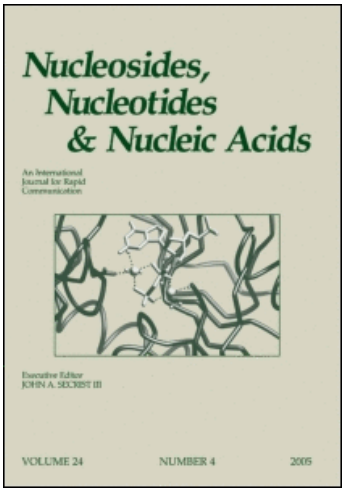

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Propeller Twisting in Single Crystals of Nucleosides

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To cite this Article Wilson, C. C. and Tollin, P.(1987) 'Propeller Twisting in Single Crystals of Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 6: 3, 643 — 653
To link to this Article: DOI: 10.1080/07328318708069993
URL: http://dx.doi.org/10.1080/07328318708069993

NUCLEOSIDES & NUCLEOTIDES, 6(3), 643-653 (1987)

PROPELLER TWISTING IN SINGLE CRYSTALS OF NUCLEOSIDES

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ABSTRACT

Propeller twists were measured for base-paired nucleosides and nucleic acid bases. The occurrence of propeller twist outside a double helical framework is shown, and conclusions drawn on the relative magnitude of the effect in single nucleosides.

INTRODUCTION

The importance of secondary structure in the stability of nucleic acids has become increasingly apparent in recent years, and various parameters have been defined to assist in the analysis of such structure. Among these parameters, the concept of propeller twist is discussed by Dickerson[1] and subjected to a mechanical analysis by Calladine[2]. Propeller twist is defined as being the angle between the planes of two bases in a base-pair, when viewed along the long axis joining them (Figure 1).

Fibre studies of DNA samples had suggested a value of around 2° for this parameter, but in recent single-crystal studies of oligonucleotides propeller twisting is found to have a much larger value. In all such single-crystal structures studied to date, the propeller twist magnitude has been in the range of about 10-17°, and the magnitude of twist is found to be independent of the number of hydrogen bonds in the base-pair[3]. All of these twists have been of positive magnitude (see Figure 1).

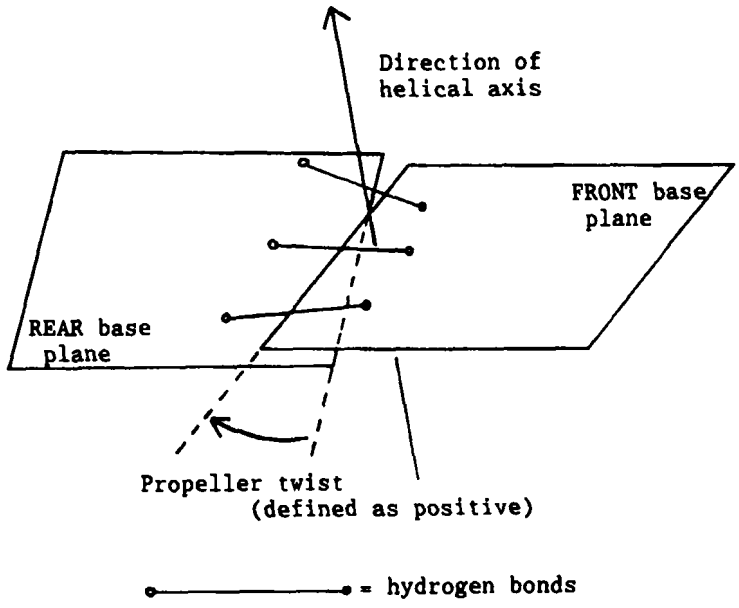


FIG. 1 (a) - Schematic view of propeller twisting in a base-pair, showing convention for the sign of the twist.

