - superior to hexose alternatives with respect to biological function.

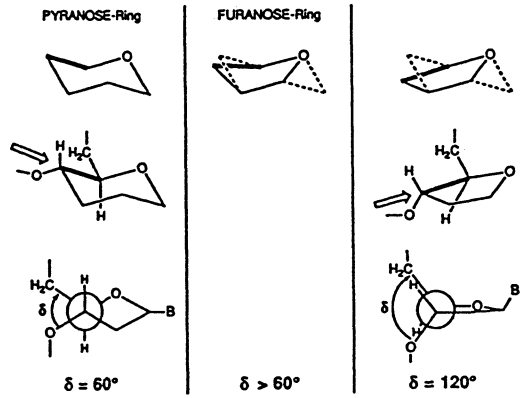
The lecture summarizes first the results of an experimental study on the pairing properties of synthetic oligonucleotides that contain 2,3-dideoxy-glucopyranose in place of 2-deoxy-ribofuranose as sugar building block. This structure type ("homo-DNA") is a highly efficient autonomous pairing system with a pairing behaviour that is in part similar to, but also in part strikingly different from, the pairing behaviour of DNA.

The 2,3-dideoxy-hexopyranose building blocks of homo-DNA possesses - according to the criterion of a structure's potential for constitutional selfassembly - a more complex structure than the hexopyranose sugars of the $(CH_2O)_6$ family. In contrast to the latter, 2,3-dideoxy-glucose should not be considered to belong to the group of potentially prebiological sugars and, therefore, the investigation of the chemistry of homo-DNA is only a model study for an exploration of the pairing properties of oligonucleotides derived from fully hydroxylated hexose sugars. Such studies are being carried out with both allose and altrose - the two hexoses which constitute the main components in glycolaldehyde phosphate aldolization mixtures - as well as with glucose as the building blocks of hexopyranosyl-(4' → 6')-oligonucleotides. The lecture describes the present state of these studies. Established already is the fact, that the pairing behaviour of such systems can be similar to, as well as drastically different from, the one shown by homo-DNA.

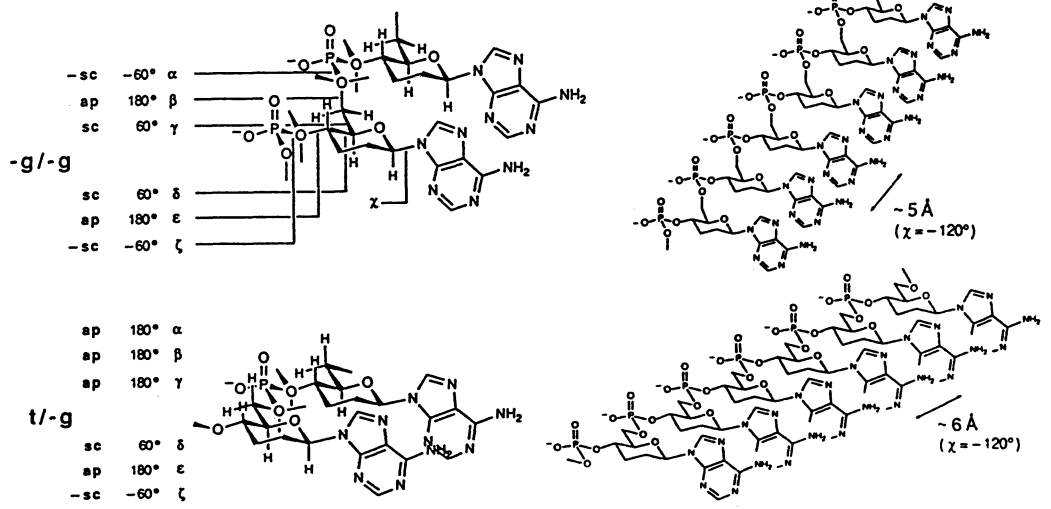
A comprehensive experimental involvement in the problem of a chemical rationalization of the natural nucleic acid's structure would require an extension of the study to hexopyranosyl- as well as to hexofuranosyl-oligonucleotide systems which have their phosphodiester link between positions other than the (4' → 6') link of the systems investigated so far. Conformational analysis of such structures predicts the existence of a variety of potential pairing systems and, most interestingly, also foresees the existence of a ribopyranosyl isomer of RNA endowed with pairing properties akin to those of homo-DNA. Experiments towards a synthesis of such a "Pyranosyl-RNA" are in progress.

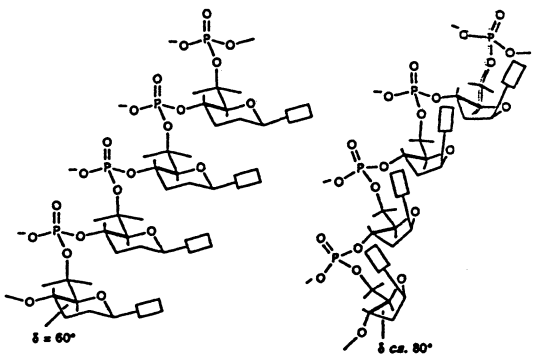






Conformational Analysis of the Homo-DNA Backbone :
the two repetitive conformations





Homo-DNA: Summary of Experimental Observations

- Homo-DNA oligonucleotides form antiparallel purine-pyrimidine duplexes which are **more stable** than the corresponding DNA duplexes.

- The higher thermodynamic stability of Homo-DNA versus DNA duplexes is due not to greater binding energy, but rather to a **less negative entropy** of duplex formation.

- In Homo-DNA **adenine and guanine pair strongly with themselves:** the base pairing selectivities in Homo-DNA are different from those operating in DNA.

- In Homo-DNA **guanine/isoguanine and xanthine/2,6-diaminopurine** form base pairs which are comparable in strength to guanine/cytosine.

