Note added in proof: The Technical Editor revealed during a routine check for structure duplication that the crystal structure of TETRA had already been published (Spek, 1972). Our e.s.d.'s for the TETRA structure are, however, about three times smaller than those in the above publication.

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1-(2,3-Dideoxy-*erythro*-β-D-hexopyranosyl)cytosine: an Example of the Conformational and Stacking Properties of Pyranosyl Pyrimidine Nucleosides. A Crystallographic and Computational Approach*

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Abstract

$C_{10}H_{15}N_3O_4$, $M_r = 241.25$, orthorhombic, $P2_12_12_1$, $a = 7.4013$ (4), $b = 8.7563$ (5), $c = 17.392$ (1) Å, $V = 1127.1$ (1) Å^3, $Z = 4$, $D_m = 1.42$, $D_x = 1.422$ Mg m^{-3}, Ni-filtered Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å, $\mu = 0.895$ mm^{-1}, $F(000) = 512$, $T = 293$ K, final $R = 0.044$ for 1024 unique observed [$F \geq 6\sigma(F)$] reflections. The conformational parameters are in accordance with the IUPAC–IUB Joint Commission on Biochemical Nomenclature [*Pure Appl. Chem.* (1983), **55**, 1273–1280] guidelines. In order to assess the possible use of pyranosyl-modified pyrimidine nucieosides in the design of new synthetic oligonucleotides, the conformational and packing proper-

* Structural Studies on Modified Nucleosides. Part XIV. Part XIII: De Winter, Blaton, Peeters, De Ranter, Van Aerschot & Herdewijn (1991*e*).

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ties of 13 structures were examined. From this study, it becomes clear that the pyrimidine-base geometry is independent of the sugar ring type (furanosyl- or pyranosyl-like). The bases are always positioned in an equatorial orientation on the pyranoside sugar, which means that the sugar adopts a $_4C^1$ conformation in α- and $^4C_1$ in β-enantiomers. As a result of the anomeric effect the O5′—C1′ bond length is 0.020 (4) Å shorter than the C5′—O5′ distance (C1′ is the anomeric C atom). The O5′—C1′—N1—C2 torsion angle χ in the 13 nucleosides is centered around 244 (8)° and varies from 196.4 (3) to 287.0 (2)°. Molecular-mechanics calculations on uncharged pyranosyl nucleosides are found to be less accurate compared with semi-empirical quantum-chemical methods or molecular-mechanics calculations on charged molecules. It is also shown that, aside from steric forces, electrostatic interactions are important in the orientation of the base with respect to the sugar ring. Crystal-packing analysis reveals that the pyranosyl nucleosides show a similar tendency for base stacking to that observed for the corresponding furanosyl nucleosides.

Introduction

During recent years it has been shown that oligonucleotides could be used to regulate gene expression *in vivo* by hybridizing to mRNAs and thereby blocking the translation process (see *e.g.* Green, Pines & Inouye, 1986). However, the use of these anti-sense oligonucleotides is limited *in vivo* by their sensitivity to cellular or serum nucleases and by their limited penetration capabilities into cells. In order to overcome these difficulties, several strategies have been developed. Replacement of the phosphodiester bonds by methylphosphonates (Ts'o, Miller, Aurelian, Murakami, Agris, Blake, Lin, Lee & Smith, 1988) or phosphorothioates (Marugg, van den Bergh, Tromp, van der Marel, van Zoest & van Boom, 1984), replacement of the β-deoxynucleosides by their α-enantiomers (Morvan, Rayner, Imbach, Thenet, Bertrand, Paoletti, Malvy & Paoletti, 1987) and covalent attachment of intercalating agents to oligo-α-deoxynucleotides (Thuong, Asseline, Roig, Takasugi & Hélène, 1987) or oligo-β-deoxynucleotides (Asseline, Thong & Hélène, 1983) increase considerably the resistance to nucleases.

Another potential approach could be the replacement of the five-membered furanosyl ring by a larger six-membered pyranosyl sugar ring. The resulting oligonucleotides are also stable against *endo-* or *exo*-nucleases (Augustyns, Van Aerschot, Urbanke & Herdewijn, 1991) but the synthesis of the individual pyranosyl nucleosides is, however, a cumbersome, time and energy intensive process. Furthermore, the hydroxyl groups of the phosphodiester linkages can be attached onto the sugar ring in many different configurations and it is difficult to predict, at least in the absence of any *a priori* knowledge from *e.g.* modeling studies, which pyranosyl configuration has to be used for the synthesis of stable, easily hybridizing oligonucleotides. Therefore, molecular-modeling techniques could be very useful in the design of these modified oligonucleotides but then a prerequisite knowledge of the conformational behavior of the individual building blocks, *in casu* the modified pyranosyl nucleosides, is required. In this context and since only a few X-ray structures of pyranosyl pyrimidine nucleosides were available from the Cambridge Structural Database (CSD; Allen, Kennard & Taylor, 1983), we started an extensive X-ray study on crystals of both α- and β-pyranosyl nucleosides (De Winter, Blaton, Peeters, De Ranter, Van Aerschot & Herdewijn, 1991*a–e*), in order to derive a 'standard' pyranosyl pyrimidine nucleoside conformation. This 'standard' structure might be used as a starting building block for the modeling of the DNA-modified oligonucleotide hybrid. The results of the conformational analyses are compared with molecular-mechanical and semi-empirical quantum-chemical calculations in order to assess their possible use in the prediction of conformations and to affirm the crystallographic findings.

