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Polymorphism of Pyridine-*N*-oxide and Its Deuterated Analogues

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ABSTRACT: The aggregation of pyridine-*N*-oxide molecules in the solid state is very sensitive to small changes of the hydrogen/deuterium (H/D) exchange of the molecules and the thermal conditions during the crystallization process. The *in situ* crystallization of a partial deuterated pyridine-*N*-oxide allows the characterization of a low-temperature crystallographic phase.

Introduction

Hydrogen/deuterium (H/D)-exchange, the smallest possible modification of a molecule, is generally seen as a nondominating parameter as far as the crystal structures or physical properties of the molecule are concerned. It has been purposefully used to gradually improve some physical properties of inorganic materials. These observed property changes are connected to altered phase transitions in the fully deuterated materials. However, related phenomena are almost unknown for purely organic materials. All the more amazing are the recent findings that even the substitution of the solvent water by heavy water is a useful strategy to control the polymorph formation of the simple amino acid glycine.[1] And only very recently, the existence of an additional low-temperature crystallographic phase for perdeuteropyridine was discovered, in contrast to the case of nondeuterated pyridine.[2]

Results and Discussion

One major challenge is to obtain crystals in a polymorphic system. Besides methods such as slow down nucleation and other methods, an alternate approach could be the crystallization of deuterated isotopic polymorphs. The observable crystallographic isotope effect of a *per*deuterated organic compound immediately leads to the question of whether a *partial* H/D-exchange results in a measurable isotope effect and at which level of substitution such an isotope effect would set in. We present here the crystallization behavior of partially deuterated pyridine-*N*-oxides (PNO).

Indeed, partial deuteration influences the crystal packing of pyridine-*N*-oxide and allows the characterization of a low-temperature crystallographic phase. Pyridine-*N*-oxide is a crystalline hygroscopic substance and is used as a common laboratory chemical in preparative organic chemistry. The crystal structure of pyridine-*N*-oxide was first described by Ulku[3] and reinterpreted by Herbstein in the space group $P4_12_12$ (phase I).[4] The aggregation of pyridine-*N*-oxide molecules in the solid state is comparable to a group of small aromatic compounds such as benzonitrile,[5] fluorobenzene,[6] and alloxan.[7] Although different in their chemical and physical properties, these compounds crystallize in the same chiral space group $P4_12_12$ with similar cell dimensions. The crystal structures have four molecules in the unit cell, in which the 2-fold molecular axis coincides with the crystallographic 2-fold axis and forms 4_1-helical chains along the *c*-axis.

The purity of the prepared compounds **1**–**3** was established by NMR spectra (Supporting Information). To elucidate the kinetics of the crystallization process, the deuterated pyridine-*N*-oxides **1**, **2**, and **3** and the nondeuterated pyridine-*N*-oxide were investigated using different DSC measurement strategies. The thermograms in Figure 1a show that the pyridine-*N*-oxides, regardless of the H/D substitution pattern, melt in the well-known melting zone[8] of 60–69 °C and crystallize in a phase (I) after heating and subsequent cooling.

Single crystal X-ray analyses of **2** and **3** carried out by us at −30 °C show identical crystal structures as determined for pyridine-*N*-oxide. Depending on the degree of H/D exchange, a slight change in unit cell constants and cell volumes of **2** and **3** is observed. Surprisingly, a completely different crystallization behavior is observed when the pyridine-*N*-oxides are cooled to −100 °C and then slowly heated in steps of 5 K per minute. The pyridine *N*-oxides show a solid−solid phase transition forming a low temperature phase (II) (Figure 1b and the Supporting Information).

To investigate phase II of the deuterated compounds **1**, **2**, and **3**, suitable single crystals for X-ray diffraction were grown *in situ* using a computer-controlled device that applies a focused CO_2 laser beam along the cooled capillary.[9] The monodeuterated pyridine-*N*-oxide **1** crystallized from the undercooled melt isostructural to pyridine-*N*-oxide in the tetragonal space group $P4_12_12$. In contrast, the trideuterated pyridine-*N*-oxide **2** was first cooled to −50 °C, a temperature 10° below the solid−solid phase transition, and then subsequently, crystal growth was carried out. Following this procedure, it was possible to obtain single crystals of the low temperature phase (phase II). Phase II of the partially deuterated pyridine-*N*-oxide **2** crystallizes in the orthorhombic space group $P2_12_12_1$, a nonisomorphic subgroup of the tetragonal space group $P4_12_12$,[10] with two molecules in the asymmetric unit ($Z' = 2$). The crystal structures of phases I and II of **2** are not superimposable.

