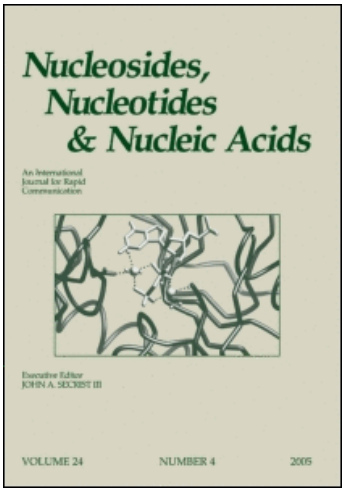

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NMR Studies of Triplex Formation - Recognition of C•G Base Pairs by New Heterocyclic Systems

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NMR STUDIES OF TRIPLEX FORMATION - RECOGNITION OF C•G BASE PAIRS BY NEW HETEROCYCLIC SYSTEMS

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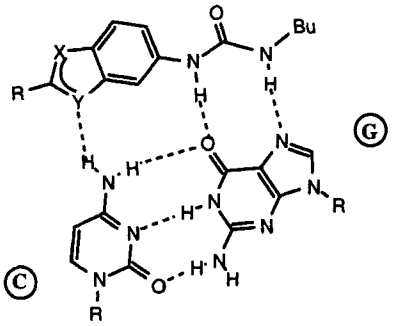
Abstract: Sequence specific recognition of double stranded DNA by oligonucleotides is an important process for selective control of gene expression. However, triple-helix formation is limited to recognition of DNA homopurine strands. We report herein the NMR recognition studies of C•G base pairs by new heterocyclic systems like benzimidazole and benzoxazoles bearing an urea donor function designed to bound to the O4 and N7 atoms of guanosine base.

Triplex forming oligodeoxyribonucleotides (TFO) can interact with double-stranded DNA to form a triplex[1]. Accordingly, TFOs can be used to interfere with biological processes in view of selective control of gene expression (antigene strategy). Unfortunately, this approach has a major intrinsic limitation since triplex formation can only be observed within the major groove of oligopurine-oligopyrimidine DNA targets by means of Hoogsteen hydrogen bond recognition of the polypurine strand[2]. Extension of the recognition pattern to homopurine sequences interrupted by a pyrimidine represents a real challenge. We propose to rationally design heterocyclic motifs having the capacity to make hydrogen bonds with C•G Watson-Crick base pairs.

Herein, we describe three heterocyclic bases (HB) which manifest C•G base pair recognition as shown by NMR studies (Scheme). Namely, we have synthesized benzimidazole, benzoxazole derivatives as well as the Zimmerman base (ZB)[3] for comparison.



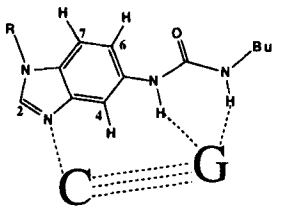
HB1: R = H, X = NR, Y = N
HB2: R = CH_3, X = O, Y = N
HB3: R = CH_3, X = N, Y = O

Scheme

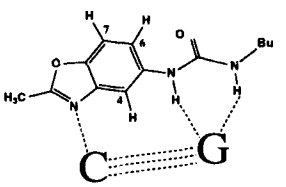
The complexation study was performed in $CDCl_3$ by: i) direct titration of the C•G base-pair (2.5 mM) with heterocyclic bases (HB1, HB2 and HB3, 1 to 20 mM) ii) reverse titration of HBi (2.5 mM) with C•G (1 to 20 mM) and iii) equimolar titration of the complex HBi-C•G with increasing concentrations.

During the titration of the heterocyclic bases (HB) (2.5 mM) with increasing concentrations of C•G base-pair (1 to 20 mM), we observed significant chemical shift variations of urea protons by 0.7 ppm for HB1 and 1.1 ppm for HB2 and HB3, respectively at 20 mM. This indicate a better recognition of the C•G base-pair by oxazole derivatives than by the corresponding imidazole. We have also observed the chemical shift variations during the equimolar titration of ternary complex C•G•HB (1.1.1) in increasing concentrations . In contrast, direct titration of C•G (2.5 mM) with increasing concentrations of HB (1 to 20 mM) show stable chemical shift variation for all concentrations supporting the formation of a stable complex even at low concentration.

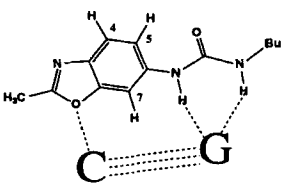
Figures display the chemical shift variations of the aromatic protons vicinal to the urea recognition site. These variation are probably due to a blocked orientation of the aromatic system. We have also synthesized the Zimmerman base (ZB)[3] for a comparison study. By comparing the observed data, we could confirm a similar mode of recognition with approximatively the same values for the proton chemical shift variations.



