[14] The complete structure of $4(\mathbf{1}_2\cdot I^-)\cdot 4Na^+\cdot 9C_3H_6O\cdot 17H_2O$ is a catemer. The main motif is the $\mathbf{1}_2\cdot I^-$ unit. There are two independent $\mathbf{1}_2\cdot I^-$ units in the unit cell and both have very similar conformations. Sodium ions and solvent molecules surround these groups, but in contrast to the anions, there are two types of sodium ions in the structure. One is pentacoordinated. Three coordination sites are occupied by carbonyl groups of neighboring cyclopeptides, one by the oxygen atom of a bound acetone molecule, and the remaining coordination site is occupied by a water molecule. This cation has a trigonal bipyramidal coordination geometry. The other sodium ion is merely tetrahedrally coordinated. Again three coordination sites are occupied by carbonyl groups of neighboring cyclopeptides and on the remaining coordination site sits a water molecule. In addition, there are two independent uncoordinated acetone molecules and five independent water molecules in the asymmetric unit.

[15] The calculations were performed on a Silicon Graphics Workstation using the program Cerius^2 (Molecular Simulations Inc.) and the Dreiding 2.21 force field: S. L. Mayo, B. D. Olafson, W. A. Goddard III, *J. Phys. Chem.* **1990**, *94*, 8897 – 8909.

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First O–H–N Hydrogen Bond with a Centered Proton Obtained by Thermally Induced Proton Migration**

Thomas Steiner,* Irena Majerz,* and Chick C. Wilson*

There is great current interest in the strongest types of hydrogen bonds, both in the chemical and the biological fields.[1] In contrast to "normal" and weak hydrogen bonds, which are primarily electrostatic $X^{\delta-}$–$H^{\delta+}\cdots Y^{\delta-}$ interactions,[2, 3] very strong hydrogen bonds have a quasi-covalent character.[4] In such a three-center four-electron bond X–H–Y, the H atom is involved in two partial covalent bonds of comparable bond orders. Very strong hydrogen bonds are stable in solution and in crystals, but have also been proposed to occur in intermediates of chemical[5] and enzymatic[6] reactions. In particular the latter proposal has led to heated and controversial discussions.[7] Very strong homonuclear hydrogen bonds (X–H–X) are experimentally well accessible, and numerous examples of centered or almost centered geometries have been reliably found by neutron diffraction experiments.[8] For heteronuclear hydrogen bonds, the structural information is much poorer. There are a few examples of X-ray crystal structures with O–H–N bonds in which the H atom has at least similar distances to O and N,[9, 10] but accuracies are poor, and not a single case was found as yet in neutron diffraction studies.[11] We now have been able to produce for the first time an exactly centered O–H–N hydrogen bond and characterize it by neutron diffraction. To achieve this goal, we used the effect of thermally induced proton migration, which we monitored by variable-temperature time-of-flight Laue neutron diffraction.

A good model system to study very short O–H–N hydrogen bonds are adducts of pentachlorophenol (PCP) with pyridine bases.[12, 13] The pK_a values of PCP and pyridine are similar, and suitable substitutions at the pyridine ring allow fine tuning of its pK_a value to match the one of PCP in an optimal way.[14] In a series of X-ray crystal structures, substituted pyridine · PCP complexes were found to crystallize as formally molecular or ionic adducts linked by hydrogen bonds $O–H\cdots N$ or $O^-\cdots H–N^+$, respectively, depending on the base selected.[15] The shortest hydrogen bond was found in crystalline 4-MePy · PCP (4-MePy = 4-methylpyridine), in which the $O\cdots N$ distance is 2.515(4) Å at 80 K,[10] and the H atom is situated approximately midway between the O and N atoms (Table 1). However, X-ray diffraction does not allow to determine the position of the H atom with an accuracy that is sufficient for a quantitative discussion.

To characterize the hydrogen bond in 4-MePy · PCP reliably, we determined the crystal structure by means of neutron diffraction (ND) at 20 K. The extremely short hydrogen bond ($O\cdots N$ 2.506(2) Å) has the center of gravity of the vibrating proton slightly off-center in the direction of the N atom (N–H 1.206(6), O–H 1.309(7) Å, N–H–O 170.4(6)°, Table 1). This represents by far the shortest O–H–N hydrogen bond for which ND data has been obtained. The most interesting observation, however, came as a complete surprise to us, and emerges from comparison with the X-ray crystal structures at room temperature[16] and at 80 K.[10] The overall crystal

Table 1. Geometrical parameters of the hydrogen bond in 4-MePy · PCP.