In the oligonucleotide studies, and in analyses of the parameters involved in secondary structure details, the appearance of propeller twisting has been within the framework of a double helix. The appearance and magnitude of propeller twisting would appear to be a consequence of the secondary structure of the helix (backbone geometry and base-pair sequence) and, together with various other parameters such as base roll, tilt, slide and helix twist[1], plays an important role in the packing of bases along the axis of the double helical structure. The efficient stacking of bases, especially purine bases, is an important aspect of nucleic acid structure and propeller twisting is one of the means by which a favourable configuration can be attained.

Since propeller twisting seems to be so strongly tied in with the overall structure of a double helical oligonucleotide, most analyses have examined the effect in such systems exclusively. In order to examine the presence or otherwise of propeller twisting outside the double helical framework, one must examine single-crystal structures of

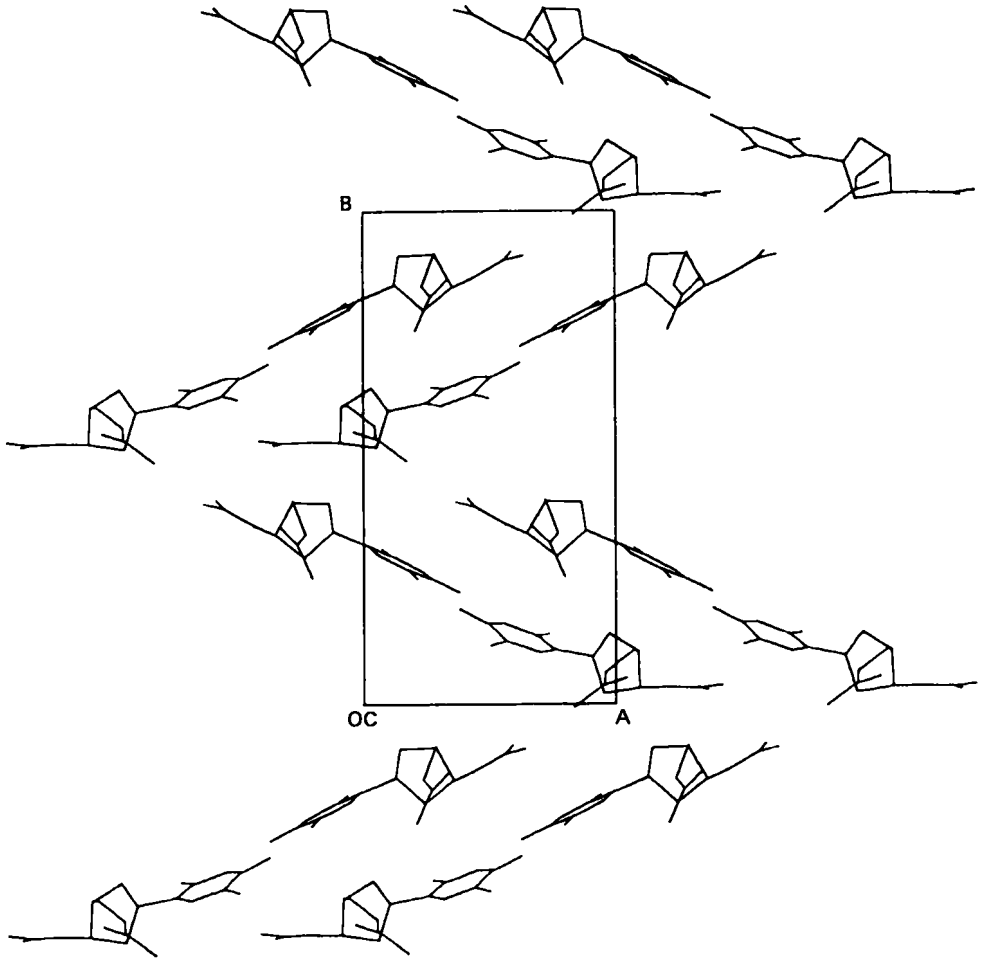


FIG. 2 - Propeller twisting in the crystal structure of 3',5'-Di-O-acetylthymidine, viewed from the side.

mononucleosides. In our own recent work, we have studied nucleosides with acetylated sugar groups, with a view to inducing base-pairing by interrupting alternative hydrogen bonding schemes. One aim of this work was to study propeller twisting and base-pairing patterns in such induced pairs.

