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^{13}C CP MAS and high-resolution ^{1}H, ^{15}N NMR study of ureido sugars

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Abstract

Ureido sugars with eight various alkyl groups at N-3 were studied by means of ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy in $CDCl_3$ solution and a ^{13}C CP MAS technique in the solid state. The analysis of chemical shifts and coupling constants suggests the *Z,Z*-anti conformation of the ureido part of molecule. Differences of δ between the liquid and solid state are observed for the C-2, C-6, and OMe carbon atoms of the D-glucopyranose moiety, as well as the splitting of the anomeric carbon C-1 and OMe signals. The possibility of various conformations in the solid state are discussed. IR spectra of solid ureido sugars indicate that both NH groups are involved in hydrogen bonding. On the other hand, dilution with $CDCl_3$ followed by ^{1}H NMR showed that N-1–H forms a stronger bond than N-3–H.

Keywords: Ureido sugars; ^{13}C CP MAS solid-state NMR; ^{1}H NMR; ^{15}N NMR

1. Introduction

Ureido sugars have attracted considerable attention as starting materials in the synthesis of nitrosoureido sugars [1] as well as their acetylated derivatives [2], which are important antitumor agents in the treatment of cancer. Some are in clinical use, for example, streptozotocin [3] [2-deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose], or chlorozotocin [4] {2-deoxy-2-[(2-chloroethyl)-3-nitrosoureido]-D-glucopyranose}. Ureido sugars are also intermediates in the preparation of derivatives of polyhydroxylated

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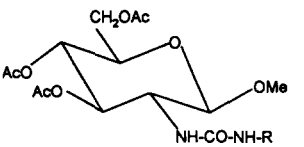
bicyclic heterocycles with nitrogen such as glucofuranoimidazolidin-2-ones [5] or sugar oxazoline [6].

As a part of our continuing work on new methods of synthesis and the physicochemical properties of ureido sugars [7], we report the application of high-field ^{1}H NMR and ^{13}C CP MAS NMR to the study of structural and conformational characteristics in solution and the solid state.

2. Results and discussion

The ureido sugars were methyl 3,4,6-tri-*O*-acetyl-2-(3-alkylureido)-2-deoxy-β-D-glucopyranoside derivatives with the following alkyl groups:



1 R = ethyl	5 R = i-butyl
2 R = propyl	6 R = pentyl
3 R = i-propyl	7 R = $CH_2CH_2CH(CH_3)_2$
4 R = butyl	8 R = allyl

^{1}H NMR.—The complex multiplets of glucose protons are difficult to differentiate when NMR spectra are recorded at lower frequency, however the 500-MHz spectra allowed the interpretation of all components of the signals. The magnitude of the coupling constants were determined by line separation rather than by line fitting. In some cases (H-6a, H-6b) the values of J were confirmed by simulation of the respective part of the spectrum by means of the RACOON computer program.

^{1}H NMR chemical shifts and proton–proton coupling constants are collected in Table 1 from which it can be seen that the glucopyranose ring adopts the $^{4}C_{1}$ conformation. The recognition of the anomeric configuration is based conventionally on $^{3}J_{H\text{-}1,H\text{-}2}$ and the relatively large vicinal couplings (7.9–8.2) of the anomeric protons are typical for a diaxial configuration of H-1 and H-2, thus confirming the presence of the β anomer in all compounds. Chemical shifts and coupling constants (Table 1) for the D-glucopyranose protons are in agreement with those reported for 2-(3-arylureido)-2-deoxy-D-glucopyranoses [5], substituted aryl 2-acetamido-2-deoxy-β-D-glucopyranosides [8], or *O*-acetylated 2-deoxy-2-formamido(or thioformamido)-D-glucopyranoses [9].

The replacement of one alkyl group by another has some influence on the chemical shifts and coupling constants of H-1 and H-2, all other values within the sugar moiety remain the same. The anomeric proton (H-1) was slightly deshielded in **1** compared to δ H-2 in other compounds. Some deshielding effect was also observed on δ H-2 in **1**.