- Complementary base sequences of Homo-DNA and DNA do not pair: **Homo-DNA is an autonomous artificial pairing system.**

MELTING TEMPERATURES (°C) OF HEXAMER – DUPLEXES

15 - 20 µM Nucleotide, 150 mM NaCl, 10 mM Tris pH 7

dd-BBBBBB
BBBBBB-dd
dd-BBBBBB
BBBBBB-dd

HOMO-DNA

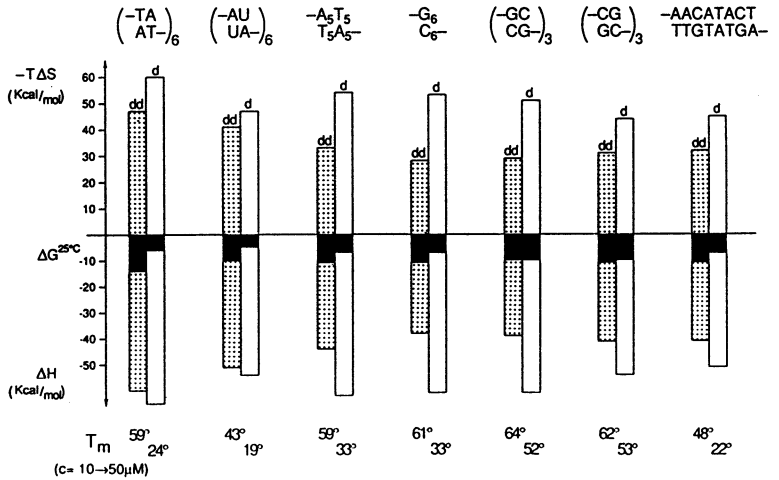
		A	T	G	C
ADENINE	A	47			
THYMINE	T	20	—		
GUANINE	G	<15	—	38	
CYTOSINE	C	<15	—	58	—

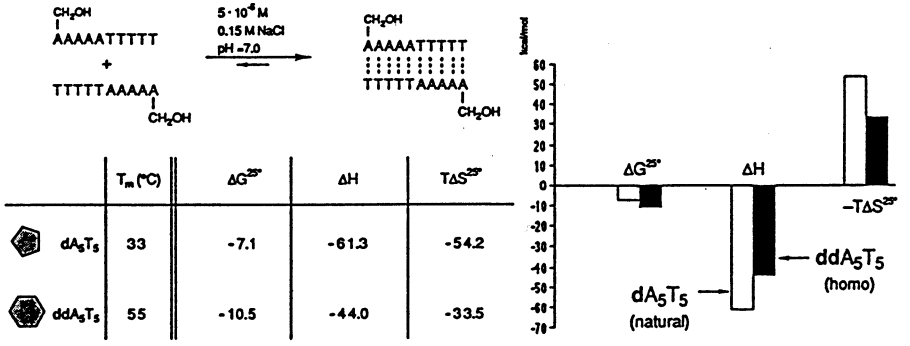
DNA

	A	T	G	C
A	—			
T	< 5	—		
G	—	—	+	
C	—	—	48	—

MARKUS BOEHRINGER, HANS-JÖRG ROTH, JÜRG HUNZIKER, FREDI GIGER, DR. CHRISTIAN LEUMANN

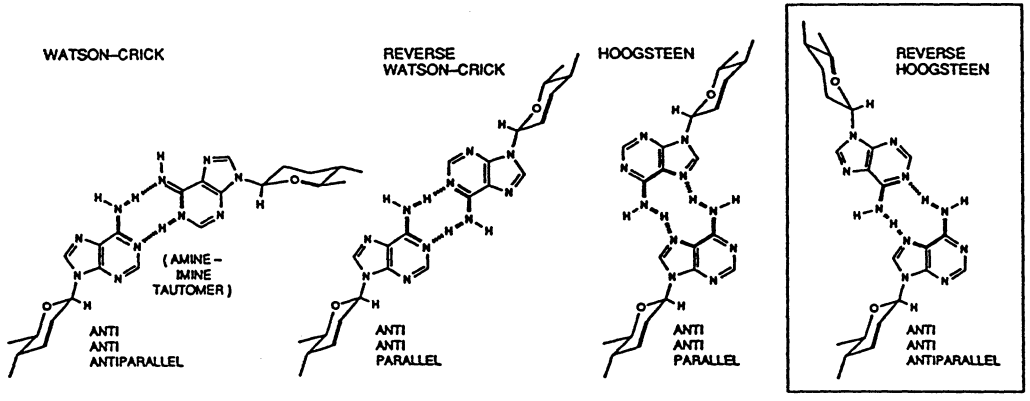
Thermodynamic Data of Homo-DNA(=dd)- and DNA(=d)-Oligonucleotide Duplexation



