Structure of 9-β-D-Arabinofuranosyl-8-morpholinoadenine Dihydrate. An Arabinoside in the *syn* Conformation

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Abstract

The crystal structure of 9-β-D-arabinofuranosyl-8-morpholinoadenine dihydrate has been determined by X-ray diffraction techniques using diffractometer data. The compound crystallizes in the orthorhombic space group $P2_12_12_1$ with $a = 17\cdot833$ (1), $b = 19\cdot436$ (1), $c = 5\cdot128$ (1) Å, $Z = 4$. The crystal structure was solved by the multisolution tangent method and refined by full-matrix least-squares calculations to a final R value of 0·039 for 2182 reflections. The molecule assumes the *syn* conformation about the glycosyl bond with $\chi = -142\cdot1°$ and is further stabilized by an intramolecular hydrogen bond (2·739 Å) between the O(5') hydroxyl and the N(3) site of the base. The morpholine ring at the C(8) position is in the chair conformation. The arabinose ring exhibits the C(3')-*endo*, C(4')-*exo* ($^3T_4$) pucker, contrary to the usual C(2')-*endo* pucker for a *syn* base. The conformation about the exocyclic C(4')–C(5') bond is *gauche*$^+$ with $\chi = 53\cdot0°$. All potential hydrogen-bonding sites are engaged in hydrogen bonding. One of the water molecules is tetrahedrally coordinated and is hydrogen bonded to the N(6) and N(7) sites of the same base while the other is trigonally coordinated to three neighboring nucleosides.

Introduction

The structure determination of 9-β-D-arabino-furanosyl-8-morpholinoadenine (8-morpholino-ara-A) was undertaken as part of a program of research in these laboratories to understand further the stereochemical properties of the nucleic acid constituents and their analogs. The 5'-hydroxy proton in the ^{1}H NMR spectrum [90 MHz, in (CD$_3$)$_2$SO] of 8-morpholino-ara-A resonates as a multiplet at δ 5·24 p.p.m., which is in the same region (δ 5·2–5·9 p.p.m.) as the chemical shifts of the 5'-hydroxy proton resonances of

adenosine, ara-A and their 8-pyrrolidino and 8-piperidino derivatives. This value is appreciably upfield from those of the 5'-hydroxy proton resonances of the 8-methylamino and 8-n-butylamino derivatives of both ara-A and adenosine. The NMR chemical-shift data would suggest that 8-n-butylaminoadenosine and the 8-methylamino derivatives of both adenosine and ara-A take up *anti* conformations in d_6-dimethyl sulfoxide solution. Indeed, this has been confirmed recently by the X-ray structure determination of 8-n-butylamino-ara-A (Neidle, Sanderson, Subbiah, Chattopadhyaya, Kuroda & Reese, 1979) where the *anti* conformation is stabilized by an intramolecular hydrogen bond between the N–H substituted on C(8) and the O(5') atom. The relatively high-field chemical shift of the 5'-hydroxy proton resonance of 8-morpholino-ara-A on the other hand would suggest that in d_6-dimethyl sulfoxide solution, it takes up the *syn* conformation stabilized by an intramolecular hydrogen bond between O(5')–H and the base N(3) site. This is in accordance with the results of the present X-ray crystallographic study.

Experimental

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X-ray intensities were measured on an Enraf–Nonius CAD-4 automated diffractometer using Cu $K\alpha$ radiation. Intensities of 2229 independent reflections were measured, of which 47 were observed to be less than $1 \cdot 5\sigma(I)$ where $\sigma(I)$ is the standard deviation of the intensity. The data were corrected for Lorentz and polarization factors and an empirical absorption correction was applied based on the variation of the $\bar{1}04$ reflection at $\chi = 90°$ as a function of φ.

Structure determination and refinement

The structure was solved by direct methods using the program *MULTAN* (Germain, Main & Woolfson, 1971). A Fourier synthesis calculated with 155 $|E|$'s > $1 \cdot 7$ revealed clearly the positions of 17 non-hydrogen atoms. A subsequent Fourier map revealed the positions of the remaining atoms in the structure. The atoms were refined by full-matrix least-squares methods, initially with isotropic temperature factors. The H atoms were then located from a difference Fourier map. Further cycles of refinement with anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the H atoms gave a final R value of 0·039.* Hughes's (1941) type of weighting scheme, viz $w = 1 \cdot 0$ for $F_o \leq 4F_{min}$ and $w = 4F_o/F_{min}$ for $F_o > 4F_{min}$ with $F_{min} = 2 \cdot 5$, was used during the final stages of refinement. The average ratios of the final shifts to their estimated standard deviations were 0·06 and 0·10 for the non-hydrogen and H atoms respectively. The scattering factors for C, N and O were those of Cromer & Waber (1965) and those for H were from Stewart, Davidson & Simpson (1965).

