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Synthesis and ^{15}N NMR of d[CGT($^{15}\text{N}^6$)ACG] and d[CGT(CGT)($^{15}\text{N}1$)ACG]

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SYNTHESIS AND ^{15}N NMR OF $\text{d}[\text{CGT}(^{15}\text{N}^6)\text{ACG}]$ AND $\text{d}[\text{CGT}(^{15}\text{N}^1)\text{ACG}]$

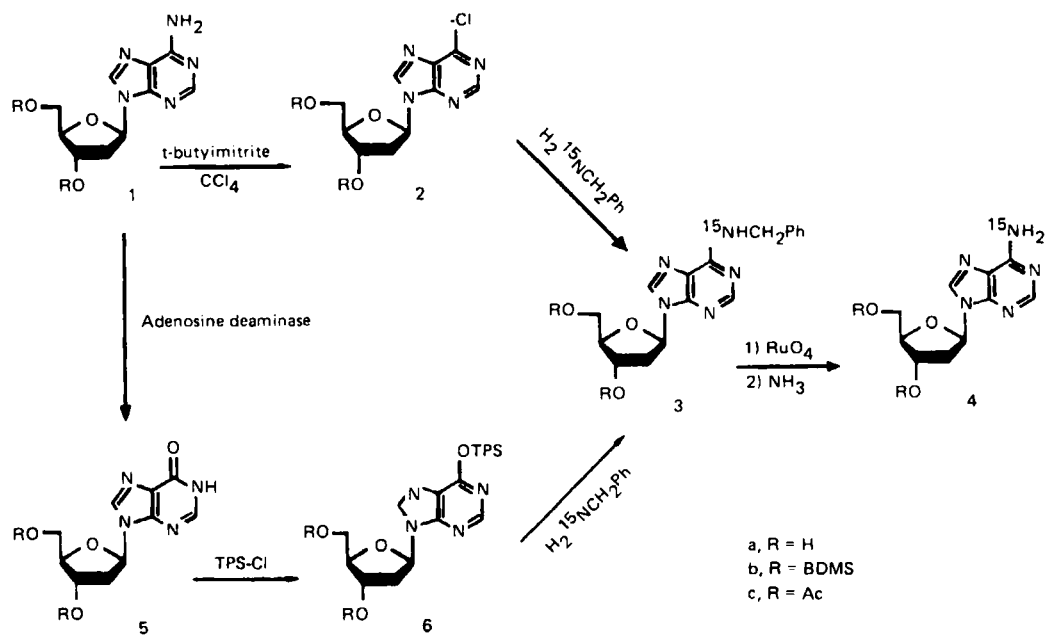
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Abstract. Deoxyadenosine has been converted to 6- ^{15}N deoxyadenosine, which in turn has been transformed to 1- ^{15}N deoxyadenosine. Each of these ^{15}N derivatives was then incorporated into the hexanucleoside pentaphosphate $\text{d}(\text{CGTACG})$ via a phosphoramidite procedure. The monomers and the hexamers were characterized by ^1H and ^{15}N nmr.

The introduction of ^{15}N to the 6 position was carried out by the two routes shown in Scheme I. In one route a 6-chloropurine derivative (2) was reacted with ^{15}N benzylamine while in the alternative route an O^6 -sulfonyl inosine derivative (6c) was used. In each case the displacement reaction was effected in high yield. Debenzylation of 3 under reductive conditions was not successful, but was achieved in high yield using ruthenium tetroxide oxidation to the corresponding 6-benzoyl compound.^{1,2} The $^{15}\text{N}^1$ derivative was then obtained by alkylation of 4b with benzyl bromide followed by Dimroth rearrangement and subsequent oxidative debenzylation.

The oligonucleotide synthesis was carried out by a phosphoramidate method in which the cyanoethyl group was used for phosphate protection.^{3,4} Purification by hplc⁵ gave 720 OD₂₆₀ (13.2 μmole) of $\text{d}[\text{CGT}(^{15}\text{N}^1)\text{ACG}]$ and 500 OD₂₆₀ (8.7 μmole) of $\text{d}[\text{CGT}(^{15}\text{N}^6)\text{ACG}]$. The ^{15}N chemical shifts were recorded over the temperature range of 5° to 80°C. The ^{15}N resonances of the monomers show a linear temperature dependence, while the hexamers display the sinusoidal curve of a helix-to-coil transition (Figure 1). Using the monomer temperature dependence as a baseline, duplex formation is accompanied by an upfield shift of ca. 2.4 ppm for the $^{15}\text{N}^1$ resonance (hydrogen bond acceptor) and a downfield shift of ca. 1.9 ppm for the $^{15}\text{N}^6$ resonance (hydrogen bond donor). These shifts are consistent in both magnitude and direction with ^{15}N shifts reported from monomer studies^{6,7} and from ^{15}N enriched *E. coli* DNA.⁸

Separate experiments were carried out to measure the ^{15}N relaxation times and NOEs, which allowed determination of the correlation time, τ_c (data not shown). These results are consistent with the correlation time determined for the same molecule by proton nmr.⁹ Thus, ^{15}N nmr is a sensitive monitor of the helix-to-coil transition. Moreover, by using specifically ^{15}N labeled molecules, ^{15}N nmr may provide unique access to local structural phenomena in large molecules.



Scheme I

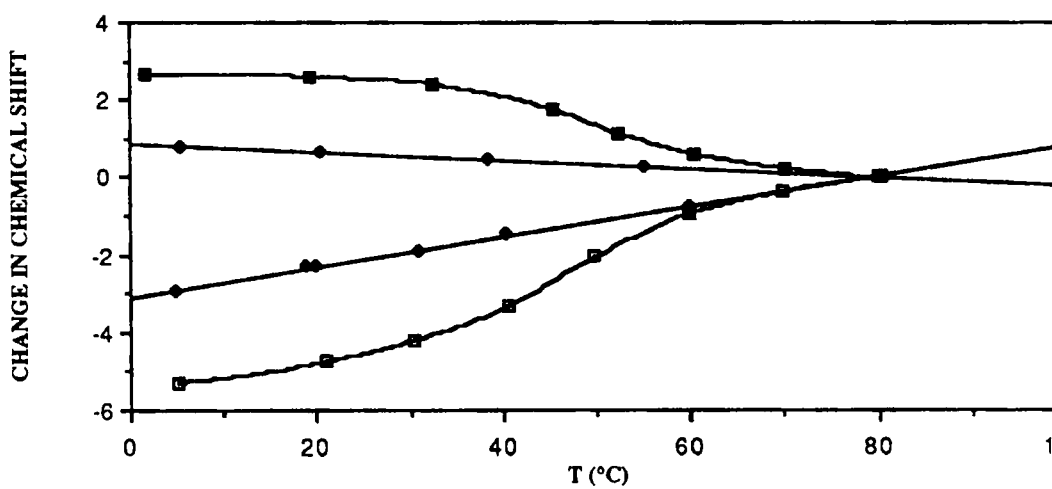


FIGURE 1

Acknowledgments

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