At the same time the crystal packings of the pyranosyl structures were examined and searched for recurring stacking patterns. In the solid state of normal furanosyl nucleosides base stacking is very specific since several recurring stacking patterns are found in the different crystalline environments (Bugg, Thomas, Sundaralingam & Rao, 1971). Usually, only partial base overlap is accomplished by superimposing the polar substituents $-NH_2$, =O, =N— or a halogen of one base over the aromatic π system of the adjacent base (Saenger, 1984; Bugg, Thomas, Sundaralingam & Rao, 1971). To design a stable oligo hybrid it is essential that the modified nucleosides are able to stack in the same manner as the normal furanosyl nucleosides since it is mainly this stacking force which stabilizes the DNA double helix (Hanlon, 1966; DeVoe & Tinoco, 1962).

This paper thus presents the crystal structure determination of 1-(2,3-dideoxy-*erythro*-β-D-hexopyranosyl)cytosine and the compilation of the conformational theoretical calculations, and the base-stacking study.

X-ray structure determination

Experimental

Colorless needle-shaped crystals were crystallized from a methanol–dioxane solution, 0.70 × 0.30 × 0.10 mm. Density measured by flotation in *n*-

heptane/CCl_4. Weissenberg photographs showed systematically absent reflections $h00$ with h odd, $0k0$ with k odd and $00l$ with l odd. Hilger & Watts computer-controlled diffractometer, cell constants by least-squares refinement of the θ angles of 30 reflections with $30 \le 2\theta \le 50°$, ω scan, $[(\sin\theta)/\lambda]_{max} = 0.5878$ Å^{-1}, $-8 \le h \le 0$, $-10 \le k \le 10$, $-20 \le l \le 20$. Intensities of four standard reflections (008, 041, $\bar{1}24$, $\bar{2}31$) monitored every 50 reflections showed no significant decrease in intensity, 4018 reflections measured, 1102 unique reflections of which 1024 were considered observed with $F \ge 6\sigma(F)$. Data reduction with a locally modified version of the *REDU*4 (Stoe & Co., 1985) program, Lorentz and polarization corrections. No absorption corrections. Scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B) and for H from Stewart, Davidson & Simpson (1965). Anomalous-dispersion corrections were included for all non-H atoms (Ibers & Hamilton, 1964). The structure was solved by *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). Refined on F by full-matrix least squares, first with isotropic temperature factors and finally anisotropically. All H atoms were found in a difference synthesis and they were included in the refinement with a fixed temperature factor B 1.3 times the B_{eq} value of their parent atoms. Final $R = 0.044$, $wR = 0.060$, with $w = 1/[\sigma^2(F_o) + 0.0004F_o^2]$, $S = 0.83$. Largest parameter shift/e.s.d. = 0.05. Minimum and maximum residual electron density -0.24 and 0.15 e Å^{-3}. The number of reflections per refined parameter 1024/199 = 5.1. All calculations were performed on a Digital PDP-11/73 microcomputer using *SDP* (B. A. Frenz & Associates, Inc., 1985) and *PARST* (Nardelli, 1983).

Discussion

A *PLUTO* view (Motherwell & Clegg, 1978) of the title compound with the atomic numbering scheme is shown in Fig. 1. The final atomic coordinates and equivalent isotropic thermal parameters are given in Table 1.

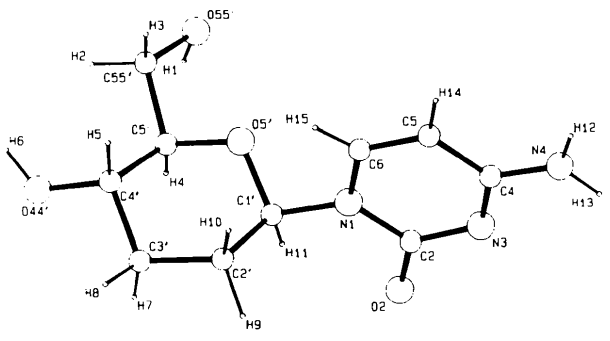


Fig. 1. A *PLUTO* plot (Motherwell & Clegg, 1978) of the title compound with atomic numbering scheme.

Table 1. *Atomic coordinates and equivalent isotropic temperature factors* (Å$^2 \times 10^4$) *for the title compound, with e.s.d.'s in parentheses*

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
N1	0.5129 (3)	0.9855 (3)	−0.0399 (1)	393 (4)
C2	0.4900 (4)	0.9302 (3)	0.0346 (1)	392 (7)
O2	0.3340 (3)	0.9197 (3)	0.0617 (1)	527 (5)
N3	0.6362 (3)	0.8908 (3)	0.0762 (1)	432 (5)
C4	0.8003 (4)	0.9097 (3)	0.0473 (2)	412 (7)
N4	0.9411 (3)	0.8744 (3)	0.0926 (1)	515 (7)
C5	0.8282 (4)	0.9646 (4)	0.0283 (2)	485 (7)
C6	0.6837 (4)	1.0013 (4)	−0.0700 (1)	467 (7)
C1′	0.3574 (4)	1.0220 (3)	−0.0876 (1)	405 (7)
C2′	0.3352 (5)	1.1928 (3)	−0.0987 (2)	511 (8)
C3′	0.1894 (5)	1.2273 (4)	−0.1580 (2)	524 (8)
C4′	0.2191 (4)	1.1364 (3)	−0.2313 (2)	457 (7)
C5′	0.2406 (4)	0.9667 (3)	−0.2109 (1)	396 (7)
O5′	0.3886 (3)	0.9487 (2)	−0.15883 (9)	416 (5)
O44′	0.0676 (3)	1.1606 (3)	−0.2787 (1)	676 (7)
C55′	0.2848 (4)	0.8667 (3)	−0.2796 (2)	471 (8)
O55′	0.2932 (3)	0.7090 (2)	−0.2593 (1)	540 (5)