Table 1
^{1}H NMR data ($CDCl_3$, δ in ppm, J in Hz) [a] for peracetylated methyl β-D-glucopyranosyl ureas **1–8**

Atom	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
H-1	4.54d	4.45d	4.41d	4.48d	4.39d	4.46d	4.43d	4.43d
$J_{1,2}$	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3
H-2	3.67ddd	3.4ddd	3.54ddd	3.60ddd	3.53ddd	3.57ddd	3.58ddd	3.59ddd
$J_{2,NH}$	8.4	7.9	6.5		7.5		7.8	7.9
$J_{2,3}$	10.3	10.3	10.2	10.3	10.1	10.4	10.3	10.3
H-3	5.24dd	5.18dd	5.14dd	5.20dd	5.14dd	5.18	5.16	5.20dd
$J_{3,4}$	9.3	9.4	9.3	9.4	9.3	9.4	9.4	9.3
H-4	5.07dd	5.07dd	5.08dd	5.07dd	5.08dd	5.08	5.07	5.10dd
$J_{4,5}$	9.9	9.7	9.6	9.8	9.6	9.8	9.8	9.8
H-5	3.75ddd	3.70ddd	3.69ddd	3.72ddd	3.68ddd	3.72ddd	3.70	3.69ddd
$J_{5,6a}$	2.5	2.5	2.4	2.4	2.4	2.4	2.5	2.4
$J_{5,6b}$	5.0	4.8	4.7	4.9	4.7	4.8	4.8	4.7
H-6a	4.30dd	4.30dd	4.30dd	4.30dd	4.31dd	4.30dd	4.30dd	4.30dd
$J_{6a,6b}$	12.2	12.3	12.3	12.3	12.3	12.3	12.3	12.3
H-6b	4.14dd	4.13dd	4.14dd	4.14dd	4.14dd	4.14	4.14	4.14dd
N-1–H		4.82d	4.44d		4.42d		4.62d	4.37d
N-3–H		5.12	4.80		5.04t	5.08	4.97	

[a] Spectra were recorded at 500 MHz.

Z/E-Isomerism in substituted ureas has been widely studied but the preferred conformation of ureido sugars has not been established. The arrangement about at least three carbon–nitrogen bonds C-2–N-1, N-1–C(O), and C(O)–N-3 needs to be recognized. Generally, 1,3-disubstituted alkylureas can exist in solution as a mixture of isomers (*Z,Z*), (*Z,E*), and (*E,Z*). For example, in *N,N'*-diglycosyl-*N*-(2-tiazolinyl)thiourea the conformation was *Z,Z*, fixed by an intermolecular hydrogen bond NH · · · N. Also in other thioureylenedisaccharides the *Z,Z* orientation was proposed [10]. On the other hand, the observed chemical shifts and large $J_{H\text{-}2,NH}$ couplings of thiourea bridge protons agree with an antiperiplanar disposition between these protons. Room temperature and low temperature spectra showed the presence of only a single conformer.

Two isomers were assigned by NMR measurements in thioformamidopyranoses [5] where the barrier to rotation around the N–CS bond was high enough to observe *E* and *Z* isomers simultaneously (in $CDCl_3$ solution), although the *Z* isomer dominated. Both isomers showed the same antiperiplanar conformation about the C_{sugar}–NHC(S)R bond which was supported by the NOE data. In 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-thioformamido-β-D-glucopyranose, H-2 resonated at 5.55–5.32 ppm for the *Z* isomer and at 3.79 ppm for the *E* isomer ($\Delta\delta$ 1.6 ppm). In formamidoglucopyranoses this difference is smaller (0.8 ppm). The sugar proton geminal to the amide group is indicative of the *Z* or *E* configuration for these series of compounds, because the carbonyl (thiocarbonyl) group anisotropy causes deshielding of H-2 in the *Z* isomer, thus giving the differences in the chemical shift of this proton. Synthetic procedures gave high yields of the anomeric mixture of the *O*-acetylated 2-(3-arylureido)-2-deoxy-D-glucopyranoses which complicated analysis of the NMR spectra. ^{1}H and ^{13}C NMR spectra showed [5] some