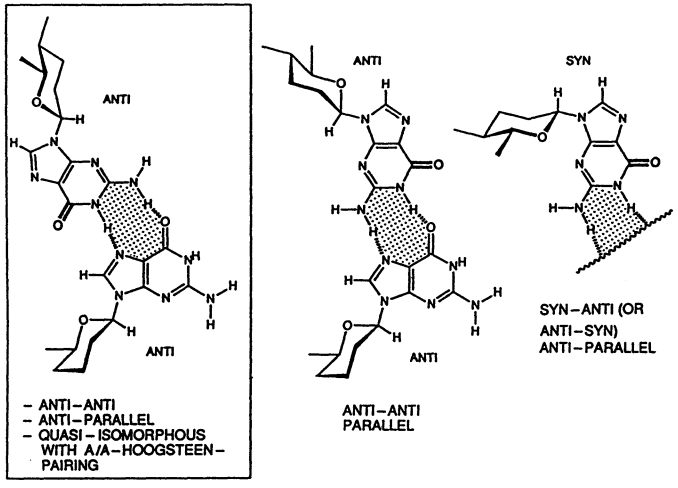


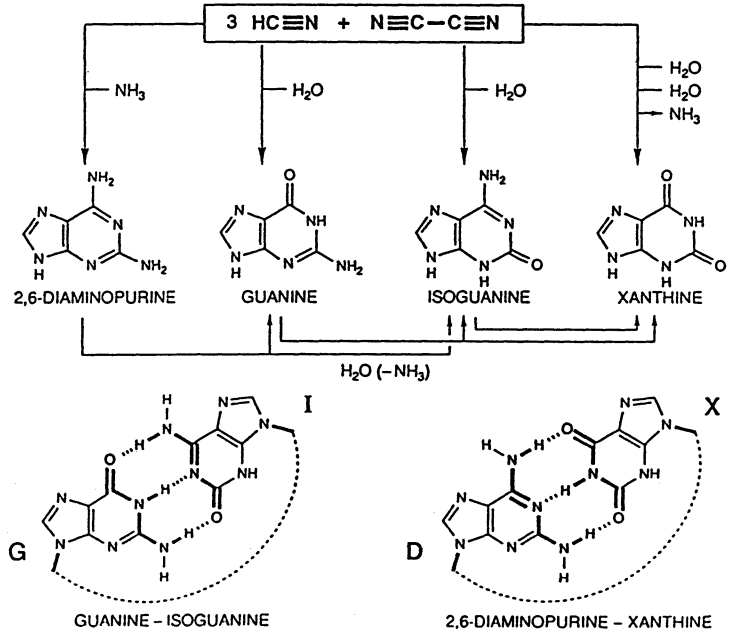
	T_m (°C)	$\Delta G^{25°}$	ΔH	$T\Delta S^{25°}$
dA_5T_5	33	-7.1	-61.3	-54.2
ddA_5T_5	55	-10.5	-44.0	-33.5

HOMO-DNA: TOPOLOGIES OF ADENINE – ADENINE PAIRING



HOMO-DNA: GUANINE–GUANINE PAIRING





HOMO-DNA: PURINE–PURINE PAIRING

MELTING TEMPERATURES (°C) OF HEXAMER–DUPLEXES:

15-20μM Nucleotide
150mM NaCl
10mM Tris pH 7

dd-BBBBBB BBBBBB-dd
dd-BBBBBB BBBBBB-dd
dd-BBBBBB BBBBBB-dd
dd-BBBBBB BBBBBB-dd

		A	H	D	X	I	G
ADENINE	A	47					
HYPOXANTHINE	H	<7	—				
2,6-DIAMINOPURINE	D	41	<5	36			
XANTHINE	X	14	—	63	—		
ISOGUANINE	I	43	12	39	16	42	
GUANINE	G	<15	<15	<15	18	61	38

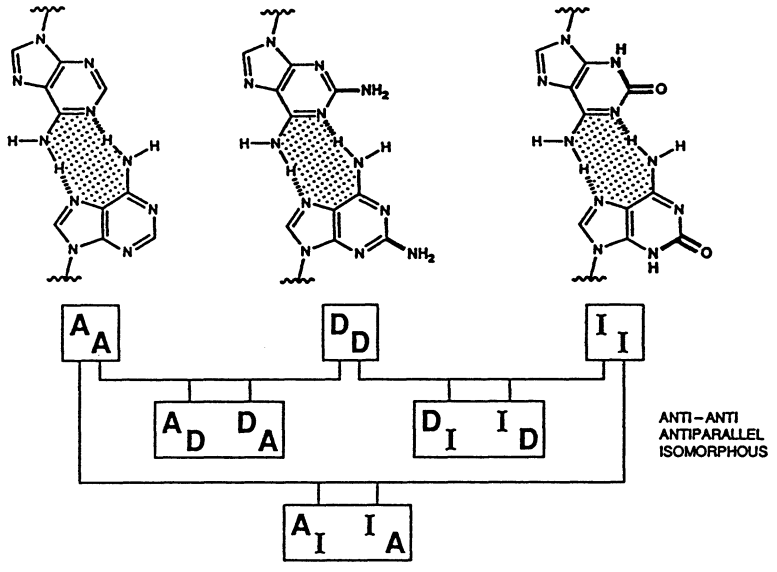
~40 HOOGSTEEN (BIDENTATE)

~60 WATSON–CRICK (TRIDENTATE)

— NO PAIRING OBSERVED

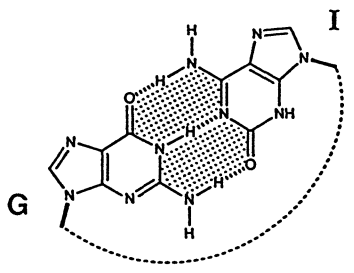
KATRIN GROEBKE, MARKUS BOEHRINGER, HANS-JÖRG ROTH, JÜRG HUNZIKER, ULF DIEDERICHSEN, DR. WILLIAM FRASER, DR. CHRISTIAN LEUMANN

HOMO-DNA: ISOMORPHOUS PURINE-PURINE PAIRS OF THE ADENINE-ADENINE HOOGSTEEN TYPE

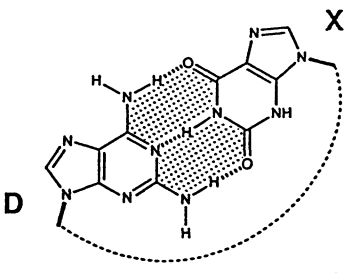


HOMO-DNA: PURINE-PURINE PAIRING

GUANINE - ISOGUANINE



2,6-DIAMINOPURINE - XANTHINE



WATSON-CRICK-TYPE
ANTIPARALLEL
ANTI / ANTI
ISOMORPHOUS

EXAMPLES

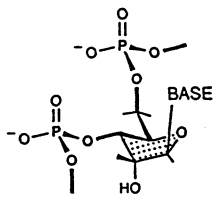
-IIIGGG GGGIII-	T_m = 57 ° (17 µM)
-IIGIGG GGIGII-	56 ° (19 µM)
-IGIGIG GIGIGI-	55 ° (22 µM)
-IIIIII GGGGGG-	61 ° (18 µM)

