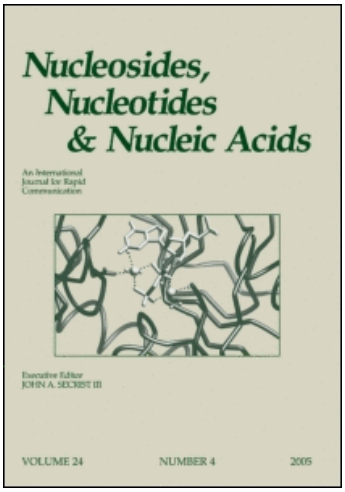

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Reaction Mechanism for the Diastereocontrolled Synthesis of Phosphorothioate DNA by the Oxazaphospholidine Approach

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ABSTRACT

Reaction mechanisms for the diastereoselective synthesis of deoxyribonucleoside 3′-cyclic phosphoramidites as well as dinucleoside phosphite intermediates by the oxazaphospholidine approach were analyzed by means of ab initio molecular orbital calculations at the HF/6-31G* level. These reactions are essential for the diastereoselective synthesis of phsophorothioate DNA.

Quite recently, we have reported a highly diastereoselective synthesis of dinucleoside phosphorothioates by using nucleoside 3′-oxazaphospholidine derivatives and a novel class of activators, dialkyl(cyanomethyl)ammonium salts (oxazaphospholidine approach).[1] One of the advantageous points of the oxazaphospholidine approach is that optically pure phosphoramidite monomers can be synthesized from readily accessible enantiopure 1,2-aminoalcohols. It has been reported by Agrawal et al.[2] that the reaction of a 5′-*O*-DMTr-nucleoside with a 2-chloro-1,3,2-oxazaphospholidine derivative *trans*-**1a**, which is derived from (1*R*, 2*S*)-ephedrin,

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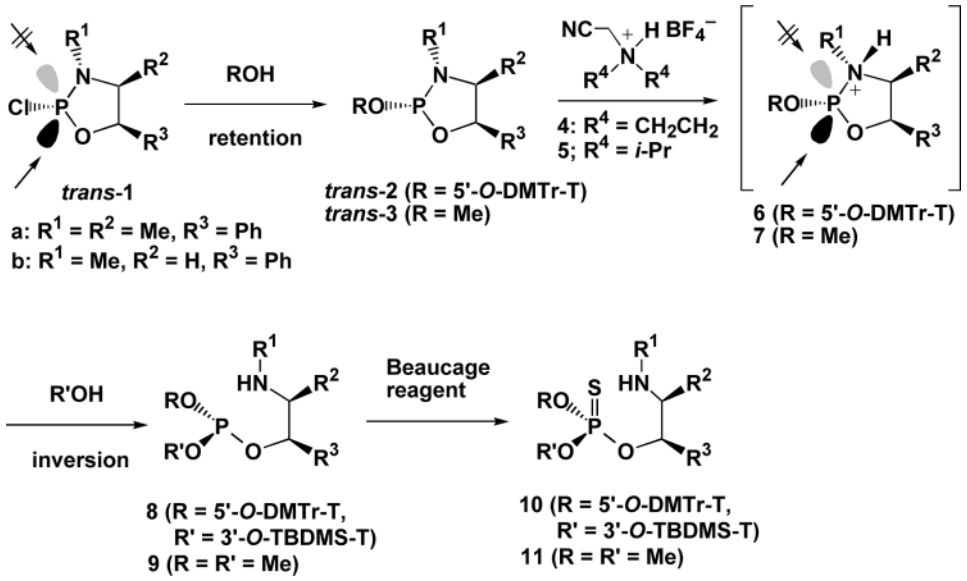

Scheme 1.

proceeds through an unusual S_N2 reaction with the retention of the *P*-configuration to give the corresponding diastereopure nucleoside 3′-cyclic phosphoroamidite *trans*-**2a** (Sch. 1). However, the mechanism of this stereospecific reaction is still unclear. In order to elucidate the unique reaction mechanism, ab initio molecular orbital calculations were carried out for model compounds. The optimized structure of *trans*-**1a**, obtained at the HF/6-31G* level, indicate that there are no LUMO located on the backside of the leaving chlorine atom. Interestingly, there exist two lobes of LUMO located on both the backsides of N^3 and O^1 atoms. The hydroxy group of an alcohol would preferentially attack at the phosphorous atom from the backside of the N^3 atom with retention of the *P*-configuration to give the *trans* product. On the contrary, the nucleophilic attack of an alcohol to the phosphorous atom from the backside of the O^1 atom would give rise to the *cis* product. The latter process, however, inherently interrupted because of the steric hindrance of the N^1-methyl group. We have successfully obtained the optimized transition state structures of model compounds for these reactions. The results of calculations indicated that the activation energy for the formation of *trans*-**3b** was found to be lower than that for the *cis* product.

In the previous paper, we have demonstrated that the diastereoselectivity of the internucleotidic bond formation depends on both the substituent groups on the oxazaphospholidine ring and the dialkyl(cyanomethyl)ammonium salts. We have ultimately found that a monomer *trans*-**2** and an activator **4** were highly effective for the diastereoselective reaction. In the case of using highly bulky activator **5**, a significant loss of diastereoselectivity was observed in the condensation reaction. To elucidate the mechanism of the diastereoselective condensation, MO calculations for *N*-protonated oxazaphospholidine intermediate **7a** and transition state models

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consisting of an *N*-protonated oxazaphospholidine, dialkyl(cyanomethyl)amine, and alcohol were carried out. A detail quantum chemical analysis of the diastereoselective condensation is now in progress.

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