Pergamon

Tetrahedron Letters, Vol. 38, No. 9, pp. 1659-1662, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00156-1

Conformational Restriction by Intramolecular Hydrogen Bonding. Carbohydrate-Carbohydrate Self-Assembly.

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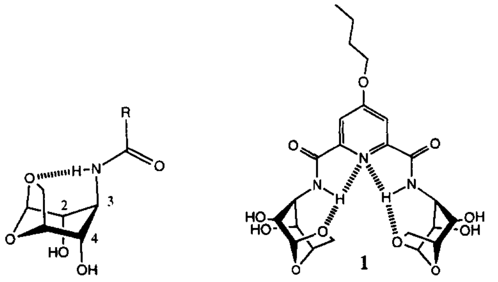
Abstract: NMR data (chemical shifts, NOEs, coupling constants and variable temperature experiments), FT-IR data and MM2* molecular mechanics calculations have allowed us to demonstrate that 3-amido-1,6-anhydro-3-deoxy-β-D-glucopyranose acts as a hydroxyl-based interaction unit and provides conformational control of self-recognition processes by intramolecular hydrogen bonding.

The study of recognition processes involving carbohydrates is a topic of current interest[1]. Hydrogen bonding and lipophilic interactions have been proposed as the major forces accounting for specificity of carbohydrate-carbohydrate self-assembly in natural systems[2]. The study of the carbohydrate OH···OH hydrogen bond energetics, cooperativity[3], and the influence of intramolecular hydrogen bonds on the formation of intermolecular H-bonds[4a, b], is fundamental to the understanding of the basis of these recognition processes.

Different synthetic receptors employ sugar hydroxyl groups as hydrogen bonding centers for molecular recognition of carbohydrates in non polar media[4]. H-bonds are highly directional as well as one of the strongest intermolecular forces[5]. H-bonding involving neutral amidic-type NH and carbonyl groups has played a predominant role in the design of unique self-assembled supramolecular structures[6a-c]. The possibility of generating self-assembled supramolecular structures based on intermolecular H-bonding of hydroxyl groups has not been demonstrated until very recently[6d, e].

As a part of a project to develop simple carbohydrate model systems[7] for the study of the relative contributions of the different forces involved in carbohydrate recognition events, this work reports on the use of 3-amido-1,6-anhydro-3-deoxy-β–D-glucopyranose as a hydroxyl-based interaction unit, and on its ability to provide conformational control of self-recognition processes by intramolecular hydrogen bonding[8].

The first step to achieve a well defined self-assembled structure is the control of the three dimensional structure of the monomeric unit. Receptor **1**[9], where the *interaction unit* is present, has been designed for the purpose of OH···OH hydrogen bonding-mediated self-assembly. Molecular modelling of **1** demonstrates that the linkage of the spacer to position 3 of the sugar, via an amide moiety, could allow the formation of an intramolecular NH···O1 hydrogen bond, thus fixing the conformation around the NH-C3 bond. This particular orientation



Interaction Unit   Receptor

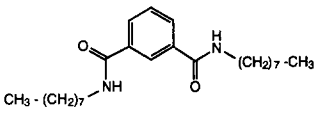
Scheme 1

places both hydroxyl groups (OH2 and OH4) pointing outwards, hence allowing the self-assembly of the carbohydrate receptor. Furthermore, the formation of intramolecular $NH\cdots N_{Py}$ hydrogen bonds, involving a pyridine spacer[8b], allows complete control of the conformation of the molecule by locking the dicarboxylic moiety in a *cis-out* conformation[10]. Indeed, MM2* calculations[11] predict this rotamer as the most energetically favourable[12], with a $NH\cdots O1$ distance (2.3 Å) in agreement with the array of intramolecular hydrogen bonds shown in scheme 1.

Conformational analysis of **1** by NMR in $CDCl_3$ showed that the pyranoid ring in solution is a $^1C_4$ chair[13]. Experimental distances obtained from NOEs[14a] and H-N-C3-H3 diedral angles obtained from vicinal $^3J_{NH,H3}$ values[14b] are in agreement with the geometry of **1** calculated by MM2*.