EXAMPLES

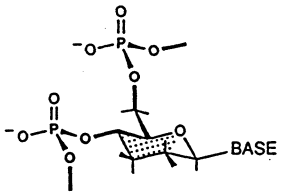
- DDDDDD XXXXXX -	63 ° (10 µM)
- XXXDDD DDDXXX -	57 ° (9 µM)

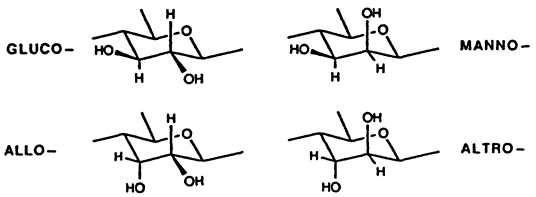
K. GROEBKE
DR. W. FRASER
J. HUNZIKER

β-RIBOFURANOSYL-NA



β-HEXOPYRANOSYL-NAs





Allose-NA (**Octa**mers)

Melting Temperatures (°C) of Duplexes

5-10 µM
150 mM NaCl
10 mM TRIS; pH 7

	A	U	G	C
ADENINE	A 16			
URIDINE/THYMINE	U <0	—		
GUANINE	G		13	
CYTOSINE	C		<10	—

HOMO-DNA (**Hexa**mers)

15-20 µM
150 mM NaCl
10 mM TRIS; pH 7

	A	T	G	C
A	47			
T	20	—		
G		—	38	
C	<15	—	58	—

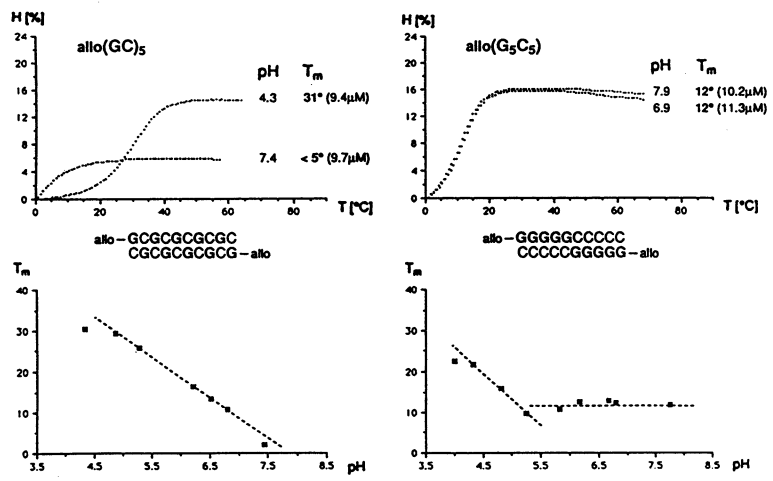
40 HOOGSTEEN (BIDENTATE) 60 WATSON-CRICK (TRIDENTATE)

Markus Böhringer, Hans-Jörg Roth, Jürg Hunziker, Andreas Helg, Reto Fischer, Alfred Giger, Dr. William Fraser, Dr.Christian Leumann

		Tm (10 µM Oligomer, 150 mM NaCl, 10 mM buffer) pH 7	pH 4.3
DNA	d - CGCG AATT CGCG GCGC TTAA GCGC - d	58°	44°
HOMO-DNA	dd - —————— —————— - dd	86°	75°
ALLOSE-NA	allo - ——— UU ——— ——— UU ——— - allo	< 3°	20°