T [K]	O–H [Å]	H–N [Å]	Δ(X–H) [Å]	$O\cdots N$ [Å]	O–H–N [°]
RT, X-ray[16]	1.09(6)	1.47(6)	–	2.552(4)	170(5)
200	1.228(11)	1.306(11)	– 0.078(11)	2.525(4)	170.5(10)
150	1.229(11)	1.300(11)	– 0.071(11)	2.519(4)	169.6(10)
125	1.241(10)	1.288(10)	– 0.047(10)	2.519(4)	169.6(10)
100	1.258(8)	1.265(8)	– 0.007(8)	2.513(3)	170.1(8)
80	1.266(8)	1.255(8)	0.011(8)	2.513(3)	170.9(8)
80, X-ray[10]	1.22(4)	1.29(4)	–	2.515(4)	176(5)
60	1.275(10)	1.249(10)	0.026(10)	2.515(4)	170.9(10)
45	1.279(8)	1.242(8)	0.037(8)	2.513(3)	170.8(8)
20[a]	1.309(7)	1.206(6)	0.103(7)	2.506(2)	170.4(6)

[a] Measured on a different crystal than that at the other temperatures.

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packing is always the same, but at room temperature the H atom of the hydrogen bond is (on time average) closer to the O atom, at 80 K it is roughly in the center, and at 20 K it is slightly closer to the N atom. Several factors can lead to such an effect,[17] and to gain further insight into this potentially important matter, we performed a variable-temperature ND study on the substance.

Variable-temperature single-crystal ND is an exceptionally powerful experimental technique. In conventional ND on steady-state sources, the collection of a data set for a substance such as 4-MePy · PCP takes several days. The recently developed time-of-flight Laue diffraction method[18] and suitable large area detectors allow routine data acquisition in substantially shorter times. Using a crystal of about 22 mm^3 volume, we were able to collect ND data at seven temperatures in the range 45 – 200 K at a rate of one data set per day (by using the time-of-flight Laue diffractometer SXD of the ISIS facility, see Experimental Section). The structure is ordered at all temperatures, and no sign of a phase transition is observed. The center of gravity of the proton alters with temperature, gradually migrating from being closer to the O atom (at high temperature) to being closer to the N atom (at low temperature; Table 1). Such a phenomenon has not, to our knowledge, been observed before. The proton migration amounts to about 5×10^{-4} Å K^{-1}, and the equidistant position is passed through at around 90 K. In Figure 1, the structure is

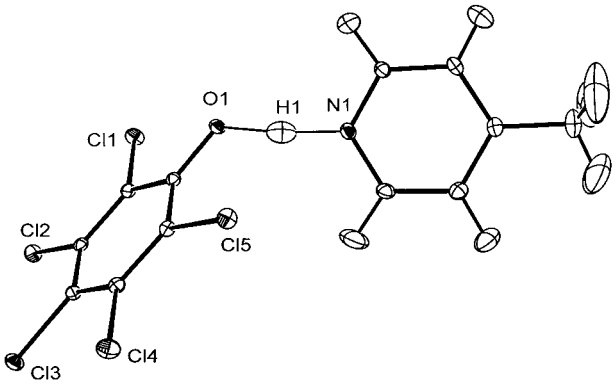

Figure 1. Neutron diffraction crystal structure of 4-MePy · PCP at 100 K. Displacement ellipsoids are drawn at the 30% probability level. The displacement amplitude of H1 is larger along the hydrogen bond than perpendicular to it, but is in no way exceedingly large when compared with those of the other H atoms in the structure.

drawn with the H atom closest to the center (100 K); the O–H and H–N distances differ by less than one standard uncertainty. In Figure 2, only the hydrogen-bonded atoms are drawn for all temperatures, showing how the H atom migrates over a distance of almost 0.1 Å in the temperature range 20 – 200 K (see the figure legend for details).

The structural data in Table 1 must be put in the context of all other published ND data of hydrogen bonds between O and N centers. This is best done by using the crystal correlation method.[19] Figure 3a shows a scatterplot of N–H against O–H distances; the small dots indicate data from published ND crystal structures, and represent exclusively strongly asymmetric hydrogen bonds either of the type O–H···N or N–H···O. The central part of the plot, which has been empty until now,[11] is populated by our data on pyridine · PCP complexes.[20] The line of dots at roughly equal N–H and O–H distances shows the thermally induced proton migration in 4-MePy · PCP. It is seen that O–H and N–H distances are well correlated over the whole range, without any sudden changes in slope or other discontinuities (Figure 3a). This parallels earlier observations in homonuclear O–H–O hydrogen bonds,[19, 21] and is in line with solution NMR spectroscopic data of other O–H–N-bonded systems.[22] The scatterplot of the O–H (or H–O) distance against the O···N separation, Figure 3b, shows a smooth correlation with two branches, one representing O–H···N and the other N–H···O hydrogen bonds. The two branches join at an O···N distance of about 2.51 Å.

