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Molecular geometry and optical activity of *N*-nitroso-2,2,6,6-tetramethylpiperidines generated by spontaneous crystallization and inclusion complexation with optically active diols

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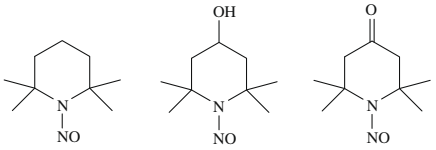
ABSTRACT

Three sterically strained *N*-nitrosamines and their inclusion complexes with optically active diols (TADDOLs) were obtained and their solid state crystal structures are described. Owing to the formation of *N*-nitroso-4-hydroxy-2,2,6,6-tetramethylpiperidine **2** as spontaneously resolvable conglomerate crystals (space group $P3_2$) its solid state CD was measured. The crystal structures of the inclusion complexes revealed that in all cases the guest nitrosamines assume chiral conformations as seen by their chiroptical spectra. The optically active nitrosamines are configurationally labile and rapidly racemize in solution. The solid state structures revealed that in order to avoid an allylic 1,3-strain [$A^{(1,3)}$], caused by an interaction of the nitrosamino group with the methyl substituents, the piperidine ring in **1** and **2** assumes a chair conformation significantly flattened at the amino nitrogen whereas in the 4-oxo derivative **3** the piperidine ring assumes a twist-boat conformation.

1. Introduction

N-Nitrosamines have attracted considerable interest over the past two decades since many compounds of this class are known to be potential carcinogens and mutagenic agents.[1] Since the molecular geometry and conformational properties critically influence the biological activity, the stereochemistry of *N*-nitrosamines has been the subject of many experimental and theoretical investigations.[2] In the case of piperidines a substitution of the nitrogen with an NO group strongly affects the conformation of the six-membered ring and the orientation of substituents. Due to so called allylic 1,3-strain [$A^{(1,3)}$][3,4] caused by an interaction of the planar *N*-nitrosamine system with the nearly coplanar equatorial substituents at C-2 and C-6 of *N*-nitroso-*cis*-2,6-dimethylpiperidine, this compound exists in solution almost exclusively in a diaxial conformation.[5] Similarly, its 2,6-diphenyl analogue prefers the sterically constrained diaxial conformation in the solid state as well as in solution, to relieve the more severe $A^{(1,3)}$ strain.[6]

However, in the case of *N*-nitroso-2,2,6,6-tetramethylpiperidine **1**, the $A^{(1,3)}$ strain cannot be avoided by inversion of the ring but instead the molecule may assume a non-chair conformation and/or increase a pyramidal character of the amino nitrogen. Continuing an interest in the stereochemistry and spectroscopy of *N*-nitrosamines,[4,7] we performed structural and spectroscopic studies on the sterically overcrowded compounds **1**–**3**.



1 **2** **3**

4, $R^1 = R^2 = CH_3$
5, $R^1 = R^2 = (CH_2)_5$

The introduction of the NO group at the nitrogen atom lowers the symmetry of the secondary amines and in the absence of any improper symmetry axis, *N*-nitrosamines **1**–**3** are chiral and may exist in two enantiomeric forms. Their chirality results from a hindered rotation about the partial double N–N bond and interconversion between the enantiomers may occur by rotation of the NO group or, as in case of **1** and **3**, by inversion of the six-membered ring. A chiral discrimination occurring during the complexation of *N*-nitrosamines with the optically active diols (*R*,*R*)-**4** and (*R*,*R*)-**5** allowed us to obtain the compounds **1**–**3** in the optically active forms and measure their solid state CD spectra. Furthermore, the 4-hydroxy derivative **2** crystallizes as a conglomerate that leads to spontaneous generation of chirality.[8]

2. Results and discussion

N-Nitrosamines **1**–**3** were prepared by nitrosation of the corresponding amines with HNO_2.

