Tetrahedron Vol. 42, No. 14, pp. 4057 to 4067, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00
Pergamon Journals Ltd.

AN ASSESSMENT OF THE REACTIVITY OF GUANOSINE AND SOME OF ITS DERIVATIVES TO ELECTROPHILES BY ^{15}N-NMR SPECTROSCOPY.

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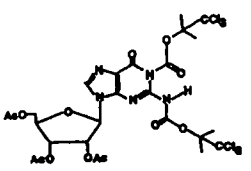
(*Received in UK* 24 *April* 1986)

Summary:

^{15}N-NMR spectra of guanosine and uridine and several of their amide-protected derivatives have been studied. The nucleophilicity of the N^7 of the guanosine, in some of its O^6 and N^1 substituted derivatives, has been studied by following the ^{15}N chemical shift of the protonated species in the presence of CF_3COOH. The formation of the N^7 protonated species, the magnitude of its ^{15}N chemical shift and the potential of the N^7 to undergo methylation reaction in a particular protected derivative of guanosine throws light on the efficiency of a protecting group to protect the guanine residue against an electrophile.

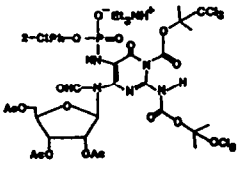
It has emerged very recently that the protections of the exocyclic amino functions of DNA and RNA aglycones are not quite enough to obtain pure oligonucleotides, that are free of undesirable base modifications[1-22]. It has been indeed shown that there is a considerable formation of by-products if the imide functions of N^2-protected guanine, uracil and thymine residues are not suitably protected[1-11]. Several protecting groups have therefore been introduced to remedy the latter problem in nucleic acid synthesis[8-23]. Recently, it has been observed that the chemical reactivity of the fully protected guanine residue, in oligonucleotide synthesis, is indeed influenced, by the exact location of the protecting group on the O^6 or N^1 of the lactam function[23]

We have thus reported[23] that the N^7 of N^1,N^2-bis(2,2,2-trichlorobutyloxycarbonyl)-2',3',5'-tri-O-acetyl guanosine (A) reacted with the 2-chlorophenylphosphoro-bis-(1,2,4-triazolide) (B) giving an imidazole ring-opened N^7-phosphoramidate (C) while 2-N-(p-t-butylbenzoyl)-6-O-(2-nitrophenyl)-2',3',5'-tri-O-acetyl guanosine (D) was completely stable under the latter reaction condition. We herein report our ^{15}N-NMR studies of a few guanosine O^6 protected



A

B



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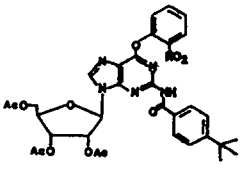

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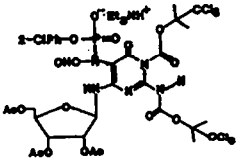


C

derivatives (3-pyridyl-[24], 2-nitrophenyl-[14], 4-nitrophenylethyl-[22]) and show how these $\underline{O}^6$ protecting groups affect the electron density distribution of resulting purine system. We have subsequently examined the effect of such redistributed electron density in the protected guanine residues on their chemical reactivities toward electrophilic reaction conditions, such as protonation and methylation, enabling us to define the "electronic criteria" that a $\underline{O}^6$ protecting group of an appropriately substituted guanine derivative must fulfil in order to protect the structural integrity of the guanine residue.

At the outset of this work, we anticipated a similarity in behaviour of the ^{15}N chemical shifts of the $\underline{N}^1$ of the $\underline{C}^6$ substituted guanosines and the $\underline{N}^3$ of $\underline{C}^4$ substituted uridines because of their comparable state of hybridization in both systems. It was, therefore, decided first to explore and unambiguously assign the ^{15}N resonances of the $\underline{C}^4$ substituted uridines and then use this knowledge to distinguish between the $\underline{N}^1$ and $\underline{N}^3$ of $\underline{C}^6$ substituted guanosines.

