The First [2.2]Pyridonophane: Preparation, Structure and Hydrogen Bond Pattern with Water

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The dimethoxydiselena[3.3]pyridinophane **3** was prepared and transformed into 7,15-dihydroxy[2.2](2,6)pyridinophane **5a** in 35% yield; the X-ray analysis of **5** proved the tautomeric structure **5b**, in which [2.2]pyridonophane units are linked by water molecules to form infinite, hydrogen bonded layers.

Keywords characterizing the synthetic and theoretical challenges related to cyclophanes are: transannular strain caused by clamping, reactivity affected by steric strain, chiroptical properties of twisted species, electronic through-space interactions of layered structures, intramolecular charge-transfer complexes.[1]

In connection with the development of pyridinophanes suitable for the formation of self-organizing, numerously hydrogen-bond linked, oligomeric or polymeric structures, we encountered the question of whether the well known prototropic pyridol–pyridone **1a** ⇌ **1b** equilibrium could be affected by linking two units to yield a sterically deformed, clamped [2.2]phane skeleton of type **5**.

According to the literature the 4-hydroxypyridine **1a** is the minor component in the tautomeric equilibrium especially in polar solvents when the oxo-form **1b** is stabilized by hydrogen bridges (*cf.* Fig. 1).[2] A comparison of IR and Raman spectra of 4-pyridone **1b** with those of 4-pyridinium ions and a rationalization of the dipole moment lead to the estimate that the upper limit of the contribution to 4-pyridone **1b** by the dipolar resonance structure **1b'** is 10–15%.[3a] The equilibrium shifts towards the pyridinol **1a** as the medium becomes less polar and less protic because the carbonyl oxygen of **1b** is less solvated.[3b] Even a strong self-association of pyridones leading to significant shifts in the protomeric equilibrium has been observed.[3c] This self-association can be minimized by the choice of a polar solvent. Nevertheless, 4-pyridones still exhibit an aromatic nature and do not have the properties of simple unsaturated lactams.[3d]

In previous attempts to prepare the dimethoxypyridinophane **4**, we directly coupled 2,6-bis(bromomethyl)-4-methoxypyridine **1** employing phenyllithium as a base. The pyridinophane **4** was obtained in 11% yield.[4] In comparison the selena-procedure,[5] resulting in the 8,17-dimethoxy-2,11-diselena[3.3](2,6)pyridinophane **3**, enabled us to raise the overall yield significantly (Scheme 1).† The starting material, chelidamic acid (4-oxo-1,4-dihydropyridine-2,6-dicarboxylic acid), was treated with methanol to obtain the dimethyl ester; it was then reduced to the diol and finally yielded the dibromo compound **1**.[4] Its conversion to the bisselenocyanatomethylpyridine **2** was easily achieved in dry degassed acetone.[5] The cyclisation (**1** + **2** → **3**) was carried out at room temperature, simultaneously adding solutions of **1** and **2** in ethanol–tetrahydrofuran (THF) (1:2) to a well-stirred sus-

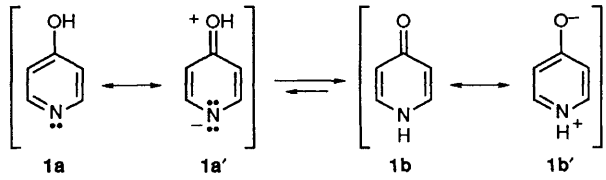
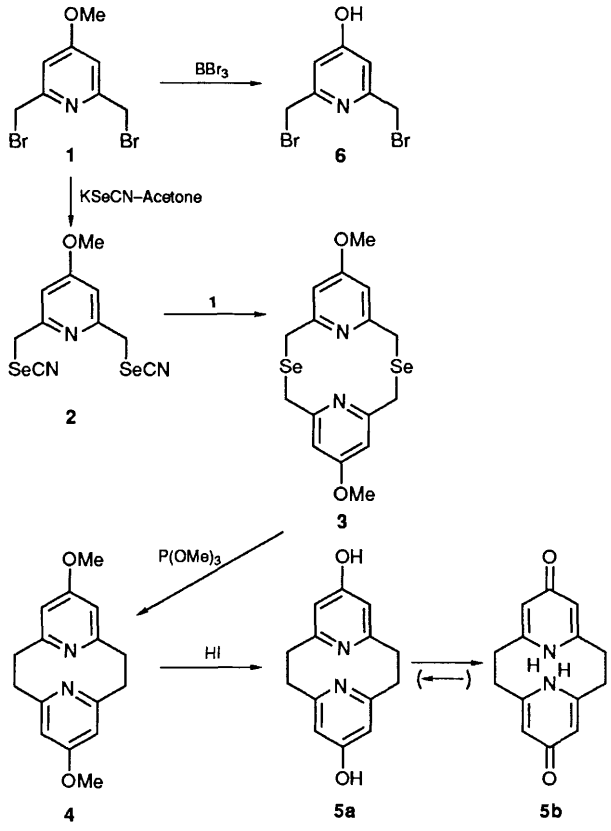