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Compound **1** is a liquid at ambient temperature but **2** and **3** are solids. The diffraction quality crystals of **2**, which were grown from water–methanol, belong to the enantiomorphous space group $P3_2$ (or $P3_1$). Usually this means that during crystallization, the racemic mixture forms a conglomerate, that is, a mechanical mixture of homochiral crystals where each single crystal contains only one enantiomer.[8]

Spontaneous generation of chirality is a rare phenomenon that receives considerable attention due to it being one of the simplest and least expensive methods for the preparation of enantiomerically pure compounds.[8] It may also be responsible for the prebiotic origin of chirality.[9] The crystal structure of **2** revealed that the piperidine ring adopts an intermediate conformation between the chair and sofa, as evidenced by the Cremer and Pople puckering parameters[10] and the hydroxyl group occupies an equatorial position. The ring is significantly flattened at the amino nitrogen, which shifts the equatorial methyl substituents out of the plane of the nitrosamino group and minimizes the $A^{(1,3)}$ strain (Fig. 1). The strain is further diminished by a pyramidalization of the amino nitrogen as shown by its displacement of 0.130 (4) Å from the plane formed by three neighbouring atoms. The O–H···O hydrogen bonds between the hydroxyl groups assemble the molecules of **2** into a helical structure running along the three-fold screw axis of the crystal.

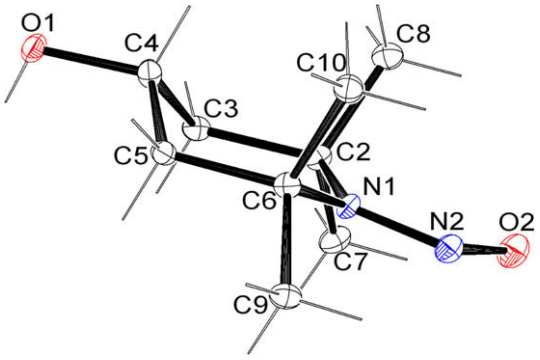


Figure 1. An ORTEP representation of **2** showing the piperidine ring conformation.

The optical activity of the single crystals of **2** was confirmed by the solid state CD spectrum taken in a KBr disk (Fig. 2), which shows a strong Cotton effect near 400 nm corresponding to the n–π^* electronic transition of the NNO chromophore. It is noteworthy that compound **2** absorbs at ca. 30 nm longer wavelengths than simple nitrosamines.[11,12] Apparently the non-planarity of the chromophore is responsible for a bathochromic shift of the n–π^* transition.

Our earlier results have shown that the resolution of racemic nitrosamines can be achieved by inclusion complexation with chiral hosts.[7a–c] Particularly useful as host compounds were the diols (*R*,*R*)-**4** and (*R*,*R*)-**5** known as TADDOLs (α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanols) which are easily accessible from (+)-tartaric acid.[13] The inclusion complexes of compounds **1**–**3** with (*R*,*R*)-**4** and (*R*,*R*)-**5** were obtained by co-crystallization of equimolar amounts of the components from toluene and hexane at room temperature. Since the nitrosamine n–π^* absorption band remains far outside the absorption range of hosts **4** and **5**, the optical activity of the guest molecules can be easily detected by CD measurements of the complexes. Thus the solid state CD of the complex **2**·**4** exhibits a strong positive Cotton effect at 404 nm (Fig. 2). The spectrum closely resembles that one shown by the crystals of the pure guest **2**. According to our helicity rule for *N*-nitrosopiperidines,[7b] the positive n–π^* Cotton effect indicates an (*R*)-configuration for guest molecule **2** (Scheme 1). Unfortunately, complex **2**·**4** does not form crystals suitable for X-ray analysis and this assignment cannot be verified by the crystal structure.

Due to the rapid racemization of the title nitrosamines, attempts to measure the CD of **2**·**4** in solution at room temperature failed. However, upon dissolution of the complex in toluene at −20 °C, a relatively strong Cotton effect was detected near 410 nm. Its intensity gradually decreases and vanished completely after ca. 2 h (Fig. 3). In an analogous experiment performed at 5 °C, complete racemization occurred after 15 min. The first-order rate constant k of racemization at −20 °C was derived from the linear regression of $\theta(t) = \exp(-2kt)$ of 0.0005 s^{-1} and corresponds to the N–N rotation energy barrier $\Delta G^{\ddagger}$ of 77.6 kJ mol^{-1}. This value

