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1,1′-[Oxybis(methylene)]bis{4-[(hydroxyimino)methyl]pyridinium} Dichloride (Obidoxime Chloride)

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Abstract. $C_{14}H_{16}Cl_2N_4O_3$, $M_r = 359{\cdot}24$, monoclinic, $C2/c$, $Z = 4$, $a = 7{\cdot}154\ (3)$, $b = 12{\cdot}663\ (5)$, $c = 18{\cdot}348\ (5)$ Å, $\beta = 98{\cdot}07\ (4)°$, $d_{calc} = 1{\cdot}45$ Mg m^{-3}; μ(Cu $K\alpha$) = 3·73 mm^{-1}; $R_w = 0{\cdot}06$ for 756 reflections. The structure was solved by conventional techniques. The compound, a potent antidote against nerve agents and organophosphate pesticides by reactivation of phosphylated acetylcholinesterase, has the (*E*,*E*) configuration at the oxime moieties. The possibility of π localization in the pyridinium rings is discussed.

Introduction. Some pyridinium oximes are potent reactivators of the enzyme acetylcholinesterase (AcChoE) inhibited by organophosphates, thereby restoring the normal transmission of nerve impulses after intoxication with these anticholinesterases. Hence, pyridinium oximes are used or considered for use as antidotes against poisoning with organophosphates both of the pesticide and of the nerve-agent type (Ellin & Wills, 1964; Sidell, 1974).

The efficacy of the reactivation reaction depends in each case on the specific combination of the structure of the oxime and of the organophosphate moiety on the enzyme. For example, monoquaternary 1-benzyl-2-[(hydroxyimino)methyl]pyridinium bromide (benzyl-P_2A bromide) and the bisquaternary 1,1′-[oxybis-(methylene)]bis{4-[(hydroxyimino)methyl]pyridinium} dichloride (obidoxime, Toxogonin®) are highly effective reactivators of AcChoE inhibited with ethyl dimethylphosphoramidocyanidate (tabun; de Jong, Benschop, Van den Berg, Wolring & de Korte, 1981), whereas 4′-carbamoyl-2-[(hydroxyimino)methyl]-1,1′-[oxybis(methylene)]dipyridinium dichloride (HI-6) is effective against the enzyme inhibited with 1,2,2-trimethylpropyl methylphosphonofluoridate (soman; de Jong & Wolring, 1980). In a previous paper we reported the structure of benzyl-P_2A salts (Van Havere, Lenstra, Geise, Van den Berg & Benschop, 1982). We now report the structure of obidoxime.

Obidoxime [m.p. 484·5–485 K (dec.)] was obtained from E. Merck, Darmstadt, Federal Republic of Germany. Colourless single crystals were obtained by slow evaporation at room temperature of an aqueous solution of the product.

The structure has been determined from data obtained at room temperature on an Enraf–Nonius CAD-4 diffractometer using Ni-filtered Cu $K\alpha$

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Table 1. *Positional parameters as fractions of the cell edges, with e.s.d.'s in parentheses, and thermal parameters*

Isotropic temperature parameters (Å²) of non-hydrogen atoms are calculated from anisotropic thermal parameters according to Lipson & Cochran (1968) [$B_{iso} = 8\pi^2(U''_{11}\,U''_{22}\,U''_{33})^{1/3}$], assuming equal volume of the 50% probability region. E.s.d.'s are *ca* 0·2 Å². All anisotropic thermal parameters were physically acceptable. H atom $H_j(x)$ with $j = 1, 2$ is attached to atom x.

	x	y	z	B_{iso}
Cl	0·2070 (3)	0·1449 (1)	0·1592 (1)	4·24
O(1)	−0·5000	0·6485 (5)	−0·2500	3·85
O(2)	−0·0839 (7)	0·3141 (3)	0·1399 (2)	3·91
N(1)	−0·3040 (7)	0·5464 (4)	−0·1611 (3)	3·00
N(2)	−0·1077 (7)	0·3369 (4)	0·0657 (3)	3·26
C(2)	−0·343 (1)	0·6028 (5)	−0·1043 (4)	3·45
C(3)	−0·3096 (9)	0·5646 (5)	−0·0336 (3)	3·00
C(4)	−0·2323 (9)	0·4653 (5)	−0·0211 (3)	2·82
C(5)	−0·189 (1)	0·4074 (5)	−0·0812 (3)	3·20
C(6)	−0·228 (1)	0·4491 (5)	−0·1499 (4)	4·01
C(7)	−0·1949 (9)	0·4252 (5)	0·0518 (3)	3·27
C(8)	−0·333 (1)	0·5903 (5)	−0·2378 (3)	3·76
H(O1)	−0·011 (7)	0·251 (4)	0·132 (3)	3·70
H(C2)	−0·376 (7)	0·657 (4)	−0·103 (3)	3·70
H(C3)	−0·371 (7)	0·603 (4)	0·003 (3)	3·70
H(C5)	−0·112 (7)	0·342 (4)	−0·066 (3)	3·70
H(C6)	−0·229 (7)	0·425 (4)	−0·178 (3)	3·70
H(C7)	−0·239 (7)	0·461 (4)	0·081 (3)	3·70
H1(C8)	−0·352 (7)	0·528 (4)	−0·278 (3)	3·70
H2(C8)	−0·234 (7)	0·637 (4)	−0·236 (3)	3·70

