MAGNETIC RESONANCE IN CHEMISTRY, VOL. 35, 203–208 (1997)

NOTE

NMR Studies on a New Type of Sugar Isourea Ethers

Gábor Tóth,[1]* István Pintér,[2] József Kovács[2] and Rainer Haessner[3]

[1] Technical University Budapest, Technical Analytical Research Group of the Hungarian Academy of Sciences, Institute for General and Analytical Chemistry, Szt. Gellért tér 4, H-1111 Budapest, Hungary

[2] Central Research Institute for Chemistry, Hungarian Academy of Sciences, POB 17, H-1525 Budapest, Hungary

[3] Technische Universität München, Organisch-Chemisches Institut, D-85747 Garching, Germany

New representatives of sugar isourea ethers were synthesized. Their tautomerism, isomerism and conformational behaviour were investigated by different ^{1}H and ^{13}C NMR methods. © **1997 by John Wiley & Sons, Ltd.**

Magn. Reson. Chem. **35**, 203–208 (1997) No. of Figures: 6 No. of Tables: 2 No. of References: 11

Keywords: sugar phosphinimines; ureido sugars; ^{1}H NMR; ^{13}C NMR; TOCSY; ROESY; HMQC; HMBC

Received 8 August 1996; accepted 30 September 1996

INTRODUCTION

Transformation of sugar phosphinimines[1] (iminophosphoranes) led to the simple synthesis of ureido derivatives of sugars.[2–5] Recently, we have examined the reaction of *N*-(tetra-*O*-acetyl-*β*-D-glucopyranosyl)-*P*,*P*,*P*-triphenylphosphinimine[1] (**1**) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**) with CO_2 and 4-dimethylaminopyridine to link two monosaccharide units with a non-glycosidic bond (Scheme 1). Unexpectedly, not only the target molecule 1,2:3,4-di-*O*-isopropylidene-6-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosylaminocarbonyl)-α-D-galactopyranose (**3**) was obtained in 18% yield, but also a new isourea ether with three sugar substituents, i.e. *N*,*N*′-bis(tetra-*O*-acetyl-*β*-D-glucopyranosyl)-*O*-6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoso)isourea (**4**), was isolated in 6% yield.[6]

The IR spectra of **3** and **4** substantiated the presence of NH, acetoxy, urethane and isourea groups. The structure and signal assignment for **3** and elucidation of the tautomerism, isomerism and conformational analysis of **4** are discussed in this paper.

EXPERIMENTAL

Compounds

1,2:2,4-Di-*O*-isopropylidene-6-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosylaminocarbonyl)-α-D-gal-actopyranose (**3**): m.p. 76–80 °C; $[\alpha]_D = -29.6$ ($CHCl_3$, $c = 2$); IR (KBr), *ν*NH 3440, *ν*C = O 1754, 1660 cm^{-1}.

N,*N*′-Bis-(tetra-*O*-acetyl-*β*-D-glucopyranosyl)-*O*-6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoso)isourea (**4**): m.p. 185–190 °C; $[\alpha]_D = -31.6$ ($CHCl_3$, $c = 2$); IR (KBr), *ν*NH 3396, *ν*C = O 1754, *ν*C = N 1660 cm^{-1}; FAB-MS, *m*/*z* 963 ($M^+ + H$).

NMR spectroscopy

The numbering of the H and C atoms of **3** and **4** in Tables 1 and 2 differs from the *Chemical Abstracts* nomenclature and is depicted in Scheme 1.

NMR spectra were measured on a Bruker DRX-500 spectrometer at room temperature in $CDCl_3$. Chemical shifts are given on the δ scale (ppm). ^{1}H NMR spectra were referenced to internal TMS and ^{13}C NMR spectra to the solvent ($\delta CDCl_3 = 77.0$ ppm). In the 1D measurements, 64K data points were used for the FID.

500 MHz phase-sensitive NOESY spectrum.[7] Relaxation delay $D_1 = 1.5$ s, mixing time 500 ms, 90° pulse 11.5 μs, sweep width 10 ppm in F_1 and F_2, 2K points in t_2, 256 experiments in t_1, quadrature detection in t_2, and TPPI in t_1 dimensions, linear prediction to 512 and zero filling up to 1K real points in F_1 and apodization with a $\pi/2$-shifted squared sine bell in both dimensions.