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* Lists of structure factors, anisotropic thermal parameters and least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34945 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
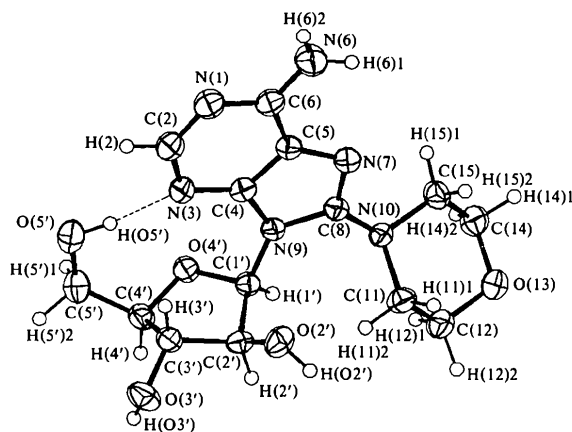

Fig. 1. An *ORTEP* drawing of 9-β-D-arabinofuranosyl-8-morpholinoadenine with the atom numbering.

Table 1. *Positional parameters ($\times 10^4$ for nonhydrogen atoms; $\times 10^3$ for hydrogen atoms) and the isotropic temperature factors of all the atoms of the title compound*

The e.s.d.'s are given within parentheses. The equivalent isotropic temperature factor for the nonhydrogen atoms is computed using the expression $B = 8\pi^2(U_1 U_2 U_3)^{2/3}$ where U_1, U_2, U_3 are the r.m.s. amplitudes along the principal axes of the thermal ellipsoid.

	x	y	z	B (Å²)
N(1)	10579 (1)	6889 (1)	5163 (5)	3·16
C(2)	10076 (1)	6470 (1)	6225 (6)	3·13
N(3)	9563 (1)	6601 (1)	8036 (4)	2·71
C(4)	9570 (1)	7264 (1)	8764 (5)	2·34
C(5)	10071 (1)	7757 (1)	7896 (5)	2·49
C(6)	10600 (1)	7549 (1)	6027 (5)	2·80
N(6)	11111 (1)	7982 (1)	5019 (6)	3·75
N(7)	9927 (1)	8386 (1)	9040 (4)	2·58
C(8)	9353 (1)	8270 (1)	10577 (5)	2·31
N(9)	9107 (1)	7591 (1)	10527 (4)	2·23
C(1')	8450 (1)	7323 (1)	11882 (4)	2·19
O(4')	8620 (1)	6655 (1)	12836 (3)	2·54
C(2')	7755 (1)	7240 (1)	10103 (5)	2·39
O(2')	7764 (1)	7667 (1)	7894 (4)	3·10
C(3')	7782 (1)	6478 (1)	9390 (5)	2·46
O(3')	7101 (1)	6209 (1)	9431 (4)	3·41
C(4')	8052 (1)	6176 (1)	11965 (5)	2·63
C(5')	8405 (2)	5473 (1)	11892 (7)	3·56
O(5')	9000 (1)	5406 (1)	10079 (6)	4·15
N(10)	9043 (1)	8756 (1)	12252 (4)	2·37
C(11)	8269 (1)	8984 (1)	11720 (5)	2·77
C(12)	7990 (1)	9402 (1)	14005 (6)	3·06
O(13)	8463 (1)	9988 (1)	14474 (4)	3·34
C(14)	9219 (1)	9763 (1)	14953 (5)	3·22
C(15)	9524 (1)	9353 (1)	12690 (5)	2·81
O(W1)	6110 (1)	5722 (1)	12076 (5)	3·77
O(W2)	6629 (1)	8560 (1)	8521 (6)	4·40
H(2)	1007 (2)	600 (1)	560 (7)	4·47
H(6)1	1109 (1)	842 (1)	552 (7)	4·43
H(6)2	1140 (2)	790 (1)	399 (8)	5·51
H(1')	834 (2)	759 (1)	1341 (6)	3·31
H(2')	733 (1)	737 (1)	1130 (6)	2·66
H(O2')	742 (2)	800 (1)	792 (8)	5·22
H(3')	818 (1)	643 (1)	795 (6)	2·46
H(O3')	684 (2)	610 (1)	963 (7)	4·39
H(4')	762 (2)	617 (1)	1320 (7)	3·70
H(5')1	864 (2)	536 (2)	1402 (10)	7·80
H(5')2	802 (2)	507 (2)	1179 (9)	6·87
H(O5')	916 (2)	583 (2)	959 (8)	6·02
H(11)1	821 (1)	933 (1)	1009 (6)	2·74
H(11)2	794 (1)	859 (1)	1122 (6)	2·67
H(12)1	804 (2)	913 (1)	1542 (7)	4·92
H(12)2	745 (2)	958 (1)	1378 (8)	4·94
H(14)1	951 (2)	1019 (2)	1494 (7)	4·74
H(14)2	930 (2)	956 (1)	1664 (9)	6·22
H(15)1	1002 (2)	924 (1)	1297 (7)	4·73
H(15)2	957 (2)	966 (1)	1108 (7)	4·65
H(W1)1	608 (2)	536 (1)	1260 (8)	5·63
H(W1)2	569 (2)	586 (2)	1164 (10)	7·66
H(W2)1	666 (2)	892 (2)	800 (12)	7·92
H(W2)2	623 (2)	846 (2)	744 (11)	7·88