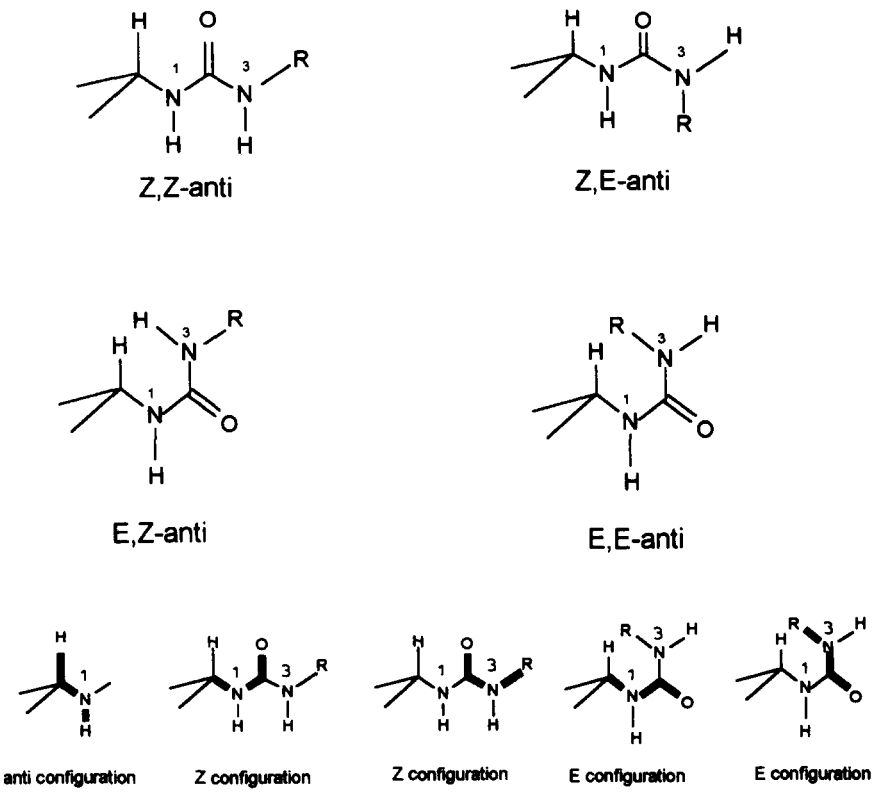


Fig. 1. Orientation of the ureido group with respect to the sugar.

analogies with those of the respective thioureas, although the replacement of the C = S by a C = O group results in an upfield shift of 0.6–0.8 ppm and δ H-2 is in the range 3.99–4.15 ppm. In ureido sugars **1–8**, δ H-2 is 3.7–3.5 ppm suggesting the *Z*-anti orientation of this fragment of the molecule. Further arguments concerning the structure of ureido sugars were obtained from analysis of the ^{13}C and ^{15}N NMR spectra. Rules for configurational assignments in compounds of the series $C_{sugar}(H_{sugar})$–N(H)–C(X)–H proposed by Avalos et al. [9] predict a sugar proton and a carbon atom joined to the functional group: δ H-2 (*Z*) > δ H-2 (*E*) and δ C-2 (*Z*) < δ C-2 (*E*). The chemical shift of C-2 of isomer *Z* is ca. 54 ppm and of *E* ca. 63 ppm [9]. The values of δ C-2 in ureido sugars **1–8**, 55.3–56.1 ppm in $CDCl_3$ solution [7] and 53.5–56.0 ppm in solid (Table 2), are in agreement with the proposed *Z,Z* orientation.