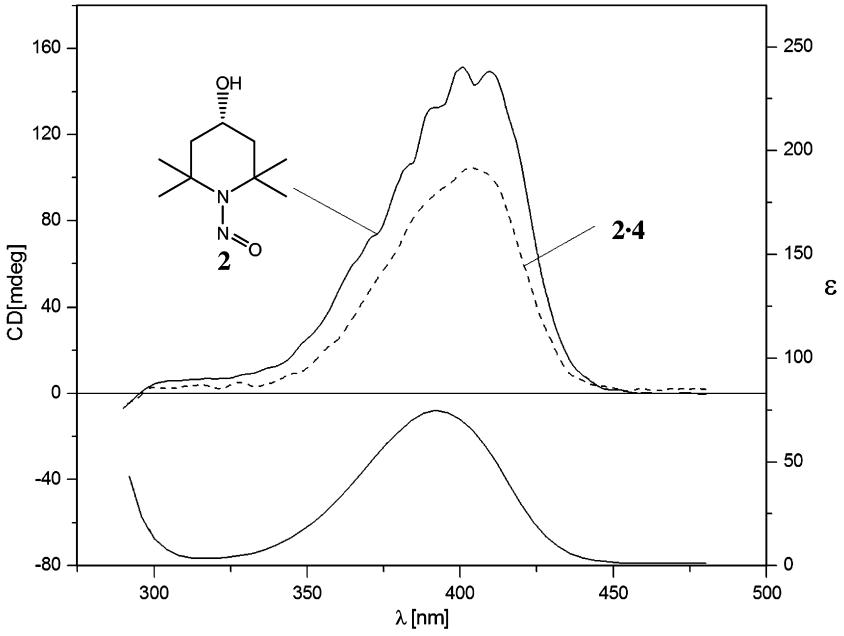
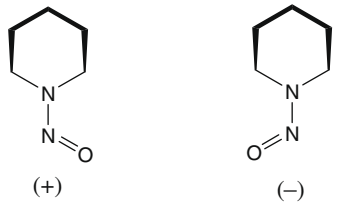


Figure 2. Solid state CD spectra of the nitrosamine **2** and the complex **2**·**4** taken in KBr disks (solid and broken line, respectively) and UV-vis spectrum of **2** measured in methanol.



Scheme 1.

is significantly lower than that found for **1** (82 kJ mol^{-1}) from the ^{1}H NMR measurements.[14,15] These values are unusually low in comparison with typical nitrosamines such as *N*-nitrosopiperidine (93.0 kJ mol^{-1}),[15] that results from the significant deviation of the nitrosamino chromophore from planarity

The non-planarity of the nitrosamino chromophore in **1** is suggested by a bathochromic shift of its n–π^* transition (λ_{max} 397 nm in cyclohexane). Although **1** is itself a liquid, it forms a crystalline complex with (*R,R*)-**5**. Thus the geometrical parameters of the guest molecule **1** trapped in the chiral host lattice were determined by X-ray structural analysis (Fig. 4).

In the asymmetric unit there is one molecule of (*R,R*)-**5** and one molecule of **1** forming a host–guest pair via hydrogen bond between the hydroxy group of the host and the nitroso group of the guest molecule. The piperidine ring of **1** assumes a conformation intermediate between the chair and sofa (Fig. 5). The absolute configuration of the guest **1** embedded in the host matrix of (*R,R*)-**5** was determined as *pS* (planar chirality).[16] The solid state CD spectrum of **1**·**5** shown in Figure 5 exhibited a positive Cotton effect at 375 nm that according to the helicity rule also points to the (*pR*)-configuration of the guest molecule. In the case of **1**, the racemization can occur not only by rotation of the nitroso group, but also by inversion of the piperidine ring. Since the energy barrier of the second process is much lower (less than 25 kJ mol^{-1})[17] than that of the first one, the CD cannot be measured in solution.

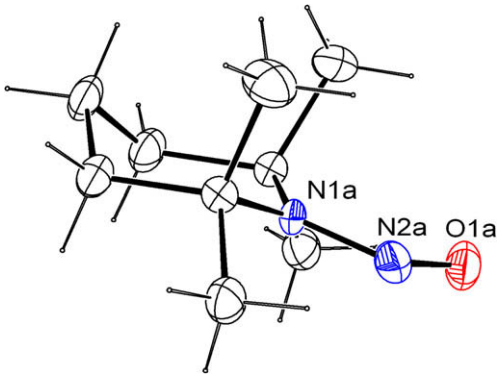


Figure 4. An ORTEP drawing of the guest molecule (*pR*)-**1** in the inclusion compound **1**·**5**.

The crystal structure of **3** revealed that the nitrosamine molecules are disordered and that each site in the crystal is occupied by two enantiomers in an 88:12 ratio. The piperidine ring assumes a twisted-boat conformation that diminishes the interaction between the methyl substituents and the nearly planar nitrosamine moiety. The two components occupying the same site in the crystal show the enantiomeric piperidine ring conformations whereas the *N*-nitroso group is common to both components (Fig. 6).