A similar phenomenon of a low temperature phase with $Z' > 1$ was observed for 1,4-bis(phenylethynyl)cyclohexane-1,4-diol.[11] These experimental results contradict Ostwald's step rule and the suggestion that crystal structures with $Z' > 1$ may represent kinetically trapped forms before the packing finally rearranges with $Z = 1$.[12,13] Based on our DSC studies, it is possible to assume a formation of the low temperature phase of the deuterated pyridine-*N*-oxides **1** and **3**, similar to **2**. Interestingly, phase II of **2** is not found to show the requirements of a thermodynamically stable phase with strong intermolecular interactions.

The crystal packing of phases I and II show that the two phases primarily differ in intermolecular CH···O contacts below the sum of the van der Waals radii (2.6 Å). The known high temperature phase I exhibits C−H···O and C−D···O contacts (2.42 Å) with the nitrogen atom neighboring C2. In contrast, the crystal structure of the low temperature phase II shows several different C−H···O and C−D···O contacts in the range 2.29–2.51 Å (Figure 2).

In addition to the contacts involving hydrogen atoms in the *ortho*-positions of pyridine-*N*-oxide, contacts are found which include hydrogen atoms in the *meta*-positions of pyridine-*N*-oxide.

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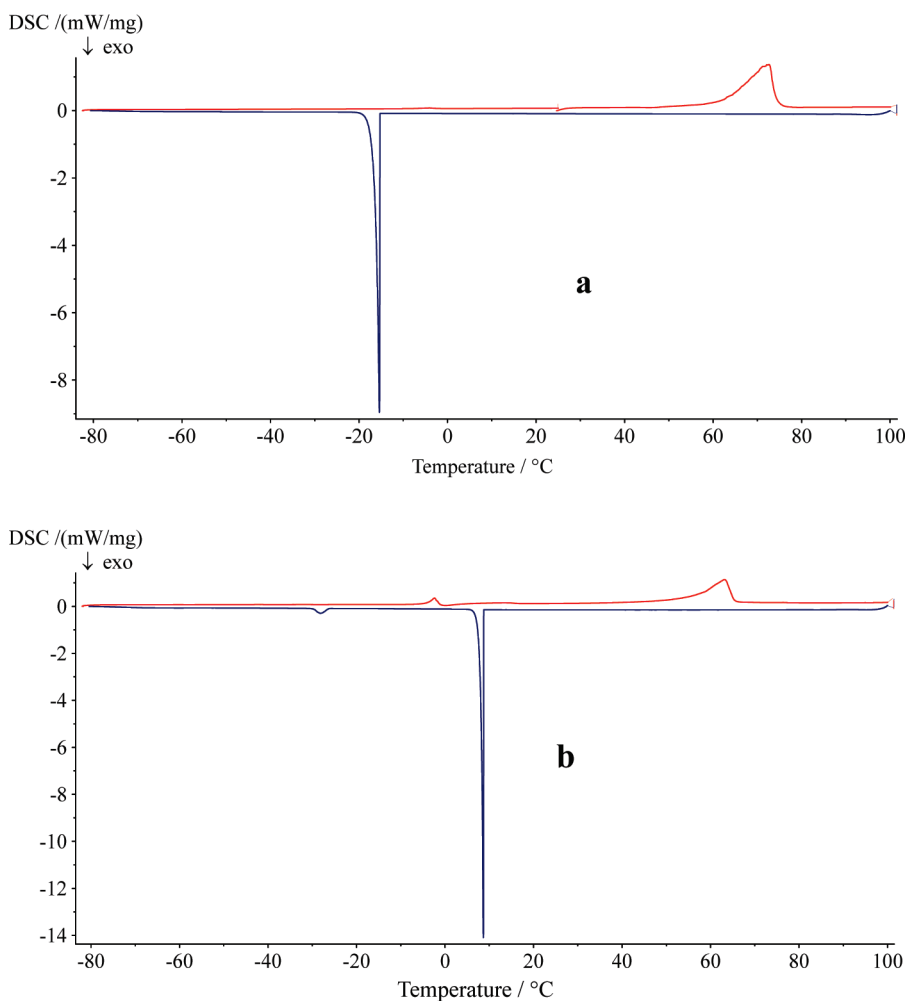
Figure 1. Thermal behavior of (a) pyridine-*N*-oxide (PNO) during heating and subsequent cooling (RT/+100 °C/−100 °C/RT) and (b) the deuterated pyridine-*N*-oxide **2** during cooling and subsequent heating (RT/−100 °C/+100 °C/RT).
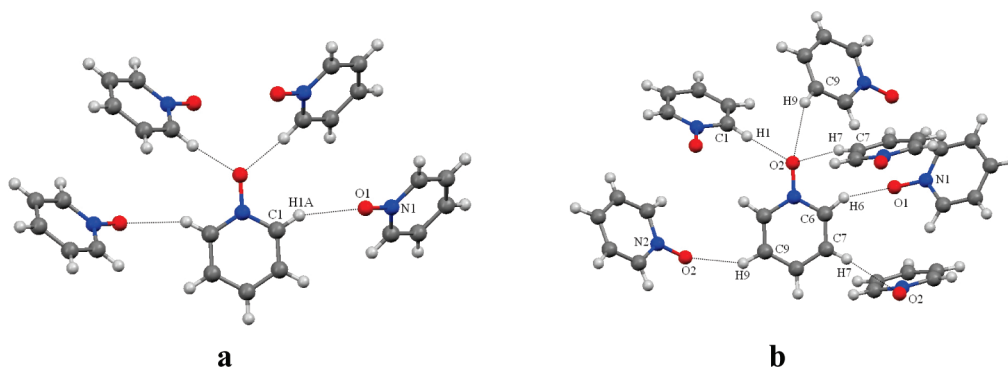