Results

The atomic coordinates of both the non-hydrogen and H atoms are given in Table 1. Fig. 1 shows an *ORTEP*

Table 2. *Bond lengths* (Å) *and angles* (°) *in* 9-β-D-*arabinofuranosyl-8-morpholinoadenine dihydrate*

Base

N(1)–C(2)	1·328		C(5)–N(7)	1·380
N(1)–C(6)	1·358		C(6)–N(6)	1·344
C(2)–N(3)	1·328		N(7)–C(8)	1·311
N(3)–C(4)	1·342		C(8)–N(9)	1·391
C(4)–C(5)	1·384		C(8)–N(10)	1·391
C(4)–N(9)	1·379		N(9)–C(1')	1·458
C(5)–C(6)	1·404			

C(2)–N(1)–C(6)	117·7		N(1)–C(6)–N(6)	119·0
N(1)–C(2)–N(3)	129·4		C(5)–C(6)–N(6)	122·5
C(2)–N(3)–C(4)	111·9		C(5)–N(7)–C(8)	104·4
N(3)–C(4)–C(5)	125·6		N(7)–C(8)–N(9)	113·5
N(3)–C(4)–N(9)	128·3		N(7)–C(8)–N(10)	124·4
C(5)–C(4)–N(9)	106·2		N(9)–C(8)–N(10)	122·0
C(4)–C(5)–C(6)	117·0		C(4)–N(9)–C(8)	105·1
C(4)–C(5)–N(7)	110·9		C(1')–N(9)–C(4)	128·9
C(6)–C(5)–N(7)	132·1		C(1')–N(9)–C(8)	125·7
N(1)–C(6)–C(5)	118·4			

Arabinose

C(1')–O(4')	1·420		C(2')–O(2')	1·404
C(1')–C(2')	1·547		C(3')–O(3')	1·411
C(2')–C(3')	1·526		C(4')–C(5')	1·505
C(3')–C(4')	1·523		C(5')–O(5')	1·417
C(4')–O(4')	1·446			

C(2')–C(1')–O(4')	106·2		C(3')–C(2')–O(2')	112·3
C(2')–C(1')–N(9)	113·6		C(1')–C(2')–O(2')	113·9
O(4')–C(1')–N(9)	108·6		C(2')–C(3')–O(3')	114·6
C(1')–C(2')–C(3')	102·5		C(4')–C(3')–O(3')	115·6
C(2')–C(3')–C(4')	100·2		C(5')–C(4')–O(4')	107·4
C(3')–C(4')–O(4')	104·0		C(5')–C(4')–C(3')	117·4
C(4')–O(4')–C(1')	109·4		C(4')–C(5')–O(5')	114·4

Morpholine

N(10)–C(11)	1·475		C(12)–O(13)	1·438
N(10)–C(15)	1·460		O(13)–C(14)	1·438
C(11)–C(12)	1·510		C(14)–C(15)	1·509

C(11)–N(10)–C(15)	109·8		C(11)–C(12)–O(13)	111·3
C(11)–N(10)–C(8)	117·5		C(12)–O(13)–C(14)	109·7
C(15)–N(10)–C(8)	113·6		O(13)–C(14)–C(15)	111·5
N(10)–C(11)–C(12)	109·1		C(14)–C(15)–N(10)	109·0

Table 3. *Conformational parameters in the nucleoside moiety of* 9-β-D-*arabinofuranosyl-8-morpholinoadenine dihydrate*

The e.s.d.'s are about 0·4° for the torsion angles.