Table 1.* Bond lengths, bond angles and selected torsion angles are given in Table 2. Table 3 summarizes all the intermolecular hydrogen bonds. All bond lengths and bond angles are within the normal range (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). The orientation of the χ torsion angle (O5′—C1′—N1—C2) along the N-glycosidic bond is in the *anti* range [229.4 (2)°]. The chair puckering for the sequence C1′—C2′—C3′—C4′—C5′—O5′ can be described using the method of Cremer & Pople (1975) with phase angles $\varphi_2 = 84$ (2) and $\theta_2 = 174.3$ (2)° and a total puckering amplitude $Q = 0.569$ (2) Å.

The crystal packing is determined partly by hydrogen bonds (Table 3) and partly by base-stacking forces between bases related to each other by the 2_1 axis along b [d_{mean} between the planes = 3.1 (1) Å, dihedral angle = 4.6 (1)°]. A *PLUTO* plot (Motherwell & Clegg, 1978) of the crystal packing is shown in Fig. 2.

Conformational analysis

Experimental

The compound names and the abbreviations used throughout this paper are listed in Table 4. Although they are not pyranosyl nucleosides in the chemical sense, the crystal structures of 1-[(2*R*,6*R*)-6-hydroxymethyl-1,4-dioxan-2-yl]uracil and its 5-bromouracil analog were also subjected to investigation since the overall conformations of the molecules strongly

* Lists of structure factors, anisotropic thermal parameters, bond lengths and angles involving H atoms, least-squares planes and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54567 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: GE0271]

Table 2. *Bond lengths* (Å), *bond angles* (°) *and selected torsion angles* (°) *for the title compound, together with the pyranose-ring geometric parameters as obtained from the rigid-ring fragment or from weighted averaging, with e.s.d.'s in parentheses*

	Title compound (GS121)	Rigid-ring fragment	Weighted averaging Average	Min.	Max.
C1′—C2′	1.516 (3)	1.510 (8)	1.513 (3)	1.490 (5)	1.528 (7)
C2′—C3′	1.523 (3)	1.525 (6)	1.522 (2)	1.516 (2)	1.534 (3)
C3′—C4′	1.519 (3)	1.502 (5)	1.519 (2)	1.494 (6)	1.533 (7)
C4′—C5′	1.536 (3)	1.522 (7)	1.521 (4)	1.505 (3)	1.538 (7)
C5′—O5′	1.430 (2)	1.422 (6)	1.433 (3)	1.423 (2)	1.446 (4)
O5′—C1′	1.415 (2)	1.420 (5)	1.413 (3)	1.398 (5)	1.441 (4)
N1—C2	1.394 (2)				
N1—C6	1.375 (3)				
N1—C1′	1.454 (3)				
C2—O2	1.250 (3)				
C2—N3	1.347 (3)				
N3—C4	1.325 (3)				
C4—N4	1.342 (3)				
C4—C5	1.415 (3)				
C5—C6	1.331 (3)				
C4′—O44′	1.407 (3)				
C5′—C55′	1.516 (3)				
C55′—O55′	1.426 (3)				
O5′—C1′—C2′	110.7 (2)	110.5 (4)	110.8 (3)	107.5 (3)	112.3 (2)
C1′—C2′—C3′	111.0 (2)	109.1 (3)	109.1 (6)	105.3 (2)	111.1 (3)
C2′—C3′—C4′	111.2 (2)	110.6 (3)	110.5 (4)	108.6 (2)	112.7 (2)
C3′—C4′—C5′	109.1 (2)	111.3 (3)	110.7 (2)	109.1 (2)	112.2 (2)
C4′—C5′—O5′	109.4 (2)	110.5 (4)	110.1 (2)	107.9 (4)	111.2 (2)
C5′—O5′—C1′	112.3 (2)	112.1 (3)	112.0 (3)	109.6 (3)	113.9 (4)
C6—N1—C1′	119.3 (2)				
C2—N1—C1′	120.6 (2)				
C2—N1—C6	120.0 (2)				
N1—C2—N3	119.4 (2)				
N1—C2—O2	119.2 (2)				
O2—C2—N3	121.4 (2)				
C2—N3—C4	120.0 (2)				
N3—C4—C5	121.9 (2)				
N3—C4—N4	117.4 (2)				
N4—C4—C5	120.7 (2)				
C4—C5—C6	118.0 (2)				
N1—C6—C5	120.5 (2)				
N1—C1′—O5′	105.7 (2)				
N1—C1′—C2′	112.0 (2)				
C3′—C4′—O44′	107.3 (2)				
O44′—C4′—C5′	111.3 (2)				
C4′—C5′—C55′	113.5 (2)				
C55′—C5′—O5′	105.6 (2)				
C5′—C55′—O55′	111.9 (2)				
O5′—C1′—C2′—C3′	53.9 (2)	58.4 (6)	59 (1)	53.9 (2)	64.4 (2)
C1′—C2′—C3′—C4′	−50.4 (2)	−53.1 (6)	−53.1 (8)	−49.3 (4)	−56.2 (2)
C2′—C3′—C4′—C5′	52.1 (2)	51.3 (6)	51.8 (6)	48.2 (3)	56.3 (6)
C3′—C4′—C5′—O5′	−58.0 (2)	−54.0 (7)	−55 (1)	−44.8 (3)	−58.1 (4)
C4′—C5′—O5′—C1′	64.2 (2)	60.1 (7)	61 (1)	54.8 (2)	66.4 (5)
C5′—O5′—C1′—C2′	−62.0 (2)	−63.3 (6)	−63.4 (8)	−59.8 (3)	−68.2 (5)
C6—N1—C1′—C2′	−73.3 (2)				
C2—N1—C1′—C2′	108.8 (2)				
C6—N1—C1′—O5′	47.3 (2)				
C2—N1—C1′—O5′	−130.6 (2)				
C2′—C3′—C4′—O44′	172.8 (2)				
C3′—C4′—C5′—C55′	−175.7 (2)				
O44′—C4′—C5′—C55′	66.0 (2)				
O44′—C4′—C5′—O5′	−176.3 (2)				
C55′—C5′—O5′—C1′	−173.2 (2)				
C4′—C5′—C55′—O55′	−176.5 (2)				
O5′—C5′—C55′—O55′	63.6 (2)				

