JOESTON, M. D. & SHAAD, L. J. (1974). *Hydrogen Bonding*, pp. 287–290. New York: Marcel Dekker.
LEISEROWITZ, L. (1976). *Acta Cryst.* B**32**, 775–802.
LIN, C. T., PAUL, I. C. & CURTIN, D. Y. (1974). *J. Am. Chem. Soc.* **96**, 3699–3701.
MAURIN, J. K., PAUL, I. C. & CURTIN, D. Y. (1992*a*). *Acta Cryst.* C**48**. In the press.
MAURIN, J. K., PAUL, I. C. & CURTIN, D. Y. (1992*b*). *Acta Cryst.* C**48**. In the press.
MAURIN, J. K., PAUL, I. C. & CURTIN, D. Y. (1992*c*). *Acta Cryst.* C**48**, 1819–1821.
MAURIN, J. K., PAUL, I. C. & CURTIN, D. Y. (1992*d*). *Acta Cryst.* C**48**, 1821–1823.
OSSART, A., SAUVAITRE, H. & PINEAU, P. (1967). *J. Chim. Phys. Phys. Chim. Biol.* **64**, 953–956.
PADMANABHAN, K., PAUL, I. C. & CURTIN, D. Y. (1989). *Acta Cryst.* B**45**, 411–416.
PATIL, A. O., CURTIN, D. Y. & PAUL, I. C. (1984). *J. Am. Chem. Soc.* **106**, 348–353.
PATIL, A. O., CURTIN, D. Y. & PAUL, I. C. (1985). *Isr. J. Chem.* **25**, 320–326.
PATIL, A. O., CURTIN, D. Y. & PAUL, I. C. (1986). *J. Chem. Soc. Perkin Trans.* 2, pp. 1687–1692.
PENNINGTON, W. T., PATIL, A. O., CURTIN, D. Y. & PAUL, I. C. (1986). *J. Chem. Soc. Perkin Trans.* 2, pp. 1693–1700.
RASTOGI, R. P., SINGH, N. B. & SINGH, R. P. (1977). *J. Solid State Chem.* **20**, 191–200.
SINGH, N. B. & SINGH, R. P. (1981). *J. Solid State Chem.* **38**, 211–218.
SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.
SHELDRICK, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
WALBORSKY, H. M., BARSH, L., YOUNG, A. E. & IMPASTATO, F. J. (1961). *J. Am. Chem. Soc.* **83**, 2517–2525.

Acta Cryst. (1993). B**49**, 96–101

Structural Studies on DNA-Binding Drugs: Crystal Structure and Molecular Dynamics Studies of Triazoloacridinones

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Abstract

Structural and conformational studies on two 8-substituted triazoloacridinone antitumor agents, C1295 and C1303, have been carried out to compare the conformation of the (aminoalkyl)amino side chain and the effect of C-8 substitution. Crystal data for 5-[2-(diethylamino)ethylamino]-8-methyl-6*H*-[1,2,3]-triazolo[4,5,1-*de*]acridin-6-one (C1295), $C_{20}H_{23}N_5O$, $M_r = 349.4$, triclinic, $P\bar{1}$, $a = 12.200\ (1)$, $b = 14.890\ (1)$, $c = 5.185\ (1)$ Å, $\alpha = 93.54\ (1)$, $\beta = 102.21\ (1)$, $\gamma = 80.61\ (1)°$, $V = 907.9\ (1)$ Å^3, $Z = 2$, $D_x = 1.278$ g cm^{-3}, λ(Cu $K\alpha$) = 1.54178 Å, $\mu = 6.2$ cm^{-1}, $F(000) = 372$, $T = 293$ K, $R = 0.061$ for 1631 observed reflections; for 5-[2-(diethylamino)-ethylamino]-8-hydroxy-6*H*-[1,2,3]triazolo[4,5,1-*de*]-acridin-6-one (C1303), $C_{17}H_{17}N_5O_2$, $M_r = 323.4$, monoclinic, $P2_1/n$, $a = 15.823\ (2)$, $b = 5.790\ (1)$, $c = 16.856\ (2)$ Å, $\beta = 98.59\ (1)°$, $V = 1526.9\ (2)$ Å^3, $Z = 4$, $D_x = 1.404$ g cm^{-3}, λ(Cu $K\alpha$) = 1.54178 Å, $\mu = 7.5$ cm^{-1}, $F(000) = 680$, $T = 293$ K, $R = 0.054$ for 1303 observed reflections. There is a difference in the orientation of the (aminoalkyl)amino side chain in the two compounds in the solid state, but molecular dynamics simulations indicate that in the gas phase the orientation is very similar. This difference could result from the different crystal packing in the case of C1303, due to the presence of an intermolecular hydrogen bond. Preliminary drug–DNA modeling studies indicate that the higher biological activity of C1303 may be attributed to the availability of the OH group which could form an extra hydrogen bond with DNA.

