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SYNTHESIS AND CRYSTAL AND MOLECULAR STRUCTURE OF 1,2-DI(*N*-PIPERIDYL)ETHANE-BIS-*N*-OXIDE TETRAHYDRATE

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ABSTRACT

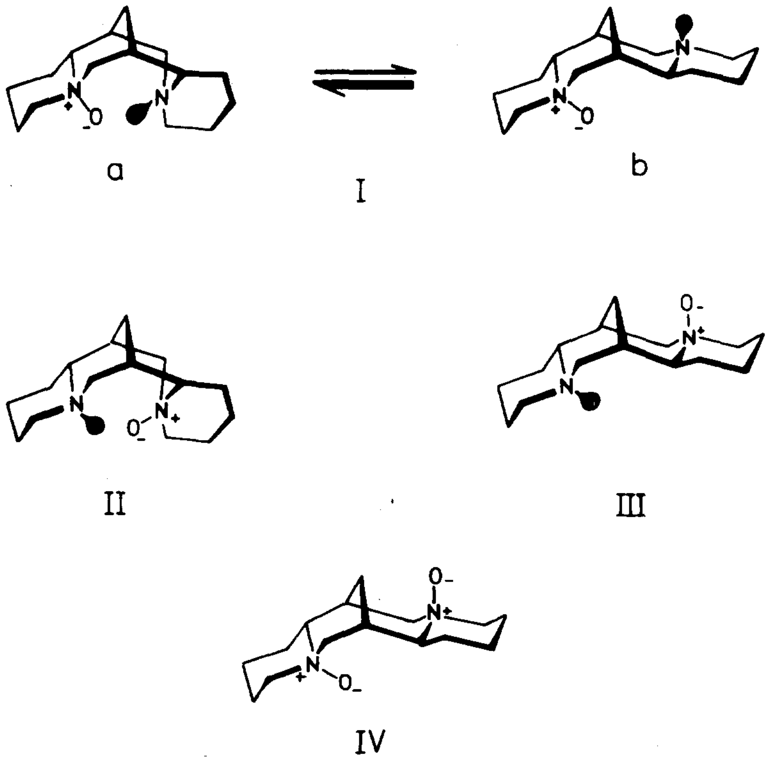
1,2-Di(*N*-piperidyl)ethane-bis-*N*-oxide (VIII) has been synthesized and obtained in crystalline form as VIII · $4H_2O$. IR spectra of these crystals and IR and ^1H NMR spectra of the solutions of VIII are presented and discussed. The pK'_{MCS} and pK'_{H_2O} values for VIII and for similar systems as well as for sparteine and its derivatives are reported and analysed, and structural conclusions are drawn. In a MCS/H_2O (8:2, v/v) system the "cisoidal" rotamers (with intramolecular H bond) seem to prevail for both VIII · H^+ and VIII · $2H^+$ cations, while in H_2O solutions the "transoidal" forms are predominant. Solid state IR spectra indicate that in VIII · $HClO_4$ the VIII · H^+ cation exists in "cisoidal" form and in VIII · $2HClO_4$ the appropriate cation is in "transoidal" conformation and involved in H-bond association with perchlorate anions.

Full X-ray structure determination for VIII · $4H_2O$ is reported. The VIII molecules are located on centres of symmetry. The results are discussed and compared with predictions. The fine network of H bonds in the crystals of VIII · $4H_2O$ is discussed in detail and explanation of the behavior of H_2O molecules in VIII · $4H_2O$ on heating is given.

INTRODUCTION

Systematic investigations of the structure and properties of various isomeric sparteine-mono-*N*-oxides (I, II, III) as well as interesting properties of recently obtained sparteine-bis-*N*-oxide (IV) [1] encouraged us to compare the structure and properties of the compounds (I—IV) with those of mono- and bis-*N*-oxides of simpler cyclic diamines for which the "cisoidal" and "transoidal" orientations of the two N—O or of the N—O and amino functions could be adopted more easily than for compounds I—IV (Scheme 1). Investigations carried out hitherto have indicated that II, III and IV have rigid structures, with frozen conformations, and only in the case of I an equilibrium of conformers Ia and Ib is observed [1] (see Scheme 1).

Model building studies of various simple cyclic diamines have suggested that it would be desirable to investigate primarily the structure and properties of 1,2-dipiperidyl-ethane-*N*-oxides (VII and VIII).



Scheme 1

EXPERIMENTAL

Apparatus, methods, reagents

The IR spectra were recorded on Perkin-Elmer 180 and Perkin-Elmer 580 spectrophotometers using 0.4 M solutions in $CDCl_3$ and 0.1 mm cells with NaCl windows. For solid-state spectra the KBr disc technique was used. ^1H NMR spectra were obtained on a 60 MC Varian EM-360 spectrometer using 10% $CDCl_3$ solutions and TMS as an internal standard. Four-ångström molecular sieves were applied to dry the $CDCl_3$ solutions and the drying process was carried out for 3—4 h immediately before the IR or ^1H NMR spectra were recorded. The pK'_{MCS} values were determined by potentiometric titration in a mixture of methoxyethanol (MCS) and water (8:2, v/v) using an automatic microtitration device from Radiometer SA, Copenhagen. The principles of the pK'_{MCS} measurements have been described earlier [2]. Elemental analyses were carried out using a Perkin-Elmer 240 automatic analyser. Melting points were measured by means of Tottoli apparatus (Büchi Co. Ltd.). For derivatographical analysis an OD102 MOM Derivatograph (Hungary) was used. The progress of the reactions was controlled by TLC on plastic plates (2.5 × 5.0 cm) covered with silica gel type HF with a mixture of acetone and 5% acetic acid (5:2) as developing phase (unfolded doubly). The chromatographic spots were made visible by means of iodine vapor and/or Dragendorff's reagent. The solvents used were purified using common methods described in the literature. The piperidine used for the synthesis of V was a commercial product. $ClCH_2COCl$ was obtained from $ClCH_2COOH$ and PCl_3 according to the procedure described earlier.

N-*(*N*-piperidylacetyl)piperidine (V)*

Compound V was obtained by treating piperidine with $ClCH_2COCl$ according to ref. 3 (70% yield). The raw product was purified by fractional crystallization from n-hexane. The ^1H NMR spectrum in $CDCl_3$ agrees with that described in ref. 4a.

M.p. = 65—66°C is 27°C higher than the value given in ref. 4a and 17° higher than that in ref. 4b. $pK'_{MCS} = 8.05$ (Table 1). X-ray structure analyses (V [5a], V · $HClO_4$ [5b]) proved the expected structure.