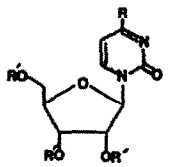
^{15}N assignments of substituted uridines (Table 1)

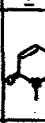
The ^{15}N chemical shifts for the $\underline{N}^1$ and $\underline{N}^3$ of uridine (16) are conveniently assigned by ^{15}N - ^1H coupled spectra in DMSO in which the $\underline{N}^3$ - ^1H coupling of 89.1 Hz is easily detectable[25]. Both $\underline{N}^1$ and $\underline{N}^3$ resonances have large negative NOE; it is the $\underline{N}^3$ in uridine which has a larger NOE (ca. -4.9) because of effective longitudinal relaxation by dipole-dipole interaction

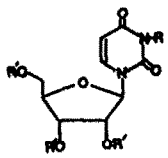
Table 1: ^{15}N chemical shifts[a] of uridine and some of its C^4 substituted derivatives.

Compound	N^1	N^3	N-substituent
1	-220.7	-149.4	-92.3
2	-221.3	-151.3	-65.8
3	-221.8	-149.9	-93.0
4	-221.6	-151.4	-67.6
5	-221.2	-117.6	-62.4
6	-222.6	-119.3	-
7	-214.8	-124.8	-197.5
8	-215.2	-140.6	-225.1
16	-237.8	-223.7	-
17	-241.9	-225.6	-
18	-228.4	-172.1	-287.7
19	-241.7	-193.9	

[a] Measurements were carried out at 303 K in 0.8 M solutions, except for 8 (0.4 M), 17 (0.8 M), 19 (0.35 M) in chloroform. The data for 16 and 18 are taken from the literature for comparison (ref. 25 and 27).



COMPOUNDS	1	2	3	4	5	6	7	8	16
R =									NH_2
R' =	Ac	Ac	Ac	Ac	Ac	Ac	Ac	Ac	H



16: R = R' = H

17: R = H; R' = Ac

18: R = Bz; R' = Ac

through the N^3-H whereas the N^1 has a smaller NOE (ca. -2.5) because of the dipole effect of the sugar protons[25-27]. Both N^3 and N^1 of the C^4 and N^3 substituted uridines could also be unambiguously assigned by a large negative NOE for N^1 and a complete absence of NOE for the N^3 resonance. A comparison of the ^{15}N data of the C^4 substituted uridines 1 to 8 in Table 1 show their close similarity with that of cytidine (18) because of the analogy of their electronic structures. It is the N^3 resonances in 1 to 8 which are most affected both because of change of its state of hybridization and the inductive or mesomeric effect of the C^4 substituent. On the other hand, the N^3 resonance of an N^3 substituted uridine (19) is deshielded by 32 ppm, as compared to the N^3 of 17, which can be explained by the fact that the N^3 is becoming a "tris

amide type". In compounds 1 to 8, the N^1 atom has a chemical shift of ca. -221 ppm except for compounds 7 and 8. In 7 and 8 the C^4-pyridone nitrogen is devoid of its lone pair and is electronically very similar to that of N^1 of the

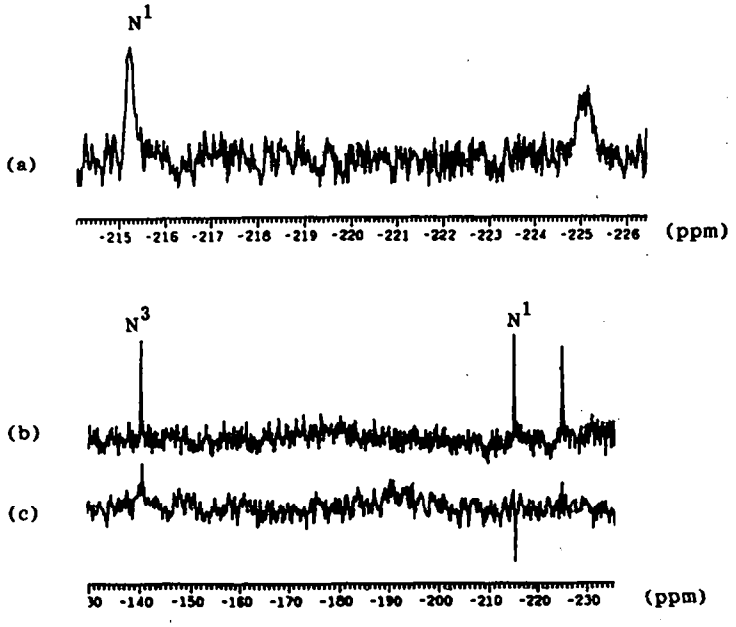


Fig. 1: ^{15}N-NMR spectra of compound 8: (a) proton coupled spectrum where N-pyridone shows a complex multiplet at ca. 225 ppm and the N^1 appears as a broad signal at ca. 215 ppm. ; (b) decoupled mode without NOE showing the N^3, N^1 and N-pyridone; (c) decoupled mode with NOE showing larger NOE for N^1 than for N-pyridone.