Additional experimental evidence for the presence of the $NH\cdots O1$ hydrogen bond in solution in the *interaction unit* is provided by FT-IR (CH_2Cl_2) and variable temperature ^{1}H-NMR ($CHCl_3$) studies[15]. Model compounds **4** and **5**, as well as protected amides **2** and **3** were used to determine its existence (Figure 1).

The FT-IR spectra[16] of compounds **2**, **3**, **4** and **5**, recorded at two different concentrations, show a sharp amide N-H stretching vibration[15a] between 3500 - 3350 cm^{-1}, which can be attributed to free or intramolecular hydrogen bonded species[15]. Indeed, only in compound **4** at the highest concentration studied (5mM) was any evidence for intermolecular hydrogen bonded species observed, with only a very weak band appearing at around 3312 cm^{-1}.



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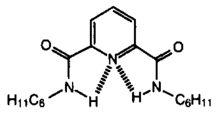

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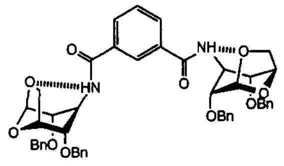

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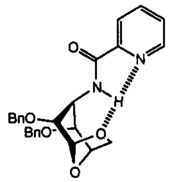

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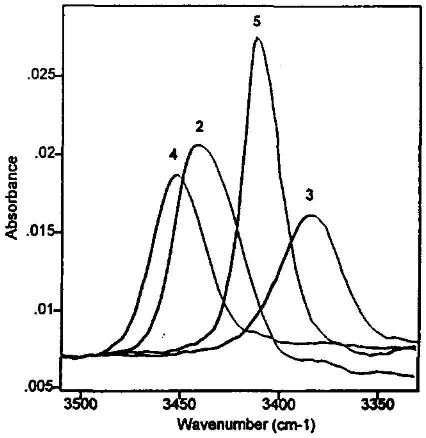

Fig.1. FT-IR spectra of the N-H stretch region of **2**, **3**, **4**, and **5** in CH_2Cl_2 at 5 mM concentration

In figure 1, the free N-H stretching vibration of **4** can be observed at the highest frecuency of 3450 cm^{-1}, as expected, whereas the corresponding ν_{NH} is shifted 12 cm^{-1} to lower frequency in compound **2**. This shift may be attributed to the formation of an intramolecular hydrogen bond between $NH\cdots O1$[17]. A similar trend is observed when the ν_{NH} of compounds **5** and **3** are compared, where the corresponding shift is 25 cm^{-1}. The intramolecular hydrogen bonds between $NH\cdots N_{Py}$ in compounds **5** and **3** produce a shift of 42 and 55 cm^{-1} when compared with compounds **4** and **2**, respectively.

The ^{1}H-NMR chemical shifts (299 K, $CDCl_3$) of the NH resonances of **4** (6.18 ppm) and **2** (6.61 ppm), as well as those of the pyridine-based compounds **5** (7.54 ppm) and **3** (8.50 ppm) also appear to agree with an increasing involvement of the corresponding NH in intramolecular hydrogen bonding. Thus, the combined FT-IR and NMR evidence suggests that the $NH\cdots O1$ hydrogen bond is indeed present in solution, thus restricting the conformation around the HN-C3 linkage.

The self-assembly process of **1** in $CDCl_3$ was studied by ^{1}H-NMR, monitoring the concentration and temperature dependence of the OHs and NH chemical shifts and coupling constants. OH chemical shifts and temperature coefficient values for **1** clearly varied upon dilution from 5 mM to 0.05 mM. On the other hand, the NH resonances were unmodified (Table 1). Variable temperature ^{1}H-NMR experiments (299-319 K) of **1** - **5** in $CDCl_3$ showed small temperature coefficients for the NH resonances. However, those measured for the OH2 and OH4 signals for **1** were larger (-0.0075 and -0.014 ppm/K, respectively) at the highest concentration. The order of these values is consistent with involvement in intermolecular hydrogen bonds[15c, d].