Boat-type conformations of the guest molecule **3** were also detected in the crystal structure of the inclusion complex **3**·**5$_2$**·H_2O (Fig. 7). The N–NO group is disordered over two positions and the occupancy factors of the two orientations are close to 0.5. For this reason, the solid state CD spectrum does not show a measurable Cotton effect in the region of the nitrosamine n–π^* transition, however, it exhibits a relatively strong CD band with a pronounced vibronic structure at 265 nm corresponding to the ketone n–π^* excitation (Fig. 8). Its sign is determined by the geometry of the six-membered ring and thus the absolute conformation of the

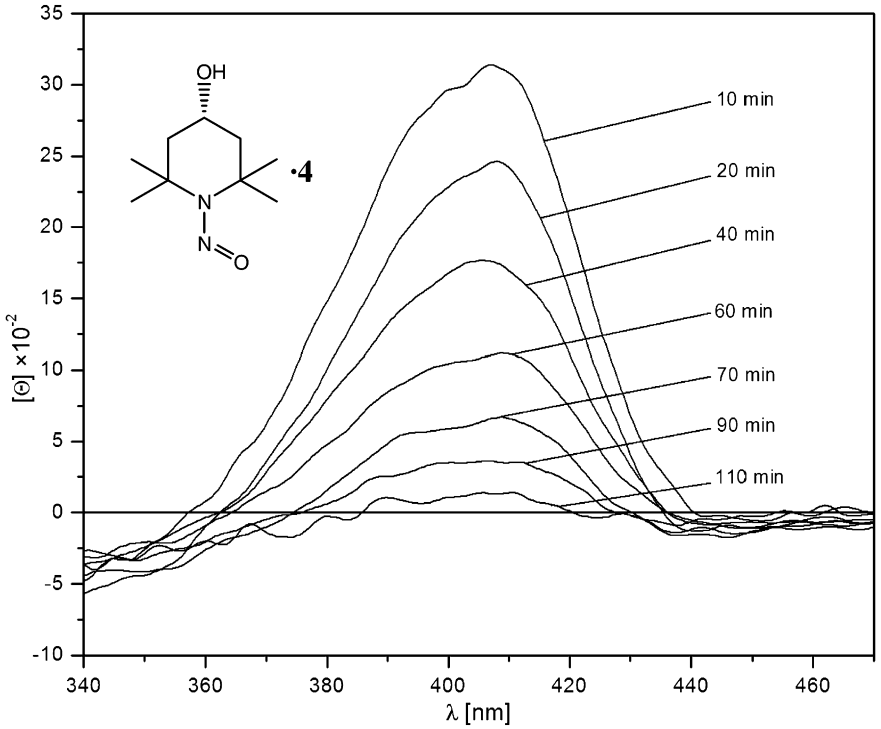


Figure 3. Decay of the CD signal of the complex **2**·**4** at −20 °C in toluene.

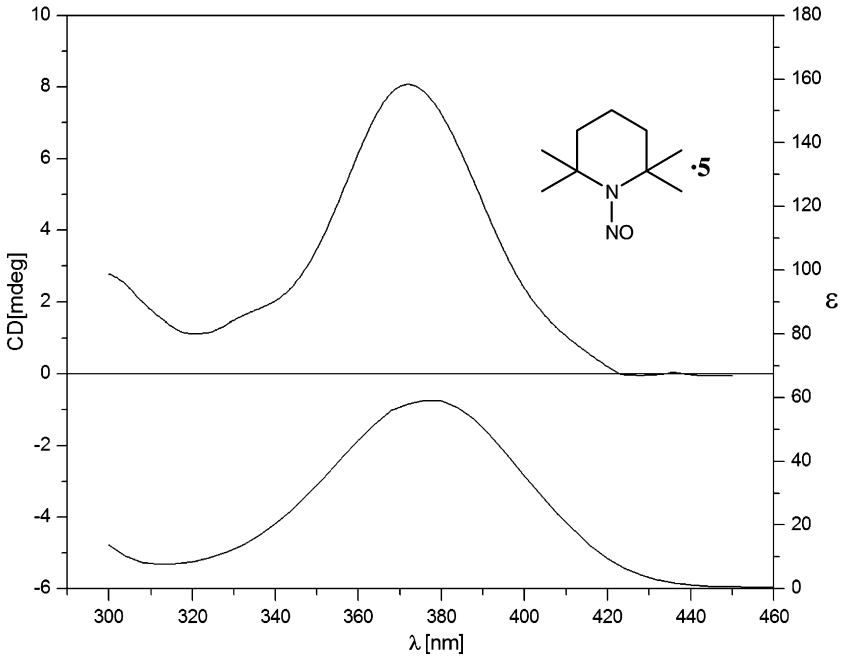


Figure 5. Solid state CD spectrum of the complex **1**·**5** taken in KBr disks and UV–vis spectrum of **1** measured in cyclohexane.