N-*(*N*-piperidylacetyl)piperidine-*N*-oxide perchlorate*

N-(*N*-piperidylacetyl)piperidine in CH_3OH solution was neutralized with $HClO_4$. Then a stoichiometric amount of *m*-chloroperbenzoic acid, in small amounts of $C_2H_5OC_2H_5$, was added. After 15 min, ethyl ether was added and a white precipitate was obtained. It was separated on a foam-glass funnel, washed with ethyl ether and dried in the air (yield = 97%).

M.p. = 157—159°C (decomposition). Elemental analysis: calculated: N, 8.57; C, 44.10; H, 7.04(%); found: N, 8.56; C, 43.92; H, 7.08(%). $pK'_{MCS} = 5.90$.

*1,2-di(*N*-piperidyl)ethane (VI)*

Reducing compound V with $LiAlH_4$ in ethyl ether solution according to ref. 3 we obtained a product (95% yield) with the same physical properties as that described in ref. 3.

pK'_{MCS} (1) = 6.10; pK'_{MCS} (2) = 9.10 (Table 1).

*1,2-di(*N*-piperidyl)ethane-bis-*N*-oxide (VIII)*

A quantity (2.94 g; 0.015 M) of VI was dissolved in 3 ml of CH_3OH and treated with 3.04 ml of 30% H_2O_2 ($\sim$0.30 M). The progress of the reaction was controlled chromatographically*. After about 6 h (room temperature) the reaction was over. The excess of H_2O_2 was decomposed with Pd/asbestos.

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*At this concentration of VI and 20-fold excess of H_2O_2, the TLC technique does not record mono-*N*-oxide (VII) formation. The formation of VII can be easily recorded by the use of a solution of VI diluted several times with CH_3OH and with a small excess of H_2O_2.

After 12 h the catalyst was separated by filtration and the filtrate was concentrated by evaporation (to about one third of the starting volume) using a rotary evaporator at lowered pressure. The product was crystallized from the final solution (95% yield) and then recrystallized from warm CH_3OH solution (3 ml) to which 10 ml of acetone was added. Four grams (88%) of the product (m.p. = 134—135°C — melting with decomposition) were obtained.

Elemental analysis: $C_{12}H_{24}N_2O_2 \cdot 4H_2O$ (300); calculated: N, 9.33; C, 48.00; H, 10.67(%); found: N, 9.29; C, 48.06; H, 10.60(%).

TDA results: at 111°C 12% loss of mass is observed and it corresponds to a removal of two water molecules in an endothermic reaction; at 140—150°C, exothermic pyrolytic decomposition takes place. IR spectra are presented in Fig. 1. Attempts to recrystallize VIII from various solvent systems always led to amorphic products or to crystals of the same IR spectra.

^1H NMR spectrum (VIII): 3.87 ppm — 4H singlet; 3.22 ppm — 8H asymmetric quartet; 2.25 ppm — 4H multiplet; 1.63 ppm — 8H multiplet. pK'_{MCS} (1) = 2.70; pK'_{MCS} (2) = 8.20; pK'_{H_2O} (1) = 3.20, pK'_{H_2O} (2) = 6.60 (Table 1).

Perchlorates of compound VIII

VIII · $HClO_4$. One hundred milligrams of VIII · $4H_2O$ was dissolved in five drops of CH_3OH and ethyl ether added till faint turbidity appeared. The mixture was then dropped into the CH_3OH solution of $HClO_4$ (4:1) to reach pH 5 (five drops). The precipitate was separated by decantation. The total yield after recrystallization from acetone was 80 mg (73%).

M.p. = 117°C (decomposition). Elemental analysis: calculated: N, 8.53; C, 43.80; H, 7.61(%); found: N, 8.39; C, 43.93; H, 7.61(%). IR spectrum — see Fig. 2.

VIII · $2HClO_4$. A solution of 100 mg of VIII · $4H_2O$ in 1 ml of CH_3OH was dropped into a 1:3 mixture of $HClO_4$ and CH_3OH to obtain a pH of 1—2. Ethyl ether was added to precipitate the crystals which were separated by decantation and washed with a mixture of CH_3OH and $C_2H_5OC_2H_5$ (1:8). The product was recrystallized from a $CH_3OH/C_2H_5OC_2H_5$ system. Total yield was 86%.

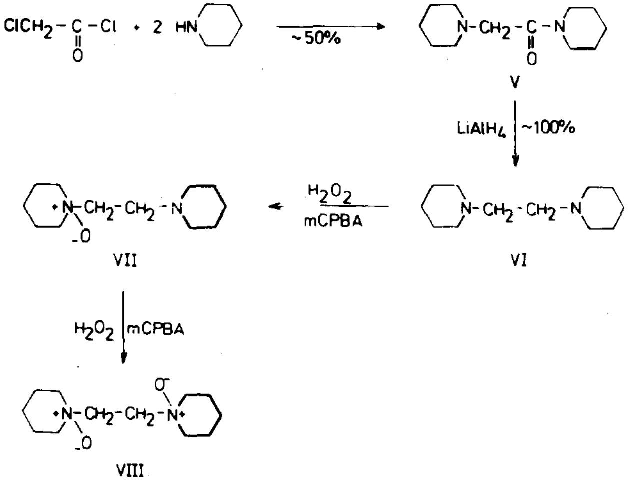
M.p. = 191—210°C (decomposition). Elemental analysis: calculated: N, 6.53; C, 33.60; H, 6.06(%); found: N, 6.34; C, 33.82; H, 6.05(%). IR spectrum — see Fig. 2.

pK'_{MCS} values for sparteine and its derivatives

The pK'_{MCS} values for sparteine, its *N*-oxides (II, III, IV) and for 2-oxosparteine (IX) and its *N*-oxide (X) agree with those reported earlier [1, 6].

SYNTHESIS, PROPERTIES AND STRUCTURAL CONSIDERATIONS

1,2-Di(*N*-piperidyl)ethane (VI) has already been described [3], but its *N*-oxides have not been known till now. We obtained compound VI in a two-step reaction through amide V [3] according to Scheme 2. Compound VI could be easily converted into its bis-*N*-oxide (VIII) by treating it with either H_2O_2 or *m*-chloroperbenzoic acid. The reaction from VI to VIII proceeds through the mono-*N*-oxide (VII) stage, but this intermediate product has not been isolated as yet. Attempts to obtain 1,2-di(*N*-piperidyl)-ethane-mono-*N*-oxide (VII) are in progress now and the present work deals with bis-*N*-oxide (VIII) only.