Table 1. ^{1}H-NMR Chemical Shifts, Coupling Constants, and Temperature Coefficents of NH and OH Resonances of **1** at Two Different Concentrations

		Compound 1		
Signal	Concentration (mM)	δ (ppm)	$\Delta\delta/\Delta T^b$ (ppm/K)	$^3J^a$ (Hz)
OH2	5.00	3.34	$-7.5\cdot10^{-3}$	9.2
OH2	0.05	2.94	$-2.7\cdot10^{-3}$	10.3
OH4	5.00	3.66	$-1.4\cdot10^{-2}$	2.5
OH4	0.05	2.99	$-5.1\cdot10^{-3}$	5.1
NH	5.00	8.60	$-2.9\cdot10^{-3}$	7.8
NH	0.05	8.53	$-2.4\cdot10^{-3}$	8.4

[a] Data at 298 K [b] Measured between 297 K and 313 K

With regard to the $^3J_{H,OH}$ couplings, OH2 and OH4 behave differently. $^3J_{H2,OH2}$ is independent of both concentration and temperature. The measured value of $\cong$ 10 Hz indicates a particular orientation of the hydroxyl proton, probably involved in an intramolecular hydrogen bond (with O5 or O4). On the other hand, at the highest concentration (5 mM), $^3J_{H4,OH4}$ varies from 2.5 Hz to 5.4 Hz between 297 K and 313 K. The value measured at low concentration (0.05 mM) is 5.0 Hz, regardless of temperature. This behavior is consistent with a particular orientation of the OH4 group at high concentration, probably involved in an intermolecular hydrogen bond. However, OH4 is free at low concentration.

These results indicate that the self-assembly process of the acyclic receptor **1** is mediated by intermolecular OH···OH hydrogen bonding and not by the amide.

The characterization of the agreggation process and of its energetics[18] is currently in progress.

Acknowledgments: Financial support by DGICYT (PB93-0127) is gratefully acknowledged. M.L.P. thanks Comunidad de Madrid for a FPU Fellowship.

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9. Receptor **1** was synthesized by coupling 4-butoxypyridine-2,6-dicarboxylic acid[4c] with the precursor of the interaction unit, 3-amino-1,6-anhydro-3-deoxy-2,4-dibenzyl-β-D-glucopyranoside, in dry CH_2Cl_2 with 1,3-dicyclohexylcarbodiimide and 4-dimethylaminopyridine at room temperature (95%), followed by catalytic hydrogenolysis of the benzyl groups with Pd (10%) on active carbon (85%). The amine was synthesized starting from D-glucose and following the classical synthesis of Cerny's epoxides[19]. These epoxides have been opened with sodium azide to give the corresponding 3-azide derivative (90%). By reduction with lithium aluminum hydride, 3-amine-1,6-anhydro-3-deoxy-2,4-dibenzyl-β-D-glucopyranoside was obtained (86%). All new products gave satisfactory spectroscopic data and elementary analysis.
10. We have used the name of *cis-in*, *cis-out* , and *trans* conformers, to describe the rotation around the $C_{aromatic}$-CO bond, depending on the situation of the carbonyl oxygen relative to the N_{Py}: both cis to the N_{Py} (*cis-in*), both trans to the N_{Py} (*cis-out*), and one cis-one trans (*trans*).
11. Molecular Mechanics Calculations were carried out using MM2* according to the GB/SA solvent model for chloroform. Initially, 9 structures were calculated for each rotamer (*cis-in, cis-out, trans*) by rotating the torsion around the N-C3 bond. The structure generation was performed maintaining the OH in a fixed orientation.
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16. Spectra were recorded at a resolution of 4 cm^{-1} on a (Perkin Elmer System 200 FT-IR) equipped with a DTGS detector, in a 0.1 mm fixed pathlength liquid cell fitted with the solvent in the cell. The absorbance scale in the figure 1 is normalized for each compound.
(Nicolet 520B FT-IR spectrometer)
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18. ^{1}H-NMR dilution experiments for **1** only show changes in the OH resonances. Dilution data were fitted for a dimerization process, to give $K_a = 50\ M^{-1}$. We thank Dr. C. A. Hunter (University of Sheffield) for kindly providing the fitting program.
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(*Received in UK* 2 *December* 1996; *revised* 23 *January* 1997; *accepted* 24 *January* 1997)