

## Structure of $N,N'$ -(2,4-Pyrimidinediyl)dipyridinium Dichloride Monohydrate

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Dedicated to Professor Maciej Wiewiórowski on the occasion of his 70th birthday

**Abstract.**  $C_{14}H_{12}N_4^{2+} \cdot 2Cl^- \cdot H_2O$ ,  $M_r = 325.2$ , monoclinic,  $P2_1/n$ ,  $a = 17.429$  (2),  $b = 14.337$  (1),  $c = 5.9788$  (5) Å,  $\beta = 97.37$  (1)°,  $V = 1481.6$  (3) Å<sup>3</sup>,  $Z = 4$ ,  $D_x = 1.458$  g cm<sup>-3</sup>,  $\lambda(\text{Cu } K\alpha) = 1.54178$  Å,  $\mu = 38.3$  cm<sup>-1</sup>,  $F(000) = 672$ ,  $T = 290$  K,  $R = 0.030$  for 1831 observed reflexions. The C–N<sup>+</sup> bonds between the pyrimidine and pyridinium rings are 1.453 (3) and 1.459 (3) Å. The pyridinium rings are twisted in the opposite sense out of the pyrimidine plane by 6.2 (3) and 6.1 (3)°. The geometry around the C(4)–N<sup>+</sup> link indicates more internal strain than at C(2)–N<sup>+</sup>. All C<sub>α</sub>–H groups of the pyridinium moieties participate in H-bonding as do the C(5)–H and C(6)–H groups of the pyrimidine moiety. The water molecule H-bonds the two independent Cl<sup>-</sup> anions and is an acceptor in a weak C–H...O hydrogen bond.

**Introduction.** This paper continues our studies on the structure of nucleobase-derived pyridinium salts which are known as fluorescent ionic side products in oligonucleotide synthesis by the phosphotriester method and as synthetic intermediates in nucleoside chemistry (Adamiak, Biała & Skalski, 1985; Adamiak, Biała, Gdaniec, Mielewczyk & Skalski, 1986). In the previous paper (Jaskólski, Skalski, Adamiak & Adamiak, 1987) we reported the structure of a 6-pyridinium analog of guanine. Here we describe the structure of a 2,4-dipyridinium analog of uracil in its monohydrated dichloride salt. The present  $N,N'$ -(2,4-pyrimidinediyl)-dipyridinium dication is an interesting system for studies on the conformation of polycyclic aromatics. It can provide information on the behavior of the pyridinium cation in such a system and is a particularly useful probe for the steric *ortho* interactions which are different at the two substitution sites.

**Experimental.** Suitable crystals from 2-propanol–water solution. Crystal 0.2 × 0.3 × 0.4 mm, Syntex P2<sub>1</sub> diffractometer, graphite monochromator, Cu  $K\alpha$  radiation. Cell parameters from least-squares treatment of

setting angles of 15 reflexions ( $22.8 < 2\theta < 31.6^\circ$ ).  $\theta:2\theta$  profiles measured for 2037 unique  $+h+k+l$  reflexions with  $2\theta \leq 115^\circ$  [max.  $(\sin\theta)/\lambda = 0.547 \text{ \AA}^{-1}$ ] and with  $0 \leq h \leq 19$ ,  $0 \leq k \leq 15$ ,  $-6 \leq l \leq 6$ ; profile analysis according to Lehmann & Larsen (1974). No significant intensity variation (<2.6%) for two standard reflexions measured every 1.5 h. No absorption correction. 1831 observed reflexions with  $I \geq 2\sigma(I)$ . Positions of the Cl<sup>-</sup> ions deduced from a Patterson map, remaining non-H atoms located from a Fourier map. Full-matrix least-squares refinement on  $F$ ,  $w = \sigma^{-2}(F)$ . All H atoms located in a  $\Delta F$  map and included in the refinement. Final refinement: anisotropic non-H atoms, isotropic H atoms, empirical isotropic-extinction parameter  $x$  used to correct  $F_c$  according to  $F'_c = F_c(1 - xF_c^2/\sin\theta)$ , which converged at  $x = 28(5) \times 10^{-8}$ ,  $R = 0.030$ ,  $wR = 0.039$ ,  $S = 4.83$ ,  $(\Delta/\sigma)_{\text{max}} = 0.04$ , largest peak in final  $\Delta F$  map = 0.29, largest trough =  $-0.19 \text{ e \AA}^{-3}$ . Computer programs: *SHELX76* (Sheldrick, 1976) and local programs (Jaskólski, 1982), molecular illustrations drawn using *ORTEPII* (Johnson, 1976) and *PLUTO* (Motherwell & Clegg, 1978). Atomic scattering factors from *International Tables for X-ray Crystallography* (1974).