We have noticed, in several recently reported structures of acetylated nucleosides, a significant propeller twist within a hydrogen bonded base-pair. In 3',5'-Di-O-acetyl-5-bromo-2'-deoxyuridine [ABDU][4], 3',5'-Di-O-acetylthymidine [AT][5] (Figure 2), 2',3',5'-Tri-

Table 1
Data used for analysis of propeller twists

(Estimated error of 1° on all measured values)

Nucleosides CSSR No	Mnemonic	Compound Name	Groups	Sign of Twist	Magnitude without subs. (in degrees)	Magnitude with subs. (in degrees)
3018	BRADOM	8-BROMO-2',3'-O-ISOPROPYLIDENE-ADENOSINE MONOHYDRATE	1 4	-	25	14
3018	BRADOM	"	1 6	-	37	32
S.FUJII,T.FUJIWARA,K.TOMITA (1976). NUCLEIC ACIDS RES., 3, 1985.						
3099	BRINOS10	8-BROMOINOSINE	1 4	+	8	8
H.STERNGLANZ,J.M.THOMAS,C.E.BUGG (1977). ACTA CRYST., B33, 2097.						
10256	GUANSH10	GUANOSINE DIHYDRATE	1 5		0	0
U.THEWALT,C.E.BUGG,R.E.MARSH (1970). ACTA CRYST., B26, 1089.						
11318	HXURID	5-HYDROXYURIDINE	1 4		0	+-5
U.THEWALT,C.E.BUGG (1973). ACTA CRYST., B29, 1393.						
12378	LEUAUR10	5-(N-(L-LEUCYL)AMINO)URIDINE HYDRATE	1 4	+	18	19
12378	"	"	1 4		0	0
P.NARAYANAN,H.M.BERMAN (1977). ACTA CRYST., B33, 2047.						
12652	MADENS10	2'-O-METHYLADENOSINE	1 5	-	12	6
P.PRUSINER,M.SUNDARALINGAM (1976). ACTA CRYST., B32, 161.						
20558	TGUANS10	6-THIOGUANOSINE MONOHYDRATE	1 5		0	0
U.THEWALT,C.E.BUGG (1972). J.AM.CHEM.SOC., 94, 8892.						
21061	TMSADS10	5'-METHYLTHIO-ADENOSINE	1 4	+	12	10
N.BORKAKOTI,R.A.PALMER (1978). ACTA CRYST., B34, 867.						