pyrimidone moiety. It thus appears that this lone-pair is shared to the rest of the pyridone-pyrimidone system, which exerts an overall electron-withdrawing influence to the pyrimidone, causing the deshielding of N^3 and especially influencing N^1. The ^{15}N assignments of pyridone-nitrogen and the N^1 was established on the basis of the proton-coupled spectrum and the favourable NOE of N^1 (Fig. 1). For the C^4-pyridyl substituent in compounds 1 to 4, the O^4 lone pair is presumably delocalized, depending upon whether it is C-2 or C-3 oxo with respect to the pyridyl-nitrogen, to the pyrimidine ring yielding a similar chemical shift for N^1 (ca. -220 ppm) and for N^3 (ca. -150 ppm). It should be noted that the 3-pyridyl shields the N^3 a slightly more (by ca. -1.5 ppm) as expected, as opposed to the 2-pyridyl while the chemical shifts of pyridyl-nitrogen are in agreement with the literature data[28,29]. Finally, when O^4 is substituted with S^4 in 5 and 6, the N^3 resonance is deshielded due to the usual "β effect" which has been already documented in ^{13}C- and ^{15}N-NMR spectroscopy[24,30,31]; consequently the pyridyl nitrogen in 5 is also deshielded by 30 ppm as compared to 1.

^{15}N assignments of C^6 substituted N^2-protected guanosines (Table 2)

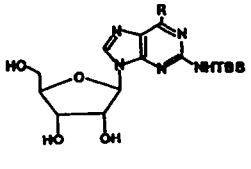
The exocyclic amino function of the guanosine is normally protected by an acyl group for oligonucleotide synthesis. Thus the presence of p-t-butylbenzoyl (TBB) group at the N^2 position in 21 has a profound influence on the ^{15}N chemical shifts of all purine-nitrogens. Each nitrogen atom of 21, especially N^3, is

deshielded as compared to the nitrogens of guanosine (20). A comparison of ^{15}N shifts of 21 with compounds 9 to 15 in Table 2 shows that a C^6 substitutent shields the N^7 to ca. -140 ppm and N^9 to ca. -210 ppm. These values are very similar to those found for adenosine[25] which can be rationalized by an activation of the aromatic ring by the C^6 substituent which is further delocalized to the imidazole part. The "azine-like" N^7 is more affected than the "pyrrole-like" N^9. In the C^6 substituted guanosines 9 to 15, the pyrimidine moiety is fully aromatic and hence a direct unambiguous assignments of N^1 and N^3 are difficult. However, as the N^1 in C^4 substituted uridine derivatives (Table 1), the N^3 of C^6 substituted guanosines 9 to 15 are at best expected to experience a long range influence of the C^6 substitution and is, therefore, expected to have a steady chemical shift which turned out to be true, showing the absorption of the N^3 of 9 to 15 indeed at ca. -160 ppm. On the other hand, the N^1 absorption of compounds 9 - 15 showed a critical dependence (Table 2) to the

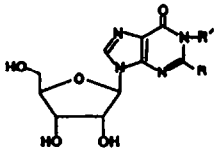
Table 2: ^{15}N chemical shifts[a] of some purines and some C^6 substituted guanosines

Compound	N^1	N^3	N^7	N^9	N^2	N-substituent
9	-155.9	-160.4	-140.6	-210.0	-243.2	-60.3
10	-156.3	-160.8	-140.9	-210.2	-243.3	-62.9
11	-154.2	-159.4	-141.1	-210.1	-243.1	-73.8
12	-129.4	-158.6	-139.5	-210.8	-243.3	-65.5
13	-157.7	-160.7	-141.1	-210.2	-243.5	-13.7
14	-166.1	-158.0	-140.3	-210.6	-243.1	-10.5
15	-155.4	-159.3	-141.7	-209.7	-243.4	-224.9
20	-232.5	-215.4	-133.6	-211.3	-307.8	-
21	-227.0	-195.6	-131.8	-207.8	-248.4	-
22	-223.3	-198.0	-219.1	-203.5	-246.9	-

[a] Measurements were carried out at 303 K in 0.25 M solution, except for 20 and 21 (0.5 M), 22 (0.4 M) and 14 (0.6 M, 313 K) in DMSO.



