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^{13}C, ^{15}N CP MAS and high resolution multinuclear NMR study of methyl 3,4,6-tri-*O*-acetyl-2-(3′-arylureido)-2-deoxy-β-D-glucopyranosides

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Abstract

Four new derivatives of methyl 3,4,6-triacetyl-2-deoxy-(3′-arylureido)-β-D-glucopyranoside were studied by ^{1}H, ^{13}C, ^{15}N NMR in $CDCl_3$ solutions and by ^{13}C, ^{15}N NMR in the solid state. The replacement of one aryl substituent by another has no influence on the proton and carbon chemical shifts within the sugar moiety, in solution. The differences in ^{13}C chemical shifts $\Delta = \delta_{liquid} - \delta_{solid}$ are significant for C-3 (deshielding of -3.4 to -3.8 ppm), C-5 and OMe but not observed for C-2, where the ureido substituent is linked, thus indicating that this fragment of the structure is rigid. The values of Δ in ^{15}N chemical shifts of N-3′ are -2.3 to -2.8 ppm (increase of shielding in the solids); the effect of replacement of substituent at aromatic ring is larger than the contribution of intermolecular H-bond interaction. The values of 15.5–16.1 Hz for $^{1}J_{C\text{-}1'\text{-}N}$ and 21.2–21.5 Hz for $^{1}J_{CO\text{-}N}$ indicate that the two C–N-3′ bonds are of significant double bond character. © 1996 Elsevier Science Ltd.

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1. Introduction

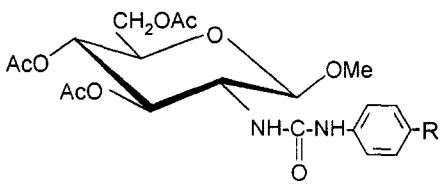
An unsymmetrically substituted urea is a frequent structural feature of many biologically active compounds such as, for example, enzyme inhibitors and pseudopeptides. In recent years the ureas or thioureas with sugar substituents have attracted considerable attention [1]. Ureido sugars are interesting as starting materials in the synthesis of nitrosoureido sugars, which exhibit antitumor activity. Some of them are used in the clinical treatment of cancer for example, streptozotocin [2-deoxy-2-(3′-methyl-3′-nitrosoureido)-D-glucopyranose] [2], or chlorozotocin {2-deoxy-2-[(2′-chloroethyl)-3′-nitrosoureido]-D-glucopyranose} [3] and many others can be tested for this application.

The series of substituted ureido sugars, the derivatives of methyl 2-deoxy-β-D-glucopyranoside and alkyl amines [4] and amino acids [5] have been recently synthesized and studied by means of NMR spectroscopy in solution and in the solid state [6,7]. As part of our continuing work on new methods for synthesis and on the determination of the structure and hydrogen bonding of ureido sugars, we report the study of three ureido glucopyranosides with aromatic substituents. Specifically ^{15}N-enriched (95%) derivatives were prepared in order to gain more spectral data and facilitate the assignments, and also as a prelude for the studies of *N*-nitrosoureido sugars.

2. Results and discussion

The synthesis of 2-(3′-arylureido)-2-deoxy-D-glucopyranoses was reported by Avalos et al. in 1993 [8]; the reaction of 2-amino-2-deoxysugars with aryl isocyanates yielded anomeric mixtures of the *O*-acetylated derivatives which could be separated further and/or analyzed by NMR. We synthesized the ureido sugars from methyl-2-deoxy-2-(4-nitrophenoxy carbonylamino)-β-D-glucopyranoside and obtained methyl 3,4,6-tri-*O*-ureido-2-deoxy-2-[3′-arylureido]-β-D-glucopyranosides i.e. only the β anomer of the sugar residue. It is worth mentioning that applying the respective ^{15}N-enriched amine enables an easy way of synthesizing ^{15}N-labelled aminosugar derivatives.

The compounds **1–4** (see Scheme 1) were 3,4,6-triacetyl derivatives, however the remaining glucopyranose protons give complex multiplets even in 500 MHz spectra, in some cases (H-3, H-5) the values and assignments of coupling constants were confirmed



1 R = H; **2** R = CH_3; **3** R = OCH_3; **4** R = Cl

Scheme 1.