22834	IPADOS	2',3'-O-ISOPROPYLIDENE-ADENOSINE	1 5	-	32	25
S.SPRANG,D.C.ROHRER,M.SUNDARALINGAM (1978). ACTA CRYST., B34, 2603.						
23154	ADMOPM	ADENOSINE-5'-O-METHYLPHOSPHATE METHANOL SOLVATE	1 5	+	16	15
J.D.HOOGENDORP,G.C.VERSCHOOR,C.ROMERS (1978). ACTA CRYST., B34, 3662.						
24352	CYADOT	8,2'-CYCLOADENOSINE TRIHYDRATE	1 5	+	0	2
S.NEIDLE,G.L.TAYLOR,P.C.COMLING (1979). ACTA CRYST., B35, 708.						
24383	DMURID	5-DIMETHYLAMINO-URIDINE	1 4	+	9	22
E.EGERT,H.J.LINDNER,W.HILLEN,H.G.GASSEN (1979). ACTA CRYST., B35, 920.						
24812	ZADENH10	2-AZA-ADENOSINE HEMIHYDRATE	1 5		0	0
P.SINGH,D.J.HODGSON (1979). ACTA CRYST., B35, 973.						
29794	CORDCP	3'-DEOXY-ADENOSINE (CORDYCEPIN)	1 5	+	26	18
M.M.RADWAN,H.R.WILSON (1980). ACTA CRYST., B36, 2185.						
31814	THPSUR	4-THIO-PSEUDOURIDINE	1 4		0	0
31814	"	"	1 4		0	0
C.L.BARNES,S.W.HAWKINSON,P.W.WIGLER (1980). ACTA CRYST., B36, 2299.						
35047	ADPRFS10	BIS(ADENOSINE) PROFLAVINE SESQUISULFATE HYDRATE	1 6	-	6	4
P.SWAMINATHAN,E.WESTHOF,M.SUNDARALINGAM (1982). ACTA CRYST., B38, 515.						
35768	BAYKER	2',3'-O-ISOPROPYLIDENE-5'-DEOXY-6(R),5'-CYCLO-5,6-DIHYDROURIDINE	1 4	+	1	5
Y.YAMAGATA,S.FUJII,T.FUJIWARA,K.-I.TOMITA,T.UEDA (1981). BIOCHIM.BIOPHYS.ACTA, 654, 242.						
39226	SAHCYA10	S-ADENOSYL-L-HOMOCYSTEINE HYDRATE	1 6	+	0	2
H.-S.SHIEH,H.M.BERMAN (1982). ACTA CRYST., B38, 1513.						
39594	BIVVIL	2',3'-O-(TETRAISOPROPYL-1,3-DISILOXANEDIYL)-CYTIDINE	1 4	-	2	2
J.D.HOOGENDORP,C.ROMERS (1982). ACTA CRYST., B38, 2738.						