COMPOUNDS	9	10	11	12	13	14	15	16
R =								



16: R = NH_2; R' = H

21: R = 4-(t-butyl)bensamido
R' = H

23: R = NH_2; R' = CH_3

26: R = R' = H

nature of the C^6 substituent. The N^1 chemical shifts for the O^6 substituents in compounds 9 to 11 and 13 is -154 to -158 ppm depending upon the exact electronic nature of the O^6-substituent. The C^6-N-substituent in 15 was not found to influence the N^1 chemical shift anyway differently (truly "isoelectronic") than in compound 11. This is presumably partly because of delocalization of the C^6-nitrogen lone pair to the pyrimidone moiety. As already noticed, the C^6-sulfur in 12 has a drastic effect on the N^1 chemical shift which goes downfield to reach the value of -129.4 ppm. Substituents in any other position of guanosine do not produce so strong changes on its ^{15}N chemical shifts. For example, in N^1-methyl guanosine (23), the N^3, N^7 and N^9 have almost identical chemical shifts as that of guanosine (20) but the N^1 goes upfield by 3.3 ppm because of +I effect of the methyl group; however, the protonation study (vide infra) has clearly shown that the N^1-methyl group significantly alters the nucleophilicity of N^7 (Table 3).

Protonation studies (Table 3)

The ^{15}N chemical shifts of the N^7 is expected to be influenced by its effective nuclear charge, its symmetry in the valence electron and by its effective excitation energy ($n\rightarrow\pi^*, \pi\rightarrow\pi^*$)[32]. Table 2 shows that a protecting group or a substituent either at O^6 or N^1 of guanosine has a definite effect on the nitrogen chemical shifts of purines. However, a comparison of the N^7 chemical shifts amongst 20, 21 and 23 and 9, 13, and 14 in neutral DMSO and in their acidic solutions (Table 3) clarifies that the reactivity of the N^7 toward electrophiles can not be estimated, even qualitatively, from the ^{15}N chemical shifts alone in any of these media but from the magnitude of the difference in $\delta^{15}N$ shift.

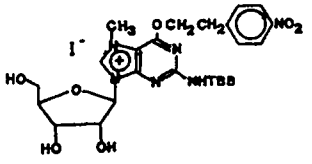
What we considered important is to understand how a protecting group on O^6 actually influences the nucleophilicity of N^7 and which are the O^6 protecting groups (O^6-alkyl vs. O^6-aryl) that are safe to use for employing guanosine in electrophilic reaction conditions! In the Table 3, the effect of C^2-amino substituent is obvious through the comparison of chemical shifts of guanosine (20) and inosine (25). With 1 equivalent of acid (CF_3COOH) in inosine (25), the N^7 moves by almost 11 ppm[33] while the N^7 in guanosine, under a similar acidic condition, moves upfield by 75 ppm, establishing the electron-donating effect of the C^2-amino function (Fig. 2). On the other hand, the N^7 in N^2-TBB-guanosine (21), under a similar acidic condition, was shielded by 25 ppm (Fig. 2). The nucleophilic character of the N^7 in 21 is therefore much poorer than in 20.

Table 3. Study of the ^{15}N chemical shifts[a,b] of guanosine derivatives upon protonation and methylation at 313 K.