Table 1
^{1}H NMR data ($CDCl_3$, δ in ppm, J in Hz) for peracetylated methyl β-D-glucopyranosyl ureas **1–4**

Atom	1	2	3	4
H-1	4.40 d	4.40 d	4.39 d	4.41 d
$J_{1,2}$	8.2	8.3	8.35	8.4
H-2	3.52 ddd	3.76 ddd	3.74 ddd	3.81 ddd
$J_{2,NH}$	[a]	9.3	[a]	8.4
$J_{2,3}$	9.8	9.3	9.6	9.4
H-3	5.27 dd	5.21 dd	5.22 dd	5.20 dd
$J_{3,4}$	9.8	9.3	9.6	9.8
H-4	5.07 dd	5.03 dd	5.04 dd	5.08 dd
$J_{4,5}$	9.2	9.8	9.5	9.8
H-5	3.66 ddd	3.61 ddd	3.65 ddd	3.64
$J_{5,6a}$	4.8	4.8	4.8	4.8
$J_{5,6b}$	2.4	2.4	2.3	2.0
H-6a	4.28 dd	4.11 dd	4.26 dd	4.31 dd
J_{6a-6b}	12.2	12.2	12.3	12.2
H-6b	4.12 dd	4.11 dd	4.12 dd	4.13 dd
N-1′–H	5.78	5.59 d	5.40	5.70 d
N-3′–H	7.62 d	7.40 s	7.20 d	7.62
$^*{}^1J^{15}_{N-H}$	89.4		89.8	

Chemical shifts for OMe, OAc, and aromatic protons are not given.
[a] Not resolved.

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. The vicinal couplings $^3J_{H\text{-}1,H\text{-}2}$ of 8.2–8.4 Hz of the anomeric protons are typical for diaxial configuration of H-1 and H-2, confirming the presence of the β anomer. The data from Table 1 are indicative of the $^4C_1$ conformation of the peracetylated methyl-β-D-glucopyranose ring. The chemical shift of the H-2 proton and the large couplings $^3J_{H\text{-}2,NH}$ indicate, as considered earlier [6], that a (*Z*)-anti-disposition of the urea framework exists in solution. In the ^{1}H NMR spectra of ^{15}N enriched ureido sugars **1** and **3** the signal of N-3′–H proton is split into a doublet with $^1J_{NH}$ 8.9 Hz. The changes of chemical shifts of ureido protons are observed, as in the case of ureido sugars with alkyl substituents [6]. Upfield shifts upon dilution in $CDCl_3$ (ureido sugars are not soluble in non-polar solvents such as cyclohexane) resulted from breaking of intermolecular NH · · · O hydrogen bonds. The signals of N-3′–H protons appeared ca. 2 ppm downfield (7.2–7.6 ppm) compared to those of C-1′–H (5.4–5.8 ppm) in the spectra of all compounds.

The ^{13}C chemical shifts for ureido sugars **1–4** are given in Table 2. The solution data are in agreement with those reported for 2-(3-arylureido)-2-deoxy-D-glucopyranoses by Avalos et al. [8], when taking into account that the compounds have different substituents at the anomeric carbon. ^{1}H and ^{13}C chemical shift assignments of substituted aryl 2-acetamido-β-D-glucopyranosides have been also given by Roy et al. [9]. The replacement of one aryl substituent by another has no influence on the proton and carbon chemical shifts or the coupling constants of the sugar moiety, as measured in solution.

Table 2
^{13}C NMR data (δ in ppm, J in Hz) in $CDCl_3$ (a), and in solid state (b), for peracetylated methyl β-D-glucopyranosyl ureas **1–4**