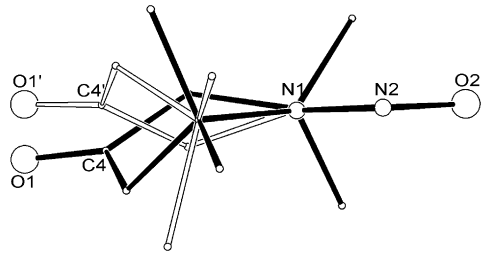


Figure 6. A twisted-boat conformation of **3** viewed along the piperidine N1–C2 bond. The disordered minor component is shown with empty lines (notice an approximately mirror-plane relationship between the two disordered piperidine rings connected to a common nitroso group).

guest molecule can be easily predicted by the simple octant rule (Scheme 2).[18] The N–N rotation energy barrier $\Delta G^{\ddagger}$ assigned by the variable temperature ^{1}H NMR measurements in DMSO-d_6 is of 93.1 kJ mol^{-1}.

3. Conclusion

In conclusion, the crystal structures of the sterically congested *N*-nitroso-2,2,6,6-tetramethylpiperidines revealed that in order to avoid the allylic 1,3-strain ($A^{(1,3)}$), caused by an interaction of the nitrosamino group with the methyl substituents, the piperidine ring in **1** and **2** assumes a chair conformation significantly flattened at the amino nitrogen whereas in the 4-oxo derivative **3**, the piperidine ring assumes boat-type conformations. All three nitrosamines easily form crystalline inclusion complexes with optically active diols (TADDOLs) in which the guest nitrosamines assume chiral conformations that was manifested by their CD spectra in the solid state. Furthermore, in the case of **2** during the crystallization of the compound as a conglomerate, a spontaneous generation of chirality occurs. Due to the rotation of the N–NO group or inversion of the piperidine ring, the optically active nitrosamines rapidly racemize in solution.

4. Experimental

4.1. General

The *N*-nitrosamine **1** was obtained following the literature method.[19] The *N*-nitrosamines **1** and **2** were prepared by *N*-nitrosation of the corresponding amines with HNO_2.[20] ^{1}H and ^{13}C NMR spectra were obtained with Varian Unity Plus spectrometer at 500 and 125 MHz, respectively. The deuteriated solvents were used as an internal lock for ^{1}H and ^{13}C NMR. The solid state CD

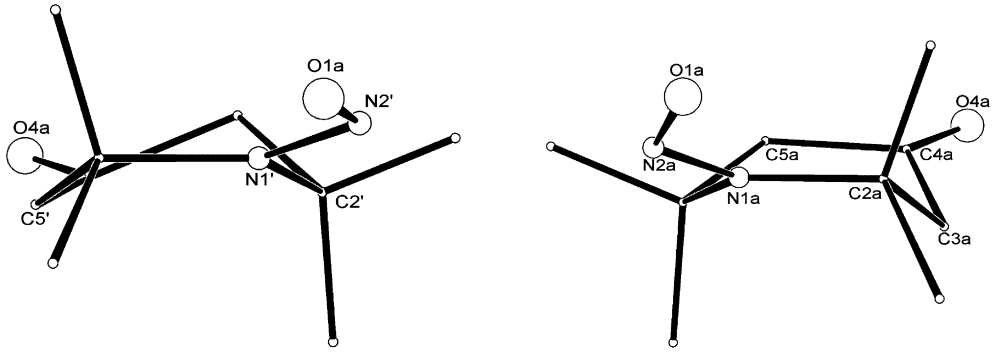


Figure 7. Two conformers of **3** occupying the same site in crystals of **3**·**5**$_2$ · H_2O.