Introduction

There has been great interest recently in the development of synthetic antineoplastic agents that complex with DNA (Zee-Cheng & Cheng, 1978; Zee-Cheng, Podrebarac, Mennon & Cheng, 1979; Showalter, Johnson, Werbel, Leopold, Jackson & Elslager, 1984). The availability of a large number of synthetic intercalating antitumor drugs has led to renewed interest in the mode of action of intercalators. Structural studies show that the DNA-intercalating agents currently under development as antitumor drugs share the common structural feature of an aromatic

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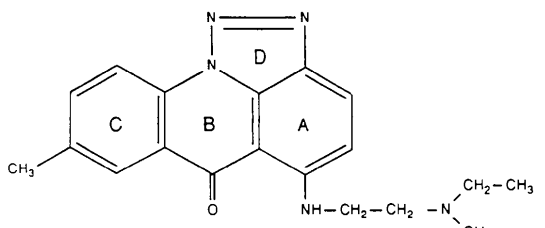
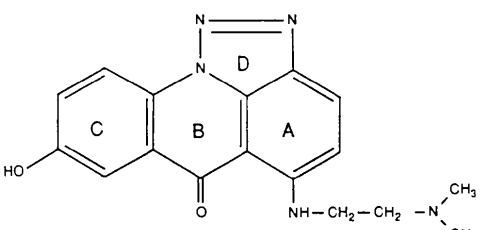
nucleus to which are attached either one or two flexible side chains. Anthracenediones (ametantrone, mitoxantrone), anthrapyrazoles, pyrazoloacridines, and acridine-4-carboxamides are other drugs that belong to this broad class of compounds. The presence of an (aminoalkyl)amino side chain at a strictly defined position is crucial for the biological activity of these compounds, and the distance between the amino groups plays an important role.

Triazoloacridinones (Chalody, Martelli & Kanopa, 1990) belong to the imidazoacridinone class of compounds in which the acridine chromophore is modified by the addition of an extra five-membered triazolo ring and a variable substitution at C-8. The (aminoalkyl)amino side chains, which are important for biological activity, are present. The hypothesized role of the added pyrazole ring is to increase the electron density of the system and to make the chromophore more resistant to enzymatic reduction to radical species (Showalter, Fry, Leopold, Lown, Plambeck & Reszka, 1986). In order to study structure–activity dependence, we have carried out crystal structure and molecular dynamics studies on two of these compounds, namely C1295 and C1303, which have different substituents at C-8 (see scheme below).



C1295



C1303

Experimental

Both 8-Me and 8-OH substituted 5-[(aminoalkyl)-amino]-6*H*-*v*-triazolo[4,5,1-*de*]acridin-6-ones, (C1295 and C1303), were synthesized as described earlier (Chalody, Martelli & Kanopa, 1990). Needle-shaped crystals of both compounds were grown from mixtures of methanol and chloroform by slow evaporation. Lattice cell parameters and the intensities were measured at 292 K on a Rigaku AFC-5 diffractometer using the $\omega/2\theta$ scan mode to a 2θ value of 120.0°. The intensities of three standard reflections were measured every 100 reflections and showed a variation of less than 3% during the data collection. Lorentz and polarization corrections were applied, but no correction was made for absorption.

Table 1. *Summary of crystal data*

	C1295	C1303
Formula	$C_{20}H_{23}N_5O$	$C_{17}H_{17}N_5O_2$
M_r	349.4	323.4
a (Å)	12.200 (1)	15.823 (2)
b (Å)	14.890 (1)	5.790 (1)
c (Å)	5.185 (1)	16.856 (2)
α ( )	93.54 (1)	90.00
β ( )	102.21 (1)	98.59 (1)
γ ( )	80.61 (1)	90.00
Crystal system	Triclinic*	Monoclinic
Space group	$P\bar{1}$	$P2_1/n$
V (Å^3)	907.9 (1)	1526.9 (2)
Z	2	4
D_x (g cm^{-3})	1.278	1.404
μ(Cu $K\alpha$) (cm^{-1})	6.2	7.5
$F(000)$	372	680
T (K)	292	292
Reflections collected	2841	2633
Unique data $>3\sigma(I)$	1631	1303
Range of		
h	0 to 13	0 to 17
k	−15 to 16	0 to 6
l	−5 to 5	−17 to 15
R_{int}	0.009	0.011
R (%)	6.1	5.4
wR (%)	6.2	5.5
$(\Delta/\sigma)_{max}$	0.04	0.03
$\Delta\rho_{max}$	0.20	0.35
$\Delta\rho_{min}$	0.19	0.24
No. of parameters	303	267

* The standard reduced-cell parameters are: a = 5.185, b = 12.200, c = 14.890 Å, α = 80.61, β = 86.46, γ = 77.79 .