resemble those of the pyranoside nucleosides. In total, 13 pyrimidine structures from 12 different X-ray studies were examined, *i.e.* three α- and ten β-anomers. Of those 13 structures only four were available from the CSD and retrieved (NORDA and B, C-SUBST1 and 2). Except for C-SUBST1, 2 and the title compound, which are all cytosine nucleosides, the others are uracil or thymine derivatives. In

Table 3. *Geometry of intermolecular hydrogen bonds* (Å, °) *in the crystal structure of the title compound, with e.s.d.'s in parentheses*

X—H···*Y*		*d*(H···*Y*)	*d*(*X*···*Y*)	*X*—H···*Y*
O55′—H1···O44′	(1)	1.77 (4)	2.783 (2)	172 (3)
O44′—H6···O2	(2)	2.09 (4)	2.955 (2)	161 (2)
N4—H12···O2	(3)	2.14 (3)	2.984 (2)	171 (2)
N4—H13···O55′	(4)	2.24 (3)	3.183 (3)	164 (2)

Equivalent positions: (1) $-x, y-\frac{1}{2}, -z-\frac{1}{2}$; (2) $-x+\frac{1}{2}, 2-y, z-\frac{1}{2}$; (3) $1+x, y, z$; (4) $x+\frac{1}{2}, \frac{3}{2}-y, -z$.

none of the examined structures is the crystallographic residual index *R* larger than 0.055 and the average e.s.d. on the bond lengths is 0.005 Å; minimum (for LKII5) and maximum (for AVII56) mean values are 0.002 and 0.01 Å respectively (despite the presence of the heavy atom Br, no absorption corrections were applied to the latter structure). All structures have been refined to a maximum shift/e.s.d. of 0.33. Co-crystallization of solvent water molecules has been observed in three structures (LKII5, NORDB and C-SUBST), but these solvent molecules are all well located and well refined with reasonable temperature factors and e.s.d.'s. The asymmetric unit of GSII115 does contain a partially disordered dioxane solvent molecule, but apparently this has no influence on the e.s.d.'s of the compound (mean e.s.d. on bond lengths is 0.004 Å).

Throughout this paper the weighted means x_m with standard errors σ_m of N parameters x_i with their e.s.d.'s σ_i have been calculated using the formulae (Domenicano, Serantoni & Riva di Sanseverino, 1977):

$$x_m = \sum_{i=1}^{N} (x_i/\sigma_i^2) \Big/ \sum_{i=1}^{N} (1/\sigma_i^2)$$

$$\sigma_m = \left\{ \sum_{i=1}^{N} [(x_i - x_m)^2/\sigma_i^2] \Big/ (N-1) \sum_{i=1}^{N} (1/\sigma_i^2) \right\}^{1/2}.$$

The method of Sheldrick & Akrigg (1980) was used for the derivation of the averaged pyranosyl

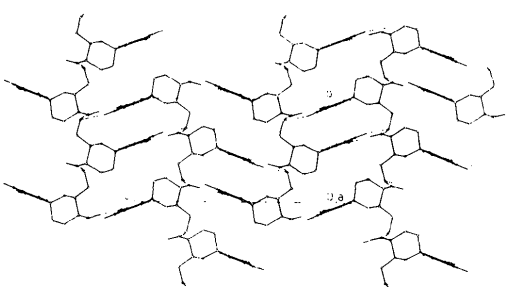


Fig. 2. A *PLUTO* plot (Motherwell & Clegg, 1978) of the crystal along **a** showing the packing. Thin lines indicate hydrogen bonds.

Table 4. *List of the compounds in this study, with average bond-length e.s.d.'s, base types and abbreviations used*