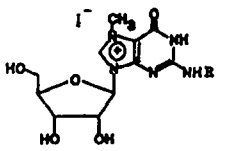
Compound	Concentration of acid	N^1	N^3	N^7	N^9	N^2	N-substituent
20	0 equiv.	-233.9	-215.2	-134.4	-211.1	-307.7	
	1.0 equiv.	-232.7	-218.1	-211.0	-204.4	-301.4	
	2.0 equiv.	-232.8	-218.3	-214.8	-204.3	-301.3	
	1.8 equiv.	-232.2	-217.2	-211.2	-205.6	-303.0	
23	0 equiv.	-237.2	-215.8	-133.3	-212.3	-300.4	
	1.0 equiv.	-235.7	-217.0	-232.8	-208.3	-297.0	
	2.0 equiv.	-235.1	-217.8	-	-207.1	-296.0	
24	0 equiv.	-231.9	-217.9	-220.8	-207.1	300.1	
	1.0 equiv.	-232.2	-218.1	-220.9	-207.2	300.3	
21	0 equiv.	-226.6	-195.0	-132.1	-207.4	-248.3	
	1.0 equiv.	-226.3	-196.3	-156.8	-205.3	-248.0	
	2.0 equiv.	-226.3	-196.8	-166.3	-204.5	-248.0	
25	0 equiv.	-206.6	-167.1	-131.9	-206.6	-	
	1.0 equiv.	-206.2	-167.3	-141.2	-205.6	-	
	2.0 equiv.	-205.9	-167.4	-147.7	-204.9	-	
9	0 equiv.	-157.7	-160.9	-141.5	-210.6	-243.5	-61.9
	1.0	-157.0	-160.8	-142.0	-209.6	-243.1	-113.1
	2.0	-158.3	-161.1	-142.8	-209.5	-243.1	-159.2
26	0 equiv.	-159.6	-160.5	-141.5	-209.4	-242.9	-177.3
13	0 equiv.	-157.3	-160.5	-141.1	-209.9	-243.5	-13.5
	1.0 equiv.	-157.4	-160.8	-142.1	-209.9	-243.4	-13.5
	2.0 equiv.	-157.5	-161.0	-143.5	-209.8	-243.4	-13.5
14	0 equiv.	-166.1	-158.0	-140.3	-210.6	-243.1	-10.5
	1.0 equiv.	-166.5	-157.9	-145.5	-210.2	-243.1	-10.6
	2.0 equiv.	-167.1	-157.9	-150.0	-209.4	-243.0	-10.6
27	0 equiv.	-170.3	-154.7	-225.7	-205.3	-242.9	-10.7

[a] compounds 9, 20 and 24 were recorded as 0.8 M solution; 13, 14, 21, 23 and 25 were recorded in 0.6 M solution; 26 and 27 were recorded in 0.4 M solution.

[b] study of 20 with 1.8 equiv. of acid is sited for the sake of comparison from literature (ref. 25 & 27)



27



28: R = 4-(t-butyl)benzamido

24: R = H

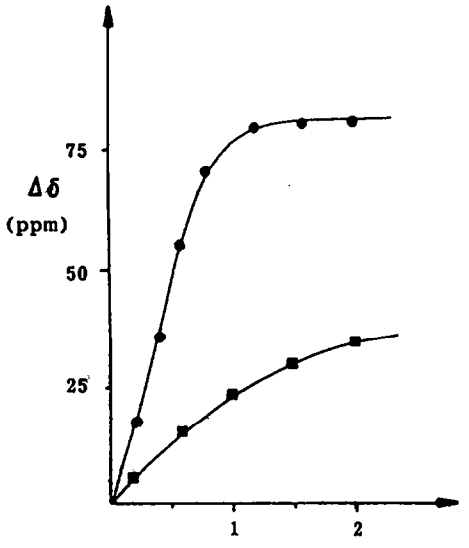


Fig. 2: ^{15}N chemical shift changes of N^7 of 20 (●) and 21 (■) as a function of added CF_3COOH.

This reduced nucleophilic reactivity is also supported by methylation studies with 20 and 21 by methyl iodide in dimethylformamide at 20° C which showed that the half-lives of N^7-methylation of 20 and 21, to give 24 and 22 respectively, are 50 and 165 min respectively.

The ^{15}N chemical shifts of the C^6 substituted guanosine derivatives 9, 13- and 14 along with the result of protonated and methylated derivatives are shown in Table 3. Since all guanosine derivatives in this work has a N^2-TBB group, the observed ^{15}N chemical shifts, in protonation and methylation experiments in Table 3, is attributed to the electronic effect of the C^6 substituent. The data for N^1-methyl guanosine (23) are also shown for comparison. The N^7 in compounds 9 and 13 moved only 0.5 and 1 ppm upfield, respectively, upon protonation. Compound 13 was completely resistant to methylation reaction condition (vide supra); the N^7 of 9 was also found to be completely resistant to methylation while its pyridyl-nitrogen, as expected, got methylated to give 26 which was isolated and characterized in the usual way. The N^7 of C^6-(4-nitrophenylethyl-) derivative 14, upon protonation, moved upfield by 5 ppm, suggesting that the N^7 is not completely deactivated. This is also corroborated by the fact that the 14 can be methylated (vide supra) at N^7 to give 27 with a half-life of 300 min. (compare half-lives of methylation of 20 and 21 which are respectively 50 and 165 min!). Compound 27, which was also isolated and characterized as a pure compound, has ^{15}N shifts which are very similar to N^7-methyl-N^2-TBB-guanosine (22) (Table 3).