Both structures were solved by the direct-methods program *SHELXS*86 (Sheldrick, 1985). The structures were refined by the full-matrix least-squares method (based on F_o) using the *SHELX*76 programs (Sheldrick, 1976). The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = \sigma^{-2}$. All the H atoms were located from difference Fourier synthesis and were included in the refinement with isotropic thermal parameters. The coordinates of all the atoms, anisotropic thermal parameters for the non-H atoms, and isotropic thermal parameters for the H atoms were varied. A summary of the crystal data and structure refinement is given in Table 1.*

50 picoseconds (ps) molecular dynamics calculations on C1295 and C1303 were carried out using the *QUANTA/CHARMM* software (Polygen Corporation, Waltham, MA) running on a Silicon Graphics Iris computer. Energy-minimized (by the adopted-basis Newton–Raphson method, ABNR) structures

* Lists of structure factors, H-atom coordinates, bond lengths and angles involving H atoms, and anisotropic thermal parameters for non-H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55426 (34 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: HH0624]

Table 2. *Fractional coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($Å^2 \times 10^4$) *for* C1295 *and* C1303

$$B_{eq} = (1/3)\Sigma_i \Sigma_j B_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j .$$

	x	y	z	B_{eq}
C1295				
N1	3283 (3)	630 (2)	−1957 (7)	33 (1)
C2	2636 (4)	−205 (3)	460 (9)	38 (1)
C3	1903 (4)	−356 (3)	2109 (10)	44 (2)
C4	1092 (4)	349 (3)	2576 (9)	42 (2)
C5	941 (4)	1237 (3)	1501 (8)	36 (1)
C6	1718 (4)	2231 (3)	−1365 (8)	34 (1)
C7	2676 (4)	2948 (3)	−4319 (8)	36 (1)
C8	3463 (4)	2954 (3)	−5863 (9)	38 (1)
C9	4208 (4)	2168 (3)	−6099 (9)	40 (2)
C10	4175 (4)	1383 (3)	−4845 (9)	39 (1)
C11	2483 (3)	654 (3)	−512 (8)	32 (1)
C12	1686 (3)	1396 (3)	−120 (8)	31 (1)
C13	3370 (4)	1397 (3)	−3301 (8)	34 (1)
C14	2603 (3)	2187 (3)	−2987 (8)	32 (1)
N15	3902 (3)	−235 (2)	−1959 (8)	43 (1)
N16	3507 (3)	−729 (3)	−485 (8)	46 (1)
O17	1057 (2)	2946 (2)	−1128 (6)	40 (1)
C18	3528 (6)	3802 (4)	−7200 (12)	55 (2)
N19	130 (3)	1901 (3)	1987 (8)	39 (1)
C20	−645 (4)	1864 (3)	3729 (10)	41 (2)
C21	−1198 (4)	2822 (3)	4372 (10)	42 (2)
N22	−1909 (3)	3263 (3)	2044 (7)	42 (1)
C23	−1926 (5)	4260 (4)	2303 (13)	58 (2)
C24	−914 (6)	4535 (5)	1607 (24)	84 (3)
C25	−3070 (4)	3036 (4)	1715 (10)	51 (2)
C26	−3774 (6)	3192 (7)	−1019 (15)	86 (3)
C1303				
N1	1563 (2)	1631 (8)	−878 (3)	36 (1)
C2	1859 (3)	4636 (10)	−1562 (3)	35 (1)
C3	2420 (4)	6214 (10)	−1838 (3)	39 (2)
C4	3284 (3)	5905 (10)	−1623 (3)	36 (2)
C5	3641 (3)	4056 (9)	−1110 (3)	32 (1)
C6	3300 (3)	539 (9)	−289 (3)	30 (1)
C7	2717 (3)	−2615 (10)	463 (3)	34 (1)
C8	2073 (3)	−3945 (10)	678 (3)	38 (2)
C9	1225 (3)	−3439 (11)	342 (3)	39 (2)
C10	1039 (4)	−1626 (11)	−170 (3)	39 (2)
C11	2219 (3)	2897 (9)	−1074 (3)	34 (1)
C12	3084 (3)	2469 (9)	−818 (3)	30 (1)
C13	1700 (3)	−280 (9)	−366 (3)	30 (1)
C14	2556 (3)	−769 (9)	−64 (3)	30 (1)
N15	796 (3)	2570 (9)	−1251 (3)	42 (1)
N16	983 (3)	4386 (9)	−1661 (3)	43 (1)
O17	4046 (2)	−39 (6)	−32 (2)	39 (1)
O18	2222 (3)	−5764 (7)	1188 (3)	50 (1)
N19	4493 (3)	3801 (8)	−900 (3)	34 (1)
C20	5133 (3)	5407 (11)	−1112 (3)	34 (1)
C21	5412 (3)	4737 (10)	−1912 (3)	35 (2)
N22	6181 (3)	5962 (8)	−2071 (3)	36 (1)
C23	6406 (5)	5020 (15)	−2823 (5)	54 (2)
C24	6045 (4)	8446 (11)	−2117 (5)	46 (2)

