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Synthesis of cyclonucleosides having a C–C bridge

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1. Introduction

Natural nucleosides are of great biological importance in metabolic pathways.[1,2] The typical structure of nucleosides has two molecular fragments: D-*ribo*- or D-2′-deoxyribopentofuranose as the sugar moiety and a purine or pyrimidine aglycone. These two moieties are covalently bonded from N_1 of pyrimidine (uracil, thymine and cytosine) or N_9 of purine (adenine and guanine) to $C_{1'}$ of the glycone in a β-configuration (Fig. 1).

The molecular geometry of nucleosides induces different conformations, which usually involve the determination of three principal structural parameters:[3] (i) the glycosyl torsion angle χ ($O_{4'}$-$C_{1'}$-N_9-C_4 for a purine nucleoside and $O_{4'}$-$C_{1'}$-N_1-C_2 for a pyrimidine nucleoside), which determines the *syn* or *anti* disposition of the nucleobase relative to the sugar moiety (*syn* when the C_2 carbonyl of pyrimidines or N_3 of purines lies over the sugar ring and *anti* for the opposite direction); (ii) the torsion angle γ ($O_{5'}$–$C_{5'}$–$C_{4'}$–$C_{3'}$), which determines the position of the 5′-OH relative to the $C_{3'}$ carbon atom (+*sc*, *ap*, −*sc* rotamers); and (iii) the phase angle of pseudorotation *P* (0–360°) and the maximum out-of-plane pucker υ_{max} (0–50°), which determine the puckering of the furanose ring and its deviation from planarity, respectively.[4,5] The value of *P* depends up on the five endocyclic sugar torsion angles (υ_0–υ_4) and on the puckering of the furanose ring. The conformation of the furanose ring around the pseudorotational cycle alternates every 18° between the envelope (E) and twist (T) form. The conformations of the nucleoside described by these three-state models (χ, γ, *P*) are in interdependent equilibria determined by steric and

Abbreviations: Ac, acetyl; AIBN, azobisisobutyronitrile (2,2′-azobis(2-methylpropionitrile)); An, anisyl; BOM, benzyloxymethyl; Bu, butyl; Bz, benzoyl; CAN, ceric ammonium nitrate; DBU, diazadicycloundecane; DCC, dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DNA, deoxyribonucleic acid; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; Et, ethyl; HMDS, 1,1,1,3,3,3-hexamethyldisilazane; imid, imidazol-1-yl; *i*-Pr, isopropyl; LDA, lithium diisopropylamide; LiHMDS, lithium hexamethyldisilazide; Me, methyl; Ms, mesyl; nd, non determined; NCS, *N*-chlorosuccinimide; NMO, *N*-methylmorpholine-*N*-oxide; PMB, *p*-methoxybenzyl; Ph, phenyl; PMHS, polymethylhydrosiloxane; PTSA, *p*-toluenesulfonic acid; pyr, pyridine; qt, quantitative; RNA, ribonucleic acid; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; *t*-Bu, *tert*-Butyl; THF, tetrahydrofuran; Thf, tetrahydrofuranyl; TIPDS, tetraisopropyldisilyloxane; TMS, trimethylsilyl; Ts, tosyl; TTMSS, tris(trimethylsilyl)silane.

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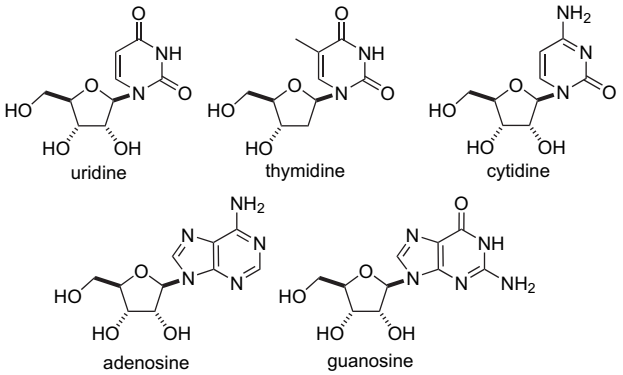

Figure 1. Classical natural nucleosides.

stereoelectronic effects (e.g., anomeric and *gauche* effects)[6] and the energy barriers between the preferred conformational states are usually low (Fig. 2).