It appears from these data that there is a considerable reduction of the nucleophilicity of N^7 with most of the C^6 substituted guanosine derivatives. This is most probably due to the delocalization of the π-electron rich imidazole system to the π-deficient pyrimidine system with a overall reduction of the nucleophilic character of the N^7. However, the present data suggests an "electronic criteria" that a O^6 protecting group of guanosine should fulfill. That such a group should not be electron-releasing to the resulting fully-aromatic purine syst-

em. This is substantiated by the fact that the O^6-alkyl substituent of 14, as the O^6 protecting group of the guanine moiety, has made the N^7 more susceptible to electrophilic reagents than the electron-withdrawing O^6-aryl group of 9 or 13.

It also should be noted that the N^7 of N^1-methyl guanosine (23), upon protonation with one equivalent of acid, moved upfield by 99.5 ppm while the N^7 of guanosine, in a similar protonation experiment, moved only by 75 ppm (Table 3). This clearly shows that the N^1 methylation enhances the nucleophilicity of the N^7. It is also established that an N^1-acyl group of a fully-protected guanosine derivative A enhances the nucleophilicity of the N^7 and gave a N^7-phosphorylated product C. All of these observations suggest that if the lactam function of the N^2-protected guanine is protected at N^1, subsequent electrophilic reactions at the N^7 can not be prevented.

Experimental

All ^{15}N-NMR spectra were recorded at 27.4 MHz on a Jeol JNM-GX-270 spectrometer equipped with a tunable probe-head of 10 mm. Routinely, the NOE suppressed-decoupled spectra (the decoupler is on during the acquisition time) were recorded using a 45° pulse angle (13 μs of pulse width), 0.8 to 1 s acquisition time for 16 K data points, zero filled to 32 K and Fourier transformed. The spectral range was 9500 Hz in order to observe the resonance from the amino group and 8200 Hz for N^2 substituted guanosines and C^4 substituted uridines. With the pulse delay set at 15 to 30 s, a useful spectrum is obtained after 2 h for 0.8 M solutions, 4 h for 0.6 M solutions, 7 h for 0.25 M solutions. A broadening factor of 2 - 3 Hz was applied before Fourier transformation. ^{15}N chemical shifts

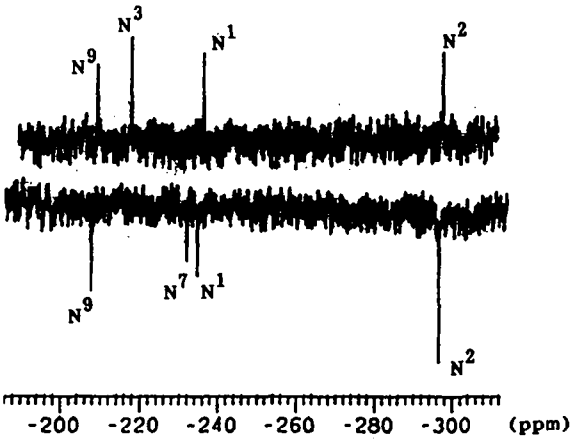


Fig. 3: ^{15}N-NMR spectra of compound 23 with CF_3COOH (1 equiv.). (a) decoupled mode without NOE where the N^7 does not appear; (b) decoupled with NOE showing negative peaks for N^9, N^7, N^1 and N^2.

are assumed to be correct to ± 0.1 ppm. As it is empirically known that a strongly protonated nitrogen atom has a shorter T_1 and a large NOE, often it is very difficult to observe the absorption of this atom because of both a short T_2 involving broad signal and a possible exchange of the acidic proton[34]. In these cases, the solution is either the reduction of the acquisition time in

order to reduce the magnitude of the negative NOE or to use this NOE to reveal a negative peak as it is shown in the fig. 3 for the compound 23. The chemical shifts were measured relative to an external solution $CH_3{}^{15}NO_2$ in CD_3NO_2 to provide the reference and the frequency lock respectively (a coaxial 4 mm capillary with 5 x 10^{-3} ml $CH_3{}^{15}NO_2$ (96%) and 0.35 ml of CD_3NO_2 and some relaxation reagent to shorten the T_1 value.)

The samples were run at 30 ± 1°C or 40 ± 1° C with either gated proton decoupling or no decoupling. A negative increment denotes an increased shielding.

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Acknowledgements:

Authors thank Wallenbergstiftelse for funds for the purchase of a Jeol GX-270 - NMR spectrometer. The generous financial supports from the Swedish Board for Technical Development is also gratefully acknowledged.