Table 3. *Bond lengths* (Å) *and angles* (°) *for* C1295 *and* C1303, *with e.s.d.'s in parentheses*

C1295

N1—C11	1.346 (5)	C8—C9	1.377 (6)
N1—C13	1.404 (6)	C8—C18	1.498 (7)
N1—N15	1.383 (5)	C9—C10	1.382 (7)
C2—C3	1.411 (6)	C10—C13	1.389 (6)
C2—C11	1.374 (6)	C11—C12	1.383 (6)
C2—N16	1.372 (6)	C13—C14	1.403 (6)
C3—C4	1.368 (6)	N15—N16	1.304 (5)
C4—C5	1.435 (6)	N19—C20	1.448 (6)
C5—C12	1.416 (6)	C20—C21	1.524 (7)
C5—N19	1.334 (6)	C21—N22	1.453 (6)
C6—C12	1.446 (6)	N22—C23	1.480 (7)
C6—C14	1.493 (6)	N22—C25	1.481 (7)
C6—O17	1.244 (5)	C23—C24	1.481 (11)
C7—C8	1.375 (6)	C25—C26	1.504 (10)
C7—C14	1.388 (6)		

N15—N1—C11	109.9 (3)	N1—C11—C12	126.4 (4)
N15—N1—C13	128.8 (3)	C2—C11—C12	128.3 (4)
C11—N1—C13	121.2 (4)	C5—C12—C6	128.1 (4)
N16—C2—C3	134.9 (4)	C5—C12—C11	114.9 (4)
N16—C2—C11	108.4 (4)	C6—C12—C11	117.0 (4)
C3—C2—C11	116.6 (4)	N1—C13—C10	122.2 (4)
C2—C3—C4	118.2 (5)	N1—C13—C14	116.3 (4)
C3—C4—C5	124.0 (5)	C10—C13—C14	121.5 (4)
C4—C5—C12	118.0 (4)	C6—C14—C7	119.9 (4)
N19—C5—C4	122.0 (4)	C6—C14—C13	123.3 (4)
N19—C5—C12	120.0 (4)	C7—C14—C13	116.9 (4)
O17—C6—C12	122.9 (4)	N1—N15—N16	107.2 (3)
O17—C6—C14	121.3 (4)	N15—N16—C2	109.1 (4)
C12—C6—C14	115.8 (4)	C5—N19—C20	126.6 (4)
C8—C7—C14	123.0 (4)	N19—C20—C21	110.2 (4)
C7—C8—C9	118.4 (4)	N22—C21—C20	111.9 (4)
C7—C8—C18	120.9 (4)	C21—N22—C23	110.2 (4)
C9—C8—C18	120.7 (4)	C21—N22—C25	108.9 (4)
C8—C9—C10	121.6 (4)	C23—N22—C25	110.8 (4)
C9—C10—C13	118.7 (4)	N22—C23—C24	112.1 (6)
N1—C11—C2	105.3 (4)	N22—C25—C26	113.6 (5)

C1303

N1—C11	1.351 (6)	C7—C8	1.369 (7)
N1—C13	1.400 (7)	C8—O18	1.358 (8)
N1—N15	1.391 (6)	C8—C9	1.407 (8)
C2—C11	1.369 (8)	C9—C10	1.363 (9)
C2—C3	1.401 (7)	C10—C13	1.383 (7)
C2—N16	1.379 (7)	C11—C12	1.395 (8)
C3—C4	1.379 (9)	C13—C14	1.403 (8)
C4—C5	1.438 (8)	N15—N16	1.316 (7)
C5—N19	1.350 (8)	N19—C20	1.458 (7)
C5—C12	1.412 (6)	C20—C21	1.530 (7)
C6—O17	1.241 (7)	C21—N22	1.467 (7)
C6—C12	1.439 (8)	N22—C23	1.472 (9)
C6—C14	1.496 (6)	N22—C24	1.455 (8)
C7—C14	1.389 (8)		