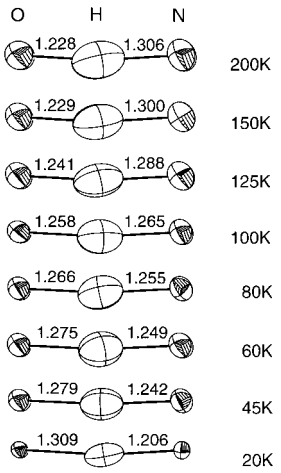

Figure 2. The hydrogen bond in 4-MePy · PCP as observed by neutron diffraction at eight different temperatures; displacement ellipsoids are drawn at the 50% probability level. The equidistant H atom position occurs at around 90 K.

Conclusions concerning proton-transfer phenomena can be drawn from the data in Figure 3a and b. A hypothetical proton transfer process along the line of the data points in Figure 3a or 3b requires a mechanism that is associated with concomitant shortening (to 2.51 Å) and subsequent widening of the O···N separation. In that case, no tunneling event is necessary. If changes in the environment of a hydrogen bond lead to suitable changes in the proton affinities of the atoms, such a mechanism should be possible, but seems quite speculative at this point. A proton-transfer event by tunneling, on the other hand, may be interpreted as a vertical jump from one branch to the other in Figure 3b. It does not require critical positioning of the O and N atoms, but since a potential well has to be penetrated, transfer rates will fall sharply with increasing O···N distances. Since the positions of the O and N atoms and their surroundings are not static, a hybrid mechanism can be envisaged that exploits initial hydrogen-bond shortening as a result of environmental fluctuations, be it stochastic or targeted as in enzymatic processes, followed by proton-tunneling through a temporarily lowered barrier.

The novel experimental finding of this work is that crystalline 4-MePy · PCP contains an O–H–N hydrogen bond with a (time-averaged) H atom position that migrates upon cooling, from a position closer to the O atom to one closer to the N atom. This effect allows the H atom position to be tuned within a 0.1 Å range merely by adjusting the temperature. The range includes the elusive geometrically centered O–H–N hydrogen bond, which has been observed experimentally for the first time (see also ref. [23]). We cannot decide herein if this is a result of a change in the thermal population of a constant but unsymmetrical hydrogen-bond potential, or of subtle changes in the hydrogen-bond potential itself. The new

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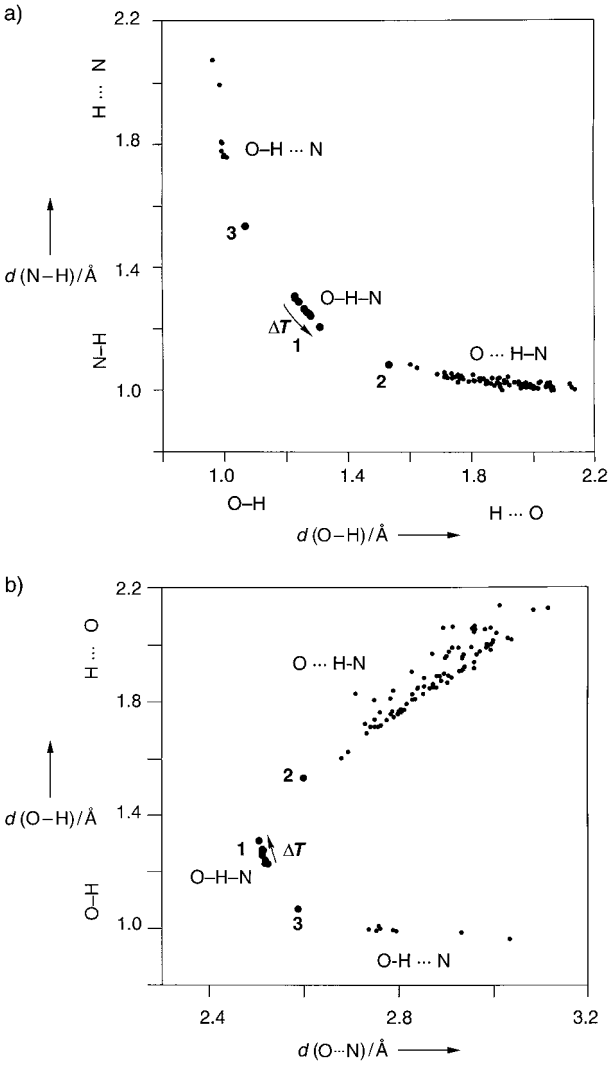