Atom	**1**		**2**			**3**			**4**
	a	c [a]	a	Δ	b	a	Δ	b	a
C-1	103.0	161.1	102.6	0.5	102.1	102.5	0.4	102.1	102.9
C-2	55.4	141.9	55.3	−1.6	56.9	55.4	1.0	56.0	55.4
C-3	72.9	154.2	72.9	−3.4	76.3	72.8	−3.8	76.6	72.7
C-4	69.0	152.7	68.9	1.4	67.5	68.9	1.1	67.8	68.7
C-5	71.7	144.2	71.6	−3.0	74.6	71.7	−1.9	73.6	71.7
C-6	62.3	148.1	62.3	1.0	61.3	62.3	1.0	61.3	62.2
OCH_3	57.0	144.2 [b]	57.0	−1.8	58.9	57.0	1.5	53.9	57.3
CH_3COO	20.5; 20.6; 20.7	129.7	20.6; 20.7; 20.8		20.2; 21.1	20.5; 20.6; 20.7		20.2; 20.8	20.8; 20.8; 20.6
CH_3COO	169.4; 170.6; 170.9	[c]	169.4; 170.7; 170.9		170.6	169.3; 170.6; 170.9		169.0; 170.9; 171.3	169.5; 170.7; 171.0
N–CO–N	155.9	[d]	156.1	0.1	156.0	156.2 [e]	0.8	155.4	155.8

Chemical shifts of aromatic carbons are not given.
[a] Coupling constants in liquid state spectra $^1J_{C-H}$.
[b] Coupling constant $^3J_{C-O-C-H} = 4.6$.
[c] Coupling constant $^2J_{C-C-H} = 6.9$, $^3J_{C-O-C-H} = 3.8$.
[d] Coupling constant $^2J_{C-N-H} = 4.6$, $^1J^{15}_{N-^{13}C} = 21.5$, $^1J_{C-1'-^{15}N} = 16.1$.
[e] Coupling constant $^1J^{15}_{N-^{13}C} = 21.2$, $^1J_{C-1'-^{15}N} = 15.5$.

One bond $^{13}C-^{1}H$ coupling constants for compound **1** were determined from the ^{13}C NMR 125 MHz spectrum recorded with gated proton decoupling. Values of ca. 160 Hz for an axial anomeric proton are observed in β anomer of methyl glycosides and D-saccharides in $^{4}C_{1}$ pyranose form; one-bond coupling constants for D-glucopyranose moieties with unprotected hydroxyl groups are of ca. 10 Hz larger [10]. In acetylated glycosides the coupling constants are within 1 Hz (the same as for those with unsubstituted hydroxyls). With increasing electronegativity of the substituent the coupling constant is increased significantly. The most widely studied has been the effect at the anomeric carbon C-1 [11]. Less attention has been paid to the other, non-anomeric $^{1}J_{C-H}$ couplings in sugar derivatives probably due to their relative inaccessibility. The problem of correlation between the magnitude of these couplings and the configuration of the corresponding carbon atoms remains open. Changes in the substituent at C-2 in the pyranose ring do not influence the $^{1}J_{C-1-H}$ value, but affect $^{1}J_{C-2-H}$ and $^{1}J_{C-3-H}$ appreciably (Table 2). In the 2-deoxy-ureido derivative **1** (with C-2–N substituent) $^{1}J_{C-2-H}$ is 142 Hz, i.e. between the value of 130 Hz for 2-deoxy-D-*arabino*-hexose derivatives (C-2–C) and those of 151 Hz found for methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (with C-2–OAc) substitution [12]. It is worth noting that $^{1}J_{C-3-H}$ is 154.2 Hz in **1**, 14 Hz higher than in methyl tetra-*O*-acetyl-β-D-glucopyranoside.

In the standard proton decoupled ^{13}C NMR spectra of **1** and **3** the signals of both carbons proximal to N-3′ (enriched in ^{15}N) appeared as doublets. The respective one bond $^{13}C-^{15}N$ coupling constants are included in Table 2. In general, the magnitude of these constants is larger than for similar compounds. One bond couplings for arylamines are of ca. -12 Hz and for amides or peptides (N–CO fragment) are of ca. -15 Hz [13]. The values of 15.5–16.1 Hz for $^{1}J_{C1'Ar-N}$ and 21.2–21.5 Hz for $^{1}J_{CO-N}$ imply that N-3′ nitrogen lone pair is more delocalized into conjugated system involving the ring and the carbonyl π-electrons and indicate that the two C–N-3′ bonds are of significant double bond character. In order to obtain structural information on solid ureido sugars we applied the techniques of cross-polarization (CP), magic angle spinning (MAS) ^{13}C and ^{15}N NMR which is complementary to X-ray crystallography. For some ureido sugars studied earlier [6,7] differences were observed between the spectra obtained in solution and in the solid state.