500/125 MHz HMQC spectrum with BIRD presaturation.[8] Relaxation delay $D_1 = 1.5$ s, presaturation delay $D_7 = 400$ ms, evolution delay $D_2 = 3.45$ ms, 90° pulse 11.5 μs for ^{1}H, 12.5 μs for ^{13}C hard pulses and 65 μs ^{13}C GARP decoupling, 1K points in t_2, sweep width 10 ppm in F_2 and 160 ppm in F_1, 128 experiments in t_1, linear prediction to 256 and zero filling up to 512 real points in F_1 and apodization with a $\pi/2$-shifted squared sine bell in both dimensions.

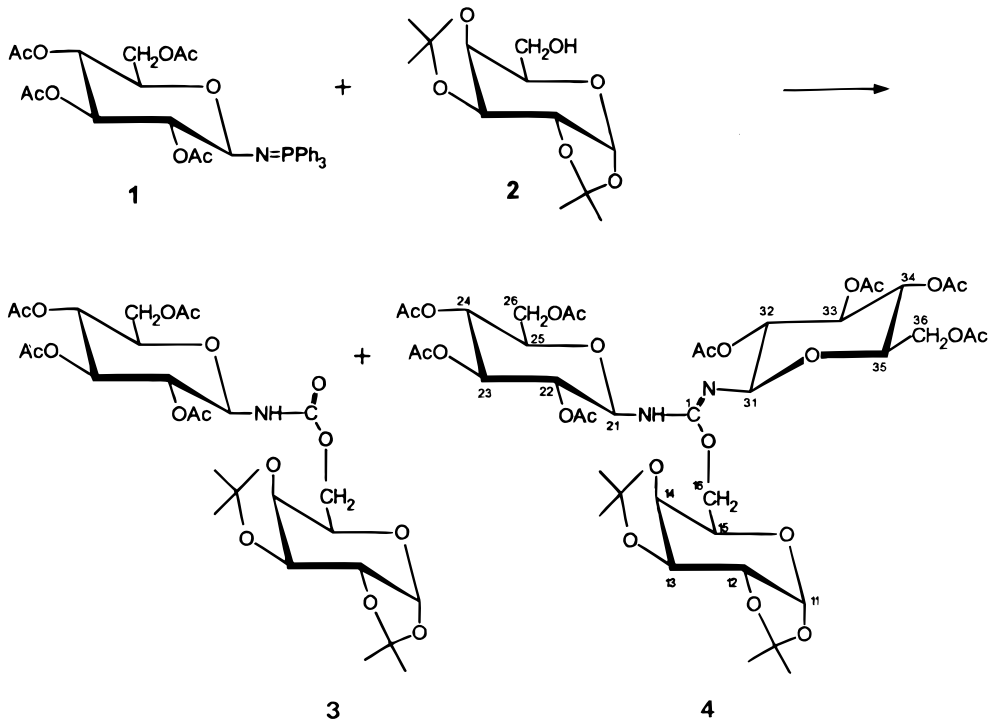
500/125 MHz HMBC.[9] Relaxation delay $D_1 = 1.5$ s, delay for evolution of long range coupling $D_6 = 70$ ms ($J = 7$ Hz), evolution delay $D_2 = 3.45$ ms, 90° pulse 11.5

* *Correspondence to*: G. Tóth.

Contract grant sponsor: National Scientific Research Fund; *Contract grant number*: OTKA T 014458; *Contract grant number*: OTKA T 014978.

Contract grant sponsor: EU Phare Accord Program; *Contract grant number*: H 9112-0060.

CCC 0749–1581/97/030203–06 $17.50



Scheme 1. Reaction route.