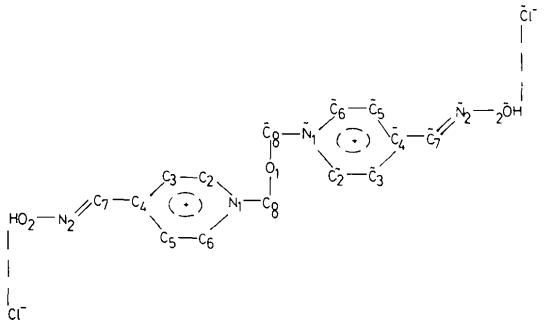


Fig. 1. Structural formula with numbering of the atoms.

radiation ($\lambda = 1{\cdot}54184$ Å). All 1219 unique reflections with $\theta < 60°$ were measured by ω scans. Cell parameters were evaluated by a least-squares procedure using 20 reflections. The data were corrected for absorption and 756 gave $I \geq 3\sigma(I)$.

Since the asymmetric unit contains half a molecule, only one Cl atom had to be located in the Patterson map. All other non-hydrogen positions were obtained using the heavy-atom Fourier technique. H positions were found from difference electron density maps. The refinement was performed with the Gauss–Seidel block method (Sparks, 1974) giving each reflection a weight based on counting statistics. The Debye–Waller temperature factor of the H atoms was kept fixed at 3·7 Å². The refinement converged to $R_w = 0{\cdot}06$, with R_w defined as $[\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ for observed reflections. The maximum noise level in the final difference Fourier map was 0·15 e Å^{-3}. Refined parameters are listed in Table 1, and the numbering of atoms is given in Fig. 1.*

Discussion. The two chemically equivalent parts of the molecule are related through a twofold axis which also renders them crystallographically equivalent.

Substituents around the C=N bonds in obidoxime are arranged in the (*E*) configuration (also called *syn* in older literature). This result confirms a recent assignment of the (*E*,*E*) configuration of obidoxime based on ^{13}C NMR spectroscopy (Waysbort, Balderman & Amitai, 1981; see also Lüttringhaus & Hagedorn, 1964). The (*Z*,*Z*) isomer of obidoxime, supposedly isolated by Russian workers (Leitis, Shimanskaya & Varslavans, 1969), seems to be more toxic and a less effective antidote than the (*E*,*E*) isomer. It has also been shown that the (*Z*) isomer of monoquaternary 4-[(hydroxyimino)methyl]-1-methylpyridinium iodide is a less potent reactivator *in vitro* than the (*E*) isomer (Poziomek, Kramer, Mosher & Michel, 1961). Interestingly, the (*E*) configuration also occurs in other pyridinium oximes with antidotal activity against intoxication with organophosphates, *e.g.* in 2-[(hydroxyimino)methyl]-1-methylpyridinium chloride (pralidoxime chloride; Carlström, 1966), and in 1-benzyl-P_2A salts (Van Havere *et al.*, 1982).

