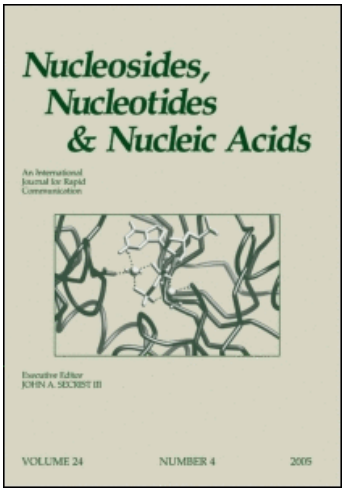


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# On the Influence of the Nature of 2-N-Protecting Acyl Groups on the Stability of Deoxyguanosine Derivatives

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# ON THE INFLUENCE OF THE NATURE OF 2-N-PROTECTING ACYL GROUPS ON THE STABILITY OF DEOXYGUANOSINE DERIVATIVES.

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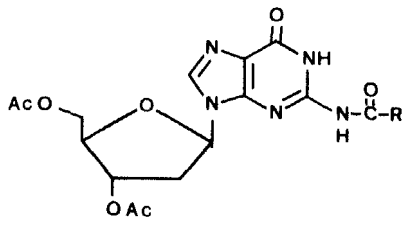
Abstract: Acid mediated variations of $^{13}$C-NMR chemical shifts and destruction kinetics of protected deoxyguanosine derivatives indicate a pronounced effect of the electronegativity of the protecting groups on their stability.

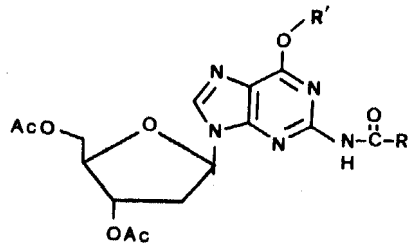


The protection of the exocyclic amino group of guanine nucleosides does not suffice to prevent base modifications during oligonucleotide synthesis [1]. The nature of the protecting group has an influence on the stability of the glycosidic bond [2]. Protection at N-1 enhances the problem [3], whereas 6-O protection leads to stable building blocks [4,5]. In one case ring opening after electrophilic attack on N-7 was demonstrated [3]. $^{15}$N-NMR experiments showed a pronounced effect of the nature of the protecting groups [6]. Our interest in this problem originated from the observation, that 2-N TCBOC protected deoxyguanosine derivatives, used in our group, were relatively labile towards phosphorous ester amide chlorides [7].

$^{13}$C-NMR spectra of the differently protected 3',5'-diacetyl guanosine derivatives **1a - d** and **2a - b** were recorded in deuteriochloroform after protonation using one equivalent of trifluoroacetic acid. The results and a comparison with those of the neutral species are summarized in the TABLES.

The stability of protected deoxyguanosine derivatives **1a - d** against $PCl_3$ (choosen as an aggressive test electrophile) (FIG.1) was tested in acetonitrile solution. Aliquots





**1a** R = TCBO(C)
**1b** p-tert.-butyl-phenyl-
**1c** p-methoxy-phenyl-
**1d** p-nitro-phenyl-

**2a** R = TCBO(C)
R'= o-nitrophenyl-
**2b** R = TCBO(C)
R'= 2,2,2-trichlorethyl-

TCBO(C) = 1,1,1-trichlor-2-methyl-2-propyl-oxy-

TABLE 1 $^{13}$C-NMR chemical shifts of protected deoxyguanosine derivatives

| | 1a | 1b | 1c | 1d | 2a | 2b |
|---|---|---|---|---|---|---|
| C-2 | δ=151.48 | 147.92 | 147.83 | 147.01 | 151.29 | 151.32 |
| C-4 | 147.91 | 147.92 | 147.64 | 147.31 | 148.30 | 148.48 |
| C-5 | 121.68 | 122.15 | 122.49 | 123.12 | 118.55 | 118.34 |
| C-6 | 155.44 | 155.58 | 155.47 | 155.35 | 153.89 | 153.37 |
| C-8 | 137.52 | 137.80 | 137.84 | 138.76 | 141.20 | 140.64 |
| C-1′ | 85.06 | 85.13 | 85.49 | 86.07 | 84.90 | 84.79 |
| C-2′ | 36.88 | 36.75 | 36.51 | 36.34 | 37.22 | 37.19 |
| C-3′ | 74.41 | 74.49 | 74.51 | 74.51 | 74.56 | 74.52 |
| C-4′ | 82.46 | 82.40 | 82.40 | 82.45 | 82.88 | 82.77 |
| C-5′ | 63.63 | 63.60 | 55.59 | 63.58 | 63.91 | 63.82 |

TABLE 2 Variation of the chemical shifts of protected deoxyguanosine derivatives on addition of one equivalent of trifluoro acetic acid.

