electronic reprint

Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

2,4-Diamino-5-(1-naphthyl)-3,5-diaza-1-azoniaspiro[5.5]undeca-1,3-diene chloride

Nikolaos C. Papandreou, Stella Makedonopoulou, Ekaterini A. Antoniadou-Vyza, Irene M. Mavridis and Stavros J. Hamodrakas

Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

2,4-Diamino-5-(1-naphthyl)-3,5-diaza-1-azoniaspiro[5.5]undeca-1,3-diene chloride

Nikolaos C. Papandreou,[a] Stella Makedonopoulou,[b] Ekaterini A. Antoniadou-Vyza,[c] Irene M. Mavridis[b] and Stavros J. Hamodrakas[a]*

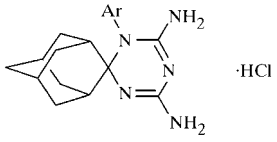
[a]Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Panepistimiopolis 157 01, Athens, Greece, [b]Institute of Physical Chemistry, NCSR Demokritos, PO Box 60228, Aghia Paraskevi 153 10, Greece, and [c]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Athens, Panepistimiopolis 157 71, Athens, Greece
Correspondence e-mail: shamodr@cc.uoa.gr

Received 5 September 2002
Accepted 17 October 2002
Online 26 November 2002

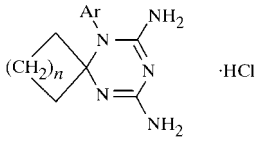
The title salt, $C_{18}H_{22}N_5^+\cdot Cl^-$, is a member of a new series of lipophilic 4,6-diamino spiro-*s*-triazines which are potent inhibitors of dihydrofolate reductase. The protonated triazine ring deviates from planarity, whereas the cyclohexane ring adopts a chair conformation. A rather unusual hydrogen-bonding scheme exists in the crystal. There is a centrosymmetric arrangement involving two amino groups and two triazine ring N atoms, with graph-set $R_2^2(8)$ and an N···N distance of 3.098 (3) Å, flanked by two additional $R_3^2(8)$ systems, involving two amino groups, a triazine ring N atom and a Cl^- anion, with N···Cl distances in the range 3.179 (2)–3.278 (2) Å. Furthermore, the Cl^- anion, the protonated triazine ring N atom and an amino group form a hydrogen-bonding system with graph-set $R_2^1(6)$.

Comment

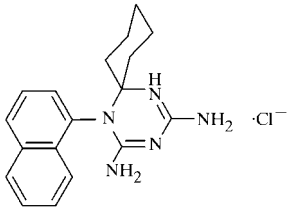
Dihydrofolate reductase (DHFR; EC 1.5.1.3) is an enzyme which catalyses the reduction of dihydrofolate to tetrahydrofolate using NADPH as coenzyme. It is of primary importance in biochemistry and medicinal chemistry, since tetrahydrofolate is a required cofactor in a number of biosynthetic processes involved in the synthesis of purines, pyrimidines and some amino acids (Blakley, 1995). An enormous number of molecules used for the selective inhibition of DHFR have been synthesized and used as antitumour (*e.g.* methotrexate) and antimicrobial (*e.g.* trimethoprim) drugs. *s*-Triazines are frequently tested in the area of non-classical antifolates, since it has been found that this class of compounds interferes with folic acid metabolism and has shown promise in cancer chemotherapy (Modest *et al.*, 1952). Following Baker's extensive reports (Baker & Ashton, 1970, 1973), several 2,2-disubstituted *s*-triazines have been studied (Marlowe *et al.*, 1995). However, for 2,2-spiro analogues of *s*-triazines, there is a complete lack of structure–activity studies in the literature to date. Therefore, two new series of lipophilic 4,6-diamino spiro-*s*-triazines, bearing a tricyclic (general type I) or cyclic (general type II) substituent at position 2 of the triazine ring, have been synthesized and are currently being tested as possible DHFR inhibitors. The detailed and accurate geometries of these compounds are needed for modelling and crystallographic studies of enzyme(DHFR)–inhibitor complexes. The size of the attached cycloalkyl chain, as well as the volume and lipophilicity of the altered monocyclic spiro ring, seem to be good parameters to vary for a systematic study of the effectiveness of these compounds. The title hydrochloride salt, (III), belongs to general type II.