**Discussion.** Atomic coordinates are listed in Table 1.\* Bond distances and angles in the  $N,N'$ -(2,4-pyrimidinediyl)dipyridinium dication are given in Table 2 and its thermal-ellipsoid representation is shown in Fig. 1. The dimensions of the two pyridinium rings are very similar and agree, within standard error, with those found in the  $N$ -(2-amino-6-purinylyl)pyridinium cation (Jaskólski, Skalski, Adamiak & Adamiak, 1987). The geometry of the pyrimidine moiety is consistent with that reported

\* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44799 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Final fractional coordinates and equivalent isotropic thermal parameters (Å<sup>2</sup>)
$$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	U <sub>eq</sub>
Cl(1)	0.12425 (4)	0.09634 (5)	0.0660 (1)	0.0544 (2)
Cl(2)	0.43142 (3)	0.14946 (4)	0.2108 (1)	0.0481 (2)
N(1)	0.1994 (1)	0.3805 (1)	0.4801 (3)	0.0417 (6)
C(2)	0.1439 (1)	0.3802 (1)	0.3086 (4)	0.0355 (6)
N(3)	0.0817 (1)	0.3273 (1)	0.2733 (3)	0.0366 (6)
C(4)	0.0755 (1)	0.2644 (1)	0.4327 (4)	0.0364 (6)
C(5)	0.1289 (1)	0.2552 (2)	0.6213 (4)	0.0438 (6)
C(6)	0.1903 (1)	0.3160 (2)	0.6368 (4)	0.0456 (8)
N(21)	0.1523 (1)	0.4475 (1)	0.1302 (3)	0.0350 (6)
C(22)	0.0943 (1)	0.4582 (2)	-0.0423 (4)	0.0402 (6)
C(23)	0.1023 (1)	0.5216 (2)	-0.2086 (4)	0.047 (1)
C(24)	0.1691 (2)	0.5738 (2)	-0.2010 (4)	0.049 (1)
C(25)	0.2263 (2)	0.5626 (2)	-0.0235 (4)	0.049 (1)
C(26)	0.2175 (1)	0.4994 (2)	0.1422 (4)	0.0437 (8)
N(41)	0.0078 (1)	0.2048 (1)	0.3902 (3)	0.0376 (6)
C(42)	-0.0382 (1)	0.2118 (2)	0.1903 (4)	0.046 (1)
C(43)	-0.1016 (1)	0.1554 (2)	0.1460 (5)	0.053 (1)
C(44)	-0.1185 (2)	0.0910 (2)	0.3035 (5)	0.054 (1)
C(45)	-0.0720 (2)	0.0855 (2)	0.5068 (5)	0.053 (1)
C(46)	-0.0089 (1)	0.1433 (2)	0.5496 (5)	0.047 (1)
O(W)	0.2639 (2)	0.2470 (2)	0.1229 (4)	0.0700 (8)