Glycosyl angle	χ	$-142\cdot1°$
Ribose ring torsions	τ_0	$-4\cdot6$
	τ_1	$-21\cdot6$
	τ_2	$37\cdot5$
	τ_3	$-41\cdot2$
	τ_4	$29\cdot3$
Sugar pucker		$^3T_4$
Phase angle of pseudorotation	P	$24\cdot5$
Maximum amplitude of pucker	τ_m	$42\cdot1$
C(3')–C(4')–C(5')–O(5')	ψ	$53\cdot0$
C(4')–C(5')–O(5')–H(O5')		$16\cdot4$

(Johnson, 1965) drawing of the molecule depicting 50% probability surfaces of the non-hydrogen atoms. Table 2 gives the bond lengths and angles. The average estimated standard deviation in the C—C, C—O and C—N bond lengths is 0·003 Å and in bond angles, 0·018°. The pertinent conformational parameters are listed in Table 3.

Discussion

Geometry of the base

The bond distances and angles in the pyrimidine part of the adenine ring are in good agreement with the average values found for the neutral base in other nucleoside structures (Voet & Rich, 1970). A notable departure from the dimensions of these adenine systems occurs in the imidazole part. The C(8)—N(9) bond length of 1·391 (3) Å is significantly longer than the average bond length (1·365 Å) in adenosine structures. This is probably due to the non-bonded interaction between the sugar and the substituent at C(8). The exocyclic angles at N(9), *viz* C(4)—N(9)—C(1') and C(8)—N(9)—C(1'), are 128·9 and 125·7° respectively which are in good agreement with the average values of 129·3 and 124·7° found in purine nucleosides with the *syn* conformation (Sprang, Scheller, Rohrer & Sundaralingam, 1978). The exocyclic angles at C(8) are close to those found in the unsubstituted adenine derivatives.

The purine ring is planar. Atoms N(1) and N(3) show the largest deviations from planarity (0·030 and 0·025 Å respectively) with deviations to opposite sides of the plane. The substituents N(6) and N(10) are displaced on the same side of the plane by 0·022 and 0·035 Å respectively, while C(1') is displaced significantly on the opposite side by 0·125 Å.

Glycosyl conformation

The glycosyl torsion angle χ [O(4')—C(1')—N(9)—C(8)] is $-142\cdot12°$. Thus the base is in the *syn* conformation with respect to the sugar. The *syn* conformation is apparently favored because of the steric interactions of the bulky morpholino group at the C(8) position of the base. Although the *syn* conformation is common in both C(8)-substituted and unsubstituted purine ribonucleosides and deoxyribonucleosides (Sundaralingam, 1975a), this is the first report of an arabinonucleoside in the *syn* conformation.

Geometry and conformation of the sugar

The bond lengths and angles of the arabinose moiety in 8-morpholino-ara-A are in reasonably good agreement with the average values found in the known

arabinonucleosides (Bunick & Voet, 1974; Sundaralingam, 1975b). A slight deviation is found in the geometry about the C(3') atom when compared with other known arabinonucleosides in the C(3')-endo conformation, viz 9-β-D-arabinofuranosyl-4-thiouracil (Saenger, 1972), 9-β-D-arabinofuranosyladenine (Bunick & Voet, 1974), 9-β-D-arabinofuranosyladenine hydrochloride (Chwang & Sundaralingam, 1974) and ara-CMP (Sherfinski, Marsh, Chwang & Sundaralingam, 1979); the endocyclic angle C(4')—C(3')—C(2') (100·2°) in 8-morpholino-ara-A is significantly smaller than the corresponding values found in the other compounds (101·6, 102·0, 101·6, 102·0°), while the exocyclic angle C(4')—C(3')—O(3') (115·56°) is significantly larger (113·3, 109·0, 112·5 and 113·4°). These differences may be attributed to the intramolecular hydrogen bonding and the syn conformation in 8-morpholino-ara-A.