Figure 2. Intermolecular C−H···O contacts in partially deuterated pyridine-*N*-oxide **2** in the space group (a) $P4_12_12$ (phase I)—H1A···O1, 2.42 Å; C1···O1, 3.24 Å; O1−H1−C1, 145.8°; N1−O1−H1, 118.3°—or (b) $P2_12_12_1$ (phase II)—H1···O2, 2.29 Å; C1···O2, 3.261 Å; O2−H1−C1, 175.9°; N2−O2−H1, 117.5°; H6···O1, 2.518 Å; C6···O1, 3.23 Å; O1−H6−C6, 131.6; N1−O1−H6, 121.2; H9···O2, 2.41 Å; C9···O2, 3.2 Å; O2−H9−C9, 139.8°; N2−O2−H9, 161.2°; H7···O2, 2.486 Å; O2···C7, 3.328 Å.

The stabilizing contribution of weak intermolecular interactions on the packing of organic molecular crystals is discussed controversially. Based on the Taylor−Kennard paper[14] on the relevance and use of the Cambridge Structural Database in understanding the properties of the C−H···O hydrogen bonds, Desiraju ruled out the importance of these hydrogen bonds as a structure determinant in crystal packing.[15]

The energy calculations for pyridine-*N*-oxide in the space groups $P4_12_12$ (phase I) and $P2_12_12_1$ (phase II) were done with the program FlexCryst.[16] This program is parametrized for all kinds of atoms contained in the CSD. The parameters are derived by data mining. This technique allows one to derive an optimal set for parameters from the database.

Thus, the low temperature phase II shows a comparable lattice energy (the lattice energy difference of phases I and II is 0.259 kJ·mol^{-1}) to that of phase I. A related situation has recently been observed in the low temperature phase of deuterated alloxan.[17] This compound also crystallizes in a low temperature phase with

Table 1. Summary of Crystal Data, Data Collection, and Refinement Parameters for 1, 2, and 3