Table 2. Bond distances (Å) and angles (°) in the dication

C(2)–N(1)	1.317 (3)	C(2)–N(3)	1.317 (3)
N(1)–C(6)	1.340 (3)	N(3)–C(4)	1.326 (3)
C(6)–C(5)	1.374 (3)	C(4)–C(5)	1.374 (3)
C(2)–N(21)	1.459 (3)	C(4)–N(41)	1.453 (3)
N(21)–C(22)	1.357 (3)	N(41)–C(42)	1.354 (3)
C(22)–C(23)	1.368 (3)	C(42)–C(43)	1.368 (3)
C(23)–C(24)	1.378 (4)	C(43)–C(44)	1.377 (4)
C(24)–C(25)	1.369 (4)	C(44)–C(45)	1.374 (4)
C(25)–C(26)	1.365 (4)	C(45)–C(46)	1.374 (4)
C(26)–N(21)	1.353 (3)	C(46)–N(41)	1.358 (3)
N(1)–C(2)–N(3)	129.4 (2)	C(4)–C(5)–C(6)	115.8 (2)
C(2)–N(1)–C(6)	113.6 (2)	C(2)–N(3)–C(4)	114.7 (2)
N(1)–C(6)–C(5)	123.4 (2)	N(3)–C(4)–C(5)	123.0 (2)
N(1)–C(2)–N(21)	115.7 (2)	N(3)–C(4)–N(41)	114.5 (2)
N(3)–C(2)–N(21)	114.9 (2)	C(5)–C(4)–N(41)	122.5 (2)
C(2)–N(21)–C(22)	119.7 (2)	C(4)–N(41)–C(42)	119.1 (2)
C(2)–N(21)–C(26)	119.2 (2)	C(4)–N(41)–C(46)	120.1 (2)
N(21)–C(22)–C(23)	119.5 (2)	N(41)–C(42)–C(43)	119.9 (2)
C(22)–C(23)–C(24)	120.0 (2)	C(42)–C(43)–C(44)	120.1 (3)
C(23)–C(24)–C(25)	119.4 (3)	C(43)–C(44)–C(45)	119.3 (3)
C(24)–C(25)–C(26)	120.1 (2)	C(44)–C(45)–C(46)	119.8 (3)
C(25)–C(26)–N(21)	119.9 (2)	C(45)–C(46)–N(41)	120.0 (3)
C(26)–N(21)–C(22)	121.1 (2)	C(46)–N(41)–C(42)	120.8 (2)

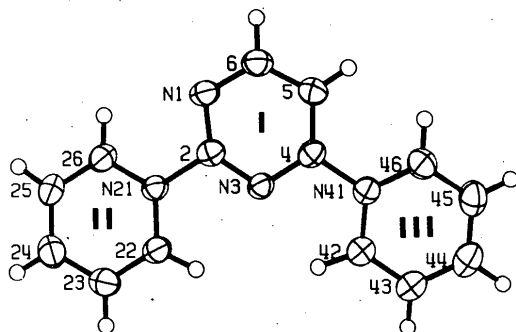


Fig. 1. Thermal-ellipsoid representation of the dication drawn at 50% probability level. H-atom spheres are on an arbitrary scale.

by Wheatley (1960) for the pyrimidine molecule. In particular, the endocyclic angles show a characteristic distribution with a very wide N–C–N angle [129.4 (2)°] and narrow C–N–C angles [113.6 (2), 114.7 (2)°]. The C–N<sup>+</sup> bonds between the pyrimidine and the pyridinium rings [1.459 (3), 1.453 (3) Å] compare very well with the value in the *N*-(2-amino-6-purinyl)pyridinium cation [1.454 (3) Å]. The C–H distances range from 0.92 (3) to 1.02 (2) Å with a mean of 0.96 Å.