Bond distances, valence angles and some torsion angles are listed in Table 2. The bond length C(4)–C(7) (1·422 Å) seems rather short for a 'normal'

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36622 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond distances* (Å), *valence angles* (°) *and some selected torsion angles* (°) *for obidoxime, with e.s.d.'s in parentheses*

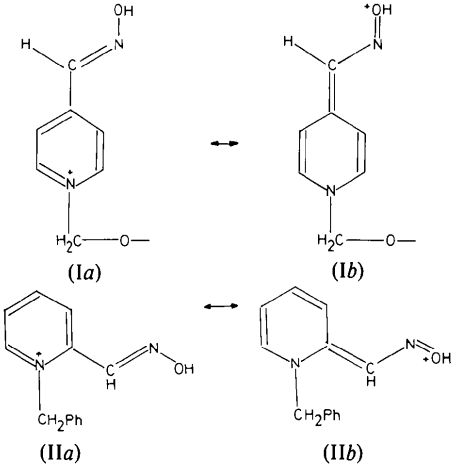
N(1)–C(2)	1·324 (3)	C(4)–C(7)	1·422 (4)
C(2)–C(3)	1·373 (4)	C(7)–N(2)	1·288 (3)
C(3)–C(4)	1·381 (3)	N(2)–O(2)	1·379 (3)
C(4)–C(5)	1·393 (3)	N(1)–C(8)	1·501 (3)
C(5)–C(6)	1·359 (5)	C(8)–O(1)	1·392 (3)
C(6)–N(1)	1·351 (4)		

N(1)–C(2)–C(3)	121·7 (3)	C(3)–C(4)–C(7)	120·0 (3)
C(2)–C(3)–C(4)	119·4 (3)	C(5)–C(4)–C(7)	121·6 (3)
C(3)–C(4)–C(5)	118·4 (3)	C(4)–C(7)–N(2)	121·2 (3)
C(4)–C(5)–C(6)	119·3 (3)	C(7)–N(2)–O(2)	111·5 (2)
C(5)–C(6)–N(1)	121·4 (3)	C(2)–N(1)–C(8)	121·4 (2)
C(6)–N(1)–C(2)	119·8 (3)	C(6)–N(1)–C(8)	118·7 (2)
N(1)–C(8)–O(1)	110·5 (2)	C(8)–O(1)–C(8')	116·1 (3)

N(2)=C(7)–C(4)–C(5)	4·7 (5)	N(1)–C(8)–O(1)–C(8')	76·6 (5)
C(2)–N(1)–C(8)–O(1)	40·1 (5)		

Symmetry code: (i) $-1-x, y, -z-\frac{1}{2}$.

Csp^2–Csp^2 bond (1·466 Å). Also, there could be a short–long–long–short pattern in the C(2)–C(3)–C(4)–C(5)–C(6) section of the pyridinium ring. These phenomena are suggestive of π localization of type (I*b*). Carlström (1966) has invoked the same rationale to explain certain features in pralidoxime iodide. On the other hand, there are arguments against it. First, it would be expected that a similar π localization (type II*b*) would occur in the closely related 1-benzyl-2-[(hydroxyimino)methyl]pyridinium bromide and methanesulphonate. In these compounds, however, the bonds C(2)–C(7) are normal (1·454 and 1·472 Å), and the distances in the C(2)–C(3)–C(4)–C(5)–C(6) part of the pyridinium ring show little of type (II*b*) alternation.



Second, indices of aromaticity (A) do not give convincing evidence. Julg & François (1967) and Julg (1971) have developed a criterion, the index of aromaticity, to assess relative degrees of delocalization from bond-length data through the equation:

$$A = 1 - \frac{225}{n} \sum_{i=1}^{n} \left(1 - \frac{d_i}{\hat{d}}\right)^2$$

where d_i is the ith bond length and $\hat{d}$ is the average of the n bond lengths. On this scale, benzene has $A = 1$ and a hypothetical Kekulé form of benzene (C=C: 1·34 Å; C–C: 1·47 Å) has $A = 0{\cdot}59$. With heteroaromatic rings one has to take into account the inherent inequivalence of CC and CX bonds. For example, we use different $\hat{d}$ values for CC (1·395 Å) and CN (1·340 Å), determined by Bak, Hansen-Nygaard & Rastrup-Andersen (1958) for pyridine. This modification gives $A = 0{\cdot}95$ (3) for the pyridinium ring of the title compound, indicating that there is no significant difference in π delocalization between this pyridinium ring and pyridine.

Table 3. *Short* O–H···Cl *interaction in obidoxime*

D–H···A	D–H (Å)	A···H (Å)	D···A (Å)	D–H···A (°)
O(2)–H(O2)···Cl*	0·98 (2)	2·0 (2)	2·973 (2)	153 (2)

* Transformation x,y,z.

The pyridinium and oxime parts of the molecule are almost planar. Relative orientations of these parts can be seen from the torsion angles (Table 2). The two pyridinium rings within one molecule are at an angle of 42 (1)°. The cation forms extra links to two symmetry-related Cl^- anions through two symmetry-related hydrogen bridges (Table 3).

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