(I)



(II)



(III)

In the crystal structure of (III), hydrochloric acid acts as a H-atom donor, protonating atom N4 at position 3 of the triazine ring. Protonation at this position was verified by the difference Fourier maps. The cyclohexane ring attached to

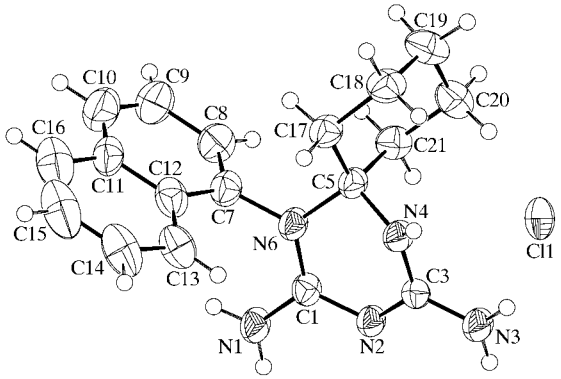


Figure 1
A view of the molecule of (III). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

  DOI: 10.1107/S0108270102019108

position 2 of the protonated triazine ring distorts the planarity of the latter, with maximum deviations of 0.24 Å for atom N4 and −0.26 Å for atom C5. The r.m.s. deviation from planarity of the atoms of the triazine ring is 0.17 Å, while the r.m.s. deviation from planarity of the naphthalene ring atoms is 0.02 Å. The cyclohexane ring adopts a chair conformation, and the plane of the naphthalene ring is almost perpendicular to that of the triazine ring.

A rather unusual hydrogen-bonding scheme exists in the crystal of (III) (Table 2 and Fig. 2). Pairs of molecules related

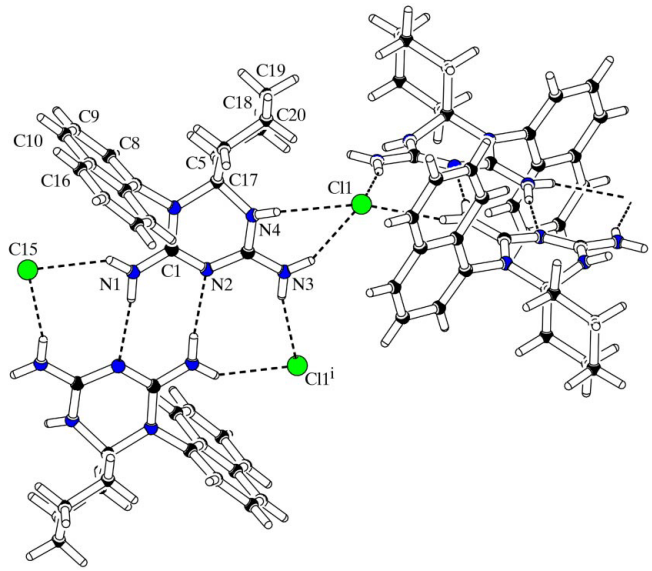


Figure 2
A view of the hydrogen-bonding scheme in the crystal of (III) [symmetry code: (i) $1-x, y-\frac{1}{2}, -\frac{1}{2}-z$].

by a centre of symmetry are joined by two hydrogen bonds (Fig. 2, dashed lines), each formed by a donor amino group (N1) and an acceptor triazine ring N atom (N2). Thus, a central ring of eight atoms is formed. This ring is flanked by two additional eight-atom rings, each formed by two amino groups, one from each molecule (N1 and N3), the triazine ring atom N2 and a Cl^- anion, Cl1 (Fig. 2). The whole hydrogen-bonding pattern has a centre of symmetry and can be described according to graph-set notation (Etter *et al.*, 1990) as $R_2^2(8)$ and $R_3^2(8)$ for the inner and outer rings, respectively. Two other hydrogen bonds, involving the Cl^- anion Cl1 and atoms N4 and N3, which act as hydrogen-bond donors, create a ring of six atoms and can be described by graph-set $R_2^1(6)$.

Experimental

A mixture of 1-(1-naphthyl)biguanide hydrochloride (2.64 g, 10 mmol), concentrated HCl (0.5 ml, 5 mmol), cyclohexanone (1.86 g, 20 mmol) and absolute ethanol (20 ml) was refluxed with stirring for about 10 h. The white crystalline precipitate was filtered off and washed with ethanol (5 ml) (m.p. 508–509 K, yield 32%). Single crystals of (III) were obtained by slow evaporation of a water–methanol (1:1) solution.