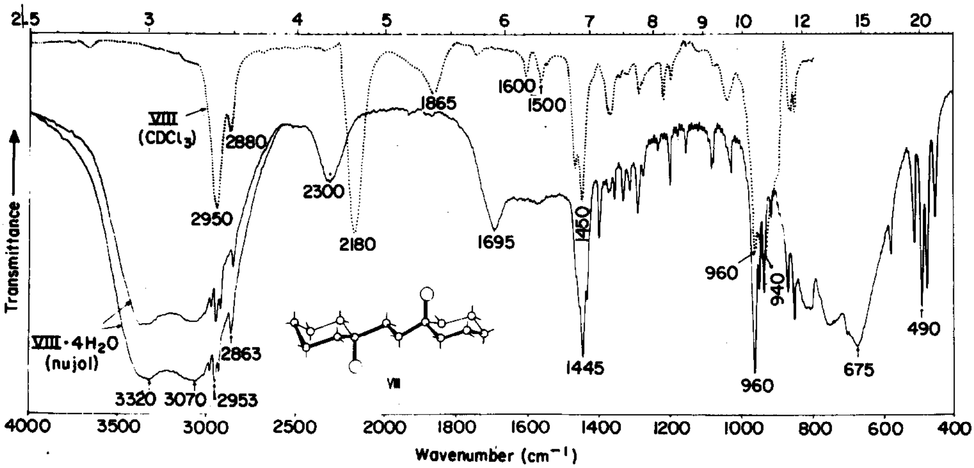


Scheme 2

1,2-Di(*N*-piperidyl)ethane-bis-*N*-oxide (VIII) easily crystallizes as a hydrate: VIII · nH_2O, the number of water molecules n being, as established from elemental analysis and X-ray studies, equal to 4. The VIII · $4H_2O$ crystals are relatively non-hygroscopic and show only some tendency to attract moisture when exposed to contact with air. They also seem to be the only stable crystalline form of VIII, since the numerous attempts to obtain another polymorphic phase have always led to the same form of VIII · $4H_2O$ or to amorphic material.

The IR spectrum of VIII · $4H_2O$ (Fig. 1) shows intense bands interpreted as stretching and bending vibrations of H-bonded OH groups, the H bonds being intermolecular ones. The positions of these bands — 3320, 3070, 2300, 1695, and ~675 cm^{-1} —attest to a very fine network of H bonds in the crystals of VIII · $4H_2O$. The $\nu\dot{N}$—O band is strong and sharp and located at 960 cm^{-1}.

VIII · $4H_2O$ dissolves slowly in chloroform but only in the presence of molecular sieves which destroy the network of H bonds by adsorbing water molecules. An IR spectrum of such a solution shows three very strong, complex



absorption bands at ~2900 cm^{-1} (νCH), ~1450 cm^{-1} (δCH) and ~950 cm^{-1} ($\nu\overset{+}{N}—\bar{O}$). A solution of VIII in $CDCl_3$ absorbs strongly at ~2180 cm^{-1} and this band can be attributed to the $\nu Cl_3C—D \cdots \bar{O}—\overset{+}{N}$ vibrations [6], see Fig. 1.

In the ^1H NMR spectrum of anhydrous VIII (in $CDCl_3$) there are, as could be expected, three groups of methylene proton signals.

(a) 4H singlet at 3.87 ppm — exocyclic α-methylene protons.

(b) 8H asymmetric quartet at 3.22 ppm — endocyclic α-methylene protons.

(c) 12H very broad multiplet at 2.25 and 1.63 ppm — β- and γ-methylene protons.

The band (c) is a complex one but it can be separated into a broad 4H multiplet, with a centre of gravity at 2.25 ppm, and a narrower 8H multiplet at 1.63 ppm. The double resonance technique unequivocally indicates that the signals at 3.22 and 2.25 ppm are conjugated, since with appropriate irradiation the former becomes a singlet while the latter one becomes an irregular doublet. The above facts imply that the broad multiplet at 2.25 ppm originates from Cβ axial or equatorial protons. Addition of TFA to the $CDCl_3$ solution of VIII results in an appreciable downfield shift of (a) and (b) bands from 3.87 and 3.22 ppm to 4.36 and 3.70 ppm, respectively. Also, the main part of the (c) band shifts downfield (from 1.63 to 1.93 ppm) and at the same time the 4H signal at 2.25 ppm completely disappears. Thus, the 2.25 ppm band is the resonance signal of the Cβ axial protons which are deshielded by the axial *N*-oxide O atoms. An addition of TFA leads to a protonation of these O atoms and they lose their partial negative charges and, in consequence, the ability of deshielding the *cis*-axial protons at Cβ.

Table 1 contains pK'_{MCS} and pK'_{H_2O} values for compounds II, III, IV and sparteine as well as for *N*-(*N*-piperidylacetyl)piperidine (V) and 2-oxosparteine (IX) and their *N*-oxides (XI and X). Analysis of the contents of Table 1 as

TABLE 1

pK′ values for some tertiary amines (R_3N) and their *N*-oxides (R_3NO) determined in methoxyethanol—water solutions (8:2, v/v), pK'_{MCS} [2], and in some cases in water solutions, pK'_{H_2O}

Compound	pK′				ΔpK′			
	MCS		H_2O		MCS		H_2O	
	(1)	(2)	(1)	(2)	(2) − (1)	(R_3N) − (R_3NO)[a]	(2) − (1)	(R_3N) − (R_3NO)[a]
Sparteine	3.05	10.26	—	—	7.21	—	—	—
Sparteine-N_{16}-oxide (II)	2.56	11.94	—	—	9.38	1.68	—	—
Episparteine-N_{16}-oxide (III)	4.25	6.70	—	—	2.45	3.56	—	—
Sparteine-bis-*N*-oxide (IV)	4.30	6.60	—	—	2.30	3.66	—	—
2-Oxosparteine (IX)	—	8.03	—	—	—	—	—	—
2-Oxosparteine-*N*-oxide (X)	—	5.90	—	—	—	2.13	—	—
N-(*N*-piperidylacetyl)-piperidine (V)	—	8.05	—	8.70	—	—	—	—
N-(*N*-piperidylacetyl)-piperidine-*N*-oxide (XI)	—	5.90	—	5.20	—	2.15	—	3.50
1,2-Di(*N*-piperidyl)ethane (VI)	6.10	9.10	6.40	9.50	3.00	—	3.10	—
1,2-Di(*N*-piperidyl)ethane-bis-*N*-oxide (VIII)	2.70	8.20	3.20	6.60	5.50	0.90	3.40	2.90

[a] In the case of diamine and diamine-mono- and -bis-*N*-oxides it is the difference between pK′ (2) of R_3N and pK′ (2) of R_3NO.

well as of spectroscopic data leads to the following preliminary structural conclusions concerning VIII and its mono- and di-protonated cations (VIII · H^+ and VIII · $2H^+$).