Fig. 1

† *Analytical data* for **3**, **5** and **6**: **3** m.p. 175–177 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.71 (s, 6H, OCH_3), 3.99 (s, 8H, CH_2Se), 6.57 (s, 4H, Ar-H); ^{13}C NMR (20.64 MHz, $CDCl_3$) δ 30.19, 55.00, 107.39, 159.55, 166.27; **5** m.p. > 308 °C decomp.; ^{1}H NMR (90 MHz, [$^2H_6$]DMSO) δ 3.04 (s, 4H, CH_2), 7.20 (s, 4H, Ar-H); ^{13}C NMR (20.64 MHz, $CDCl_3$) δ 35.09, 112.91, 156.44, 172.40; **6** m.p. 192–194 °C; ^{1}H NMR (90 MHz, [$^2H_6$]DMSO) δ 4.52 (s, 4H, CH_2Br), 7.45 (s, 6H, Ar-H); ^{13}C NMR (20.64 MHz, [$^2H_6$]DMSO) δ 28.71, 112.43, 154.00, 170.03.



Scheme 1 Synthesis of the 7,15-dihydroxy [2.2](2,6)pyridinophane

pension of an excess of $NaBH_4$ in ethanol–THF (1 : 19) over a period of 8 h.† The diselenaphane **3** was purified by column chromatography (88% yield). Deselenation was carried out by irradiation in dry trimethyl phosphite.[6] After removing the solvent by distillation under reduced pressure, the residue was recrystallized from water–ethanol to yield the phane **4** (35%). Demethylation proceeded quickly with an excess of hydroiodic acid, resulting in the dihydroxyphane **5** in excellent yield (98%). Remarkably it was not possible to follow this reaction sequence when starting with the hydroxypyridine compound **6** to yield the corresponding dihydroxydiselenaphane (*cf.* Scheme 1).

The X-ray analysis provides some exceptional features of the phane **5b**.‡ As for the pyridinophane **4**, the dioxo analogue **5b** adopts a step-type, *anti*-conformation shown by the X-ray structure (*cf.* Fig. 2).[4] The selected parameters of the pyridinophane **4** and **5b** are compared in Table 1 and Fig. 3 explains the chosen distances and angles of the pyridonophane **5b**.

Owing to the presence of the N–H binding sites of **5b**, the intramolecular N–N distance (d = 264 pm) and the angle τ (τ = 13°) are out of the range of normal values. In fact, the X-ray structure shows that **5b** no longer contains aromatic pyridine rings. The tautomeric equilibrium **5a** ⇌ **5b** in the crystal is completely shifted in favour of the oxo-species **5b**, which is stabilized *via* hydrogen-bridges to water molecules. We believe that because of the highly strained [2.2](2,6)phane structure, the deformation of the two six membered rings is also responsible for the 'freezing' of the equilibrium (*cf.* Fig. 2).