Code	Chemical name	Mean σ (Å)	Base*
α-Enantiomers			
GSII118	1-(2,3-Dideoxy-*erythro*-α-D-hexopyranosyl)-thymine[b]	0.003	T
NORDA	1-(2-Deoxy-α-D-*ribo*-hexopyranosyl)uracil[c]	0.005	U
LK159A	1-(2-Deoxy-2-fluoro-α-D-arabinopyranosyl)-5-iodouracil[f]	0.006	U
β-Enantiomers			
LK160	1-(2-Deoxy-*erythro*-β-D-pentopyranosyl)-5-iodouracil[a]	0.005	U
GSII115	1-(2,3-Dideoxy-*erythro*-β-D-hexopyranosyl)-thymine[b]	0.004	T
NORDB	1-(2-Deoxy-β-D-*ribo*-hexopyranosyl)uracil[c]	0.005	U
LK115	1-(2-Deoxy-2-fluoro-β-D-arabinopyranosyl)-thymine[d]	0.002	T
LK170	1-(2-Deoxy-2-fluoro-β-D-arabinopyranosyl)-5-ethyluracil[d]	0.005	U
AVII52	1-[(2*R*,6*R*)-Hydroxymethyl-1,4-dioxan-2-yl]uracil[f]	0.003	U
AVII56	5-Bromo-1-[(2*R*,6*R*)-6-Hydroxymethyl-1,4-dioxan-2-yl]uracil[f]	0.01	U
GS121	1-(2,3-Dideoxy-*erythro*-β-D-hexopyranosyl)-cytosine[g]	0.003	C
C-SUBST†	4-Amino-1-[4-amino-2-oxo-1(2*H*)-pyrimidinyl]-1,4-dideoxy-β-D-glucopyranuronic acid[h]	0.006	C

References: (*a*) De Winter *et al.* (1991*a*). (*b*) De Winter *et al.* (1991*b*). (*c*) Nord *et al.* (1987). (*d*) De Winter *et al.* (1991*c*). (*e*) De Winter *et al.* (1991*d*). (*f*) De Winter *et al.* (1991*e*). (*g*) This paper. (*h*) Swaminathan *et al.* (1980).

* U for uracil, T for thymine and C for cytosine.

† With two molecules in the asymmetric unit, C-SUBST1 and C-SUBST2.

ring fragment from the pyranosyl nucleoside structures. Following this procedure each pyranose ring was initially fitted with *BMFIT* (Nyburg, 1974; the fitting involved all six ring atoms) to a reference ring (*in casu* the LKII5 fragment) and subsequently to the weighted average of these fitted rings. This second fitting was then iterated until no change in the geometry of the averaged fragment was observed; the average r.m.s. deviation converged to less than 0.03 (2) Å.

Theoretical calculations were performed with the molecular-mechanics programs *ALCHEMY*II (Tripos Associates, 1989) and *CHEMMOD* (U-Microcomputers Ltd., 1989) and with the semi-empirical quantum-chemical program *AM*1 (Dewar, Zoebisch, Healy & Stewart, 1985), which is part of the *MOPAC* package (Stewart, 1989). *ALCHEMY*II was run on an IBM AT compatible, *CHEMMOD* on its dedicated U-MAN 1000 system and *MOPAC* was implemented on the IBM 3090 of the Leuvens Universitair Rekencentrum. The energy of each conformation was fully optimized until (1) the energy difference between successive iterations dropped below 0.01 kcal mol^{-1} (1 kcal mol^{-1} = 4.184 kJ mol^{-1}) (*ALCHEMY*), (2) the r.m.s. value of the function gradient was <0.01 kcal mol^{-1} Å^{-1} (*CHEMMOD*) or (3) the difference in heat of formation between consecutive iterations was <0.3 kcal mol^{-1} (*AM*1).

Discussion

The pyrimidine base. For a description of the pyrimidine-base geometry, the reader is referred to the paper of Taylor & Kennard (1982), where an accurate depiction of the base geometry of furanosyl nucleosides is given. Since for the pyranosyl bases under study the weighted means of the bond lengths and angles do not differ by more than 2σ from their comparable furanosyl-base values, it is obvious that the bases are conformationally identical and that the sugar ring type (furanosyl- or pyranosyl-like) has little or no influence on the base geometry. Only for the cytosine pyranosyls (GS121 and C-SUBST), some mean values such as the N1—C2 bond length and the C1′—N1—C2 and C1′—N1—C6 bond angles deviate by more than 5σ from their reference furanosyl values. This, however, has little physical significance since these parameters have been calculated from only three observations, two of which (C-SUBST1 and 2) have e.s.d.'s twice as large as the third (GS121). Consequently, the contribution of the former observations to the weighted mean is relatively small and the mean is biased in favor of only one observation, GS121.

The pyranosyl sugar ring. The conformation of the six-membered pyranosyl ring is different for α- and β-nucleosides. In the former a $_4C^1$ conformation is adopted while for the latter the conformation is $^4C_1$ so that the base moiety is always oriented equatorially. In a study of the pyranosyl-ring geometry, it is important that both anomers are distinguished and treated separately or converted to the correct anomeric form. In order to increase the data set the latter solution was chosen and three additional β-anomers were generated by simple inversion of the α-anomers; in total 11 β-nucleosides were investigated [obviously, 1-[(2*R*,6*R*)-6-hydroxymethyl-1,4-dioxan-2-yl]uracil and its 5-bromo analog were excluded from the calculations]. In order to reveal some common properties or to identify outliers in the data set, the iterative fitting procedure as described by Sheldrick & Akrigg (1980) was used to calculate an averaged pyranosyl rigid-body fragment. Bond lengths, bond angles and torsion angles for this ring are tabulated in Table 2. From the small average r.m.s. deviation of only 0.03 (2) Å and from the observation that all deviations fall within 1σ from the mean (minimum and maximum of 0.01 and 0.05 Å for LKI60 and GSII118 respectively), it is clear that the 11 rings are all conformationally very similar; the reason for this lies most probably in the rigidness of the pyranose ring. Results from research done by Sheldrick & Akrigg (1980) and Jeffrey (1990) point in the same direction. The Cremer & Pople (1975) puckering parameters for the sequence C1′—C2′—C3′—C4′—C5′—O5′ of the 'β-fragment'

