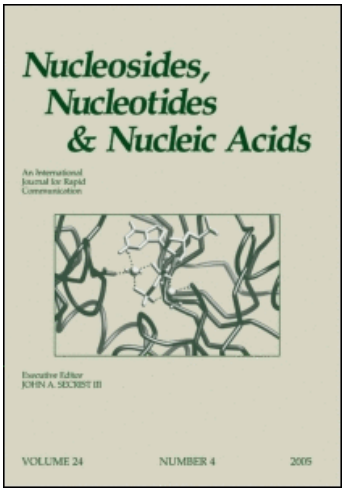

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Yet Another Mechanism of HIV Reverse Transcriptase Inhibition?

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YET ANOTHER MECHANISM OF HIV REVERSE TRANSCRIPTASE INHIBITION ?

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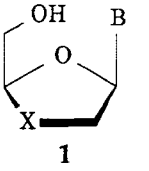
Abstract. Bicyclonucleosides like **3** are active against HIV-1 and HIV-2 after phosphorylation. They most probably act as their native bicyclic form fundamentally different, structurally, from that of AZT.

Introduction. Anti-HIV nucleosides active against both HIV-1 and HIV-2 all act, as their triphosphate derivatives, at the same reverse transcriptase (RT) site. They correspond to the general formula **1** where X stands for S, CH_2, or CHR if belonging to the *erythro* series. 2,3-Didehydro derivatives of **1** (X = CH_2) are also active (for a recent review, see ref. 1).



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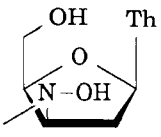

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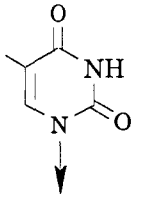

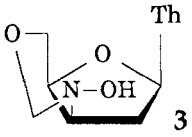

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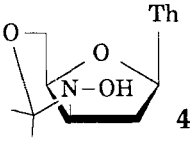

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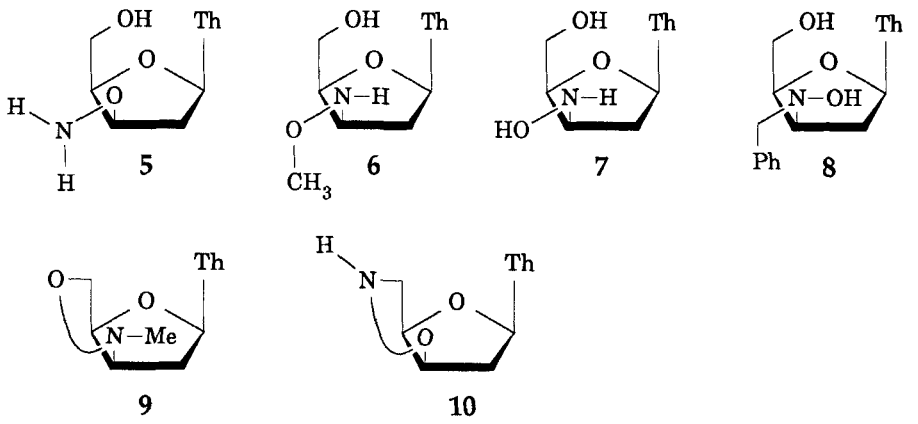
Scheme 1. Active compounds

We have described[2-4] the first examples of active β-D-*threo*-nucleosides (Scheme 1), either mono (**2**) or bicyclic (**3**, **4**). All these compounds have the common peculiarity of being nucleoside hydroxylamines but other compounds bearing this function (Scheme 2), either monocyclic (**5-8**) or bicyclic (**9-10**) were found inactive.[2-5] We describe here some preliminary studies on the possible modes of action of these novel nucleosides.

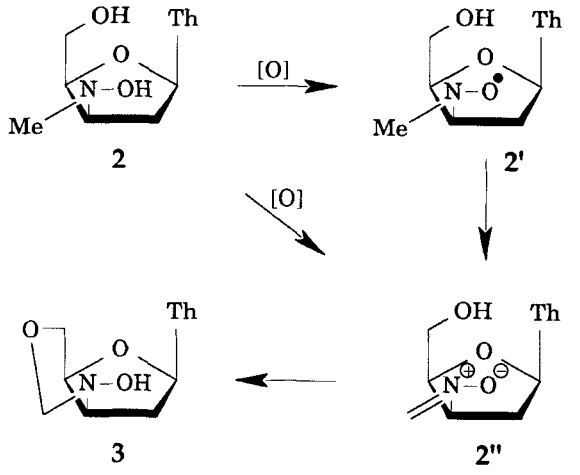
Results and Discussion. The monocyclic active nucleoside **2** can be converted to the bicyclic active **3** (Scheme 3). Upon oxidation (tetrabutylammonium periodate, 2,3-dichloro-5,6-dicyanoquinone), **2** led to **2"** which spontaneously and quantitatively cyclized to **3**. On the other hand, **2** spontaneously oxidized to the



Scheme 2. Inactive compounds

aminoxyl radical **2'**, EPR spectrum of which exhibited the expected signals and hyperfine coupling constants (a_N 14.6, $a_{H(Me)}$ 12.9, $a_{H(3')}$ 3.6, $a_{H(2' \text{ and } 4')}$ 1.0, 0.8 and 0.8 G). The decay of the EPR signals corresponds to a further oxidation of **2'** into **2"** which cyclizes to **3**.