^{13}C CP MAS NMR spectra of ureido sugars are illustrated in Figs. 1 and 2 and the ^{13}C chemical shifts measured for the solid state are collected in Table 2. The resonances in the spectra of compounds **2** and **3** can be assigned directly by comparison with the solution data because single resonance for each carbon is observed. Thus, the most interesting are the differences in chemical shifts (Table 2): $\Delta = \delta_{liquid} - \delta_{solid}$. The chemical shifts of a carbon of acyl groups are almost the same as those in solution, the signals of aromatic carbons linked to nitrogen atoms (N–CO–N–C-1′) are broader due to the residual dipolar coupling $^{13}C-^{14}N$ (this effect is not observed at C-1′ of ^{15}N substituted derivatives). The values of Δ are indicative of rigid and conformationally flexible fragments of the molecule, the latter are expected to undergo larger changes. The best illustration of this effect is the averaging of chemical shifts of aromatic carbons in **3** through rapid motion of the OCH_3 group (C-2,6 114.37 ppm) in solution whereas a locked conformation in solid state results in a significant (9.5 ppm) difference: C-3 110.16 ppm and C-5 199.72 ppm (Fig. 2). Changes of chemical shifts of sugar carbons

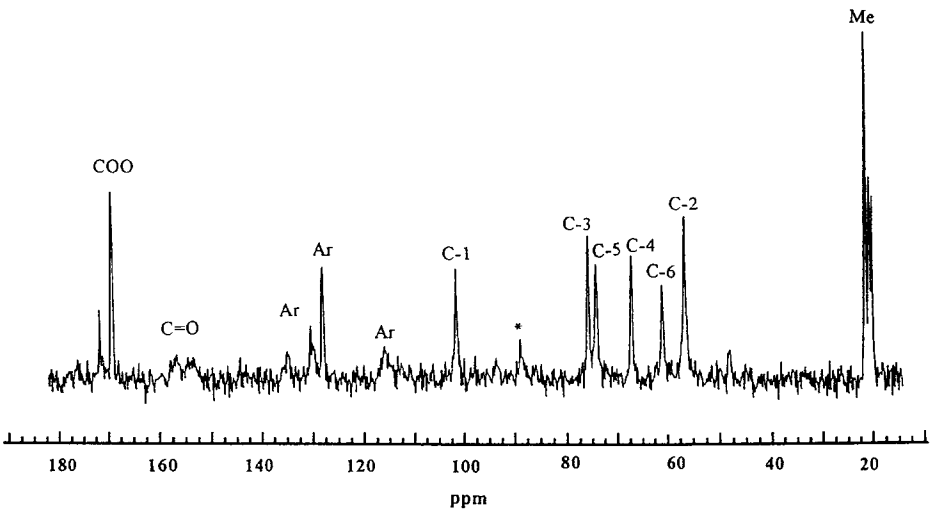


Fig. 1. ^{13}C CP MAS spectrum of compound **2** (*, spinning side band; Ar, aromatic carbon atoms).

are, however, not observed for C-2 where the ureido substituent is linked, thus indicating that this fragment of structure is rigid.

The conformation of the ureido fragment and the hydrogen bond formation by NH was monitored using ^{15}N NMR. The spectra of ureido sugars in solution recorded with the INEPT technique showed two doublets with $^{1}J_{NH} = -89$ Hz (Fig. 3). The upfield resonance was assigned to N-1′, the nitrogen linked to glucopyranose, and the downfield resonance to N-3′ nitrogen, proximal to the aromatic ring. The nitrogen resonance signal of arylamines is usually shifted to low field compared to that from alkylamines [14],