Table 1 (ctd)

CSSR No	Mnemonic	Compound Name	Groups	Sign of Twist	without subs. (in degrees)	with subs. (in degrees)
41337	SAHCYB10	S-8-AZA-ADENOSYL-L-HOMOCYSTEINE MONOHYDRATE	1 6	+	7	6
V.B.PETT,H.-S.SHIEH,H.M.BERMAN (1982). ACTA CRYST., B38, 2611.						
43305	BUVPOX	(C1'-R,C3'-R,C4'-R)-2'-DEOXY-3'-S-ETHYL-3'-THIOADENOSINE	1 5	-	12	7
B.DIMKE,E.SCHLIMME,V.ZABEL,W.SAENGER (1983). JUSTUS LIEBIGS ANN.CHEM., 1409.						
44534	CALDEY	5-BROMO-2'-DEOXYCYTIDINE	1 4	+	3	0
44534	"	"	1 4	+	9	6
J.N.LOW,P.TOLLIN,D.W.YOUNG (1981). CRYST.STRUCT.COMMUN., 10, 1369.						
	ABDU	5-BROMO-3'-5'-DI-O-ACETYL-2'-DEOXYURIDINE	1 4	+	4	6
J.N.LOW (1983). ACTA CRYST., C39, 796.						
	AT	3',5'-DI-O-ACETYLTHYMIDINE	1 4	+	17	13
C.C.WILSON,J.N.LOW,P.TOLLIN,H.R.WILSON (1984). ACTA CRYST., C40, 1712.						
	TAG	2',3',5'-TRI-O-ACETYLGUANOSINE (MONOCLINIC FORM)	1 5	-	4	2
C.C.WILSON,J.N.LOW,P.TOLLIN (1985). ACTA CRYST., C41, 1123.						
	TAA	2',3',5'-TRI-O-ACETYLADENOSINE	1 5	+	18	17
C.C.WILSON,P.TOLLIN,R.A.HOWIE (1986). ACTA CRYST., C42, 697.						
	TG (A)	2',3',5'-TRI-O-ACETYLGUANOSINE (ORTHORHOMBIC FORM)	1 5	-	12	9
	TG (B)	"	1 5	-	9	11
J.N.LOW,P.TOLLIN,C.C.WILSON,S.N.SCRIMGEOUR (1986). ACTA CRYST., C42, 700.						
Nucleic Acid Bases						
3393	BURBAD	1-METHYL-5-BROMOURACIL-9-ETHYL-8-BROMO-ADENINE COMPLEX	3	-	8	2
3393	"	"	2		0	0
S.S.TAVALE,T.D.SAKORE,H.M.SOBELL (1969). J.MOL.BIOL., 43, 375.						
3395	BUREAP	1-METHYL-5-BROMOURACIL-9-ETHYL-2-AMINOPURINE COMPLEX	3	-	6	2
3395	"	"	2		0	0
F.MAZZA,H.M.SOBELL,G.KARTHA (1969). J.MOL.BIOL., 43, 407.						
6729	CYTFUR	CYTOSINE-5-FLUOROURACIL COMPLEX MONOHYDRATE	2		0	0
6729	"	"	2	+	3	2
D.VOET,A.RICH (1969). J.AM.CHEM.SOC., 91, 3069.						
8609	EBAEBH	9-ETHYL-8-BROMOADENINE-9-ETHYL-8-BROMO-HYPOXANTHINE	3	+	4	4
T.D.SAKORE,H.M.SOBELL (1969). J.MOL.BIOL., 43, 77.						
8626	EBPETY	9-ETHYL-8-BROMO-2,6-DIAMINOPURINE-1-ETHYLTHYMINE COMPLEX	3	+	0	1
8626	"	"	2		0	0
G.SIMUNDZA,T.D.SAKORE,H.M.SOBELL (1970). J.MOL.BIOL., 48, 263.						
8627	EBPMUR	9-ETHYL-8-BROMO-2,6-DIAMINOPURINE-1-METHYLURACIL COMPLEX	3	-	1	1
8627	"	"	2		0	0
G.SIMUNDZA,T.D.SAKORE,H.M.SOBELL (1970). J.MOL.BIOL., 48, 263.						
8791	EGMCYT10	9-ETHYLGUANINE-1-METHYLCYTOSINE COMPLEX	3	+	2	2
E.J.O'BRIEN (1967). ACTA CRYST., 23, 92.						
8792	EGMFCY10	9-ETHYLGUANINE-1-METHYL-5-FLUOROCYTOSINE COMPLEX	3	+	1	1
E.J.O'BRIEN (1967). ACTA CRYST., 23, 92.						
9264	ETAMBU10	9-ETHYLADENINE-1-METHYL-5-BROMOURACIL COMPLEX	3	-	2	4
L.KATZ,K.TOMITA,A.RICH (1966). ACTA CRYST., 21, 754.						
9981	FUREAP	1-METHYL-5-FLUOROURACIL-9-ETHYL-2-AMINOPURINE COMPLEX	3	-	5	2
9981	"	"	2		0	0
F.MAZZA,H.M.SOBELL,G.KARTHA (1969). J.MOL.BIOL., 43, 407.						

(continued)

Table 1 (ctd)