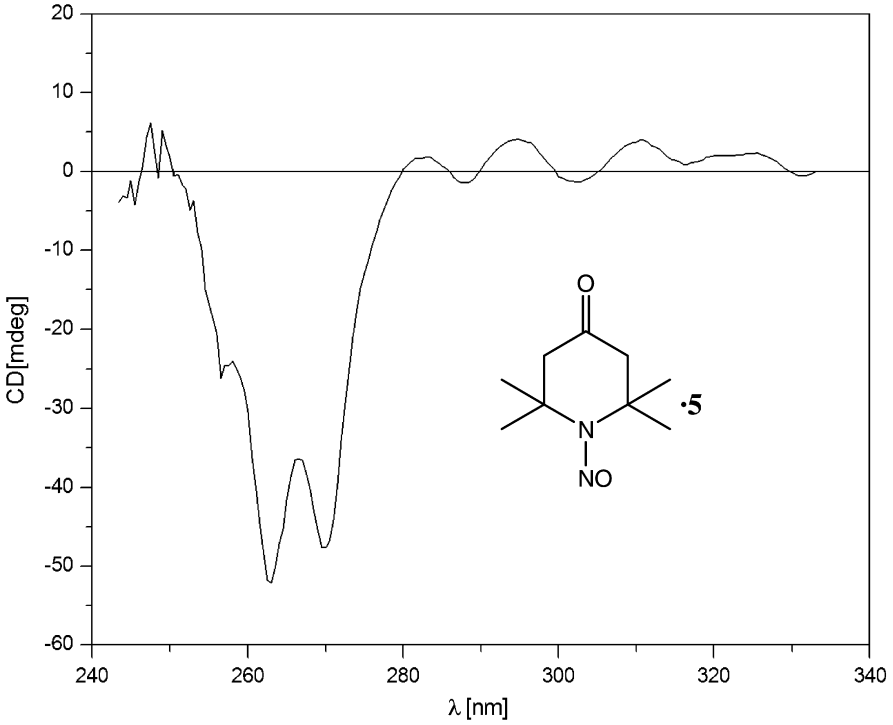
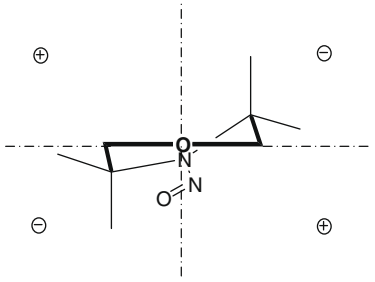


Figure 8. Solid state CD spectrum of the complex **3·5₂**·H_2O taken in KBr disk.



Scheme 2.

spectra were taken with freshly prepared KBr disks and recorded with a Jasco J-715 dichrograph. A mixture of 2–5 mg of the sample and 250 mg of dried KBr was ground and formed into a disk 0.5 mm thick and with radius of 15 mm. The disk was rotated around the optical axis and the CD recordings were made for several positions in order to check a reproducibility of the spectra.

Caution: All nitrosamines are potential chemical carcinogens, and special care should be taken in the handling and disposal of these substances.[21]

4.2. *N*-Nitroso-4-hydroxy-2,2,6,6-tetramethylpiperidine 2

Mp 96–97 °C (methanol/water); ^{1}H NMR ($CDCl_3$) δ 4.15 (m, 1H), 2.26 (br s, 1H), 2.17 (ddd, J = 2.6 Hz, 4.8 Hz and 13.3 Hz, 1H), 1.91 (ddd, J = 2.4 Hz, 4.4 Hz and 13.7 Hz, 1H), 1.83 (dd, J = 10.0 Hz and 13.4 Hz, 1H), 1.77 (s, 3H), 1.70 (m, 1H), 1.56 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 63.1, 62.1, 61.7, 50.1, 47.7, 33.1, 32.1, 29.8, 24.0. Anal. Calcd for $C_9H_{18}N_2O_2$ (186.25): C, 58.04; H, 9.74; N, 15.04. Found: C, 58.07; H, 9.88; N, 15.00.

4.3. *N*-Nitroso-2,2,6,6-tetramethyl-4-piperidinone 3

Mp 71–72 °C (toluene/hexane); ^{1}H NMR ($CDCl_3$) δ 2.69 (d, J = 4.4 Hz, 4H), 1.72 (s, 6H), 1.49 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 61.8, 61.1, 54.0, 51.7, 31.5, 26.3. Anal. Calcd for $C_9H_{16}N_2O_2$ (184.24): C, 58.67; H, 8.75; N, 15.21. Found: C, 58.66; H, 8.81; N, 15.20.