R. FISCHER
C. LEUMANN

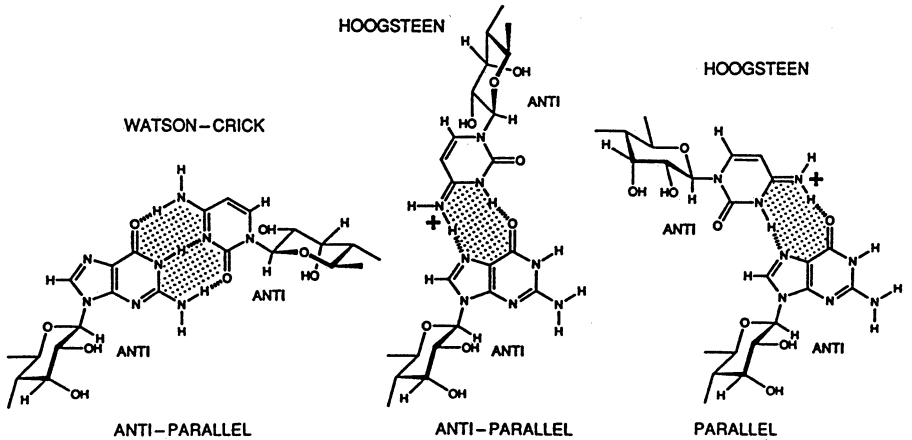
ALLOSE-NA: **GUANINE-CYTOSINE PAIRING**



c = 8.4 - 11.3 µM; 150 mM NaCl, 10 mM acetate/citrate/tris

A. HELG

ALLOSE-NA: **GUANINE-CYTOSINE PAIRING**



ALLOSE-NA: Summary of Experimental Observations

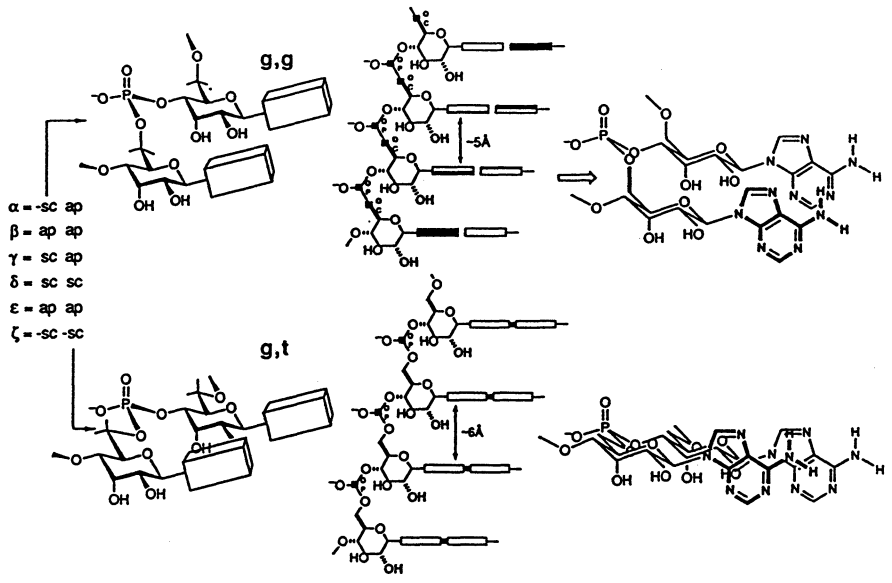
- Purine-pyrimidine pairing in allopyranosyl oligonucleotides (up to dodecamers) is very **much weaker**, and (almost certainly) of **different constitutional type**, than in either homo-DNA or DNA.

- Adenine pairs with adenine, and guanine with guanine, as in homo-DNA, but **more weakly**.

- Guanine and isoguanine pair strongly, as in homo-DNA. However, in contrast to homo-DNA, the pairing is heavily **dependent on base-pair sequence**.

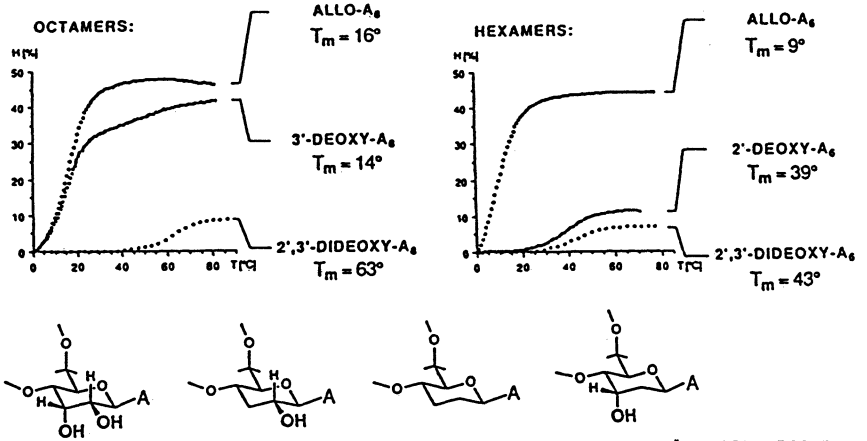
- There appears to be **no** guanine-cytosine cross-pairing to homo-DNA.

REPETITIVE CONFORMATIONS OF ALLO-PYRANOSYL-(4'→6')-OLIGONUCLEOTIDES (IDEALIZED)



SELF-PAIRING OF HEXOPYRANOSYL-ADENINE OLIGONUCLEOTIDES

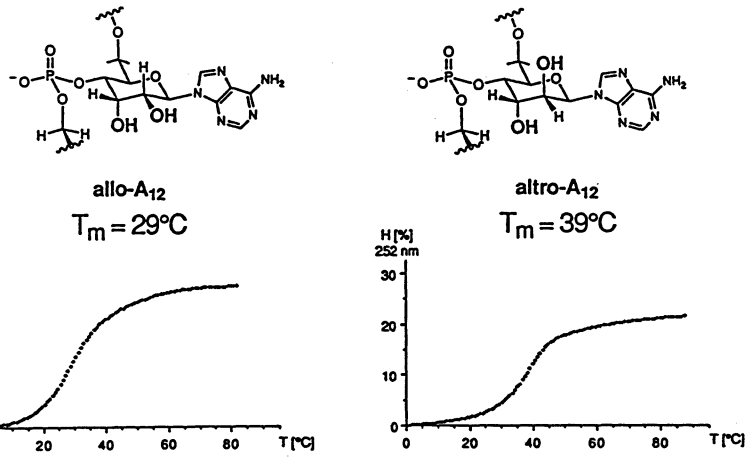
(C~10 µM, 0.15 M NaCl, 10 mM Tris, pH 7, 260 nm)



R. HAMMER, M. BÖHRINGER, R. FISCHER

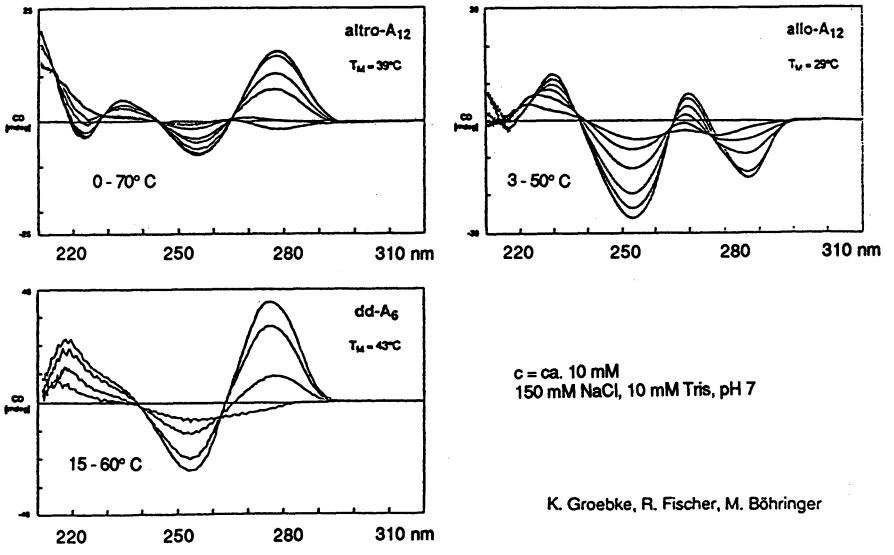
SELF-PAIRING OF ALLO- AND ALTRO-HEXOPYRANOSYL-ADENINE-DODECAMERS

(c ~ 9 µM, 150 mM NaCl, 10 mM Tris, pH 7)