The arabinose ring is in the C(3')-endo,C(4')-exo ($^3T_4$) conformation. The conformation about the exocyclic C(4')—C(5') bond is gauche$^+$ with a ψ value of 53°. The 5'-hydroxy bond O(5')—H(O5') is rotated (Table 3) from the usual trans conformation to form the intramolecular hydrogen bond with N(3) of the base. The dihedral angle between the best four-atom plane of the sugar and the adenine ring is 99·5°. As a rule the syn conformation about the glycosyl bond, the gauche$^+$ conformation about the C(4')—C(5') bond and the O(5')H···N(3) intramolecular hydrogen bond are coupled with the C(2')-endo pucker of the sugar in purine nucleosides (Rao & Sundaralingam, 1970). The present structure and 2-methylformycin (Abola, Sims, Abraham, Lewis & Townsend, 1974) are exceptions in that the above conformational features are coupled with a C(3')-endo pucker. On the other hand, formycin hydrobromide monohydrate (Koyama, Umezawa & Iitaka, 1974), which exhibits the C(2')-endo sugar pucker, has a trans conformation about the C(4')—C(5') bond. It could be that for arabinosides in the syn conformation, the C(3')-endo pucker is more favored.

Geometry and conformation of the morpholino ring

There is only one other report of a structure containing the morpholino moiety, viz 2-morpholinomethyl-5H-dibenzo[b,f]azepine (Carpy, Gadret, Goursolle, Leger & Lehuede, 1979). A comparison of the bond lengths and angles in the morpholino moiety in this structure and 8-morpholino-ara-A shows reasonably good agreement. However, the exocyclic angle C(8)—N(10)—C(11) in 8-morpholino-ara-A is significantly larger (117·5°) than the other values. This widening of the angle can be attributed to the non-bonded interaction between the sugar and the morpholino ring. A comparison can also be made with the dimensions of the morpholinium ion in morpholinium nitrate (Swaminathan & Murthy, 1976)

Table 4. Conformational parameters in morpholino and morpholinium rings

The e.s.d.'s are about 0·4° for the torsion angles of the title compound.

Ring torsions

	(i)	(ii)	(iii)	(iv)	(v)
N(10)—C(11)	−58·5°	−60·0°	−53·8°	−55·2°	−55·3°
C(11)—C(12)	58·5	59·9	60·1	58·9	58·0
C(12)—O(13)	−58·2	−57·7	−64·5	−63·7	−60·4
O(13)—C(14)	58·4	56·2	63·2	63·4	60·7
C(14)—C(15)	−58·9	−56·5	−56·8	−58·8	−58·6
C(15)—N(10)	58·5	58·1	51·9	55·5	55·7

Cremer & Pople puckering parameters

Q	0·583 Å	0·571 Å	0·589 Å	0·594 Å	0·574 Å
θ	178·6°	175·7°	174·8°	177·2°	178·8°
φ	0·8	45·9	160·3	178·5	214·1

Other torsion angles of interest

	(i)	(ii)
N(7)—C(8)—N(10)—C(11)	114·8°	
N(7)—C(8)—N(10)—C(15)	−15·21	
N(9)/C—C(8)—N(10)—C(11)	−69·9	−65·5°
N(9)/C—C(8)—N(10)—C(15)	159·9	175·3
C(8)—N(10)—C(15)—C(14)	−167·6	−179·0
C(8)—N(10)—C(11)—C(12)	169·5	178·6

References: (i) Present study. (ii) 2-Morpholinomethyl-5H-dibenzo[b,f]-azepine (Carpy et al., 1979). (iii) Morpholinium nitrate (Swaminathan & Murthy, 1976). (iv) 1:1 Morpholinium–TCNQ (Sundaresan & Wallwork, 1972a). (v) 2:3 Morpholinium–TCNQ (Sundaresan & Wallwork, 1972b).

and two other salts of morpholinium 7,7,8,8-tetracyano-p-quinodimethanide (TCNQ) (Sundaresan & Wallwork, 1972a,b). The two C—O distances in 8-morpholino-ara-A are equal (1·438 Å) and compare well with those in morpholinium nitrate (1·433 and 1·446 Å). The corresponding distances in the morpholinium TCNQ salts are somewhat shorter. The C—O—C bond angle and the C—C distances in all these structures are in good agreement.