4.4. X-ray structure analysis

X-ray data were collected with a KM4CCD diffractometer. The crystal structures were solved by direct methods with SHELXS97[22] and refined by full-matrix least-squares with SHELXL97.[22] The H atoms attached to carbon atoms were positioned geometrically. The H atoms from OH groups were located in difference Fourier maps. All structural drawings were prepared with the program ORTEP-III for Windows.[23] In the absence of significant anomalous scattering, Friedel pairs were merged for **1·5**, **2** and **3·5₂**·H_2O.

Crystal data for $C_9H_{18}N_2O_2$ **2**, M = 186.25, trigonal, space group $P3_2$, $a = b$ = 12.133(3), c = 5.804(2) Å, V = 739.9(4) Å^3, T = 100 K, Z = 3, ρ_x = 1.254 g cm^{-3}, μ(Mo Kα) = 0.089 mm^{-1}, λ = 0.71073 Å, 3949 reflections measured, 857 unique (R_{int} = 0.0524). Final residuals for 122 parameters were R_1 = 0.0482, wR_2 = 0.0772 for 780 reflections with $I > 2\sigma(I)$, and R_1 = 0.0587, wR_2 = 0.0807 for all data. In the absence of significant anomalous scattering, the absolute structure was arbitrary assigned.

Crystal data for $C_9H_{16}N_2O_2$ **3**, M = 184.24, monoclinic, space group $P2_1/n$, a = 6.0613(8), b = 16.489(2), c = 10.2529(13) Å, β = 91.166(11)°, V = 1024.5(2) Å^3, T = 180 K, Z = 4, ρ_x = 1.194 g cm^{-3}, μ(Mo Kα) = 0.085 mm^{-1}, λ = 0.71073 Å, 5023 reflections measured, 1797 unique (R_{int} = 0.0139). Final residuals for 143 parameters were R_1 = 0.0427, wR_2 = 0.1106 for 1441 reflections with $I > 2\sigma(I)$, and R_1 = 0.0538, wR_2 = 0.1178 for all data. The molecule is disordered over two sites with the occupation ratio 88:12. The atoms which are common for both positions of **3** are O2, N2, N1, C2, C6, C7, C8. On cooling, at *ca.* 157 K a phase transition occurs to a twinned triclinic $P\bar{1}$ form with Z = 16 and the unit cell parameters a = 11.7354(7), b = 17.5461(11), c = 20.9962(14) Å, α = 72.333(6)°, β = 88.839(5)°, γ = 80.015 (5)°.

Crystal data for $C_9H_{18}N_2O{\cdot}C_{34}H_{35}O_4$ **1·5**, M = 1215.48, orthorhombic, space group $P2_12_12_1$, a = 9.3865(4), b = 18.1507(7),

c = 22.0090(8) Å, V = 3749.7(3) Å^3, T = 130 K, Z = 4, ρ_x = 1.199 g cm^{-3}, μ(Mo Kα) = 0.078 mm^{-1}, λ = 0.71073 Å, 26,765 reflections measured, 3709 unique (R_{int} = 0.0495). Final residuals for 463 parameters were R_1 = 0.0396, wR_2 = 0.0699 for 3157 reflections with $I > 2\sigma(I)$, and R_1 = 0.0548, wR_2 = 0.0754 for all data.

Crystal data for $C_9H_{16}N_2O_2{\cdot}2(C_{34}H_{35}O_4){\cdot}H_2O$ **3·5$_2$**·H_2O, M = 1215.48, monoclinic, space group $P2_1$, a = 9.3808(5), b = 34.0461(17), c = 10.2416(6) Å, β = 94.782(5)°, V = 3259.6(3) Å^3, T = 100 K, Z = 2, ρ_x = 1.238 g cm^{-3}, μ(Mo Kα) = 0.082 mm^{-1}, λ = 0.71073 Å, 19,222 reflections measured, 5820 unique (R_{int} = 0.0822). Final residuals for 806 parameters were R_1 = 0.0476, wR_2 = 0.0853 for 2672 reflections with $I > 2\sigma(I)$, and R_1 = 0.1325, wR_2 = 0.1082 for all data. The guest molecule is disordered over two positions with the ratio of the occupancy factors of 53:47. The two residual highest peaks in the difference Fourier map were interpreted as two water molecules, each with the half occupancy. H atoms of these molecules were not located.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 726779–726782. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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