^{15}N NMR.—In the proton decoupled natural abundance ^{15}N NMR spectrum of **1** (not shown), two signals at −294.1 and −301.2 ppm were seen. The difference in chemical shifts was too small for unambiguous assignment based only on alkyl group increments proposed for ureas by Martin et al. [11], and the single-frequency ^{1}H–^{15}N decoupling experiments were performed to differentiate the sugar-N-1 from the N-3–CH_2CH_3. The spectrum recorded with the INEPT technique (not shown) exhibited two doublets and $^{1}J_{NH}$ 88.7 Hz for both nitrogen atoms; the downfield doublet was further split into

quartets with $^{3}J_{NH}$ 3.5 Hz (coupling to CH_3 protons), the components of the upfield doublet were slightly broader or further split into doublets with $^{2}J_{NH} < 1.3$ Hz. When the ^{1}H decoupling frequency was that of the CH_3 protons, the downfield components in the ^{15}N spectrum appeared as triplets with $^{2}J_{NH}$ 2.2 Hz (coupling to CH_2 protons). The long-range coupling disappeared when the decoupling frequency was set between that for CH_3 and CH_2, thus confirming that the downfield signal arose from the N-3 atom linked to the ethyl group. It is worth mentioning that three-bond couplings, $^{15}N–C–C–H$ or $^{15}N–C(O)–C–H$, are usually larger in magnitude than analogous two-bond $^{15}N–C–H$ couplings [12]. One bond coupling constants depend on the orientation of the lone nitrogen pair, and also on the degree of planarity around H–N–CO. The same value of $^{1}J_{NH}$ can suggest, therefore, that there is no significant change in the arrangements of atoms about N-1 and N-3. The values of $^{1}J_{NH}$ 88.7 and $^{2}J_{NH}$ 0.7 Hz were reported for $CH_3NHC(O)NHCH_3$ in Me_2SO [13]. In alkyl-*N*-nitrosoureas the values of $^{1}J_{NH}$ of 89.2–89.6 Hz in $CDCl_3$, 60.5 Hz ($^{2}J_{NH}$ 1.8 Hz) in CCl_4 and 92.5 Hz ($^{2}J_{NH}$ 0.6 Hz) in Me_2SO were measured [14]. The magnitude of $^{2}J_{N-C-H}$ of 0.6–1.8 was close to that of the *trans* H–C–N–H coupling constant average. The value of 1.3 Hz for $^{2}J_{N-C-H}$ with the sugar H-2 is within the above range, indicating that the anti conformation is probable in this part of molecule. In amido sugars [15], the amide proton was found to be anti to the sugar H-2.

Hydrogen-to-deuterium exchange rates in 2-acetamido-2-deoxy-D-glucopyranosides [16] were faster for the β anomer than for the α anomer, and suggested that in the α anomer a hydrogen bond exists between the amide proton and the oxygen of the axial methoxy group at C-1. A similar hydrogen bond is not possible in the β anomer with its equatorial methoxy group; thus, the amide proton of the β anomer is more exposed to solvent and exchanges more quickly than that of the α anomer.

Proton chemical shifts of N-1–H are in the range 4.37–4.82 ppm and N-3–H 4.80–5.12 ppm. Studies of the influence of solvent and concentration on δ NH are difficult because these signals are overlapped with multiplets of the sugar protons H-3 and H-4. However, in **5** with an *i*-butyl substituent, N-1–H appeared separately as a doublet and N-3–H as a triplet located to the left and right of the H-4 multiplet. Further experiments were therefore possible. Dilution with $CDCl_3$ from $c = 0.14$ to 0.07 mol/dm^3 caused an upfield shift of both NH signals of $\Delta\delta$ 0.14 ppm and $\Delta\delta$ 0.25 ppm for N-1–H and N-3–H, respectively. The upfield shifts result from breaking of the NH $\cdots$ O = C hydrogen bond, i.e., reducing the self-association and the N-1–H $\cdots$ O bond seemed to be stronger than that formed by N-3–H. Gradual addition (1–11 μL) of a strong proton acceptor such as Me_2SO to the 0.11 mol/dm^3 solution of **5** (in $CDCl_3$) produced a downfield shift of N-3–H of $\Delta\delta$ 0.07 ppm, and N-1–H $\Delta\delta$ 0.54 ppm confirming that N-1–H is able to form a stronger hydrogen bond with Me_2SO than N-3–H. We assume that there is no evident steric hindrance in the approach of a Me_2SO molecule either to N-1–H or N-3–H.