The morpholino ring in 8-morpholino-ara-A assumes an ideal chair conformation with the torsion angles very nearly equal in magnitude. The substituent C(8) at the N atom is in the equatorial position with the N lone-pair electrons in the axial position. A similar conformation is observed in 2-morpholinomethyl-5H-dibenzo[b,f]azepine (Carpy et al., 1979). Table 4 gives the conformational parameters in the morpholino and morpholinium rings in the above-mentioned structures. The torsion angles about the two C—N bonds in the morpholinium rings are smaller than the corresponding angles in the morpholino rings while those about the two C—O bonds are larger. The morpholinium rings are thus more flattened at the N apex due to the presence of the quarternary N atom and sharpened at the O end.

The Cremer & Pople (1975) puckering parameters Q, θ and φ (where Q is the puckering amplitude and θ and φ are the phase angles) are also listed in Table 4.
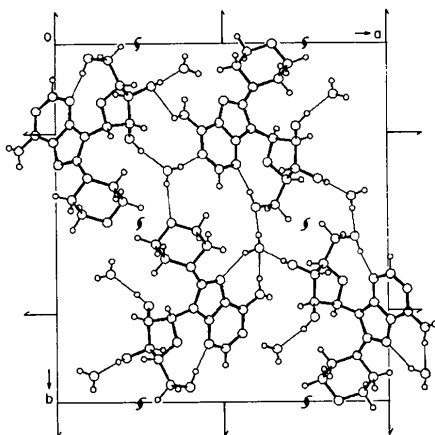
Fig. 2. A view down the c axis showing the contents of the unit cell and the intramolecular and intermolecular hydrogen bonds.

Table 5. *Hydrogen-bond distances* (Å) *and angles* (°) *in   9-β-D-arabinofuranosyl-8-morpholinoadenine   dihydrate*

D–H···A	Symmetry for A	D···A (σ 0·003 Å)	H···A (σ 0·03 Å)	$\angle D$–H···A (σ 2°)
O(5′)–H(O5′)···N(3)	(i)	2·739	1·84	169
O(2′)–H(O2′)···O(W2)	(i)	2·686	1·81	167
O(3′)–H(O3′)···O(W1)	(i)	2·741	1·95	169
N(6)–H(6)1···O(W1)	(ii)	2·926	2·07	160
N(6)–H(6)2···O(3′)	(iii)	2·953	2·47	123
O(W1)–H(W1)1···O(5′)	(iv)	2·686	1·96	161
O(W1)–H(W1)2···N(7)	(v)	2·790	2·03	153
O(W2)–H(W2)1···O(13)	(vi)	2·869	2·26	138
O(W2)–H(W2)2···N(1)	(vii)	2·799	1·90	166

Symmetry code

(i)	x, y, z	(v)	$-\frac{1}{2}+x, \frac{1}{2}-y, 2-z$
(ii)	$\frac{1}{2}+x, \frac{1}{2}-y, 2-z$	(vi)	$\frac{1}{2}-x, 2-y, -\frac{1}{2}+z$
(iii)	$\frac{1}{2}+x, \frac{1}{2}-y, 1-z$	(vii)	$-\frac{1}{2}-x, 1-y, \frac{1}{2}+z$
(iv)	$\frac{1}{2}-x, 1-y, \frac{1}{2}+z$		

Hydrogen bonding and molecular packing

All the potential hydrogen-bonding sites on the arabinose, the base and the two water molecules in the structure take part in hydrogen bonding. Fig. 2 shows the hydrogen bonding and molecular packing in 8-morpholino-ara-A. The distances and angles involved in hydrogen bonding are given in Table 5.

The hydroxyl oxygen O(5′) of the arabinose forms an intramolecular hydrogen bond with N(3) of the base [O(5′)···N(3) = 2·737 Å], a feature that has been observed in many purine nucleosides with *syn* conformation. One of the water molecules, O(W1), forms four hydrogen bonds, two of which are to the N(6) and N(7) atoms of the same base. The other, O(W2), forms three hydrogen bonds to three neighboring nucleoside molecules and one of them is with the O(13) atom of the morpholine ring.

Base-stacking interactions are not very significant. The two closest van der Waals approaches of 3·145

and 3·154 Å are between the sugar-ring oxygen O(4′) and the base atoms C(2) and N(3) of a neighboring molecule.

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