‡ *Crystal data* for **5b**: $C_{14}H_{14}N_2O_2 \cdot 4H_2O$, M = 314.3, monoclinic, space group $P2_1/c$, colourless crystals, dimensions 0.15 × 0.35 × 0.50 mm³, a = 8.413(6), b = 12.628(6), c = 8.208(4) Å, β = 118.70(4)°, U = 764.9 (7) Å³, D_c = 1.365 Mg m⁻³, Z = 2, μ(Mo-Kα) = 0.71073 Å, 1340 Symmetry independent reflections, 990 reflections with $F > 4.0\ \sigma(F)$ were used for the structure solutions (direct methods) and refinement (full-matrix least-squares, 115 parameters), non-hydrogen atoms were refined anisotropically. H-atoms localized by difference electron density determination and refined using 'riding' model. R = 0.063 [R_w = 0.067, $w^{-1} = \sigma^2(F) + 0.0010F^2$)].

Program SHELXTL-Plus: G. M. Sheldrick, SHELXTL-Plus, Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin USA, 1989. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

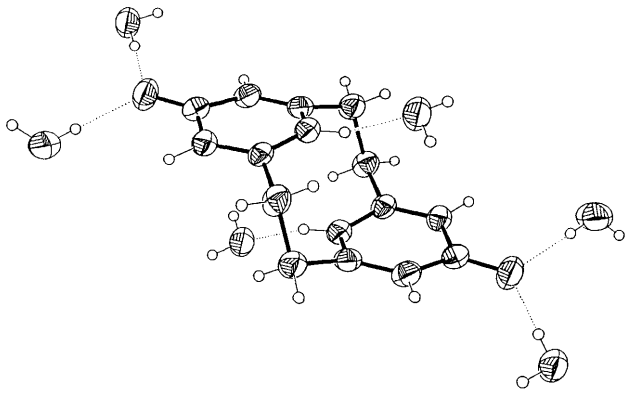


Fig. 2 Crystal structure of **5b**·4 H_2O

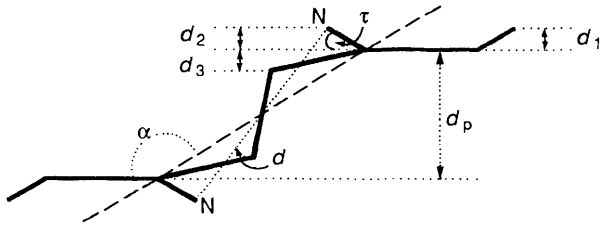


Fig. 3 Side-view of [2.2](2,6)phane

Table 1 Selected parameters of the phanes **4** and **5b** (see Fig. 3)

Parameter	4	5b
Intermol. distance/pm		
d_1	6.9	10.4
d_2	11.4	14.8
d_3	41.8	38.6
	30.2	30.9
d	253.8	263.8
d_p	224.6	221.0
Bond angle/°		
α	131.9	136.0
τ	11.6	13.0

As far as we know this is the first X-ray analysis of a pyridonophane **5b** with a lactam type structure. The distance of the carbon atoms in the pyridone rings of **5b** [*cf.* Fig. 2; bond length C(2)–C(3): 150.2(4), C(3)–C(4): 135.3 (4) pm] and the C–O bond length [127.3(3) pm] reveal oxo-functions in positions 7 and 15.[3a] In comparison to the methoxypyridinophane **4** [136.8 (5) pm], the C–O bond length is reduced significantly.[4]

The IR spectrum in the solid state supports the carbonyl structure of **5b**. We assign the high frequency band at 1645 cm^{-1} to carbonyl stretching, the low frequency band at 1550 cm^{-1} to C=C bond stretching. This high frequency band is missing completely in the IR spectrum of **4**. The UV spectrum of **5** in acetonitrile shows two bands (λ_{max} = 290 nm, A = 0.63 and λ_{max} = 360 nm, A = 0.33), indicating a pyridone structure, whereas **4** shows no significant absorbance in this region. Also, the ^{13}C NMR spectrum of **5b** indicates the presence of a carbonyl group. The ^{13}C signal of C(7) [C(15)] is shifted to δ 172.4 whereas the C(7) [C(15)] signal of **4** is found at δ 167.2.