are $\varphi_2 = 164\,(13)$, $\theta_2 = 175.7\,(9)^\circ$ and $Q = 0.566\,(9)$ Å, and describe a $^4C_1$-chair conformation which is only slightly flattened at the C4′ apex. These values are in close agreement with the puckering parameters of aldoses and ketoses ($Q = 0.55$–0.58 Å, $\theta_2 = 0$ or $180 \pm 5^\circ$; Jeffrey, 1990). Conversion to the $_4C^1$ form is simply done by inversion of the original β-coordinates and the puckering-phase angles for this 'α-fragment' are $\varphi_2 = -16\,(13)$ and $\theta_2 = 4.3\,(9)^\circ$. Although fitting to an averaged group can be an excellent procedure to reveal some basic common properties or to identify outliers in a data set, the mean bond lengths and angles of this rigid-body ring are less accurate since the ring coordinates have been calculated by simultaneously fitting all the ring atoms. Therefore, lack of a good fit on one side of the ring can result in a biased fit on the other side. Thus, conclusions drawn from these parameters only remain valid within a certain approximation. A second and more appropriate approach for the calculation of mean bond lengths or angles simply involves the calculation of the weighted means of the parameters using the formulae of Domenicano, Serantoni & Riva di Sanseverino (1977). Having performed this for all the pyranose bond lengths, angles and torsion angles, the results are tabulated in Table 2. All ring C—C lengths are centered in a narrow range around the mean value of 1.518 (4) Å [minimum and maximum distances are 1.513 (3) and 1.522 (2) Å respectively]. The mean C—O distance is 1.42 (1) Å but the O5′—C1′ distance is 0.020 (4) Å ($> 5\sigma$) shorter than the C5′—O5′ length. This shortening is most probably caused by the acquisition of partial double-bond character due to electron delocalization from the O5′ lone-pair *p*-type orbital into the antibonding σ^* orbital of the C1′—N1 bond (Jeffrey, Pople, Binkley & Vishveshwara, 1978). This so-called anomeric effect has also been observed in halogeno-1,4-dioxanes and carbohydrates (*e.g.* Angyal, 1969) and is, at least for these molecules, responsible for the preferred axial orientation of the substituents at the anomeric C atom. Quantum-chemical calculations (Jeffrey, Pople, Binkley & Vishveshwara, 1978) suggest that the C—O shortening due to electron back donation is independent of the COC*X* (*X* represents the substituent) conformation (70 or 180°), although the axial conformation (70°) is energetically slightly more stabilized than the equatorial orientation (180°). However, in all the observed α- or β-pyranosyl nucleosides the bases are oriented equatorially with a COCN torsion angle of approximately 180°. It thus seems that the energy gain due to optimal electron back donation is negligible compared with the energy loss from unfavorable steric contacts in the axial orientation of the pyranosyl nucleoside base.

The χ torsion angle. The orientation of the base moiety with respect to the pyranosyl part can be described by the O5′—C1′—N1—C2 torsion angle χ. From Fig. 3 it can be seen that χ is centered around 244 (8)° and varies from 196.4 (3) (LKI60) to 287.0 (2)° (GSII118) (it should be noted that the α-anomers have been inverted to their β-analogs). A more descriptive view of the variation of χ is given in Fig. 4, in which all the pyranosyl rings were fitted onto the averaged sugar ring fragment. At this point, it seemed interesting to compare these experimental findings with molecular-mechanics and quantum-chemical calculations. Therefore a model compound, constructed from the averaged ring fragment and the 1-thyminyl moiety (and shown in Fig. 5), was subjected to an analysis of the variation of the internal energy as a function of the torsion angle χ. The angle was rotated in steps of 10° and at each point the geometry was fully optimized using *ALCHEMY*, *CHEMMOD* (both molecular mechanics) or *AM*1

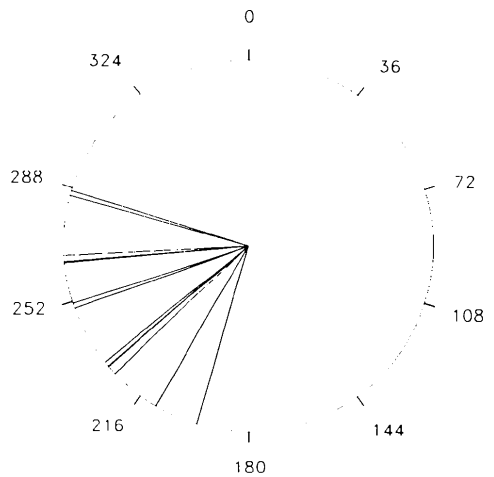


Fig. 3. Distribution of torsion angle χ. Values are in °.