Table 1 ^{1}H and ^{13}C chemical shifts (ppm) and ^{3}J(H, H) coupling constants (Hz) of compounds 3 and 4

		3[b]			4[c]	
Atom No.	$\delta^{1}H$	J^{a}	$\delta^{13}C$	$\delta^{1}H$	J^{a}	$\delta^{13}C$
11	5.51	5.1	96.1	5.50	4.6	96.1
12	4.31	2.4	70.2	4.28	2.3	70.4
13	4.60	7.8	70.5	4.56	7.9	70.6
14	4.20	1.7	70.9	4.11	1.0	70.9
15	3.97	2.8	66.1	4.04		65.4
16a	4.29		64.6	4.38		65.7
16b	4.18	7.8		4.06		
21	5.02	9.5	80.6	4.80	9.4	80.9
22	4.91	9.5	70.0	4.85	9.4	70.9
23	5.27	9.5	72.9	5.29	9.4	72.5
24	5.06	9.5	68.0	5.02	10.2	68.4
25	3.77	4.2	73.1	3.75	4.1	72.8
26a	4.28		61.6	4.28		61.7
26b	4.07	2.0		4.06	2.0	
NH	5.58	9.5		5.92	9.5	
31	—	—	—	4.37	8.5	85.7
32	—	—	—	5.03	9.7	72.7
33	—	—	—	5.22	9.7	73.7
34	—	—	—	5.06	10.0	68.6
35	—	—	—	3.87	2.1	73.1
36	—	—	—	4.27		62.5
				4.21	5.3	
1			155.3			155.7

[a] *J* values indicate the coupling constants between subsequent protons.
[b] Further signals of **3**: ^{1}H (^{13}C): CH_3, 1.32, 1.33, 1.44, 1.51 (24.6, 25.1, 26.0, 26.1); CH_3CO, 2.01, 2.03, 2.06, 2.08 (20.6, 20.7 (2×), 20.8, 169.6, 170.0, 170.6, 170.7).
[c] Further signals of **4**: ^{1}H (^{13}C): CH_3, 1.32, 1.33, 1.44, 1.45 (24.3, 24.9, 25.9, 26.0); CH_3CO, 2.01, 2.02, 2.03 (2×), 2.04, 2.06, 2.10, 2.15 [20.5 (2×), 20.6 (2×), 20.7 (2×), 20.8 (2×), 169.1, 169.3, 169.4, 169.8, 170.4, 170.5 (2×), 171.5].

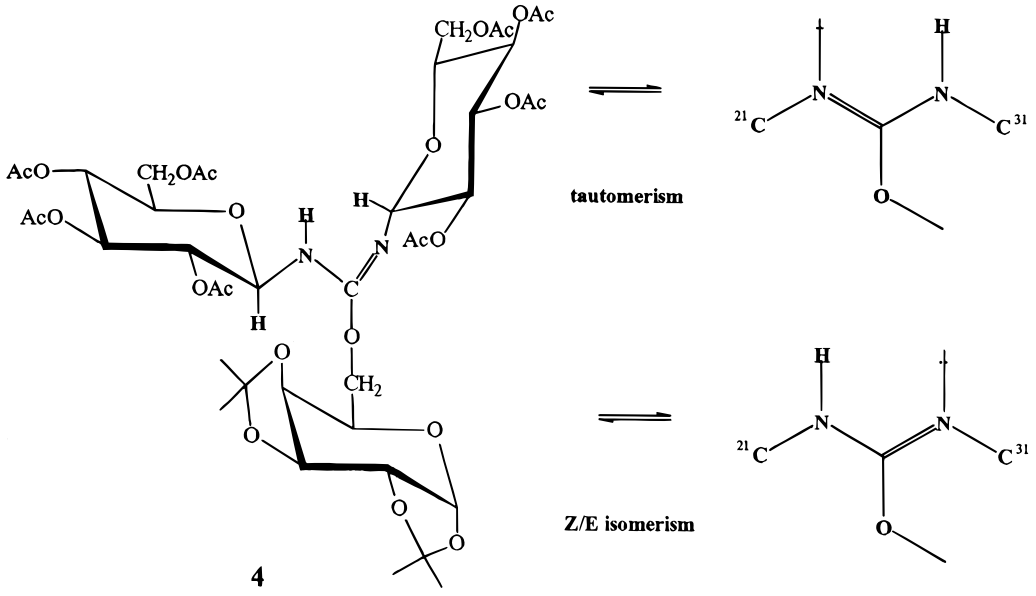


Figure 1. Tautomerism and isomerism of **4**.