C13—N1—C11	122.7 (4)	N1—C11—C12	125.6 (5)
N15—N1—C11	109.1 (5)	N1—C11—C2	106.3 (4)
N15—N1—C13	129.2 (4)	C2—C11—C12	128.1 (5)
C3—C2—C11	116.9 (5)	C6—C12—C11	117.5 (5)
N16—C2—C11	108.4 (5)	C5—C12—C6	128.2 (4)
N16—C2—C3	134.7 (6)	C5—C12—C11	114.3 (5)
C2—C3—C4	118.9 (6)	N1—C13—C14	115.8 (4)
C3—C4—C5	122.8 (6)	N1—C13—C10	122.7 (5)
C12—C5—N19	119.2 (5)	C10—C13—C14	121.5 (5)
C4—C5—N19	121.8 (5)	C6—C14—C13	124.0 (5)
C4—C5—C12	119.0 (5)	C6—C14—C7	118.4 (5)
C12—C6—O17	123.2 (5)	C7—C14—C13	117.5 (5)
C14—C6—O17	121.0 (5)	N1—N15—N16	107.5 (4)
C14—C6—C12	115.3 (4)	C2—N16—N15	108.7 (5)
C8—C7—C14	122.0 (5)	C5—N19—C20	124.7 (5)
C7—C8—O18	122.6 (5)	N19—C20—C21	110.9 (5)
C9—C8—O18	118.8 (5)	C20—C21—N22	113.3 (5)
C7—C8—C9	118.6 (6)	C21—N22—C23	107.0 (5)
C8—C9—C10	121.2 (6)	C21—N22—C24	111.6 (5)
C9—C10—C13	119.1 (5)	C23—N22—C24	111.9 (6)

(using X-ray coordinates) were used for dynamics simulations. The *SHAKE* algorithm (Van Gunsteren, 1977) was used for constraining all bonds containing H atoms. The integration time step was 0.001 ps with a bath temperature of 300 K. The coordinates of all atoms were written out for analysis every 1000 steps to a total of 50 000 steps. The final 50 structures were energy minimized by ABNR. The modeling studies on the complexes of the drugs with DNA using molecular mechanics were carried out by the software *MACROMODEL*3.0 (Still *et al.*, 1989). AMBER force-field parameters (Weiner *et al.*, 1984) were used. The hexanucleotide duplex structure $d(CGTACG)_2$ was constructed in the *B* form using the *NUCLEI* template in the *MACROMODEL*3.0 software. The drug–DNA models were prepared by intercalating the energy-minimized structures of the drugs (above) between the central bases in the duplex $d(CGTACG)_2$ and were energy minimized using the block-diagonal Newton–Raphson minimization procedure. A united atom force field was used. A

distance-dependent dielectric constant was used in all calculations. The models were minimized to an r.m.s. first derivative of 0.1 kJ $Å^{-1}$.

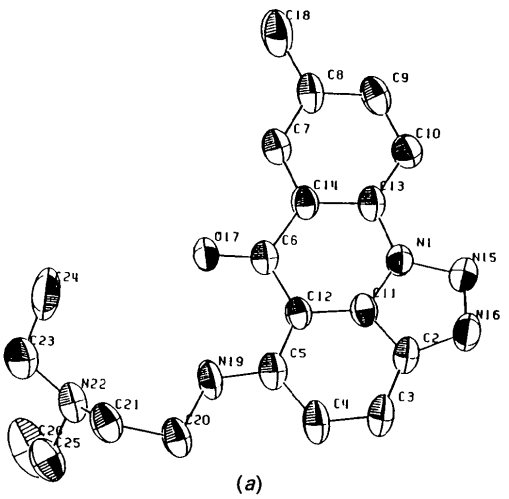
Results and discussion

The final fractional and equivalent isotropic thermal parameters for the non-H atoms are given in Table 2. Bond distances and angles involving non-H atoms are given in Table 3. Table 4 gives the torsion angles for the (aminoalkyl)amino side chain from X-ray studies and molecular dynamics (MD).