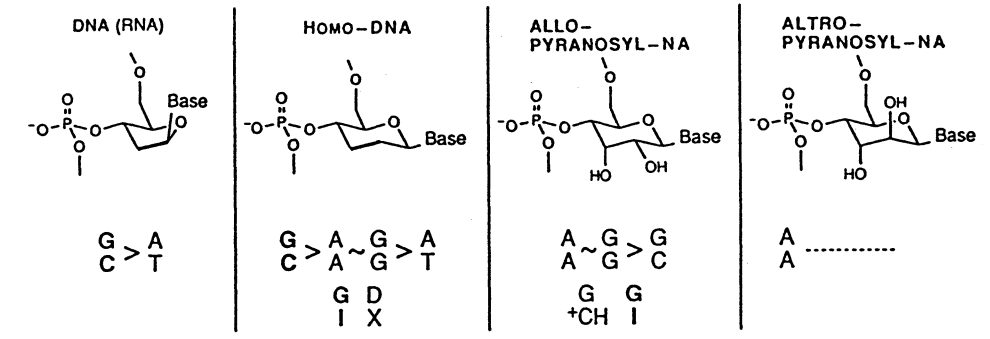
K. Groebke, R. Fischer

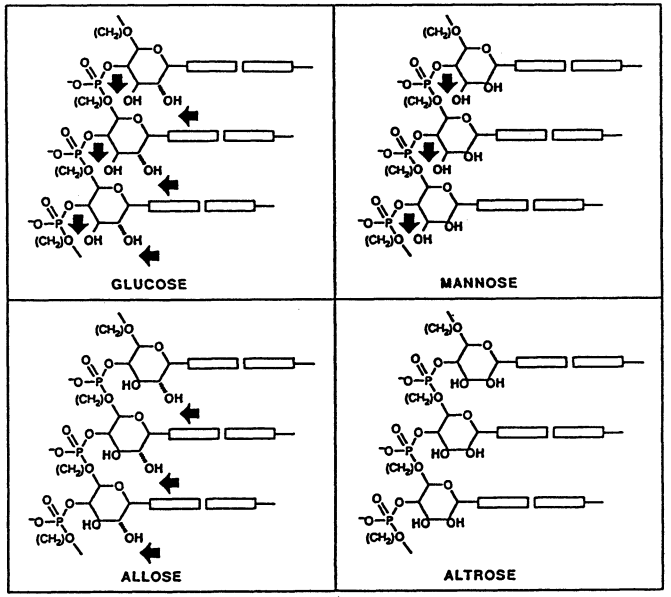
CD-SPECTRA OF ALLO-, ALTRO-2',3'-DIDEOXY- } HEXOPYRANOSYL-ADENINE OLIGOMERS



c = ca. 10 mM
150 mM NaCl, 10 mM Tris, pH 7

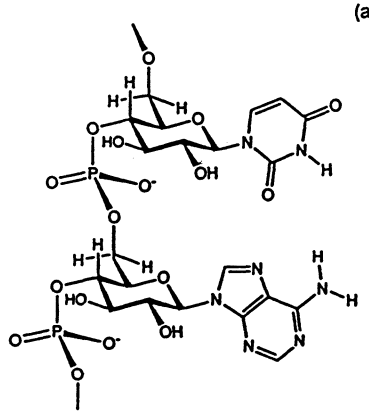
K. Groebke, R. Fischer, M. Böhringer

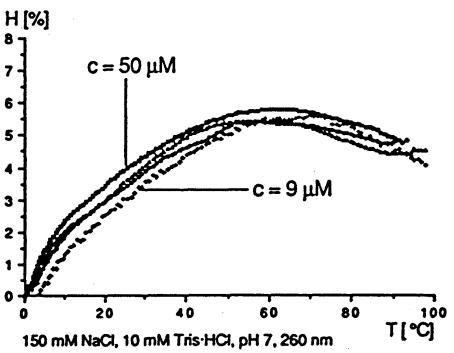




Glucose-NA: Glc-(AAAAAAUUUUUU) does not pair

(according to UV-spectroscopy)





U. Diederichsen

Constitutionally Isomeric Oligonucleotide Backbones

(Phosphodiester junctions between sugar postions)

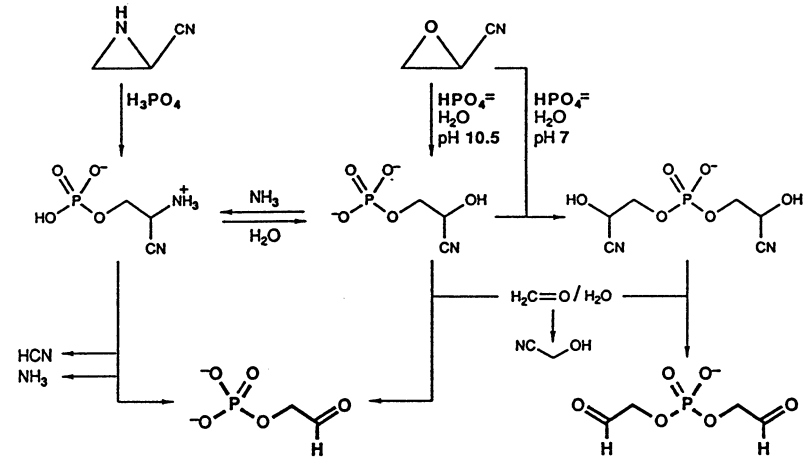
	PYRANOSES	FURANOSES
HEXO–	2'→6' ■ = 2'→4' ■ = 2'→3' 3'→6' 3'→4' 4'→6' ■ =	2'→6' 2'→5' 2'→3' 3'→6' 3'→5' 5'→6'
PENTO–	2'→4' ■ = 2'→3' 3'→4'	2'→5' 2'→3' 3'→5' RNA