μs for ^{1}H, 12.5 μs for ^{13}C hard pulses, 2K points in t_2, sweep width 10 ppm in F_2 and 220 ppm in F_1, 256 experiments in t_1, linear prediction to 512 real points in F_1 and apodization with a $\pi/2$-shifted squared sine bell in both dimensions.

500 MHz ROESY spectra.[10] Relaxation delay $D_1 = 2$ s, 90° pulse for ^{1}H, spin lock 300 ms, 1K points in t_2, spectral width 8 ppm in both dimensions, 256 experiments in t_1, linear prediction to 512 points, zero filling up to 1K.

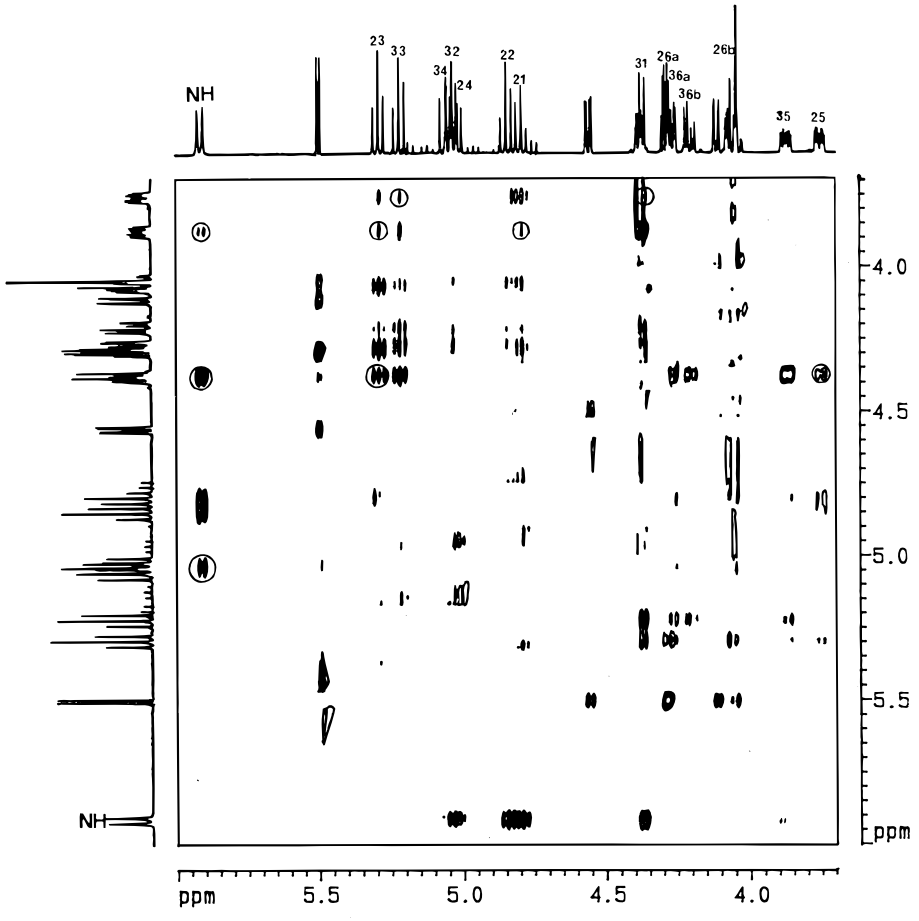


Figure 2. ROESY spectrum of **4** (− levels). Cross peaks indicating steric proximities among protons of different glucopyranosyl moieties are marked by circles.