(1) Compound VIII is a markedly stronger base than sparteine-mono- and bis-*N*-oxides III and IV in which the rigid "transoidal" orientation of the *N*-oxide and tert amino groups (III) or of both the *N*-oxide groups (IV) precludes intramolecular H bond formation.

(2) VIII is also a stronger base than 2-oxosparteine-*N*-oxide (X) and *N*-(*N*-piperidylacetyl)piperidine-*N*-oxide (XI). Basicities of the two latter *N*-oxides are lower by about 2 pK'_{MCS} units, than those of the corresponding parent amines (IX and V, respectively), while VIII is less basic than its parent amine by only 0.9 pK'_{MCS} units.

(3) The pK'_{MCS} (2) value for VIII is 1.6 units greater than for IV and from this we may conclude that, in the mono-protonated VIII · H^+ cation, an intramolecular H bond between the two *N*-oxide groups is formed. Formation of such a bond is possible only in the case of a conformer with "cisoidal" orientation of the N—O groups (VIIIc), which resembles the conformation of II · H^+ in this respect. Comparison of $\Delta pK'_{MCS}$ values for II and VIII (which are —1.68 and 0.9, respectively) indicates that the intramolecular H bond in VIII · H^+ is much weaker than that in II · H^+. In the latter case this bond is stabilized by rigid conformation with favourable orientation of the two proton-acceptor groups, while in the case of VIII these groups are free to rotate and the VIIIc form is thermodynamically less stable than the forms VIIIa and VIIIb. A

relatively high pK'_{MCS} (2) value for VIII attests to the fact that in the MCS/H_2O (8:2, v/v) solution VIII · H^+ exists as a VIIIc conformer, but this form is probably in tautomeric equilibrium with protonated forms of VIIIa and VIIIb. The absence of the $\nu\overset{+}{N}$—OH band in the solid state IR spectrum of VIII · $HClO_4$ along with the broad absorption (with distinct minima) in the 1300—800 cm^{-1} region seem to attest to the presence of intramolecular H bonding in solid-state VIII · $HClO_4$. However, the low solubility of this salt in $CHCl_3$ renders it impossible to give spectroscopic evidence for the existence of an intramolecular H bond in the crystals of VIII · $HClO_4$.

(4) Further protonation of VIII · H^+ in MCS/H_2O (8:2, v/v) solution leading to VIII · $2H^+$ is probably not connected with a severe change of conformation

$$\text{VIIIc} \cdot H^+ \overset{+\overset{+}{H}}{\not\longrightarrow} \text{VIIIa} \cdot 2H^+ \ (\text{VIIIb} \cdot 2H^+)$$

since the pK'_{MCS} (1) value for VIII is low (2.70, see Table 1) and 1.60 units less than the corresponding value for IV (4.30). In bis-protonated IV · $2H^+$ cation, the *N*-oxide functions are in "transoidal" conformation. On the other hand, in spite of the possibility of free rotations around the σN—C and σC—C bis-methylene-bridge bonds in VIII · $2H^+$, the *N*-oxide functions retain in the MCS/H_2O solution (8:2, v/v) the "cisoidal" arrangement. It is probably due to a specific solvation of VIIIc · $2H^+$ in this solvent system which seems to stabilize the intramolecular H bond in VIIIc · $2H^+$ (see Scheme 4).

There is, however, a significant change of the VIII · $2H^+$ di-cation structure in water solution. This is concluded from the pK' values for VIII in water (see Table 1). The $\Delta pK'_{H_2O}$ (pK' (2) — pK' (1)) value for VIII is 3.40, while the $\Delta pK'_{MCS}$ is 5.50. Such a large difference between $\Delta pK'_{MCS}$ and $\Delta pK'_{H_2O}$ for VIII (2.10) results from the 0.5 unit increase from pK'_{MCS} (1) to pK'_{H_2O} (1) and from the 1.6 unit decrease from pK'_{MCS} (2) to pK'_{H_2O} (2). Thus, the amount of intramolecularly H-bonded mono- and di-cations of VIII · H^+ and VIII · $2H^+$ in water solution must decrease significantly, or perhaps these forms do not exist at all in water solution as a result of solvation of the thermodynamically more stable form VIIIa (or VIIIb) with "transoidal" *N*-oxide groups.

The analysis of pK'_{MCS} and pK'_{H_2O} values for VIII (see Table 1) encourages us to propose schematically the dynamical conformational equilibria for mono- and di-cations of VIII in MCS/H_2O and H_2O solutions (Scheme 4). We assume that in MCS solutions of both VIII · H^+ and VIII · $2H^+$ the "cisoidal" (VIIIc) rotamers prevail while in water solutions the "transoidal" rotamers are predominant.

As mentioned above, the analysis of the IR spectrum of crystalline VIII · HClO indicates the VIIIc · H^+ is the only rotamer present in the crystal structure. On the other hand the pure VIIIa · $2H^+$ rotamer is probably found in the crystals of VIII · $2HClO_4$. Evidence for this can be found in the IR spectrum of this salt (nujol, KBr; Fig. 2), in which there is only one strong $\nu\overset{+}{N}O$—H band at 3120 cm^{-1} indicating that both the hydroxammonium groups are involved in the same intermolecular associations with perchlorate anions. These interactions must be rather strong since the perchlorate νCl—O band, usually very strong and with one broad maximum at ~1090 cm^{-1}, is evidently split, the positions of the two maxima being 1120 and 1030 cm^{-1}. Also, in the overtone region, instead of one band at 1980 cm^{-1}, there is a doublet with maxima at 2020 and 1890 cm^{-1}. Assuming symmetrical "transoidal" (VIIIa) structure for VIII · $2HClO_4$ and a bifurcated H bond between each hydroxammonium group and two perchlorate anions, one can propose a symmetrical system of polyassociations (presented in Scheme 5) which accounts for the perchlorate absorption band split in the IR spectrum of VIII · $2HClO_4$.