As AZT, compound **3** needs prior phosphorylation to become active.[3] Is it phosphorylated on its N-OH group or on the 5'-OH of a ring-opened metabolite ? From a chemical viewpoint, the most logical opening mechanism should be the ring-chain tautomerism of hydroxy-nitrones (2" ⇌ 3), well known in carbohydrate chemistry.[6]



Scheme 3

Quantum mechanically (semi-empirical treatment, AM1 Hamiltonian), the opening should correspond to the excitation of normal vibrational mode #37. The computation carried out on the anion of the sugar moiety of **3** (Fig. 1) showed that when the NCH_2-O5' bond was broken and the value of θ fixed to 154°, the structure relaxed to **3**, whereas for a value of θ of 124°, the open-chain compound **2"** was obtained. The ring-chain interconversion does indeed take place but the ring

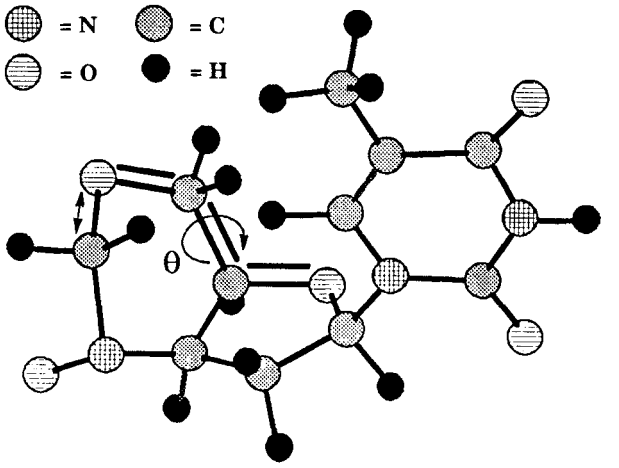


FIG. 1

tautomer **3** is considerably more stable that its open-chain counterpart **2"** as proved experimentally by the fact that it is impossible to find any trace of **2"** in the reaction medium of the cyclization of **2"** into **3** and that quantum mechanics (AM1) predicts the sugar moiety of **3** to be 88 kJ/mol more stable than its open-chain counterpart.

It follows from these experiments that, even if one cannot definitively exclude an improbable bioreduction of **3** to **2**, compound **3** should exert its biological activity in its native cyclic form. This leaves open the question of whether biophosphorylated **3** acts as a surrogate of a nucleoside (Fig 2**a**) or of a nucleoside monophosphate (Fig 2**b**). Two theroretical approaches have been used to study the feasibility of the hydroxyamino nitrogen atom of the sugar moiety of **3** acting as an electrophilic site. The first method[7] determining the electrophilic sites by monitoring the EHT interactions between the molecule and a nucleophile (H^-) indicated, as the major site for a nucleophile (base) attack, the NOH proton and did not detect any other (incipient) electrophilic site. The same treatment applied to the *(N)O*-acetyl derivative of **3** gave the acetyl carbonyl as the only electrophilic site. The second approach consisted in determining the 3D distribution of Fukui's electrophilic reactivity index computed using the density functional theory (deMon, 3-21G+ basis, Becke-Perdew gradient correction[8]). This confirmed the electrophilic properties of the hydroxyamino nitrogen atom.

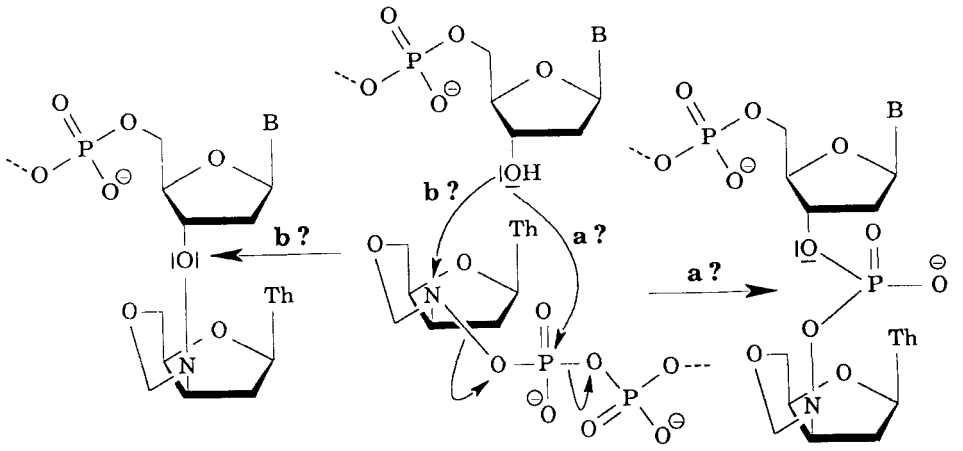


FIG. 2

Compound **3** fitted satisfactorily into an hypothesis generated by the Catalyst™ software (BioCad Corporation) using 19 classical nucleoside structures (correlation coefficient 0.91, RMS 1.82, total cost 125 *versus* 194 for the null hypothesis. When the triphosphate derivatives of the former classical nucleosides were submitted to Catalyst™, a novel hypothesis was generated. The diphosphate derivative of **3** - and not its triphosphate derivative - fitted correctly with this second hypothesis. Nevertheless, more work is needed to understand the mode of action of bicyclonucleosides like **3** and **4**.

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