Figure 3. Crystal correlation results for O–H···N and N–H···O bonds based on neutron diffraction data. a) Scatterplot of N–H versus O–H distances in O–H–N hydrogen bonds. b) Scatterplot of O–H versus O···N distances in O–H–N hydrogen bonds. Large symbols: 1: 4-MePy·PCP at eight temperatures; 2: 2,4-Me_2Py·PCP; and 3: 2-MePy·PCP.[20] Small symbols show previously published data.[11]

data allow us to draw essentially complete pictures of distance correlations in O–H–N hydrogen bonds. Finally, we add that we see here only a relatively small degree of enhanced vibration of the H atom along the hydrogen bond, indicating a potential with a well-defined single minimum.

Experimental Section

After purification of the starting materials (4-MePy (Merck) was distilled, whereas PCP (Fluka) was sublimed), the complex 4-MePy·PCP was prepared in CCl_4 in the presence of excess base. Activated charcoal was added, the mixture was heated to reflux, and then filtered. Large single crystals of the 4-MePy·PCP complex with volumes of up to 50 mm^3 were then obtained by slow evaporation (room temperature) of the solvent.

All ND experiments were performed on the SXD instrument at the ISIS pulsed-spallation neutron source, with the time-of-flight Laue diffraction method.[18] This method uses a pulsed wavelength-sorted white neutron beam, along with large area position-sensitive detectors, to allow a large volume of reciprocal space to be measured in a single crystal setting (a "frame"). Collection of a data set comprises a series of such frames, each accumulated with a stationary crystal-detector arrangement. First, ND data were collected for 4-MePy·PCP at 20 K on a single crystal of approximate dimensions $4.5 \times 3 \times 2$ mm^3 (triclinic, space group $P\bar{1}$ (no. 2), $a = 7.236(2)$, $b = 8.929(3)$, $c = 13.058(4)$ Å, $\alpha = 99.84(3)$, $\beta = 118.04(2)$, $\gamma = 103.30(2)^\circ$, $V = 685.4(4)$ Å^3, $Z = 2$). Over two days, 42 frames were collected, yielding 5612 unique reflection intensities, with acceptable data extending to about 0.45-Å resolution. The second experiment was initiated only after the 20 K structure analysis has been finished. By then, the original crystal was lost, and a new crystal had to be used (dimensions $5 \times 3 \times 1.5$ mm^3). ND data were collected at eight temperatures in the order 100, 60, 80, 150, 200, 125, 45, and 300 K (temperature stabilities better than ± 1 K) within seven days. The final 300-K data set was unusable owing to fast sublimation of the crystal. Because of the need for fast data collection, only 20 frames were collected at each temperature, leading to crystallographically slightly incomplete data sets with around 2600 reflection intensities at each of the lower temperatures (realistic crystallographic resolution about 0.65 Å) and around 1850 reflections for the three highest temperatures.

The structures were refined anisotropically (SHELXL) starting from the known X-ray crystal structure. The data/parameter ratios (for unique data $I > 2\sigma(I)$): 23.0 (20 K), 11.1 (45 K), 7.9 (60 K), 10.8 (80 K), 10.0 (100 K), 7.6 (125 K), 7.8 (150 K), 7.4 (200 K). The final crystallographic R values are 0.076 at 20 K, and between 0.082 and 0.090 at the other temperatures. These values are in the usual range for Laue-diffraction data.[18] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-156061 – CCDC-156068. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[14] A necessary (but not sufficient) condition for the formation of very short hydrogen bonds is the matching of the pK_a values of the atoms. The numerical value of $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$ for "50% proton transfer" depends on the system selected,[13b] and also on the environment. In amine·PCP adducts, very strong O–H–N hydrogen