(5) The conformation of the free-base form of VIII remains to be discussed. Conformational analysis suggested that the VIIIa rotamer should prevail*. It was, however, still an open question whether the water molecules in the crystals of VIII · $4H_2O$ stabilize this thermodynamically favourable conformation or whether the packing and intermolecular H-bond formation requirements favour another conformation (for example VIIIb). Also, the coexistence of different rotamers in the crystal lattice of VIII · $4H_2O$ could not be rejected without further investigation. All these questions could be answered only by an X-ray structure determination carried out for VIII · $4H_2O$. As a matter of fact, the structural hypotheses proposed for VIII · $HClO_4$ and for VIII · $2HClO_4$ need to be fully proved and this could be accomplished best by means of X-ray structure analysis as well. Nevertheless, we decided to undertake an X-ray investigation of VIII · $4H_2O$ in the first place, since besides the reasons outlined above we hoped to get information to explain the curious behavior of the water molecules in the crystal lattice on heating that was recorded during the derivatographical analysis and observed during the m.p. measurements. On heating, only two water molecules could be removed from the lattice of VIII · $4H_2O$ (at a temperature of 111°C) and the remaining water was liberated in a violent pyrolytic reaction at 140—150°C. Investigation of the products of the pyrolysis of VIII · $4H_2O$ is in progress now.

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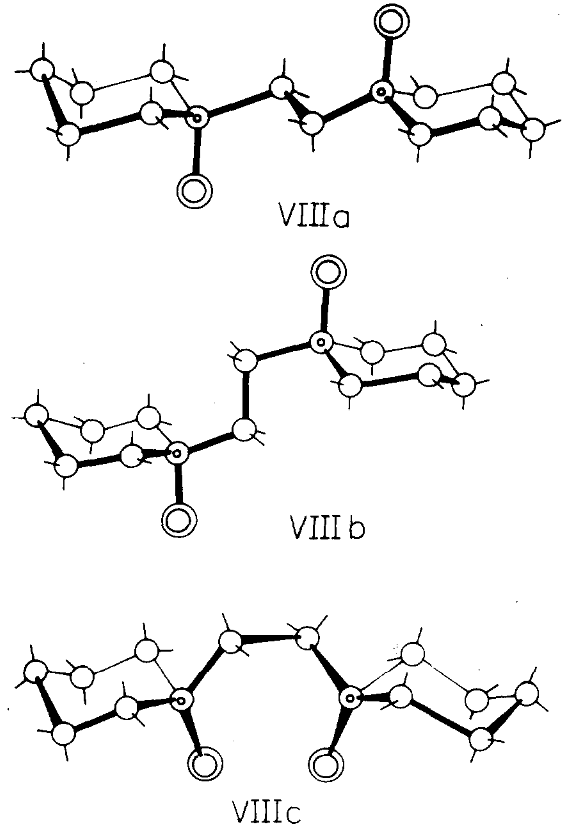
*Taking into account the isolated VIII molecule with the rings in chair conformations, the O atoms being axial, and carrying out a model building study, one will find that the possible molecular conformations are restricted to those with the bridging C—C bond (C_b—C_b) in *trans* orientation. Of these, however, the most probable are the two with both the O—N—C_b—C_b torsion angles in a *gauche* region, since in this way the number of short H · · · H repulsive contacts is minimized. In one of them, the two O—N—C_b—C_b torsion angles are of the same sign, while, in the other, they have different signs. In the latter case the distance between the two negatively charged O atoms is greater than in the former one and thus we may conclude that the preferred molecular conformation of a free VIII molecule is that described in the following way

$$\mathrm{O{-}{-}{-}N}\underset{+}{\overset{gauche}{\text{---------}}}\mathrm{C_b}\overset{trans}{\text{---------}}\mathrm{C_b}\underset{-}{\overset{gauche}{\text{---------}}}\mathrm{N{-}{-}{-}O} \qquad (A)$$

and presented as VIIIa.



Scheme 3

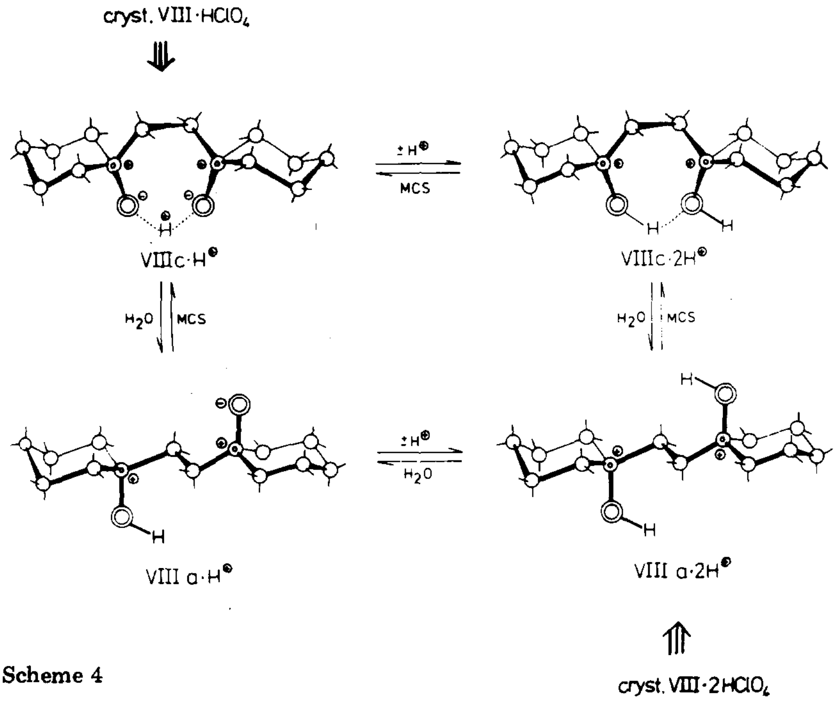
X-RAY STRUCTURE DETERMINATION

Data collection

The crystals of VIII · $n\mathrm{H_2O}$ were obtained by recrystallization from methanol acetone solution. Preliminary values of unit-cell parameters were established from precession and Bouman—de Jong photographs. From the symmetry of diffraction patterns and from systematic absences the space group was determined to be $P2_1/\mathrm{n}$.

Density measurements by the flotation method gave the value of 1.235 g cm^{-} for d_m and from this the number of water molecules in one formula unit was deduced to be $n = 4$ and the number of formula units in the unit cell (Z) was established as two. Precise unit-cell constants were determined by least-squares fit of the setting angles of 15 counter reflexions, and their values, as well as other crystal data, are presented in Table-2.