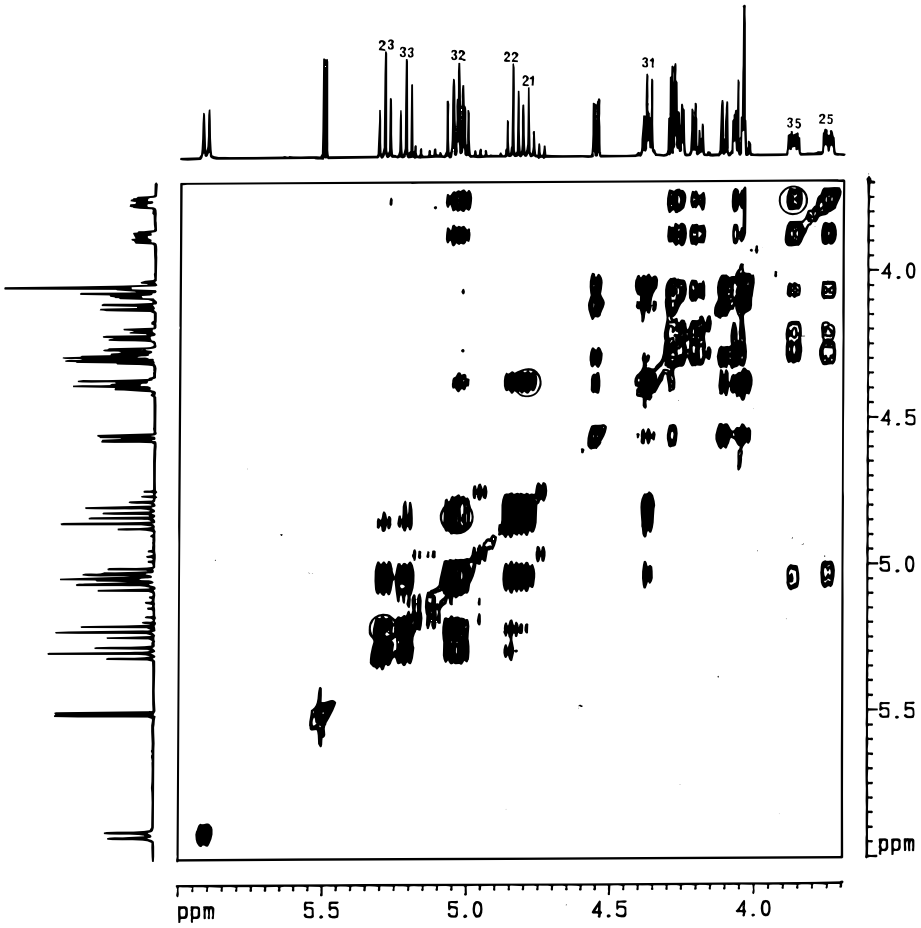


Figure 3. ROESY spectrum of **4** (+ levels). Cross peaks indicating exchange (tautomerism) are marked by circles.

500 MHz TOCSY.[11] Relaxation delay $D_1 = 2$ s, 90° pulse for ^{1}H, 90° pulse for MLEV, TRIM pulse 2.5 ms, mixing time 80 ms, spectral width 8 ppm in both dimensions, 256 experiments in t_1, linear prediction to 512 points, zero filling up to 1K.

RESULTS AND DISCUSSION

^{1}H and ^{13}C NMR signal assignments for **3** and **4** was achieved by COSY, TOCSY, NOESY, ROESY, HMQC and HMBC measurements. Characteristic chemical shifts and ^3J(H, H) coupling constants are presented in Table 1.

The NMR data unequivocally proved the interglycosidic coupling between the tetra-*O*-acetyl-β-D-glucopyranosyl and 1,2:3:4-di-*O*-isopropylidene-α-D-galactopyrano-6-yl moieties to give the new sugar carbamate **3**. The galactopyranoid unit has a twisted ring conformation, while the acetylated glucopyranoid ring preserved the $^4C_1$ conformation. The 9.5 Hz value of J(NH, 21-H) indicates a stable antiperiplanar arrangement of the two protons.

In the case of **4**, in addition to the isopropylidenegalactopyranoid substituent of the O atom, two acetylated β-glucopyranosyl units are bound to each N atom of the isourea group. For the characterization of the isourea moiety the propensity for tautomerism and isomerism may be considered (Fig. 1).

In the molecule **4** one glucopyranosyl group is attached to an NH and the other to an imine N-atom, i.e. they are not equivalent. Slow tautomerism should result in the exhibition of two different sets of signals, while fast exchange would give only one averaged series for the glucopyranosyl units. Considering the inversion of the imine N atom, in the case of slow tautomerism, the appearance of the Z/E isomers in equilibrium might be expected. On the one hand, a low activation energy of inversion leads to the averaging of each signal at room temperature, and on the other, a high energy barrier of the activation should give two separate sets.