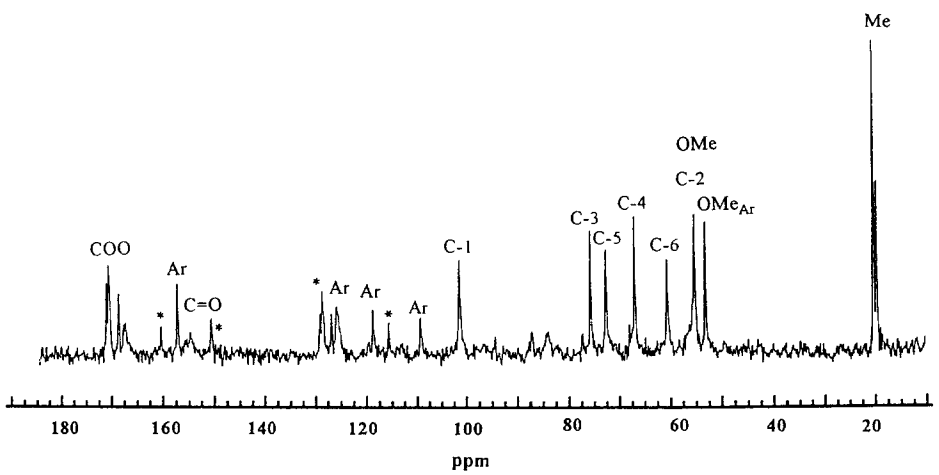


Fig. 2. ^{13}C CP MAS spectrum of compound **3** (*, spinning side band; Ar, aromatic carbon atoms).

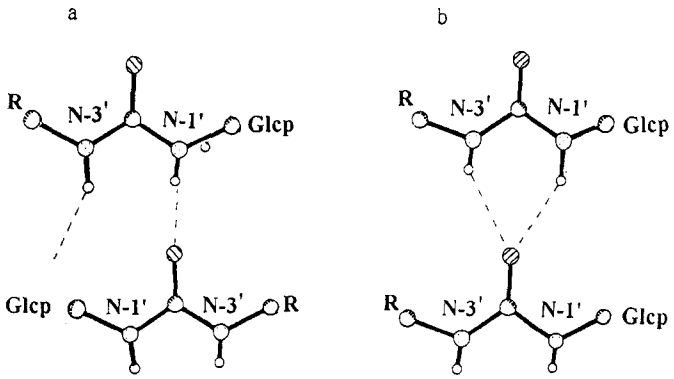


Fig. 3. Possible association models of ureido sugars in the solid state (Glcp, glucopyranose fragment, a, [17]).

because of the lone electron pair delocalization in the aromatic ring system. The replacement of the *para*-hydrogen atom by the strong electron donating methoxy group results in an increase of nitrogen shielding with an upfield shift of 3.5 ppm of N-3′ and 1.2 ppm of N-1′ observed.

The ^{15}N CP MAS NMR spectra of **1** and **3** (enriched in ^{15}N in N-3′) consist of a relatively narrow resonance from the enriched position. The chemical shifts are given in Table 3. Assuming that intermolecular NH · · · O hydrogen bonds in diluted $CDCl_3$ solution can be neglected and that in the solid ureido sugar all NH groups are involved in hydrogen bonding we calculated $\Delta = \delta_{liquid} - \delta_{solid}$ and the value of $\Delta = -2.3$ to -2.8 ppm for **1** and **3**, respectively (increase of shielding in the solid state) reflecting the effect of formation of NH · · · O=C hydrogen bonds. In amido moieties a deshielding of the nitrogen atom was observed upon hydrogen bonding of the C=O (H-bond formation of NH group of alkylamines with an electron donor). However, an opposite effect was reported for arylamines; if the lone electron pair at the amino group is involved in a delocalized π-electron system, the hydrogen bonding and protonation results in an increased shielding of the nitrogen nucleus [15,14]. It should be mentioned that the effect of intermolecular interactions involving the NH proton is less pronounced

Table 3
^{13}N chemical shifts (δ in ppm, CH_3NO_2) and in parentheses $^1J_{NH}$ coupling constants (Hz), (a) in $CDCl_3$, (b) in the solid state for peracetylated methyl β-D-glucopyranosyl ureas **1–3**

Compound		N-1′	N-3′
1	a	−297.9	−277.4
		(89.5)	(89.4)
	b		−280.2
2	a	−298.3	−278.0
		(89.3)	(89.2)
3	a	−299.2	−280.9
		(89.8)	(89.0)
	b		−280.9

than intramolecular contribution from OMe substituent although it is relatively wide apart, in the *para*-position at aromatic ring.