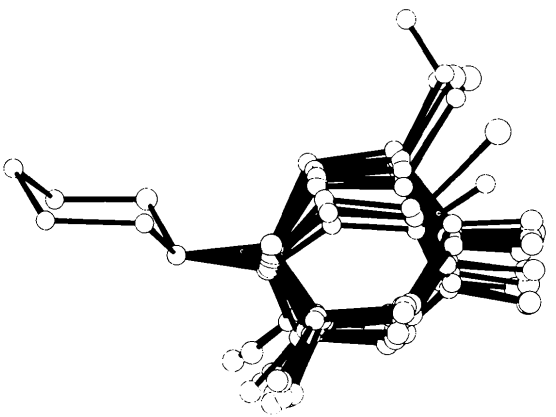
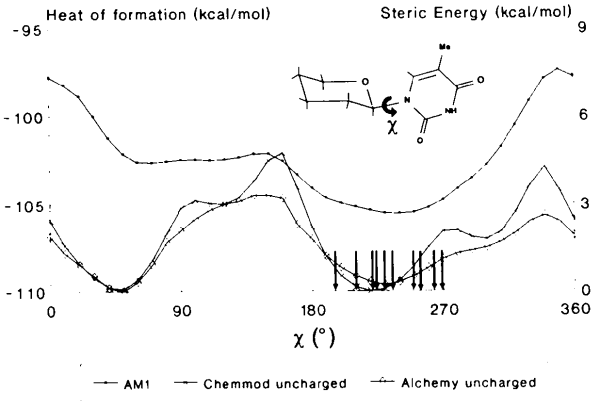
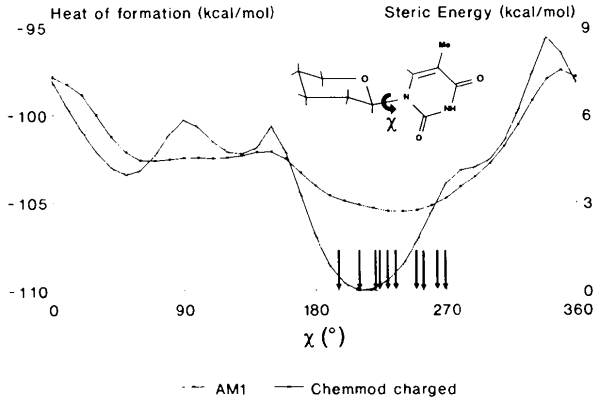


Fig. 4. A *PLUTO* plot (Motherwell & Clegg, 1978) showing all the base moieties implemented onto the averaged sugar ring fragment.

(semi-empirical quantum chemical). The molecular-mechanics calculations were performed on the uncharged model. Fig. 5(*a*) summarizes the results of these calculations and the experimental conformations are represented by arrows. From this figure it can be seen that the experimental conformations fall within the preferred conformation range as predicted from *AM*1. The semi-empirical quantum-chemical results thus agree much better than the molecular-mechanics calculations, which predict two energy minima at $\chi = 50$ and 220–230°, respectively. Therefore, the idea was raised that, aside from steric interactions, electrostatic forces could play a determining role in the orientation of the base moiety relative to the sugar ring. In this context, a *CHEMMOD* molecular-mechanics recalculation, but this time with net atomic charges from *AM*1, was performed (Fig. 5*b*). Since the net charges on O2 and O5′ are highly dependent upon the conformation (Fig. 6), the charges assigned to the model are from the conformation with $\chi = 240°$. It is noteworthy that mainly the charges on O2 and O5′ fluctuate with χ, while the charge shifts on the other base or sugar atoms are less pronounced (results not shown). From Fig. 5(*b*) it is clear that the introduction of net atomic charges leads to a considerable improvement of the molecular-mechanics results: only one energy minimum is predicted at $\chi = 210°$. Compared with *AM*1 the energy minimum is much deeper and narrower, but that is most probably the consequence of the invariability of the assigned charges. Indeed, as Fig. 6 suggests, the closer O2 and O5′ come, the more modest the charges on these atoms, which counterbalances for the larger electrostatic repulsion at smaller distances. If, however, the charges are left invariable (as is the case in the molecular-mechanics approach) and thus unable to compensate for the larger electrostatic repulsion at small distances, the repulsion will be overestimated in most of the conformations, and so will be the total energy.



(*a*)



(*b*)

Fig. 5. Variation of the steric energy (*CHEMMOD* or *ALCHEMY*) or heat of formation (*AM*1) as a function of χ for (*a*) the uncharged model and (*b*) the model with *AM*1 net charges assigned.

The N1—C1′ bond length varies from 1.450 (2) to 1.479 (5) Å with a weighted mean value of 1.459 (2) Å, significantly shorter than the average 1.49 Å for furanosyl pyrimidine nucleosides (Lin, Sundaralingam & Arora, 1971). Unlike the furanosyl pyrimidine nucleosides (Lo, Shefter & Cochran, 1975) no dependency of the glycosyl N1—C1′ bond length on χ has been observed.

Construction of the 'standard' model. As already stated above, the scope of this conformational analysis was to elucidate a standard rigid model for a pyranosyl pyrimidine nucleoside which could be used in subsequent molecular-modeling studies of modified oligonucleotides. The fragment does consist of a base moiety linked onto the pyranosyl sugar part by the *N*-glycosidic bond. Averaged geometries for the nucleoside bases can be found in the excellent book by Saenger (1984). For the pyranosyl sugar ring, the geometry of the averaged pyranosyl rigid-body fragment was used and linked onto the base

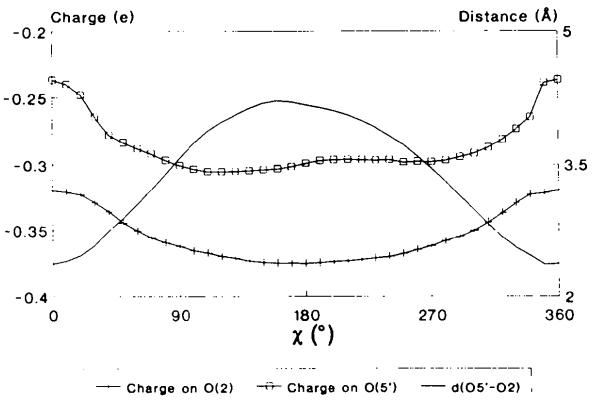


Fig. 6. Variation of the *AM*1 net atomic charges (on O2 and O5′) as a function of χ.