The appearance of two different sets for the two glucopyranosyl units in the ratio 1:1, together with the significantly high value of the J(NH, 21-H) coupling, corroborates slow tautomerism in the case of **4**. The lifetime of the tautomers must be longer than 17 ms. The observation of only one set for the glucopyranosyl substituent of the imine N atom might mean either a fast N inversion or the presence of a single stable isomer. The stereochemistry and conformational behaviour of **4** were studied with phase-sensitive 2D NOESY measurements. However, owing to the moderate size of the molecule (MW 962), the data did not allow an unambiguous differentiation between steric interactions and exchanges caused by tautomerism. With the help of ROESY measurements we could achieve the separate observation of these two effects (Figs 2 and 3). The characteristic proton–proton proximities between the two

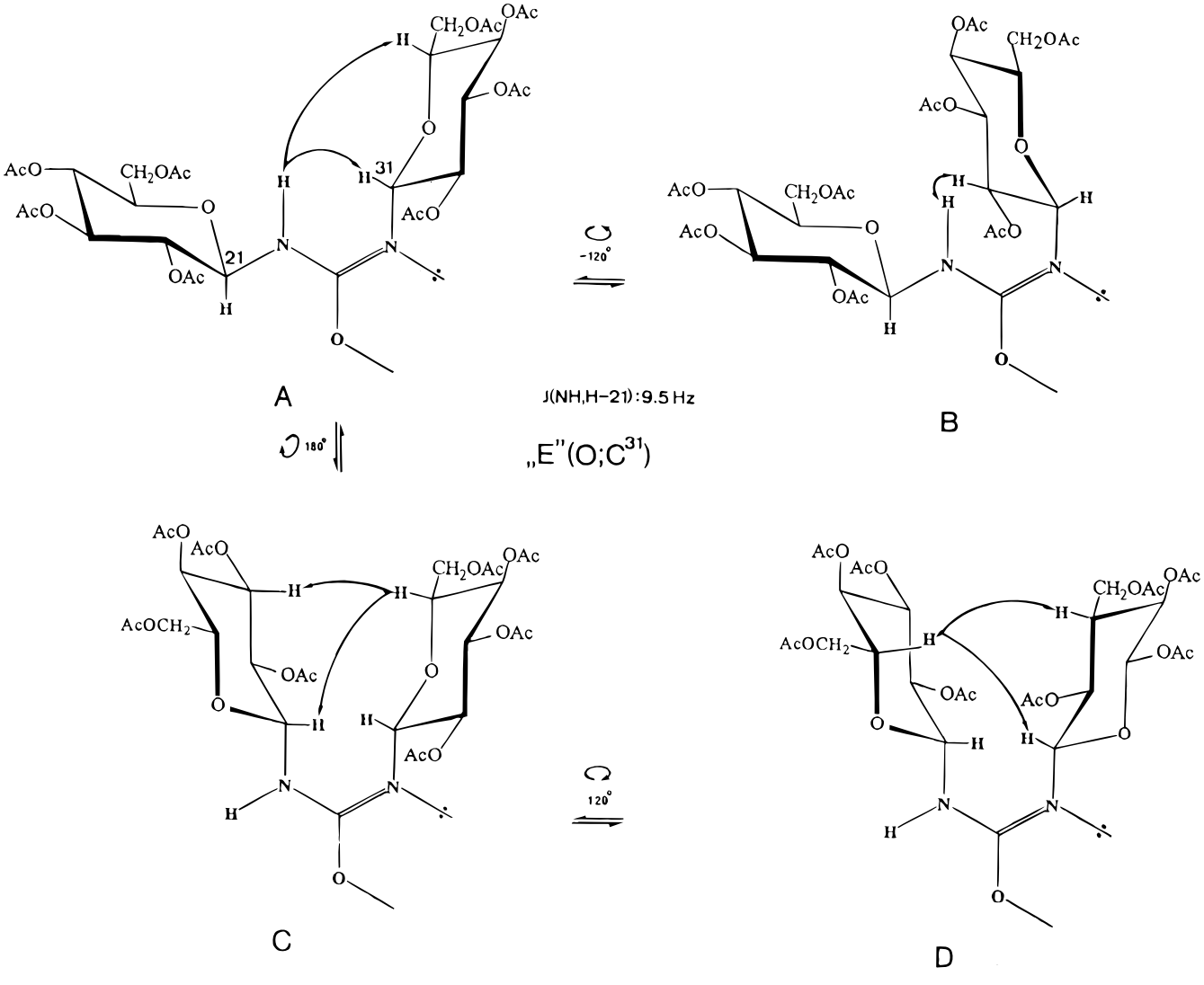
glucopyranosyl units, obtained from the − levels of the spectrum, are collected in Table 2.