| | 1a | 1b | 1c | 1d | 2a | 2b |
|---|---|---|---|---|---|---|
| C-2 | Δδ=0.42 | 1.19 | 1.48 | | 0.77 | 0.77 |
| C-4 | 0.29 | -0.39 | -0.31 | | 0.09 | 0.01 |
| C-5 | | -3.48 | -4.62 | | -2.67 | -2.36 |
| C-6 | -1.18 | -1.31 | -1.62 | | -0.85 | -0.85 |
| C-8 | 0.59 | 0.16 | 0.14 | | 0.30 | 0.17 |
| C-1′ | 1.07 | 0.77 | 0.82 | | 0.57 | 0.57 |
| C-2′ | 0.48 | 0.60 | 0.77 | | 0.35 | 0.31 |
| C-3′ | -0.14 | -0.25 | -0.37 | | -0.15 | -0.19 |
| C-4′ | 0.66 | 0.47 | 0.59 | | 0.41 | 0.39 |
| C-5′ | 0.05 | -0.04 | -0.03 | | -0.01 | -0.06 |

decomposed during aquisition

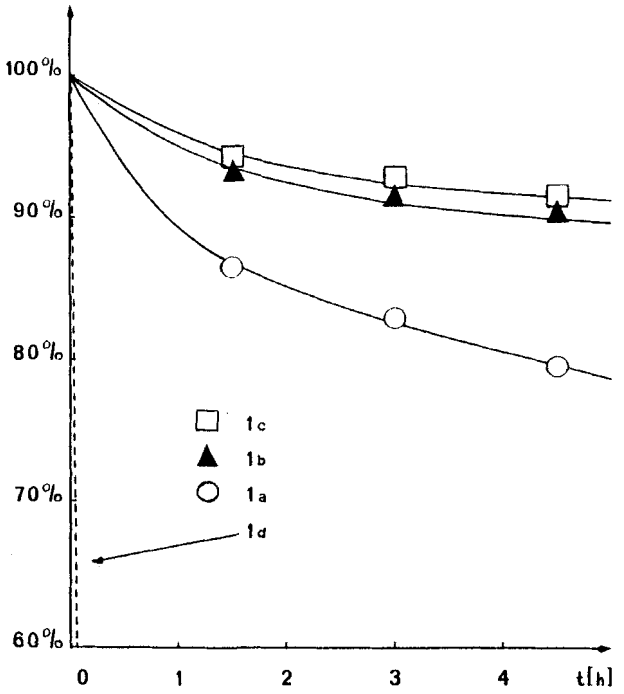



**FIG. 1 Decomposition of Protected Deoxyguanosine Derivatives by $PCl_3$ in Acetonitrile Solution**



were quenched ($NaHCO_3$), diluted to constant volume and analyzed by HPLC (RP C-18, eluent acetonitrile/water 1/1).

In $^{13}C$-NMR-spectra of the neutral molecules **1a - d** only the signal of C-2 varies systematically with the electronegativity of the protecting group. All other signals are not very sensitive to it. Protonation produces an inverse effect on C-2: compounds with more electronegative protecting groups experience a smaller shift difference. It seems, that an electronegative protecting group has already depleted C-2 of electrons, so the difference is smaller.

The effect of protonation on the $^{13}C$-signals of C-5 and C-6 might be interpreted in terms of shifting of the keto-enol-equilibrium towards the enol form as is indicated by a comparison with the protected enol compounds **2a** and **2b**.

The most instructive observation is the sensitivity of the $^{13}C$-NMR signals of potentially reactive atoms to protonation: The signals of C-8 and C-1′ are more sensitive to protonation in those compounds which bear stronger electron demanding 2-N-protecting groups. We think, that the sensitivity of these signals towards protonation can be taken as an indication of chemical reactivity towards nucleophiles (ring opening reactions on C-8 or cleavage of the glycosidic bond at C-1′). This sensitivity is decreased by 6-O-protection, as shown by the corresponding signals of **2a** and **2b** in comparison to the TCBOC-protected **1a**.

One might expect, that electronegative protecting groups decrease by mesomerism the electron density at N-7 and thus decrease the sensitivity towards acid. The observed inverse behaviour can be understood by a shift of the site of protonation from the six- to the five-membered ring of the guanine aglycon. This supports the conclusions, drawn from $^{15}N$-NMR observations by Chattopadhyaya, Lönnberg and coworkers [8].

The kinetics of destruction shown in FIG. 1 corresponds to this picture: The rate of destruction of 2-N-protected guanosine derivatives by $PCl_3$ grows with increasing electronegativity of the 2-N protecting group.



**Conclusions**

$^{13}C$-NMR shift arguments show a desabilizing effect on deoxyguanosine derivatives of electron demanding 2-N protecting groups. The glycosidic bond is desabilized as well as the five membered ring of the guanine aglycon. This effect can be overcome by 6-O protection. Also this protection group should not be electronegative.

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