Of particular interest in the present structure is the planarity of the pyrimidinediylpyridinium dication. The three rings composing the cation (Fig. 1) are planar with only slight deviations from strict planarity for the pyridinium rings [ $\chi^2$  test values [ $\sum (\Delta/\sigma)^2$ ]: I 18.2, II 32.1, III 41.8]. The pyridinium rings make angles of 6.2 (3) (I/II) and 6.1 (3)° (I/III) with the inner pyrimidine ring. The N<sup>+</sup> substituents deviate by 0.045 (2) [N(21)] and 0.021 (2) Å [N(41)] from the pyrimidine plane. The dihedral angle II/III of 10.5 (3)° illustrates that the rotations of rings II and III relative to ring I are in the opposite sense. Another way to describe coplanarity in a polycyclic system is through the use of torsion angles. Applying an algorithm similar to that of Winkler & Dunitz (1971), one can determine the twist ( $\tau$ ) between two connected triatomic groups as well as nonplanarity (pyramidalization,  $\chi$ ) of the three bonds around each of the connected atoms. In the present case  $\tau_{C(2)-N(21)} = 6.0 (3)$ ,  $\chi_{C(2)} = 0.5 (3)$ ,  $\chi_{N(21)} = 1.2 (3)^\circ$  and  $\tau_{C(4)-N(41)} = 6.2 (3)$ ,  $\chi_{C(4)} = 0.9 (3)$ ,  $\chi_{N(41)} = 0.1 (3)^\circ$ , illustrating that the atoms at which the rings are connected show negligible pyramidalization and confirming that the outer rings are both rotated by *ca* 6° from the pyrimidine plane.

There is a lot of discussion in the literature about the factors influencing the mutual orientation of aromatic rings connected *via* a single bond. It is generally accepted that there are two competing intramolecular effects, *i.e.* conjugation, favoring coplanarity, and *ortho*-substituent repulsions, driving the connected rings to perpendicular orientation, and that the balance between these effects can be significantly influenced in a crystal by intermolecular forces. Biphenyl, the standard molecule in these studies, is non-planar in the gas phase, the two rings being rotated by 42° (Bastiansen, 1949). In the crystalline state it is quasi-planar (centrosymmetric) but shows unusually large-amplitude libration along the long axis of the molecule (Charbonneau & Delugeard, 1977). Also many *ortho*-substituted biphenyl derivatives show large deviations (30° and more) from coplanarity of the two benzene rings (*e.g.* Singh, Posner & McKinney, 1987). Replacement of one or more of the C<sub>α</sub>–H groups by N appreciably relieves the steric stress but does not always lead to improved coplanarity in the crystalline state. For instance, the twist between the pyrazine and the phenyl rings in 2,5-diphenylpyrazine is 20° (Laing & Sommerville,

1976) as compared with the values of 25 and 16° reported for the ordered phase of *p*-terphenyl (Baudour, Delugeard & Cailleau, 1976). On the other hand, the dihedral angles between the central ring and the outer rings in 1,3,5-triphenylbenzene are 24, 27 and 34° (Farag, 1954) while in *s*-triphenyltriazine they are only 6.9, 7.6 and 10.9° (Damiani, Giglio & Ripamonti, 1965). Another illustration of the interplay between intra- and intermolecular factors in determining the mutual orientation of the aromatic rings is provided by the structures of various phenylpyrimidines. As a rule, 2-phenylpyrimidines exhibit only a small (<10°) tilt (Raphel, Hartung, Richter & Jaskólski, 1983) in contrast to an appreciable tilt observed in 5-phenylpyrimidines (Hartung, Raphel & Richter, 1982). This is true in 5-phenyl-2-(4-*n*-propoxyphenyl)pyrimidine (respective tilts 4.8 and 39.1°) and in 5-phenyl-2-(4-*n*-butoxyphenyl)pyrimidine (7.6 and 37.7°) (Winter, Hartung & Jaskólski, 1987) but not in the two independent molecules of 2-phenyl-5-(4-*n*-pentoxyphenyl)pyrimidine where the tilts at the 2-side of pyrimidine (7.8, 8.8°) are the same as those at the 5-side (8.3, 6.7°) (Winter, Hartung, Brandt & Jaskólski, 1987). Also, in the present case, intermolecular forces must influence the conformation of the dication since the two pyridinium rings, exposed to different steric stress, have the same orientation relative to the central ring. The difference in the intramolecular strain at the two C–N<sup>+</sup> links is illustrated by the exocyclic pyrimidine bond angles at the substitution sites [122.5 (2), 114.5 (2)° at C(4) and 115.7 (2), 114.9 (2)° at C(2)]. It should be noted that the strain in the present system with C–N<sup>+</sup> inter-ring links can be expected to be generally higher than in similar systems with C–C inter-ring links. This is due to the length of the C–N<sup>+</sup> bonds which are shorter than typical C<sub>sp<sup>2</sup></sub>–C<sub>sp<sup>2</sup></sub> bonds in the examples discussed above (1.47–1.49 Å).