	1	**2**	**2**	**3**
formula	$C_5H_4D_1NO$	$C_5H_2D_3NO$	$C_5H_2D_3NO$	C_5D_5NO
formula weight	$M = 96.11$	$M = 98.12$	$M = 98.12$	$M = 100.14$
temperature (K)	223	243	223	243
crystal system	tetragonal	tetragonal	orthorhombic	tetragonal
space group	$P4_12_12$	$P4_12_12$	$P2_12_12_1$	$P4_12_12$
cryst size (mm)	$0.2 \times 0.3 \times 0.3$	$0.1 \times 0.2 \times 0.2$	$0.2 \times 0.3 \times 0.3$	$0.1 \times 0.2 \times 0.2$
habit	cylinder	cylinder	cylinder	cylinder
color	colorless	colorless	colorless	colorless
a (Å)	5.8024(8)	5.7641(8)	7.959(1)	5.762(2)
b (Å)	5.8024(8)	5.7641(8)	10.847(2)	5.762(2)
c (Å)	13.732(3)	13.613(3)	11.025(2)	13.674(7)
V (Å^3)	462.33(14)	452.28(13)	951.9(3)	454.0(3)
Z	4	4	8	4
calc. density (g cm^{-3})	1.366	1.397	1.327	1.391
$F(000)$	200	200	400	200
no. of rflns measured	1219	1193	2489	2474
no. of unique rflns	384	401	1361	403
μ (mm^{-1})	0.10	0.10	0.095	0.099
$2\theta_{max}$ (deg)	49.99	49.96	50.00	50.02
parameters	45	45	168	45
S (F^2)	1.097	1.003	1.044	1.084
$R1$ [$I > 2\sigma(I)$]	0.0433	0.0581	0.0565	0.0431
$wR2$ (all rflns)	0.1039	0.1256	0.1376	0.1029
max. $\Delta\rho$ (e Å)	0.23/−0.14	0.268/0.219	0.237/0.238	0.275/0.196

comparable lattice energy and density to the well-known high temperature phase.[18]

In conclusion, we show that the aggregation of molecules in the solid state of the polymorphic system of pyridine-*N*-oxide is very sensitive to the thermal conditions during the crystallization process and to small changes of the isotopic substitution pattern of the molecules, using partially deuterated pyridine-*N*-oxides as examples. By controlling the thermal behavior, pyridine-*N*-oxides show an enantiotropic crystallization behavior and it is possible to observe a low-temperature phase II. Additionally in the case of **2**, phase II was characterized crystallographically.

Experimental Section

X-ray Crystallography. Single-crystal X-ray diffraction measurements of **1**, **2**, and **3** were carried out on a Bruker Smart 1000 CCD diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$). The compounds were transferred into an attached capillary. The sealed capillary was transferred to the diffractometer with a detachable cooling device. Single crystals suitable for X-ray diffraction were grown *in situ* using a computer-controlled device that applied a focused CO$_2$ laser beam along the capillary.[9] Compounds **1** and **2**: based on the geometry of the crystallization device, one ω-scan (one cycle for each measurement) was collected. Compound **3**: After successful use of the crystallization device, the capillary with the crystal of **3** was mounted on a standard goniometer and data were measured such that a hemisphere was collected. Structures were solved by the direct method, and all non-hydrogen atoms were refined anisotropically on F^2 (program SHELXTL-97, G. M. Sheldrick, University of Göttingen, Göttingen, Germany). Crystallographic crystal data and processing parameters are shown in Table 1.

Differential scanning calorimetry (DSC) thermograms were taken on DSC 204 F1 (NETZSCH, Selb, Deutschland) by program PROTEUS 4.8.5. Approximately 15 mg of each substance (using Sartorius LE26P microbalance, Goettingen, Deutschland) was balanced in an Al pan (25 μL). Dry nitrogen was used as protection and cooling gas (flow 20 mL min^{-1}). Heating rates were 5 K min^{-1}. The device was calibrated for temperature and energy with pure KNO$_3$, In, Bi, Sn, Zn, CsCl, Hg, and cyclohexane.

Supporting Information Available: Experimental data of the synthesis and characterization of the deuterated pyridine-*N*-oxides **1**, **2**, and **3**; selected bond lengths, bond angles, and intermolecular contacts of **1**, **2**, and **3**; DSC-measurements (cooling and subsequent heating); melting points of pyridine-*N*-oxide and the deuterated pyridine-*N*-oxides **1**, **2**, and **3**; NMR and IR spectra; peak parameters of pyridine-*N*-oxide and the deuterated pyridine-*N*-oxides **1**, **2**, and **3** during the DSC-measurements; and CIF-files giving X-ray data with details of refinement procedures for **1**−**3** (CCDC 767710−767713). This material is available free of charge via the Internet at http://pubs.acs.org.

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