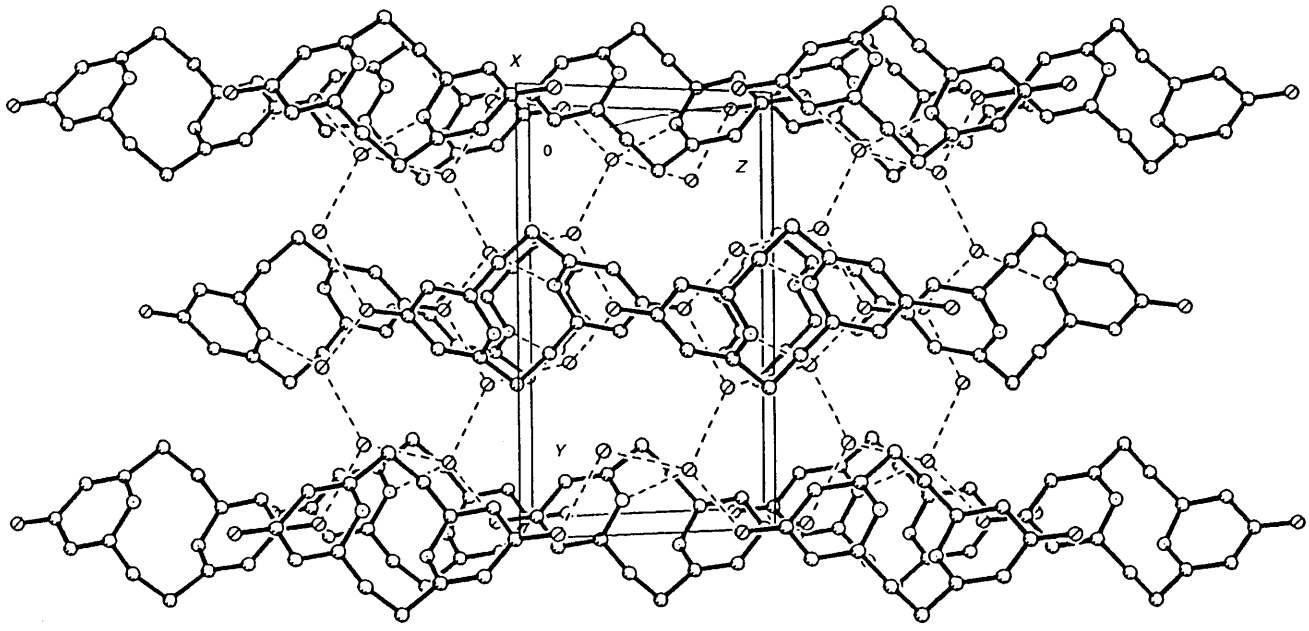


Fig. 4 Hydrogen bridges (- - - -) of layer system **5b**

Using selected solvents (H_2O–EtOH) we were able to crystallize **5b** in such a way as to form a polymer-like, layered pyridinophane system with interlinking water molecules. The two binding sites at the pyridone rings of **5b** are saturated with four antagonistic water molecules (*cf.* Fig. 2), creating one hydrogen bridge at the nitrogen and two hydrogen bridges at the oxygen site of **5b**. These hydrogen bridges link the nitrogen atom of one molecule **5b** *via* one water molecule with the next phane **5b** in the same layer. The second water molecule at the oxygen atom interlinks the stacked, stair-shaped layers, forming a hydrogen bridge to the water molecule which connects the nitrogen with the oxygen site of **5b** in the neighbouring layer (*cf.* Fig. 4).

The X-ray analysis confirms that **5b** is capable of simultaneously forming hydrogen-bond bridges at the nitrogen and oxygen atom. Moreover, this self-assembly and self-organization of interacting pyridonophanes **5b** by forming new layers *via* multiple hydrogen bridges represents a specific molecular architecture in the crystalline state. We believe that the hydrogen bridges and the strain of the molecule act in combination, shifting the equilibrium to the 4-pyridone species **5b**.

The application of the seleno-method to functionalized heteroaromatic systems opens a wide spectrum for carbon–carbon linkages leading to new strained molecules. Furthermore, the 7,15-dihydroxy[2.2](2,6)-pyridinophane **5** offers a new type of [2.2](2,6)pyridinophane with unprotected functional groups, which presents a new potential as a synthetic unit.[7,8]

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