^{13}C CP MAS.—The advent of high resolution solid-state NMR methods allowed us to extend our studies. Our interest was to gain some insight into the conformations of the ureido and sugar units without the influence of solvent. ^{13}C NMR chemical shifts were measured from a series of spectra recorded by the cross-polarization magic-angle spinning technique. The spinning speed of 3 KHz was enough to circumvent side bands.

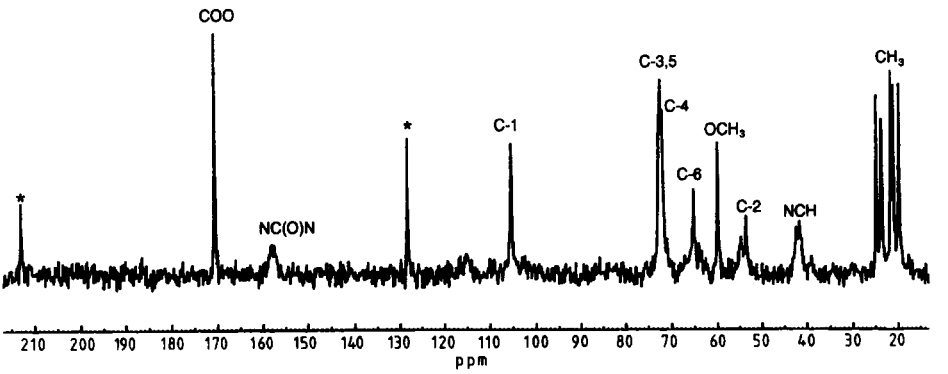


Fig. 2. ^{13}C CP MAS NMR spectrum of compound **3** (* , rotational signals).

Solid ureido sugars were obtained as white powders by evaporation of solvent in a dry atmosphere, and were not crystalline. Attempts to grow the crystals have up to now failed. In the absence of X-ray diffraction data, the interpretation of solid-state structure is not straightforward when splittings of the signals arise, i.e., when the solid-state spectrum contains more resonances than the liquid-state spectrum.

The ^{13}C CP MAS NMR spectrum of solid methyl 3,4,6-tri-*O*-acetyl-2-(3-*i*-propyl)ureido-2-deoxy-β-D-glucopyranoside (**3**) is shown in Fig. 2. The majority of the ^{13}C resonances in such a spectrum could be assigned directly by comparison with the solution data [7]. The signals of acyl group carbons are narrow and their chemical shifts are almost the same as those in $CDCl_3$ solution (Table 2). The signals of carbons bonded to nitrogen [N-1–CO–N-3, N-1–C(2), N-3–C_{alkyl}] are broader and/or split into asymmetric doublets due to the residual $^{13}C–^{15}N$ dipolar coupling [17]. These residual splittings allow the assignment of carbons in the proximity of the nitrogen atom and, in our case, allow us to distinguish the neighbouring C-2 and OMe signals. Most interesting are the differences of chemical shifts between the liquid state and the solid state spectra observed for C-2, C-6, OMe (deshielding of −1.1 to −6.5 ppm), and C-2 (increase of shielding of 1.7 to 2.5 ppm) carbons of the D-glucopyranose moiety. It is worth noting that the differences are larger for ureido sugars with smaller alkyl substituents, such as ethyl (**1**) or *i*-propyl (**3**), than for those with a longer aliphatic chain, *n*-butyl (**5**) or *n*-amyl (**6**) (Table 2). In solution, there is only one resonance for each set of chemically equivalent carbons because of rapid conformational averaging, but in the solid state several peaks may be observed for each type of carbon. The most evident example is that of **3** with the *i*-propyl moiety: in the spectra in solution in $CDCl_3$ there is one signal for a CH_3 group, whereas in the solid state spectrum, the methyl groups are not equivalent (the difference in chemical shifts is 1.1 ppm; Fig. 2). Chemical shifts of the anomeric carbon, 103 ppm, and that of OMe, 57 ppm, in $CDCl_3$ solutions are found for all the studied ureido sugars [7]. In the solid-state spectra the resonances of C-1 and OMe are moved 2–3 ppm downfield of their solution state values and, additionally in the spectra of compounds **1**, **5**, and **8** are split into unequal doublets. The ^{13}C CP MAS spectrum of **1** is illustrated in Fig. 3. It is probable that this reflects