■ retrosynthetically derivable via aldomerization pathway

= cooperative base pairing predicted by qualitative conformation analysis

□ experimentally studied (so far)

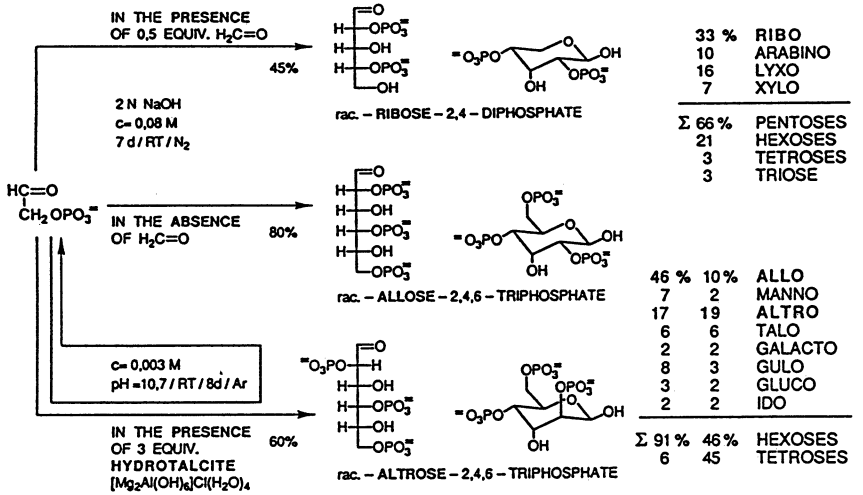
CHEMISTRY OF AZIRIDINE-2-CARBONITRILE AND OXIRANE-2-CARBONITRILE



HELV. CHIMICA ACTA (1990), 73, 1373

S. PITSCH

ALDOLIZATION OF GLYCOLALDEHYDE PHOSPHATE

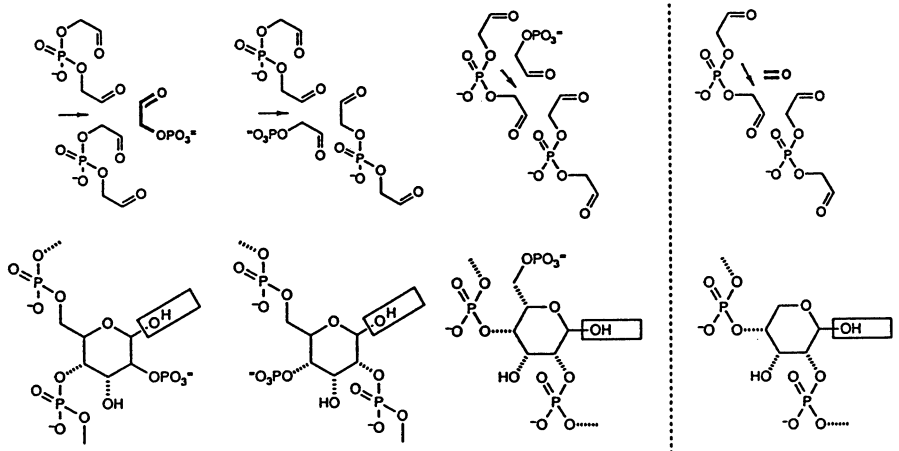


33 %		RIBO
10		ARABINO
16		LYXO
7		XYLO
Σ 66 %		PENTOSES
21		HEXOSES
3		TETROSES
3		TRIOSE

46 %	10 %	ALLO
7	2	MANNO
17	19	ALTRO
6	6	TALO
2	2	GALACTO
8	3	GULO
3	2	GLUCO
2	2	IDO
Σ 91 %	46 %	HEXOSES
6	45	TETROSES

S.PITSCH, D.MÜLLER (ETH); PROF. G.ARRHENIUS (LA JOLLA)

Potential Aldomerization Pathways for Constitutional Self-Assembly of HEXO- and PENTO-Pyranosyl-Oligonucleotide Backbones