Crystal data

$C_{18}H_{22}N_5^+\cdot Cl^-$
$M_r = 343.86$
Monoclinic, $I2/a$
$a = 24.862$ (4) Å
$b = 7.3778$ (14) Å
$c = 19.633$ (4) Å
$\beta = 101.823$ (6)°
$V = 3524.8$ (11) Å^3
$Z = 8$
$D_x = 1.296$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 16 reflections
$\theta = 11$–20°
$\mu = 1.98$ mm^{-1}
$T = 293$ (2) K
Prism, colourless
0.50 × 0.30 × 0.25 mm

Data collection

Syntex $P2_1$ diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.405$, $T_{max} = 0.615$
3095 measured reflections
2996 independent reflections
2518 reflections with $I > 2\sigma(I)$
$R_{int} = 0.015$
$\theta_{max} = 65.1°$
$h = -29 \rightarrow 28$
$k = 0 \rightarrow 8$
$l = 0 \rightarrow 23$
3 standard reflections
every 97 reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.052$
$wR(F^2) = 0.155$
$S = 1.03$
2996 reflections
239 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0784P)^2 + 5.7970P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.009$
$\Delta\rho_{max} = 0.55$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C1—N1	1.316 (3)	N4—C5	1.456 (3)
C1—N2	1.352 (3)	N6—C5	1.488 (3)
C1—N6	1.350 (3)	N6—C7	1.445 (3)
N2—C3	1.340 (3)	C5—C17	1.532 (4)
N3—C3	1.321 (3)	C5—C21	1.535 (4)
N4—C3	1.346 (3)		
N1—C1—N2	117.5 (2)	N4—C5—C17	109.2 (2)
N1—C1—N6	119.6 (2)	N6—C5—C17	111.2 (2)
N2—C1—N6	122.9 (2)	N4—C5—C21	110.5 (2)
C1—N2—C3	115.9 (2)	N6—C5—C21	110.3 (2)
N2—C3—N3	119.8 (2)	C17—C5—C21	110.3 (2)
N2—C3—N4	121.5 (2)	C1—N6—C5	118.7 (2)
N3—C3—N4	118.7 (2)	C1—N6—C7	121.8 (2)
C3—N4—C5	117.6 (2)	C5—N6—C7	118.8 (2)
N4—C5—N6	105.1 (2)		
N6—C1—N2—C3	18.3 (4)	C3—N4—C5—N6	48.0 (3)
C1—N2—C3—N4	−3.7 (4)	C1—N6—C7—C12	91.4 (3)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···Cl1^{i}	0.86	2.46	3.179 (2)	142
N1—H1B···N2^{ii}	0.86	2.24	3.098 (3)	174
N3—H3A···Cl1^{iii}	0.86	2.44	3.278 (2)	164
N3—H3B···Cl1	0.86	2.48	3.264 (2)	152
N4—H4···Cl1	0.86	2.58	3.222 (2)	133

Symmetry codes: (i) $x, \frac{1}{2}-y, \frac{1}{2}+z$; (ii) $1-x, -y, -z$; (iii) $1-x, y-\frac{1}{2}, -\frac{1}{2}-z$.

The H atoms were treated as riding atoms, with C—H distances in the range 0.93–0.97 Å and N—H distances of 0.86 Å, and their isotropic displacement parameters were allowed to refine freely.

Data collection: *CRYSTAL LOGIC* (Strause, C. E.; unpublished); cell refinement: *CRYSTAL LOGIC*; data reduction: *CRYSTAL LOGIC*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1990, 2002); software used to prepare material for publication: *SHELXL*97.

The authors thank the University of Athens for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1139). Services for accessing these data are described at the back of the journal.

References

Baker, B. R. & Ashton, W. T. (1970). *J. Med. Chem.* **13**, 1165–1170.
Baker, B. R. & Ashton, W. T. (1973). *J. Med. Chem.* **16**, 209–214.
Blakley, R. L. (1995). *Adv. Enzymol. Relat. Areas Mol. Biol.* **70**, 23–102.
Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* B**46**, 256–262.
Marlowe, C. K., Selassie, C. D. & Santi, D. V. (1995). *J. Med. Chem.* **38**, 967–972.
Modest, E. J., Foley, G. E., Pechet, M. U. & Farber, S. (1952). *J. Am. Chem. Soc.* **74**, 855–876.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (1990). *Acta Cryst.* A**46**, C-34.
Spek, A. L. (2002). *PLATON*. University of Utrecht, The Netherlands.