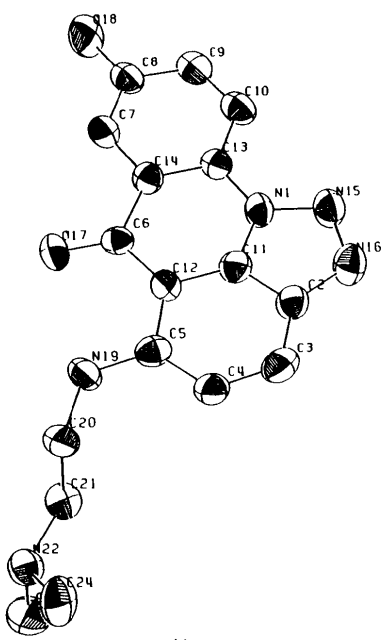
Table 4. *Torsion angles (°) for the (aminoalkyl)amino side chain*

	C1295		C1303	
	X-ray	MD	X-ray	MD
C4—C5—N19—C20	4.3	1.4	4.1	−3.7
C12—C5—N19—C20	−175.7	−177.8	−175.1	−179.6
C5—N19—C20—C21	163.5	179.5	−90.3	178.3
N19—C20—C21—N22	64.5	−37.2	−167.4	−43.8
C20—C21—N22—C23	−149.7	−72.5	−61.3	−67.0
C20—C21—N22—C24			−175.8	164.0
C20—C21—N22—C25	88.5	152.5		
C21—N22—C23—C24	81.5	144.2		
C21—N22—C25—C26	−161.5	−80.6		

Figs. 1(*a*) and 1(*b*) show the stereochemistry of C1295 and C1303, respectively, in their crystal structures. The acridine chromophore is nearly planar in both compounds with maximum deviations from the least-squares plane, defined by the 14 atoms, being 0.03 and 0.06 Å, respectively. The two outer rings of



(*a*)



(*b*)

Fig. 1. (*a*) Stereochemistry of C1295. (*b*) Stereochemistry of C1303.

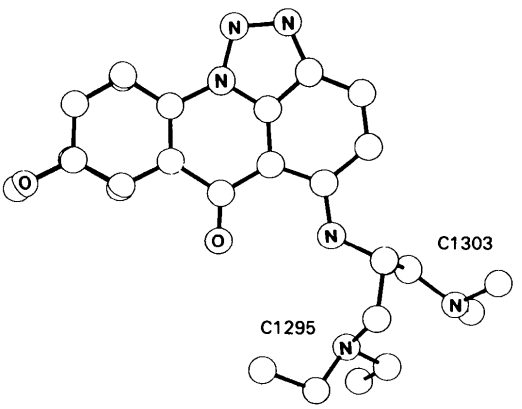


Fig. 2. Best molecular fitting of C1295 and C1303.

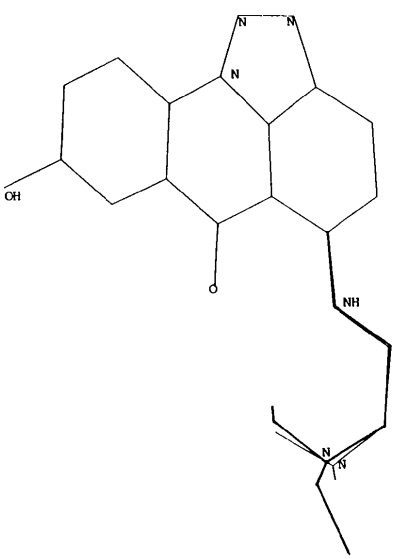
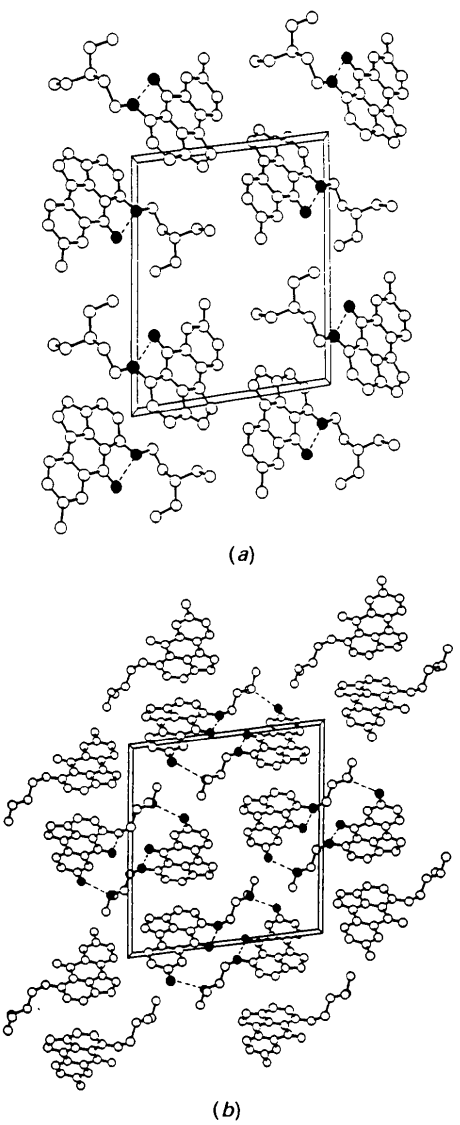