CSSR No	Mnemonic	Compound Name	Groups	Sign of Twist	without subs. (in degrees)	with subs. (in degrees)
9982	FUREHX	5-FLUOROURACIL-9-ETHYLHYPOXANTHINE	2		0	0
S.H.KIM,A.RICH (1967). SCIENCE, 158, 1046.						
11629	IMUEAD	BIS(1-METHYL-5-IODOURACIL)-9-ETHYLADENINE COMPLEX	3	-	11	11
11629	"	"	3	-	2	2
T.D.SAKORE,S.S.TAVALE,H.M.SOBELL (1969). J.MOL.BIOL., 43, 361.						
13949	MIDUAP10	BIS(1-METHYL-5-IODOURACIL)-9-ETHYL-2,6-DIAMINOPURINE COMPLEX	3		+-9	0
13949	"	"	3	-	0	2
T.D.SAKORE,H.M.SOBELL,F.MAZZA,G.KARTHA (1969). J.MOL.BIOL., 43, 385.						
14847	MTHMAD	9-METHYLADENINE-1-METHYLTHYMINE COMPLEX	3	Constrained to zero		
K.HOOGSTEEN (1963). ACTA CRYST., 16, 907.						
14937	MTYDAP	BIS(1-METHYLTHYMINE)-9-ETHYL-2,6-DIAMINOPURINE COMPLEX MONOHYDRATE	3	-	0	1
14937	"	"	3	-	7	7
T.D.SAKORE,H.M.SOBELL,F.MAZZA,G.KARTHA (1969). J.MOL.BIOL., 43, 385.						
19572	SURMAD10	1-METHYL-4-THIOURACIL 9-METHYLADENINE	3	+	2	3
19572	"	"	2		0	0
W.SAENGER,D.SUCK (1971). J.MOL.BIOL., 60, 87.						
44388	BUDVUR10	ADENINE 1-(2-CARBOXYETHYL)-URACIL	3	-	0	2
S.FUJITA,A.TAKENAKA,Y.SASADA (1983). BULL.CHEM.SOC.JPN., 56, 2234.						

O-acetylguanosine [TAG][6] and 2',3',5'-Tri-O-acetyladenosine [TAA][7], the parameter is found to have values in the range 2-17°. The existence of propeller twisting and shown by these single-crystal studies of nucleosides prompted us to study further the effect in nucleosides and nucleic acid bases.

ANALYSIS OF CRYSTALLOGRAPHIC DATA

Full listings of nucleoside and nucleic acid base structures were retrieved from the Cambridge structural database, using the Chemical Databank Service CSSR program[8]. Two types of situation were selected for analysis. Firstly, those nucleosides in which base-pairing is present. These amounted to 27 structures, plus the acetylated nucleosides ABDU, AT, TAG and TAA mentioned above. Secondly, those structures among nucleic acid base co-crystal complexes where base-pairing was found: these amounted to 26 structures. The decision to choose only co-crystal complexes in the latter case was made both to restrict the amount of data to be analysed and to improve the chances of data being available for non-self-paired bases.

The results of the studies are shown in Table 1, and were analysed according to the following divisions :

1. Self-paired nucleosides.
2. Self-paired nucleic acid bases.
3. Non-self-paired nucleic acid bases.
4. Nucleosides with 2 hydrogen bonds in a Watson-Crick type arrangement.
5. Nucleosides with 2 hydrogen bonds in a Hoogsteen type arrangement.
6. Nucleosides with 2 hydrogen bonds in a "double-Hoogsteen" type arrangement.

The base-pair types encountered in this analysis are illustrated in Figure 3. Note that "double-Hoogsteen" refers to those pairs in which two purines are involved, and both employ indole N atoms in the hydrogen bonding scheme. Figure 3 is not intended to give the precise scheme of hydrogen bonding in each structure analysed, merely the general arrangement of the bases and the number of hydrogen bonds present.

Propeller twist in these structures was measured in two ways, exclusive of and inclusive of the substituents on the base. The latter is the more correct definition, since these substituents are widely involved in the hydrogen bonding scheme and are usually regarded as part of the base plane for stacking purposes.