Table 5. *List of structures with the recurring stacking patterns*

	Space group	d (Å)	θ (°)	Halogen oriented	Methyl oriented	Carbonyl oriented	N oriented
LKI59A	$P\bar{1}$	3.5	0.0	I		+	–
AVII56	$P\bar{1}$	3.3	0.0	Br		+	–
LKII5	$P2_1$	3.2	11.6		–	+	–
LKI60*	$P2_1$	–	–	–		–	–
LKI70	$P6_5$	3.4	16.8			+	+
GS121	$P2_12_12_1$	3.1	4.6			+	+
GSII115	$C2$	3.8	4.3		+	–	–
GSII118*	$P2_12_12_1$	–	–			–	–
AVII52†	$P3_121$	3.4	10.8			–	+
		3.6	12.9			+	+
NORDA	$P2_12_12_1$	3.3	1.0			+	–
NORDB	$C2$	3.7	3.5			+	+
C-SUBST	$P2_1$	3.7	5.7			–	+

* These molecules do not stack in the solid state.
† Two different stacking patterns are observable.

part with the O5′—C1′—N1—C2 torsion angle χ fixed at 244° and a C1′—N1 distance of 1.459 Å. It should be emphasized that this angle and distance are only valid for pyrimidine bases; purine bases were excluded from the analyses (too few structures were available).

Base-stacking properties

Experimental

Calculations were performed on the parameters obtained from the crystal structure analyses summarized in Table 4. Weighted least-squares planes through the atoms of the base rings, dihedral angles between those planes, interplanar spacings and out-of-plane deviations were calculated using *PARST* (Nardelli, 1983). H atoms were not taken into account. Stacking patterns, interplanar spacings d and dihedral angles θ of the structures are listed in Table 5.

Discussion

In all the structures except 1-(2,3-dideoxy-*erythro*-α-D-hexopyranosyl)thymine and 1-(2-deoxy-*erythro*-β-D-pentopyranosyl-5-iodouracil base stacking is observed and in total four different patterns are recognizable. These stacking modes are similar to the ones observed in furanosyl nucleosides and for a depiction the reader is referred to the excellent paper by Bugg, Thomas, Sundaralingam & Rao (1971).

(1) The first pattern is found in one third of the halogenated pyranosyl nucleoside structures. In these, the halogen atoms are positioned close above the center of adjacent pyrimidine heterocycles with halogen-to-plane distances of 3.3–3.5 Å ('halogen oriented' in Table 5).

(2) The stacking pattern of GSII115 closely resembles that of the halogenated molecules. However, in this structure the 5-methyl group lies almost exactly above the center of the adjacent base ('methyl oriented').

(3) In approximately 60% of the structures, the carbonyl O atom is positioned close above the base ring of an adjacent nucleoside. However, in contrast to the previous two patterns, the carbonyl O atom is seldomly centered above the adjacent pyrimidine ring but merely prefers to form a close contact with one of the atoms of the adjacent base ('carbonyl oriented').

(4) Sometimes the stacked bases are oriented in such a way that the N atoms of the pyrimidine bases are able to form close contacts with N atoms of adjacent bases ('N oriented').

From the results of the study it is clear that base stacking in pyranosyl nucleosides is an important and perhaps just as dominant an interaction mechanism as it is in furanosyl nucleoside crystals.

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Crystallography of the Even *n*-Alkanes: Structure of $C_{20}H_{42}$

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Abstract

n-Eicosane, $M_r = 282.55$, triclinic, $P\bar{1}$, $a = 4.293\ (5)$, $b = 4.84\ (1)$, $c = 27.35\ (9)$ Å, $\alpha = 85.3\ (3)$, $\beta = 68.2\ (1)$, $\gamma = 72.6\ (1)^\circ$, $V = 503.2$ Å^3, $Z = 1$, $D_x = 0.932$ Mg m^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 0.34$ mm^{-1}, $F(000) = 162$, $T = 300$ K, $wR = 0.074$, $R = 0.090$ for 649 significant reflections out of a total of 1251 [$I > 2.5\sigma(I)$]. The triclinic even *n*-alkanes up to $n = 22$ form an isostructural series.

Introduction

It is a matter of some difficulty to obtain accurate X-ray crystal structure analyses of long-chain *n*-alkanes. By virtually whatever method they are crystallized, they invariably adopt a thin platy habit, a consequence of their underlying layer structure. Such thin plates are often slightly warped and this prevents their precise alignment on a diffractometer. The best orientation matrix obtainable usually yields cell parameters with errors substantially larger than those normally acceptable. Nevertheless, accepting these limitations, it is possible to obtain X-ray structure analyses which, although not of the highest accuracy, can yield useful structural information. We report the X-ray crystal structure analysis of *n*-eicosane, $C_{20}H_{42}$. Its relation to the crystal structures of other even *n*-alkanes is given in the *Discussion*.

Experimental

A large crystalline agglomeration (25 × 10 × 4 mm) of *n*-$C_{20}H_{42}$ (Aldrich Chemical Company Ltd) was grown from *n*-dodecane, $C_{12}H_{20}$, by slow cooling (< 0.01 K per day) over a period of two weeks. From this, a flat plate was cut (dimensions 1.5 × 0.5 × 0.1 mm) and mounted on a Picker four-circle diffractometer. Using Ni-filtered Cu $K\alpha$ radiation, unit-cell dimensions were derived from 26 reflections, $34.0 < 2\theta < 80.0^\circ$. Data were collected in the range $3.0 < 2\theta$

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