In the *N*-(2-amino-6-purinyloxy)pyridinium cation, the coplanarity of the pyridinium and pyrimidine rings [dihedral angle 2.3 (4)°] was attributed to a C–H...N hydrogen bond between a C<sub>α</sub> atom of the pyridinium ring and the N(7) atom of the purine system (Jaskólski, Skalski, Adamiak & Adamiak, 1987). In the present dication there are also short contacts between the pyrimidine N atoms and all suitable C<sub>α</sub>H groups on the pyridinium substituents [H...N distances: C(26)H(26)...N(1) 2.32 (3), C(22)H(22)...N(3) 2.31 (2), C(42)H(42)...N(3) 2.21 (2) Å]. These contacts may have some stabilizing contribution to the roughly coplanar arrangement of the three rings but the values of the C–H...N angles [103 (2), 103 (2) and 105 (1)°, respectively] exclude the possibility of intramolecular H-bond formation (Jaskólski, 1984).

There are, however, intermolecular C–H...Cl<sup>–</sup> hydrogen bonds involving all four C<sub>α</sub>–H donors on the pyridinium rings (Table 3, Fig. 2). It is not unexpected that all C<sub>α</sub>–H groups act as H-bond donors as they are

Table 3. Geometry of the H bonds

D–H...A	D–H (Å)	H...A (Å)	D...A (Å)	∠D–H...A (°)
C(5)–H(5)...Cl(1 <sup>i</sup> )	0.93 (2)	2.58 (2)	3.510 (3)	177 (1)
C(6)–H(6)...O(W)	1.00 (3)	2.31 (3)	3.180 (3)	145 (1)
C(22)–H(22)...Cl(2 <sup>ii</sup> )	0.97 (3)	2.57 (3)	3.398 (2)	143 (1)
C(26)–H(26)...Cl(1 <sup>iii</sup> )	0.94 (3)	2.67 (3)	3.368 (3)	132 (2)
C(42)–H(42)...Cl(2 <sup>ii</sup> )	1.02 (2)	2.62 (2)	3.474 (3)	142 (1)
C(46)–H(46)...Cl(1 <sup>i</sup> )	0.99 (3)	2.71 (3)	3.679 (3)	167 (2)
O(W)–H(W1)...Cl(2)	0.82 (3)	2.40 (3)	3.220 (3)	178 (2)
O(W)–H(W2)...Cl(1)	0.89 (4)	2.36 (4)	3.240 (3)	170 (3)

Symmetry code: (i)  $x, y, 1+z$ ; (ii)  $x-0.5, 0.5-y, z-0.5$ ; (iii)  $0.5-x, y+0.5, 0.5-z$ .