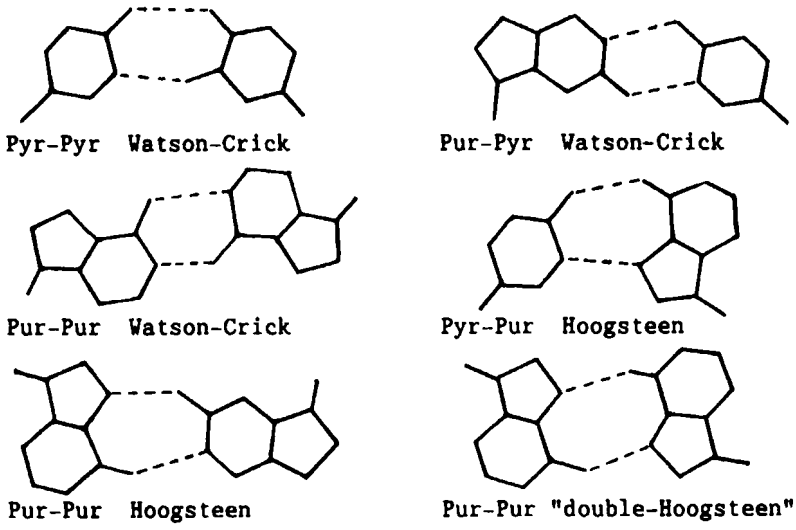
The average propeller twists in each group are given in Table 2. In all cases it can be seen that the second method of measurement (including substituents) gives a smaller value of the twist.

RESULTS OF ANALYSIS

From the average values in Table 2, several points are worthy of note.

1. Propeller Twist is Non-Zero in Many Nucleosides

   There is a definite non-zero propeller twist shown by base-paired



(Pyr = Pyrimidine base, Pur = Purine base.)

FIG 3 - Base pair types discussed in this paper.

TABLE 2

Average values of Propeller Twist
for the groups detailed below (in degrees).

Group	Number measured	Without Substituents	With
1	30	9.1	8.0
2	9	0.3	0.2
3	17	3.5	2.8
4	15	7.7	7.0
5	11	10.7	8.3
6	4	12.5	11.0

nucleosides in these single-crystal studies. While these values are on average lower than those found for complementary pairs in oligonucleotide structures, the result is significant in demonstrating the existence of propeller twist outside a double helical structure.

2. Nucleic Acid Bases Exhibit Less Twisting

There is almost no propeller twisting effect among self-paired nucleic acid bases and, while it is greater in cases where non-self-pairing is present, it is still substantially less than in nucleosides.

3. A Trend Within Nucleosides

Within the group of self-paired nucleosides, the magnitude of the propeller twist increases from Watson-Crick → Hoogsteen → double-Hoogsteen. As yet no equivalent data is available in oligonucleotide structures for comparison with these results. In only two cases to date have oligonucleotide single-crystal structures contained Hoogsteen base-pairs[9,10].

TWO RECENT EXAMPLES

Since this study was carried out, we have found in our work two further examples of base-pairing which fit in well with the expected values from this analysis.

1. An orthorhombic form of 2',3',5'-Tri-O-acetylguanosine[11], in which the propeller twist is found to be 9°. The pairing in this compound is of type 5 (Hoogsteen-like), and so the value found is in reasonable agreement with the average value found for this type of pairing.

2. 3-methylxanthine[12], being a self-paired nucleic acid base, would be expected to have no significant propeller twist and this was indeed found to be the case.

CONCLUSIONS

The most important point to emerge from this analysis is that propeller twists exist within base-paired nucleosides even outside a

double-helical framework, and in a range of crystal packing environments. However, the role of backbone and sequence effects can be seen by the fact that in the nucleosides the magnitude of the twist is reduced, there is a rather larger spread of values of the twist and the sign of the propeller twist varies when compared with the oligonucleotides (see Table 1). The oligonucleotide results show only positive results for the parameter. The existence of propeller twist does, however, appear to be common in base-paired nucleosides and it is likely to contribute to their stability.

While extensive oligonucleotide data is as yet only available for Watson-Crick pairs, the above results suggest the possibility that Hoogsteen pairs may show an even greater magnitude of twist, should the mononucleoside results carry over into oligonucleotide (double helical) milieu.

ACKNOWLEDGEMENTS

The authors would like to thank Professor H R Wilson for his interest in, and discussions of, this work.

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Received July 3, 1986.