Intensity measurements were carried out on a Syntex $\mathrm{P2_1}$ four-circle diffractometer using a crystal with dimensions 0.36 × 0.37 × 0.32 mm. Since the



Scheme 4

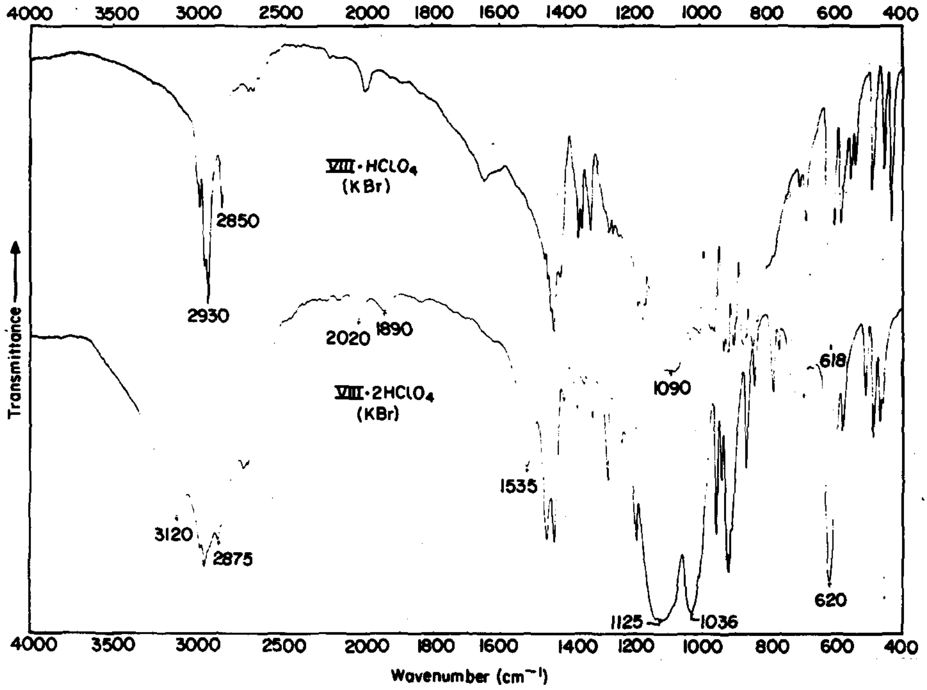
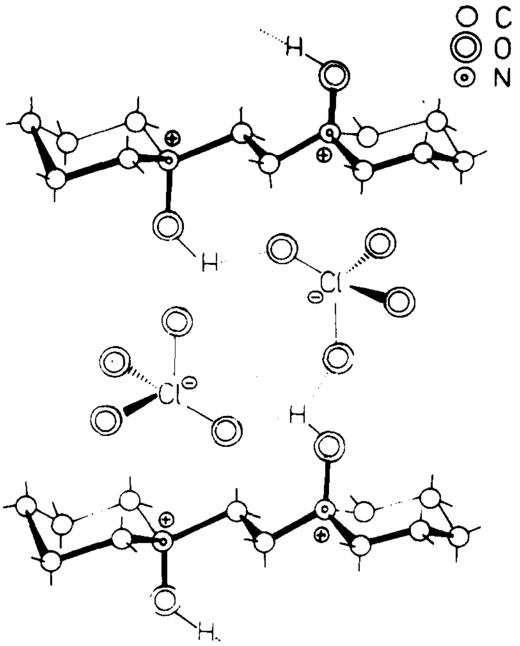


Fig. 2. IR spectra of VIII · $HClO_4$ and VIII · $2HClO_4$ (KBr).



VIII·2HClO$_4$

Scheme 5

crystals attracted some moisture from the air, this specimen was sealed in a glass capillary. Eleven hundred and ten independent reflexions were collected

TABLE 2

VIII · 4H$_2$O — crystal data

$C_{12}H_{24}N_2O_2 \cdot 4H_2O$

F.W. = 300.5
Dec. temp. = 135°C
Monoclinic
Space group $P2_1/n$

Unit-cell parameters
a = 10.488(3) Å
b = 6.773(1) Å
c = 12.411(2) Å
β = 112.6(2)°
V = 814.0 Å^3
d_m = 1.235 g cm^{-3}
d_c = 1.230 g cm^{-3}
Z = 2
F_{000} = 332
$\mu_{CuK\alpha}$ = 8.1 cm^{-1}

in a 2θ range up to 116° using graphite-monochromatized Cu$K\alpha$ radiation and a variable θ—2θ scan. Of these, 915 had $I \geqslant 1.96\sigma(I)$ and were considered observed. Structure factors were obtained from the intensities in the usual fashion. No absorption or extinction corrections were applied.

Structure solution and refinement

The structure was solved by direct methods using the computer program MULTAN [7]. Fifteen hundred and eighty-eight Σ_2 relationships were generated for 170 reflexions with $E \geqslant 1.4$. The origin was fixed by 215, 26$\bar{7}$ and 733 reflexions and the multisolution phases were assigned to reflexions $\bar{1}$22, 224 and 44$\bar{5}$. Of the eight generated sets of phases one had markedly better figures of merit, ABS FOM = 1.1372, R_{Karle} = 16.3 and COMB FOM = 3.00, and an E-map calculated for that set revealed the locations of all heavy atoms, including O atoms from water molecules. Full-matrix least-squares refinement of their parameters (four cycles in isotropic approximation to an R value of 0.151 and then four cycles using an anisotropic model to an R value of 0.112) was followed by a difference Fourier synthesis which gave the positions of all H atoms including those from water molecules. Each H atom was given an isotropic thermal parameter one unit greater than the isotropic value for the atom to which it was attached and they were allowed to contribute to structure factors although their parameters were not varied. The subsequent four cycles of full-matrix least-squares refinement converged at R = 0.061. A second ΔF map was computed from which improved H atom positions were obtained and the four cycles of refinement that followed gave R = 0.055. The function minimized in the least-squares was $\Sigma w(F_0 - F_c)^2$ with w based on counting statistics: $w = \sigma^{-2}$. At this stage, however, the weighting scheme was changed to one defined as follows

$$w = (|F_0|/F_{\mathrm{LOW}})^2 \quad \text{for} \quad |F_0| < F_{\mathrm{LOW}}$$

$$w = 1 \quad \text{for} \quad F_{\mathrm{LOW}} \leqslant |F_0| \leqslant F_{\mathrm{HIGH}}$$

$$w = (F_{\mathrm{HIGH}}/|F_0|)^2 \quad \text{for} \quad |F_0| > F_{\mathrm{HIGH}}$$

with F_{LOW} = 3.20 and F_{HIGH} = 13.01, and it caused the full-matrix least-squares refinement of the same set of variables as previously to converge at R = 0.049. Exclusion of the four most intense reflexions with $\Delta F/\sigma(F) > 50$ from the refinement yielded a better agreement and the model so obtained, for which R = 0.043 and $R_w = [\Sigma w(F_0 - F_c)^2/\Sigma w F_0^2]^{0.5}$ = 0.050, was accepted as final. The number of observations per parameter varied was 10.0.