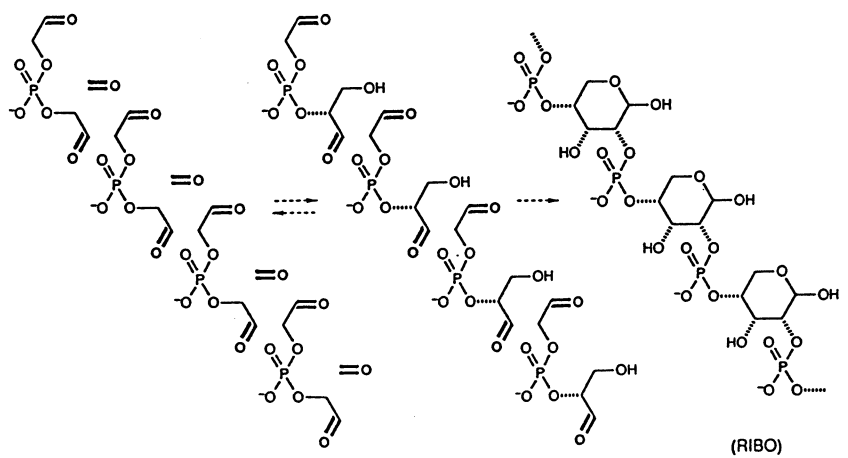
4'→6' Altropyranosyl- Allo- Gulo-

2'→6' Allopyranosyl- Altro-

2'→4' Talopyranosyl- Manno-

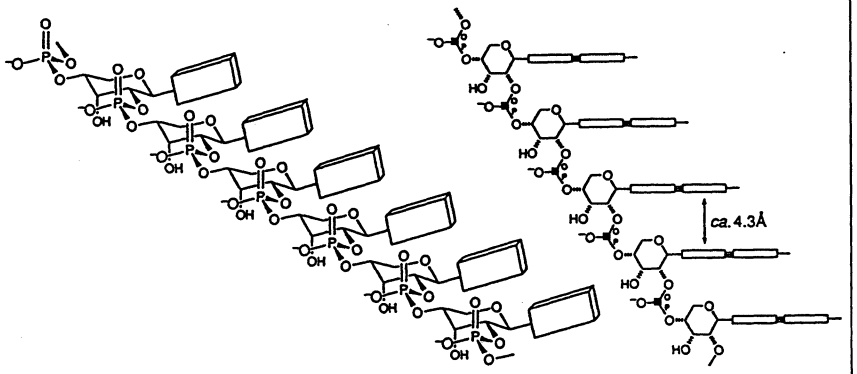
2'→4' Ribopyranosyl- Lyxo-

Oligonucleotide Backbones by Aldomerization: Retrosynthetic analysis for PENTO-pyranosyl-(2'→4')-oligonucleotide backbones



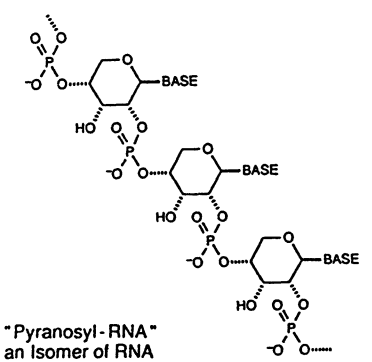
(RIBO)

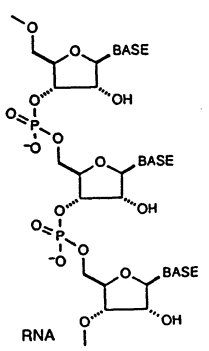
β-RIBO-PYRANOSYL-(2'→4')-OLIGONUCLEOTIDES
("PYRANOSYL-RNA")
Pairing Conformation of Backbone
(hypothetical)

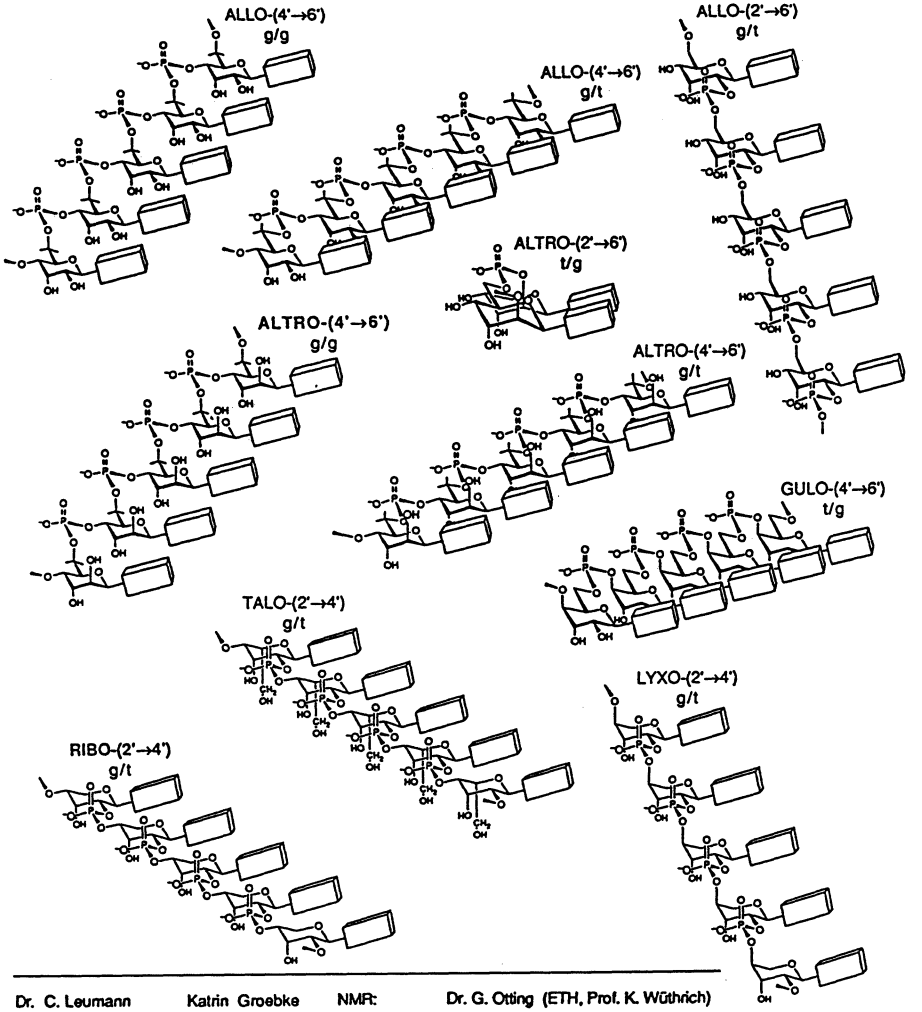


– $2 \cdot 3^4$ (idealised) backbone conformations
– 10 of them least strained (gg- as well as gt-phosphodiester groups)
– only 1 conformationally repetitive (gt)

β-RIBO-PYRANOSYL-(2'→4')-OLIGONUCLEOTIDES
("PYRANOSYL-RNA")
a target of chemical synthesis and of studies on the constitutional self-assembly of potentially self-replicating systems :







Dr. C. Leumann
H.J. Roth
M. Böhringer
J. Hunziker
Dr. M. Göbel
Dr. R. Krishnan
A. Giger
Ling Peng
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