Table 2
^{13}C NMR chemical shifts of peracetylated methyl β-D-glucopyranosyl ureas in solid state and (in parentheses) the differences $\Delta(\text{ppm}) = \delta_{\text{liquid}} - \delta_{\text{solid}}$ [a]

Atom	1	3	4	5	7	8
C-1	106.6, 104.2 (−3.4)	105.5 (−2.1)	103.2	102.0, 100.0 (1.0)	103.0	103.1, 102.5
C-2	53.5 (2.5)	53.5, 54.5 (2.5) (1.5)	56.0	55.6	55.6	53.6 (1.7)
C-3	72.7 (−1.0)	72.4	72.4	71.1	71.1	71.8
C-4	70.6 (−1.7)	72.1 (−3.2)	72.0	68.5	71.0	71.0
C-5	72.7	72.4 (2.1)	72.4 (2.0)	71.1 (1.0)	71.1	72.3
C-6	66.3 (−4.0)	65.3 (−3.0)	66.6 (−4.2)	65.3 (−2.8)	66.6 (−6.1)	63.8 (−1.1)
OMe	60.0 (−3.0)	60.0 (−3.0)	60.0 (−2.8)	60.7 (−3.7)	59.8 (−2.8)	57.9 56.4
CH_3COO	171.0	170.6	170.8	171.7 170.0 169.2	171.1	171.9 170.9 170.4
CH_3COO	20.5, 21.1	21.6, 21.1 19.8	21.5, 20.2	20.7	20.1	20.8, 20.3
NCON	157.7	157.9	158.7	158.8	159.0	158.2
C-1′	35.2	41.7	40.1 (−1.8)	46.4 br	38.7	44.3 br
C-2′	15.5 16.1	23.7, 24.8	33.0	29.5	38.7	114.0
C-3′			20.5	20.7	38.7	135.1
C-4′			13.8		26.3	

[a] $\Delta < 1$ are neglected.

the frozen rotation of the OMe group (Fig. 4) and the presence of conformation I (the only one, as indicated by single C-1, OMe resonances of **3**, see Fig. 2, Table 2) or I and II. The third conformation is not probable because of steric hindrance between the methoxy and ureido groups.

The chemical shifts of the C-6 resonances are sensitive to structural changes because of the rotation about the C-5–C-6 bond which enables different interactions. The signals of C-6 exhibited no splitting but large, downfield shifts, up to 6 ppm, compared to the averaged value in the liquid state. ^{13}C shifts of D-glucopyranose C-6 in cyclomalto-polyoses [18] were found to correlate with the torsional angle O-6–C-6–C-5–C-4, characterized by the orientations as signed as *gg* (60.4 ppm) and *gt* (62.9 ppm); a similar correlation for polysaccharides showed 62 ppm for *gg*, 62.7–64.5 ppm for *gt*, and 66 ppm for *tg*. The rotation of the acetyl group around C-5–C-6 in *O*-peracetylated-D-glucopyranose is more restricted because of the large steric requirement of the neighbouring acetyl group at C-4. There are no data reported on whether chemical shifts of C-6 in *O*-acetylated D-glucopyranose molecules follow the same direction, i.e., $tg > gt > gg$; we can only state therefore, that the orientation of CH_2-OAc in solids is significantly distinct from that in solution.