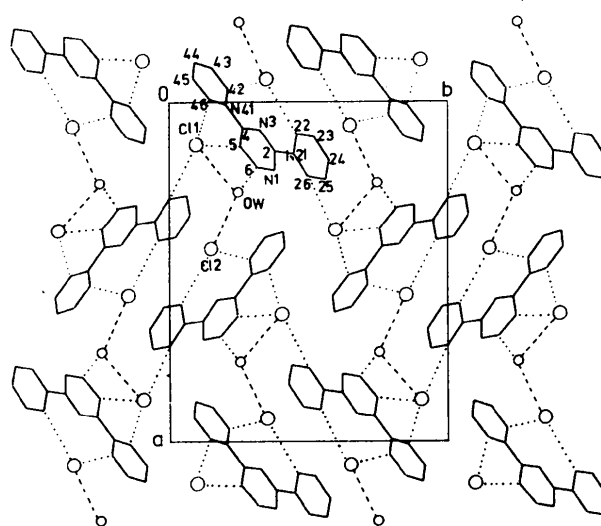


Fig. 2. Projection of the structure down *c*. Broken lines indicate O(W)–H...Cl<sup>–</sup> hydrogen bonds and dotted lines C–H...A hydrogen bonds. H atoms have been omitted for clarity.

adjacent to positively charged N atoms (Taylor & Kennard, 1982). Also, the C(5)–H and C(6)–H groups of the pyrimidine system are involved in H-bonding. The water molecule uses its H atoms to bind the two Cl<sup>–</sup> ions forming separate <sup>–</sup>Cl...HOH...Cl<sup>–</sup> anionic units. In addition, the water O atom is an acceptor in a weak C(6)–H...O(W) hydrogen bond.

The best plane through the dication makes an angle of 131.6° with the monoclinic *b* axis (Fig. 2) and in consequence the cations in the crystal can be divided into two sets (with  $x = 0, 1, \dots$  and  $x = \frac{1}{2}, \frac{3}{2}, \dots$ ) with roughly perpendicular planes.

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## Studies on Antifungal Agents. 21. Structure of (±)-*cis*-3-(4-Chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-5-(4-chlorophenoxymethyl)isoxazolidine

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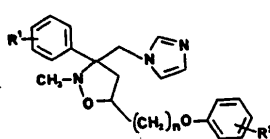
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**Abstract.** C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>, *M<sub>r</sub>* = 418.33, monoclinic, *P*2<sub>1</sub>/*n*, *a* = 13.547 (4), *b* = 7.683 (1), *c* = 19.740 (2) Å, β = 102.26 (2)°, *V* = 2007.8 Å<sup>3</sup>, *Z* = 4, *D<sub>x</sub>* = 1.384 g cm<sup>-3</sup>, λ(Mo Kα) = 0.71073 Å, μ = 3.43 cm<sup>-1</sup>, *F*(000) = 872, *T* = 297 K, final *R* = 0.051 for 3212 unique observed reflections. The X-ray analysis confirms the molecular geometry of the title *cis* compound, which is a more potent antifungal agent than the *trans* diastereomer. The individual aromatic rings are planar. The title compound has normal bond lengths and angles.

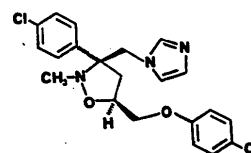
**Introduction.** Recently (Mullen, Maryniak, Swift, Allen, Mitchell, Kinsolving & Georgiev, 1987), we reported the synthesis of a series of a novel class of potent antifungal agents, the 5-phenoxyalkyl-3-phenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidines (1), via a 1,3-dipolar cycloaddition reaction of α-substituted ketonitrones with 1-alkenyl phenyl ethers. The resulting products comprised the *cis* and *trans* diastereomers of (1) which were conveniently separated by flash

chromatography on silica gel. The initial stereochemical assignment of both diastereomers was accomplished by interpretation of their NMR spectra. In general, *cis* analogs were more potent antifungal agents *in vitro* than their *trans* counterparts.

The title compound, (±)-*cis*-3-(4-chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-5-(4-chlorophenoxymethyl)isoxazolidine (2), demonstrated potent *in vitro* antifungal activity against a broad spectrum of yeast and systemic mycoses and dermatophytes. An X-ray crystal-structure determination of compound (2) was undertaken in order to define unambiguously the stereochemistry of the *cis* derivatives and allow for a consistent differentiation between the *cis* and *trans* diastereomers by NMR techniques.



(1)



(2)

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