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bonds are formed in a "critical range" of ΔpK_a values scattered roughly around 1.0.[12, 13] For substituted pyridine · PCP adducts in CCl_4 solution, an ideal ΔpK_a for "50% proton transfer" is reported as 1.6.[13a] Since a more polar environment generally favors more ionic forms, it must be expected that in crystals, a pyridine · PCP adduct with $\Delta pK_a = 1.6$ is formally ionic (N^+–H···O^-) and adducts with really 50% proton transfer are characterized by $\Delta pK_a < 1.6$. Because the influence of the crystalline environment cannot be predicted quantitatively, one cannot predict the exact hydrogen-bond geometry from a known ΔpK_a value and molecular geometry. In any case, the ΔpK_a of 0.77[12] makes 4-MePy · PCP an interesting candidate in the search for an O–H–N bond with a centered H atom ($pK_a = 5.22$ (Py), 6.03 (4-MePy), 5.26 (PCP)).[12a]

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[17] The observation that the H atom is on time-average closer to the O atom at room temperature, and closer to the N atom at 20 K could have a number of reasons: 1) The substance might be dimorphic, with one crystal form having a different kind of hydrogen bond than the other. 2) There might be gradual proton migration upon cooling; this is the effect that was actually found in the second experiment. 3) The H atom might be disordered over two positions, one closer to the O atom and the other closer to the N atom, and relative occupancies change with temperature; similar effects are known, for example, with the O–H···O hydrogen bond in benzoic acid: C. C. Wilson, N. Shankland, A. J. Florence, *J. Chem. Soc. Faraday Trans.* **1996**, *92*, 5051 – 5057. 4) The difference between the structures at room temperature and at 20 K might be nothing more than an artifact caused by experimental inaccuracies.

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[23] In 4-MePy · PCP, the hydrogen bond is geometrically centered at about 90 K. This H position is singular in geometric terms, but not the one where the O–H and H–N bonds have equal "bond orders" $s = ½$. Free O–H and N–H covalent bonds have different lengths (e.g. 0.957 and 1.012 Å in H_2O and H_3N vapor, respectively), and also O–H and N–H bonds with $s = ½$ should have different X–H distances. Even the most recent parametrization of distance/valence relations is very inaccurate for strong O–H–N bonds, because no experimental data from that region could be used,[11] but suggests that an O–H bond with $s = ½$ is 0.060 Å shorter than an N–H bond with $s = ½$. According to Table 1, this situation occurs in 4-MePy · PCP between 125 and 150 K.

Nitroglycal Concatenation: A Broadly Applicable and Efficient Approach to the Synthesis of Complex O-Glycans**

Gottfried A. Winterfeld and Richard R. Schmidt*

The mucin class of glycopeptides has attracted much attention in recent years, because it subsumes numerous structures of fundamental importance in biological processes such as fertilization, parasitic infection, inflammation, immune defense, cell-growth, and cell – cell adhesion.[1] Synthesis of the characteristic α-glycosidic linkage between 2-acetamido-2-deoxy-D-galactopyranose and the hydroxy groups of L-serine and L-threonine, however, proved difficult. Most syntheses of α-O-linked glycopeptides rely essentially on the methodology introduced by Paulsen in 1978: The glycosylations are carried out with glycosyl donors that have a non-participating azido group at position 2 as latent amino function as well as a leaving group at the anomeric center.[2, 3] Enzymatic syntheses have also been reported, for example the synthesis of Core 1 and the corresponding sialylated Core 1 structure.[4] Core structures are defined as the binding region of the saccharides directly bound to the protein.[19] Recently, we have shown that for the synthesis of the simplest mucin structure, the T_N antigen, Michael addition to 2-nitrogalactal may serve as an efficient alternative approach.[5] This fundamentally new approach has now been developed to a comprehensive and powerful methodology that provides highly stereoselective access to 3-O- and 6-O-branched mucin structures.

All mucin core structures contain at the reducing end a *N*-acetylgalactosamine α-glycosidically linked to L-serine or L-threonine. Eight core structures of mucin-type glycopeptides have been identified to date; they bear additional glycosyl residues at either position 6 or position 3 or at both positions to form complex O-glycans (Scheme 1). To demonstrate that nitroglycal concatenation is a well-suited tool for the synthesis of all members of the mucin family we strategically chose two target molecules from the 6-O-branched structures (ST_N antigen and Core 7) and one target molecule from the 3-O-branched structures (Core 1). These structures are generated by reaction sequences I – III (Scheme 2 and 3).

For reaction sequences I and II as well as for the synthesis of T_N building blocks, nitroglycal **2** is the key intermediate of our synthesis. Nitroglycal **2** can be obtained in 84% yield from protected galactal **1**[6] by using a two-step, one-pot procedure involving addition of acetyl nitrate to the glycal functionality and subsequent elimination of acetic acid (Scheme 2).[5]

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