Fig. 3. Energy-minimized structures of C1295 and C1303 from molecular dynamics (overlapped).

the chromophore are inclined at dihedral angles of 0.3 and 0.9° (C1295) and 1.4 and 2.1° (C1303) to the central heterocyclic ring. In both compounds, the triazolo ring *D* is nearly planar with the acridine ring, with deviations of 0.04 and 0.10 Å for N2 and 0.06 and 0.13 Å for N3, respectively, from the chromophore least-squares plane.

The N19—C20 bond is coplanar with the aromatic nucleus, and this part of the geometry of the molecule is governed by a strong intramolecular hydrogen bond between N19 and O17 in both compounds, with distances of 2.822 and 2.788 Å, respectively. However, the overall conformation of the (aminoalkyl)amino side chain is different in the two structures. Table 4 gives the torsion angles in the side chain. There are large differences in the angles C5—N19—C20—C21 (161.8 and −90.3°) and N19—C20—C21—N22 (66.3 and −167.4°) in the two structures, as depicted in Fig. 2, but the energy-minimized structures of C1295 and C1303 from the molecular dynamics calculations (Fig. 3) indicate that there is no major difference in the side-chain conformation between the two molecules (C1295 and C1303). Thus, the difference in the orientation of the side chain is most probably due to crystal packing forces which in case of C1303 are influenced by the intermolecular hydrogen bond (2.712 Å) involving O18(x, y, z) as donor and N22($-x$, $-y$, $-z$) as acceptor. Figs. 4(*a*) and 4(*b*) show the unit-cell packing of C1295 and C1303, respectively.



(*a*)

(*b*)

Fig. 4. (*a*) Packing diagram for C1295. (*b*) Packing diagram for C1303.

There is no sequence-specificity information available for the interaction of these drugs with DNA. We have carried out preliminary modeling studies on drug–DNA complexes. Figs. 5 and 6 show the best molecular mechanics energy-minimized models for the interaction of C1295 and C1303 with oligodeoxynucleotide d(CGTACG)$_2$ using the *MACROMODEL*3.0 software package. In the case of the C1303–DNA complex (E = −2514 kJ), the

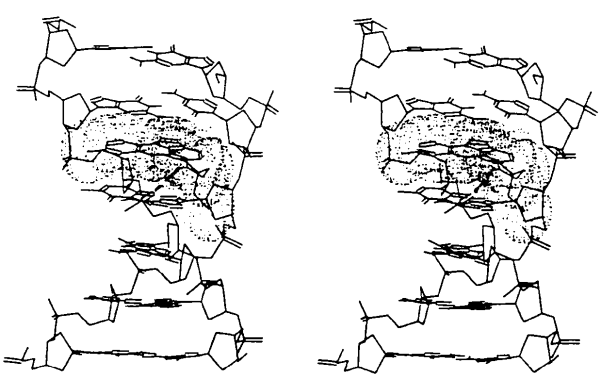


Fig. 5. Energy-minimized model of C1295–DNA complex.

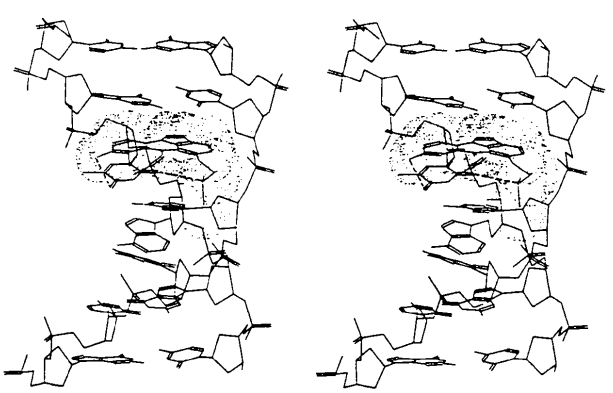


Fig. 6. Energy-minimized model of C1303–DNA complex.

drug seems to bind through two hydrogen bonds, one involving O18 of the drug and O2 of Thy3 of the base pair below (2.89 Å), and one involving N22 and O4 of Thy3 of the base pair below (2.99 Å). In the case of the C1295 complex ($E = -2480$ kJ), which has no hydroxyl group at the 8 position, it is N19 of the drug that is involved in hydrogen bonding with O4 of Thy3 with a distance of 3.03 Å. The extra hydrogen bonding in the case of C1303 could be a possible reason for the better activity of C1303 and thus the lower energy of its complex with DNA.