All calculations were carried out using Syntex XTL structure determination programs [8] and their local modifications.

Final positional and thermal parameters are given in Tables 3 and 4*.

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*A list of structure factors has been deposited with the B.L.L.D. at Boston Spa, Wetherby, Yorkshire, U.K., as Supp. Pub. No. SUP 26108 (13 pp.).

TABLE 3

Final fractional atomic coordinates × 10^4 and anisotropic temperature factors of non-hydrogen atoms. The anisotropic temperature factor is of the form exp $[-1/4\,(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N	6317(1)	4156(1)	4365(1)	3.66(4)	2.28(4)	3.60(4)	−0.12(3)	1.96(4)	−0.37(3)
O(1)	5361(1)	3725(1)	3246(1)	4.02(4)	2.67(3)	3.49(4)	−0.00(3)	1.51(3)	−0.26(3)
C(7)	5661(1)	5456(2)	4995(1)	4.11(5)	2.72(5)	4.58(6)	−0.18(4)	2.50(5)	−0.85(4)
C(6)	7511(1)	5284(2)	4263(1)	4.06(6)	3.33(5)	5.04(6)	−0.74(4)	2.59(5)	−0.34(5)
C(5)	8250(1)	4040(2)	3672(1)	4.71(6)	4.32(6)	5.86(7)	−0.42(5)	3.47(6)	−0.47(5)
C(4)	8790(1)	2131(2)	4329(1)	4.60(6)	4.93(7)	5.99(7)	0.96(5)	2.93(6)	−0.29(6)
C(3)	7603(1)	1017(2)	4468(1)	4.90(6)	3.20(5)	4.71(6)	1.08(5)	2.34(5)	0.29(5)
C(2)	6859(1)	2277(2)	5046(1)	4.50(6)	2.95(5)	3.86(5)	0.30(4)	2.16(5)	0.40(4)
O(W1)	1428(1)	1589(1)	3018(1)	5.05(4)	4.05(4)	5.03(4)	−0.78(3)	1.02(3)	0.49(4)
O(W2)	3904(1)	334(1)	2885(1)	5.65(5)	3.09(4)	9.53(7)	−0.81(4)	3.16(5)	−0.88(4)

TABLE 4

H-atom fractional coordinates × 10^3 and the isotropic temperature factors used in the least-squares calculations

	x	y	z	B(Å^2)
H(21)	753	272	585	4.3
H(22)	613	159	512	4.3
H(31)	759	−21	496	4.9
H(32)	690	53	367	4.9
H(41)	951	243	519	5.8
H(42)	919	131	388	5.8
H(51)	761	366	287	5.3
H(52)	899	478	357	5.3
H(61)	706	650	375	4.7
H(62)	816	564	510	4.7
H(71)	631	567	577	4.5
H(72)	549	665	454	4.5
H(W11)	121	258	277	5.4
H(W12)	86	87	259	5.4
H(W21)	326	78	294	6.2
H(W22)	437	115	290	6.2

RESULTS AND DISCUSSION

The potential molecular symmetry of VIII is fully retained in the structure, the molecules being located on centres of symmetry. The N—O groups are thus exactly in *trans* orientation.

The labelling sequence, torsion angles in piperidyl ring, bond distances and angles in the heavy-atom skeleton of VIII are shown in Fig. 3. The symmetry code employed in this figure is consistent with the following convention used throughout this paper:

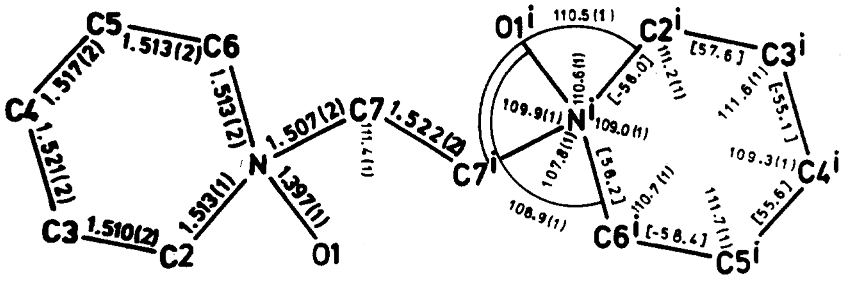

Fig. 3. Piperidyl torsion angles (in square brackets; degrees), and bond distances (Å) and angles (degrees) in the heavy-atom skeleton of VIII.

i	$1-x$	$1-y$	$1-z$
ii	$0.5-x$	$0.5+y$	$0.5-z$
iii	$0.5-x$	$y-0.5$	$0.5-z$

All C—H and O—H bond lengths are listed in Table 5. The mean O—H bond for water molecules is 0.756 Å and the H—O—H angle is 105° for the W1 molecule and 108° for W2. The mean C—H bond length is 1.00 Å while the H—C—H, C—C—H and N—C—H angles are in the range 101.8°–113.6°, with a mean of 109.1°.

The piperidyl ring adopts the usual chair conformation as seen from the torsion angles in Fig. 3. The piperidyl C—C distances agree well with those reported previously for similar systems ([5b] and references therein, [5a]), the mean C—C distance being 1.515 Å.

The mean N—C bond distance is 1.511 Å. As could be expected, it is greater than the usual amine N—C bond lengths since the N atom is a four-substituted one. The *N*-oxide N—O bond length is 1.397(1) Å.