HB1



HB2



HB3

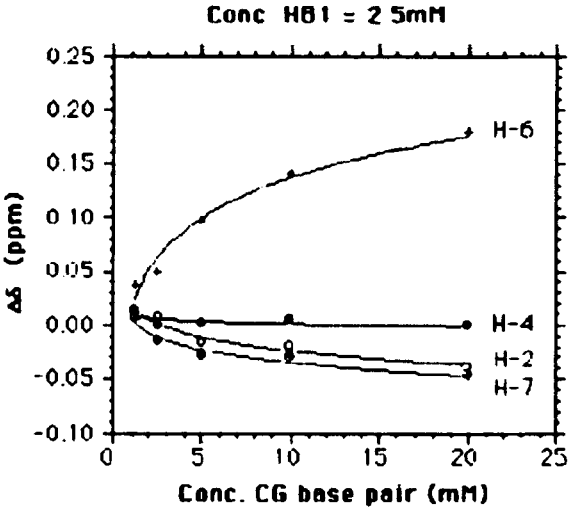


Fig.1

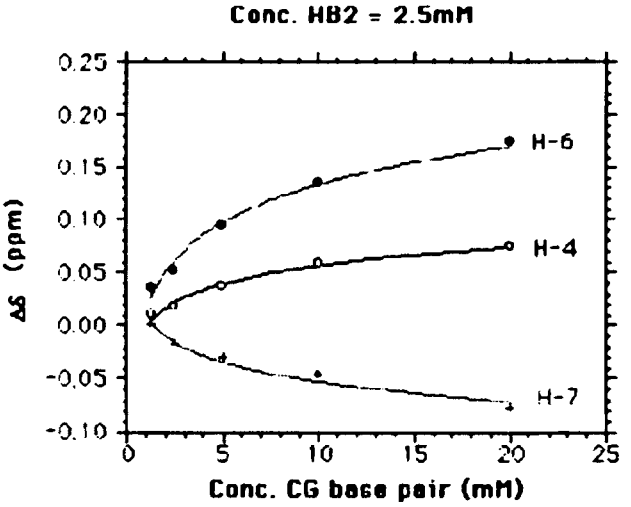


Fig.2

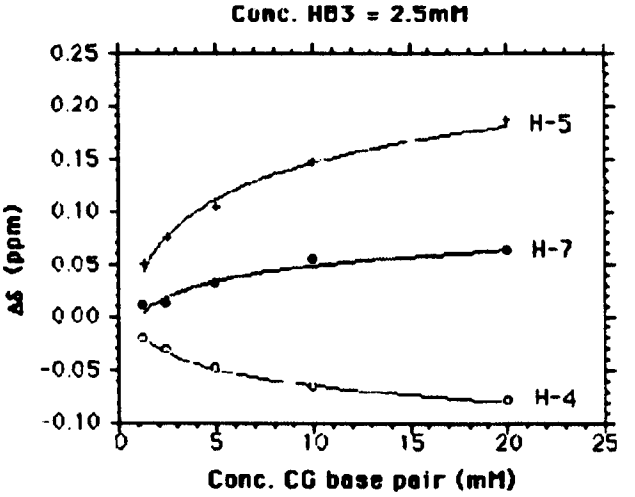


Fig.3

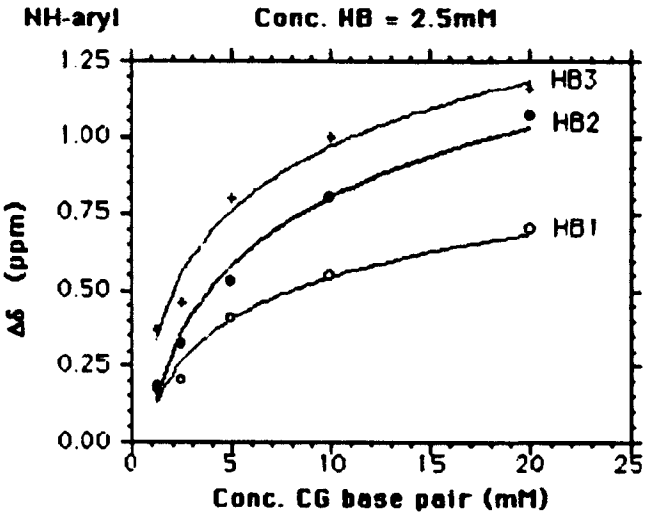


Fig.4

We have described a new and simplified hetherocyclic systems for recognition of CG base-pair in $CDCl_3$ as shown by NMR study. Our results and observations are in agreement with previous studies by Zimmerman group for such recognition processes.

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More experimental and spectral data of new compounds will be published elsewere.