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References

CHALODY, M. C., MARTELLI, S. & KANOPA, J. (1990). *J. Med. Chem.* **33**, 49–52.

SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

SHELDRICK, G. M. (1985). *SHELXS86*. In *Crystallographic Computing* 3, edited by G. M. SHELDRICK, C. KRÜGER & R. GODDARD, pp. 175–189. Oxford Univ. Press.

SHOWALTER, H. D. H., FRY, D. W., LEOPOLD, W. R., LOWN, J. W., PLAMBECK, J. A. & RESZKA, K. (1986). *Anticancer Drug Des.* **1**, 73–85.

SHOWALTER, H. D. H., JOHNSON, J. L., WERBEL, L. M., LEOPOLD, W. R., JACKSON, R. C. & ELSLAGER, E. F. (1984). *J. Med. Chem.* **27**, 253–261.

STILL, W. C., MOHMADI, F., RICHARDS, N., GUIDA, W. C., LIPTON, M., LISKAMP, R., CHANG, G., HENDRICKSON, T., DEGUNST, F. & HASEL, W. (1989). *MACROMODEL3.0*. Department of Chemistry, Columbia Univ., New York, NY 10027, USA.

VAN GUNSTEREN, W. F. & BERENDSON, H. J. C. (1977). *Mol. Phys.* **34**, 1311–1317.

WEINER, S. J., KOLLMAN, P., CASE, D., SINGH, U. C., GHIO, C., ALOGNA, G. & WEINER, P. J. (1984). *J. Am. Chem. Soc.* **106**, 765–784.

ZEE-CHENG, R. K.-Y. & CHENG, C. C. (1978). *J. Med. Chem.* **21**, 291–294.

ZEE-CHENG, R. K.-Y., PODREBARAC, E. G., MENNON, C. S. & CHENG, C. C. (1979). *J. Med. Chem.* **22**, 501–505.

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Structure of Precursors of Higher-Carbon Sugars

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Abstract

3-*O*-Benzyl-5-*C*-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-heptopyranos-6-ulos-7-ylidene)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (2), $C_{28}H_{36}O_{10}$, $M_r = 532.59$, monoclinic, $P2_1$, $a = 14.233$ (2), $b = 9.271$ (1), $c = 11.804$ (2) Å, $\beta = 114.53$ (1)°, $V = 1417.0$ (4) Å^3, $Z = 2$, $D_x = 1.248$ (1) Mg m^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 0.797$ mm^{-1}, $F(000) = 568$, room temperature, $R = 0.0472$ for 1960 reflections with $F > 6\sigma(F)$. 3-*O*-Benzyl-6-*C*-(1,2:3,4-di-*O*-isopropylidine-D-*glycero*-α-D-*galacto*-hexopyranos-6-yl)-1,2-*O*-isopropylidene-D-*glycero*-β-L-*ido*-hexofuranose (3), $C_{28}H_{40}O_{12}$, $M_r = 568.62$, orthorhombic, $P2_12_12_1$, $a = 8.912$ (1), $b = 10.154$ (2), $c = 32.704$ (5) Å, $V = 2959.5$ (8) Å^3, $Z = 4$, $D_x = 1.276$ (1) Mg m^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 0.747$ mm^{-1}, $F(000) = 1216$, room temperature, $R = 0.0375$ for 2226 reflections with $F > 6\sigma(F)$. In (2) the results of crystal structure investigations and molecular mechanics calculations suggest some rotational flexibility of bonds linking the two sugar moieties with the three-carbon chain. In (3) a network of intra- and intermolecular O—H···O hydrogen bonds exists.

Introduction

This work is a continuation of our studies concerning the X-ray crystal structures of precursors of higher-carbon sugars. α,β-Unsaturated ketones substituted at both ends of the allylic system with two different monosaccharide subunits are suitable starting materials for the preparation of higher sugars *via*, for example, osmylation of the double bond (Jarosz, 1988). The X-ray crystal structure analysis of unsaturated and saturated precursors of higher sugars provides valuable information about the conformations of these systems and makes correlation possible

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