Torsion angles involving both piperidyl and non-piperidyl atoms are shown in Table 6. It is seen from these data that the *N*-oxide bond is in an axial position so that the general rule requiring the more bulky substituent to be in an equatorial position is obeyed. Inspection of the data in Table 6 leads to the conclusion that the actual conformation of the VIII molecule in solid state is almost exactly the same as that predicted for a free molecule (see footnote

TABLE 5

C—H and O—H bond lengths (Å)

C(2)–H(21)	1.03	C(6)–H(61)	1.04
C(2)–H(22)	0.93	C(6)–H(62)	1.03
C(3)–H(31)	1.01	C(7)–H(71)	0.95
C(3)–H(32)	1.04	C(7)–H(72)	0.97
C(4)–H(41)	1.06	O(W1)–H(W11)	0.74
C(4)–H(42)	0.99	O(W1)–H(W12)	0.79
C(5)–H(51)	1.00	O(W2)–H(W21)	0.77
C(5)–H(52)	0.97	O(W2)–H(W22)	0.74

TABLE 6

Torsion angles (degrees) external to the piperidyl ring

O(1)—N—C(2)—C(3)	61.7
C(7)—N—C(2)—C(3)	−176.3
C(7)—N—C(6)—C(5)	178.2
O(1)—N—C(6)—C(5)	−62.6
$C(7^i)$—C(7)—N—O(1)	54.3
$C(7^i)$—C(7)—N—C(2)	−68.1
$C(7^i)$—C(7)—N—C(6)	172.9

p. 85) Therefore, the conformation preferred in the case of a free molecule is retained in the crystals of VIII · $4H_2O$ and we may conclude that the conformation (A) (see footnote p. 85) is advantageous, not only as far as free molecule energy is concerned, but also in that it suits the requirements of close molecular packing, of H-bond formation (with H_2O molecules) and of other intermolecular interactions in the solid state. Figure 4 is a thermal-ellipsoid ORTEP [9] drawing of the molecule of VIII.

The crystal structure contains a fine three-dimensional network of hydrogen bonds in which all water molecules and all *N*-oxide O atoms are involved. The H-bond scheme as well as the molecular packing as viewed along the c axis are shown in Fig. 5 and the H-bond geometry data are contained in Table 7. Each water molecule is involved in three H-bonds: in two of them it acts as an H donor and in one as an acceptor. The *N*-oxide O atom is an acceptor in two H bonds. O(1) is H-bonded to water(2) and water(1) molecules via their H(W22) and H(W12) atoms, respectively. The second water(2) H atom (H(W21)) is used to bind this molecule to another water(1) which in turn uses its H(W11) to form an H-bond with another water(2) molecule. The latter one is linked, via its H(W21) proton, to the water(1) molecule, originally bonded to O(1). This "cyclic" H-bond pattern is included in the H-bond network by its "external" H(W12), H(W22) and H(W11) atoms, by its O(W2) acceptor and

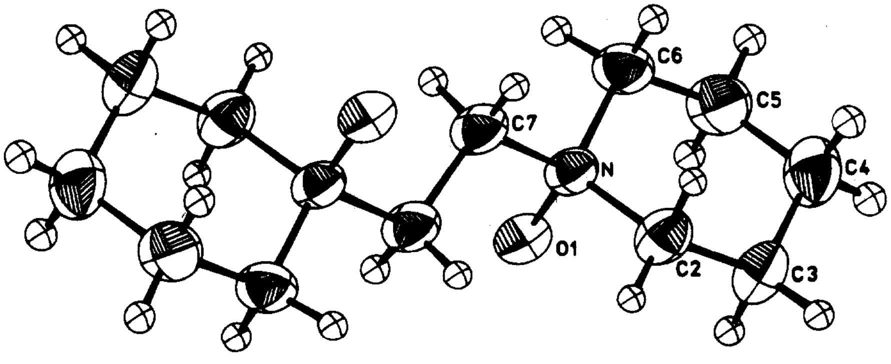

Fig. 4. Thermal-ellipsoid ORTEP drawing of the VIII molecule.

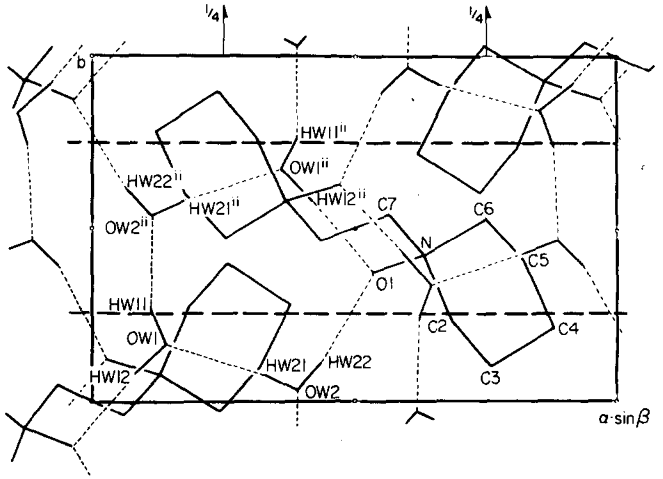

Fig. 5. Projection of the structure down the c axis. Hydrogen bonds are shown as dashed lines. All carbon H atoms have been omitted.

TABLE 7

Hydrogen-bond geometry

D	A	D···· A (Å)	H ···· A (Å)	D—H ···· A (degrees)	H
O(W2)	O(1)	2.699(1)	1.98	162.5	H(W22)
O(W1^{ii})	O(1)	2.735(1)	1.95	169.6	H(W12^{ii})
O(W2)	O(W1)	2.797(2)	2.03	172.2	H(W21)
O(W1^{iii})	O(W2)	2.740(1)	2.01	166.3	H(W11^{iii})

by the (O—N—C$_b$)$_2$ bridge from the VIII molecule, the terminal atom of which (O(1^i)) is the starting point for another similar system. The "five-membered ring" of intermolecular H-bonds as well as its connections with the entire H-bond system are easily seen from Fig. 5. Two water molecules of each type and one *N*-oxide O atom are involved in each "H-bond ring". Adding up the three H-bond O ··· O distances for each water molecule one obtains the following values: 8.272 Å for W1 and 8.236 Å for W2. The difference between these two values is not very large (0.036 Å — in fact it is the difference between the two O(W) ··· O(1) distances), but it does show that the different H_2O molecules are held in the structure of VIII · $4H_2O$ with different strengths. Thus, it is probably the W1 molecule that is removed from the lattice during the endothermic process at 111°C, since its connections in the structure are weaker.

Attempts to recrystallize the VIII · $2H_2O$ product obtained from VIII · $4H_2O$ by heating it over P_2O_5 have been, up till now, unsuccessful. Because it easily absorbs water from its environment, the above product converts readily back into VIII · $4H_2O$.

The results concerning the crystal and molecular structure of VIII · $4H_2O$ presented in this work suggest that it would be desirable to undertake X-ray structure investigations of VIII · $HClO_4$ and of VIII · $2HClO_4$. Crystals of both these compounds are anhydrous and thus there will be other factors responsible for the stabilization of the rotamers in the crystal structure.

Studies on the structures of VIII · $HClO_4$ and VIII · $2HClO_4$ are in progress.

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