On the basis of these data, an *E* configuration of the imine group and a fourfold equilibrium of the **A**, **B**, **C** and **D** conformers were established. The arrows in Scheme 2 indicate steric proximities obtained from ROESY for these conformers.

Table 2. Interglycosidic ROESY responses of compound 4

Proton	ROESY
21-H	33-H; 35-H
23-H	31-H; 33-H; 35-H
24-H	33-H
25-H	31-H; 32-H; 33-H
NH	31-H; 32-H
31-H	NH; 23-H; 25-H
32-H	NH; 25-H
33-H	21-H; 24-H; 25-H
35-H	21-H; 23-H

The reason for the disappearance of further conformers around the central isourea group might be attributed to unfavourable steric repulsions between the three sugar units. Furthermore, a preferred rotamer around the C(1)—O bond was supported by the fact that no ROESY cross peak of the 16-H_2 protons was observed with the substituents of both N atoms. The cross peaks in the + levels of the ROESY spectrum of **4** (Fig. 3) for 21-H–31-H, 22-H–32-H, 23-H–33-H and 25-H–35-H clearly indicate the existence of the tautomerism, i.e. the exchange of the NH proton between the two glucopyranosylamine moieties within a 500 ms mixing time. Further evidence for the exchange is furnished by selective 1D TOCSY experiments with a 120 ms mixing time (Fig. 4). Despite the selective excitation of 25-H with an e-burp pulse, not only the spin–spin coupled protons H-21–H-26 were observed but also the protons H-31–H-36 of the other glucopyranosyl unit appeared in the spectrum with a 0.1 H intensity of each (line a). A similar but opposite phenomenon occurred when 35-H was excited (line b). This exchange was not detected in the 2D TOCSY experiment with an 80 ms mixing time.



Scheme 2. Conformational equilibrium. Arrows indicate characteristic steric proximities obtained from the ROESY experiment.