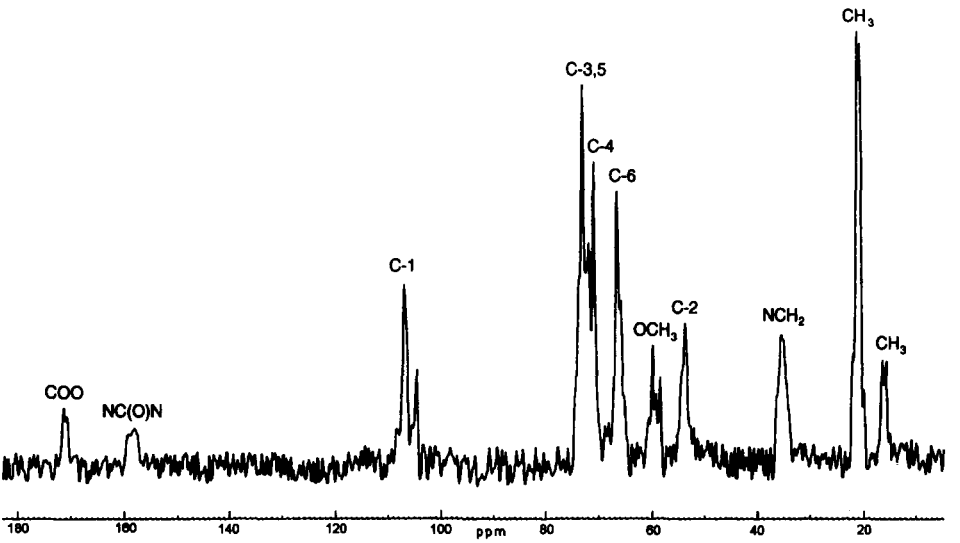


Fig. 3. ^{13}C CP MAS NMR spectrum of compound **1**.

The X-ray diffraction analyses of *N-tert*-butyl-*N'*-methylurea and *N,N'*-dicyclohexylurea indicated that the C–NH–C(O)–NH-C moiety is planar and adopts a *Z,Z* orientation in the crystal state. An interesting observation was the presence of intermolecular hydrogen bonds (only in the structure of unsymmetrical urea) with unequal distances of N · · · O 2.965 and N' · · · O 2.951 Å [19].

IR spectra.—Since solid state ^{1}H NMR spectra are not sufficiently resolved, we recorded the IR spectra from the KBr pellet in order to monitor the hydrogen bonding

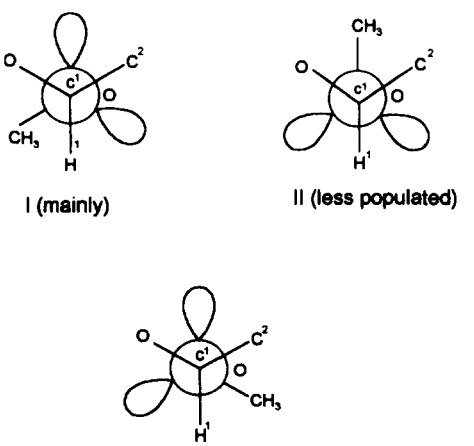


Fig. 4. Rotational isomerism of the methoxy group at the anomeric carbon.

network. A sharp NH stretching band at ca. 3450 cm^{-1} was expected, which is characteristic for monomeric NH because, for steric reasons, at least one NH proton may not form an intermolecular hydrogen bond. However, no such band was observed, but two broader absorptions were observed at lower frequency (3300 and 3340 cm^{-1}), which indicate that both N-1–H and N-3–H are involved in inter- or intra-molecular hydrogen bonds.

3. Experimental

The protected, anomerically pure ureido sugars were synthesized and purified according to the described procedures [7] from methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(4-nitrophenoxycarbonylamino)-β-D-glucopyranoside and the respective alkyl amine.

^{1}H NMR spectra were recorded on a Bruker AMX-500 spectrometer for 0.05 M solutions in $CDCl_3$; the ^{15}N NMR spectra were measured on a Bruker AM-500 spectrometer operating at 50.7 MHz using INEPT [20] and selective single frequency proton decoupling. Chemical shifts were measured for 0.5 M solutions in $CDCl_3$ and referenced to CH_3NO_2. Cross polarization magic angle spinning solid-state ^{13}C NMR spectra were recorded on a Bruker MSL-300 instrument at 75.5 MHz. Powder samples were spun at 3–4 kHz. A contact time of 5 ms, a repetition time of 6 s, and a spectral width of 20 kHz were used for accumulation of 800–2500 scans. The ^{13}C NMR chemical shifts were calibrated indirectly through the glycine CO peak observed at 176.3 ppm relative to Me_4Si.

Infrared spectra were recorded from KBr pellets on a Nicolet Magna IR-550 spectrometer equipped with a data station.

Acknowledgment

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