In an enzymatic reaction, the problem is to correlate the conformational preference demanded by the specific enzyme in the activation pathway with a particular nucleoside conformation because the nucleoside conformation in solution can differ sharply from that determined in the solid state. Consequently, any conformation–activity study based exclusively on solid-state conformational parameters would be flawed, unless both solution and solid-state conformations are known to be equivalent. One strategy for pre-organising the nucleoside conformation might be to rigidify the normally flexible nucleoside by chemical modification. To overcome this problem, the limitation of conformation of a nucleoside or nucleotide is widely used to reach a particular conformation of a rotamer to study: (i) the affinity of a biomacromolecule for its natural ligand;[7] and (ii) the molecular recognition in an oligonucleotide chain (RNA/DNA).[8] This particular conformation can be predetermined by limiting the conformational equilibrium (*syn* or *anti*, North or South, $+sc$, *ap* or $-sc$) by the elaboration of restricted polycyclic structures. Nucleosides with a restricted conformation can be classified into three families: (i) *bicyclonucleosides* obtained by bonding two atoms of the furanose moiety via an alkylene unit or analogue; (ii) *cyclic phosphoesters* obtained by forming an alkylene bridge or analogue between the phosphorus atom and the nucleobase or the furanose moiety; and (iii) *cyclonucleosides* obtained by bonding one atom of the furanose moiety and one atom of the nucleobase via an alkylene unit or analogue (Fig. 3).

For the sake of clarity, this review has been arranged to describe the synthesis of cyclonucleosides having an alkylene group between the glycone moiety and the nucleobase.

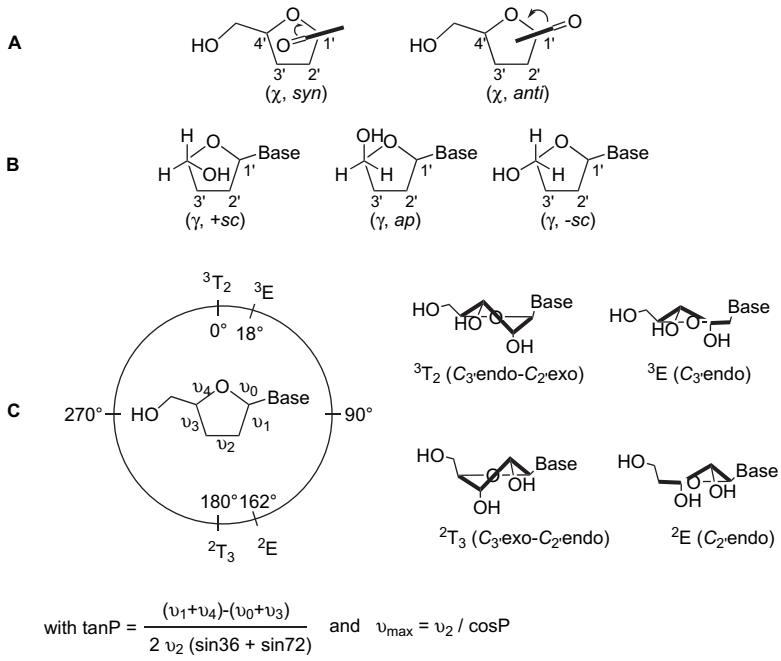

Figure 2. (A) Definition of *anti* and *syn* conformations for a pyrimidine nucleoside. (B) Definition of the torsion angle ranges for the $C_{4'}$–$C_{5'}$ bond. (C) Pseudorotational cycle of the furanose ring in a nucleoside (E=envelope and T=twist).

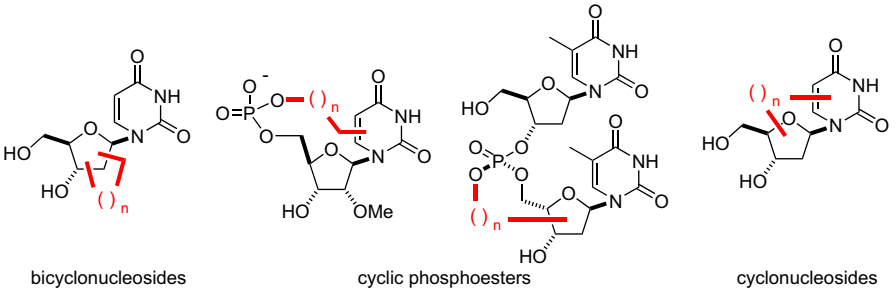

Figure 3. Different families of nucleoside analogues having a restricted conformation.