An interesting problem is the mode of association of ureido sugars bearing acetyl groups where the number of acceptor oxygens exceeds the number of proton donor group (only two NH). For steric reasons the anomeric oxygen, the carbonyl oxygen of the acetyl group located at C-3 and the carbonyl oxygen of the ureido fragment could be considered as acceptors. The *Z,Z* orientation of substituents in ureido group enables the hydrogen bonding pattern involving double acceptors, met in unsymmetrically substituted ureas where both NH formed hydrogen bonds with unequal N · · · O distances of 0.2965 and 0.2951 nm [16]. Recent X-ray studies of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3-(2-phenylethyl)ureido]-β-D-glucopyranoside [17] revealed an 'antiparallel' disposition of the two molecules linked by one NH · · · O=C interaction. However, the orientation of the molecules of ureido sugars with aromatic substituents could be 'parallel' with one or/and two NH · · · O=C hydrogen bonds. The crystal packing is frequently characterized by the separation of polar and non-polar groups and, as a consequence, the network of hydrogen bonds links the hydrophilic parts whereas alkyl groups or aromatic rings stack in columns forming the hydrophobic zone. Such a structure, with one molecule in an asymmetric unit cell, can be expected in solid aryl ureido sugars taking into account the results of solid state NMR.

3. Experimental

The ureido sugars were synthesized from methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(4-nitrophenoxycarbonylamino)-β-D-glucopyranoside and the respective substituted aniline derivative according to the described procedure [4]. The aniline and *p*-methoxyaniline ^{15}N-enriched (95%) were synthesized from benzamides and the benzamides from the appropriate acid chlorides and $^{15}NH_4Cl$ [18]. The following compounds were prepared:

*Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(3'-phenylureido)-β-D-glucopyranoside* (**1**).—Yield 77%, m.p. 194–197°C {m.p. 183 °C [19]}, $[\alpha]_D^{22}$ +12.9° (*c* 1, $CHCl_3$) {$[\alpha]_D^{22}$ +4.4° (EtOH) [20]}.

*Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3'-(4-tolueneureido)]-β-D-glucopyranoside* (**2**).—Yield 70%, m.p. 198–200°C, $[\alpha]_D^{22}$ +16.4° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{28}N_2O_9$: C, 55.75; H, 6.24; N, 6.19. Found: C, 55.78; H, 6.49; N, 6.21.

*Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3'-(4-methoxyphenylureido)]-β-D-glucopyranoside* (**3**).—Yield 80%, m.p. 182–184°C, $[\alpha]_D^{22}$ +15.2° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{28}N_2O_{10}$: C, 53.84; H, 6.02; N, 5.98. Found: C, 53.83; H, 6.18; N, 5.96.

*Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[3'-(4-chlorophenylureido)]-β-D-glucopyranoside* (**4**).—Yield 78%, m.p. 208–209°C, $[\alpha]_D^{22}$ +8.4° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}ClN_2O_9$: C, 50.80; H, 5.33; N, 5.92; Cl, 7.50. Found: C, 50.77; H, 5.38; N, 5.88; Cl, 7.76.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-500 spectrometer for 0.05 M solutions in $CDCl_3$; the ^{15}N spectra on a Bruker AM-500 spectrometer operating at 50.7 MHz using INEPT pulse sequence, chemical shifts were referenced to CH_3NO_2. Cross polarization magic angle spinning (CP MAS) 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 700–1200 scans. Chemical shifts were calibrated indirectly through the glycine CO signal recorded at 176.3 ppm relative to TMS. ^{15}N NMR spectra were recorded on a Bruker CXP-100 at 9.0 MHz, spinning speed was 2.8 kHz, a contact time 2 ms, repetition time 3.5 s; the accumulation of 20–50 scans was sufficient for observation of N-3′ signal from the ^{15}N enriched position. Chemical shifts were referenced to solid-state NH_4Cl and recalculated according to −341.2 ppm with respect to CH_3NO_2 [15].

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