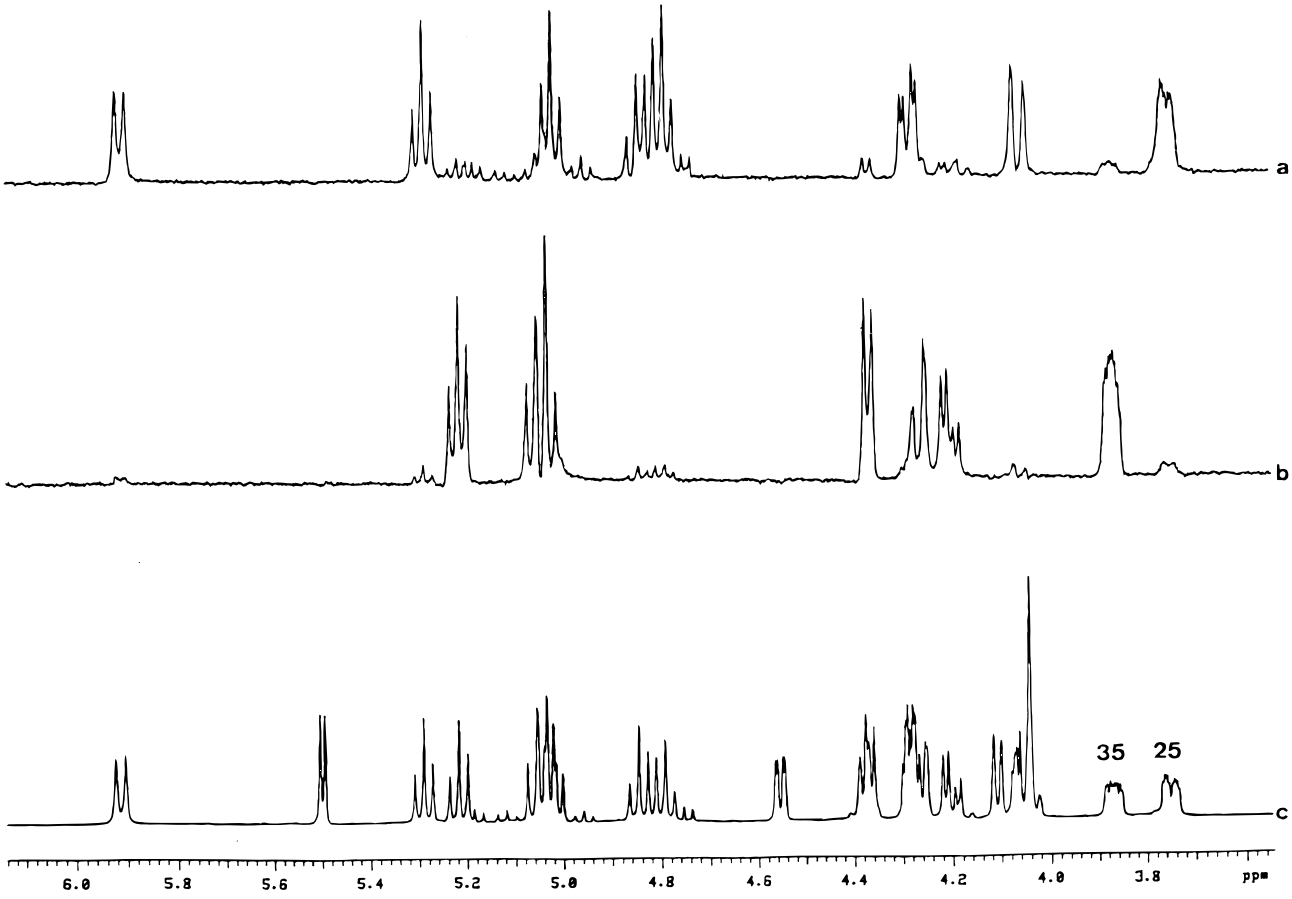


Figure 4. Selective 1D TOCSY spectra of **4**. Line a, selective excitation at 25-H; line b, selective excitation at 35-H; line c, reference ^{1}H spectrum.

Acknowledgements

The work was supported by the National Scientific Research Fund (OTKA T 014458 and T 014978). G.T. thanks the Phare-Accord Program (H 9112-0060) of the EU for supporting the Bruker Avance DRX-500 spectrometer. The authors thank Professor H. Kessler for useful discussions. G.T. gratefully acknowledges a 2 month visiting fellowship at DAAD (Germany).

REFERENCES

1. A. Messmer, I. Pintér and F. Szegö, *Angew. Chem.* **76**, 227 (1964).
2. J. Kovács, I. Pintér, A. Messmer and G. Tóth, *Carbohydr. Res.* **141**, 57, (1985).
3. J. Kovács, I. Pintér, A. Messmer, G. Tóth and H. Duddeck, *Carbohydr. Res.* **116**, 101 (1987).
4. J. Kovács, I. Pintér, G. Tóth, Z. Györgydeák and P. Köll, *Carbohydr. Res.* **239**, 95 (1993).
5. I. Pintér, J. Kovács and G. Tóth, *Carbohydr. Res.* **273**, 99 (1995).
6. I. Pintér, J. Kovács and G. Tóth, *Carbohydr. Res.* submitted for publication.
7. J. Jeener, B. H. Meier, P. Bachmann and R. R. Ernst, *J. Chem. Phys.* **71**, 4546 (1979); S. Macura and R. R. Ernst, *Mol. Phys.* **41**, 95 (1980).
8. A. Bax and S. Subramanian, *J. Magn. Reson.* **67**, 565 (1986).
9. A. Bax and M. F. Summers, *J. Am. Chem. Soc.* **108**, 2093 (1986).
10. (a) A. A. Bothner-By, R. L. Stephens and J.-M. Lee, *J. Am. Chem. Soc.* **106**, 811 (1984); (b) A. Bax and D. G. Davies, *J. Magn. Reson.* **65**, 207 (1985).
11. A. Bax and D. G. Davies, *J. Magn. Reson.* **65**, 355 (1986).

