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# The conformational behavior, geometry and energy parameters of Menshutkin-like reaction of *O*-isopropylidene-protected glycofuranoid mesylates in view of DFT calculations

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ABSTRACT

The formation of pyridinium salts in the transformation of three *O*-isopropylidene-protected mesylates of furanoid sugar derivatives under pyridine action is considered at the B3LYP/6-31+G** computation level. All the structures were optimized in the gas phase, in chloroform and water. Activation barrier heights in the gas phase were also estimated at the B3LYP/6-311++G**, MPW1K/6-31+G** and MPW1K/6-311++G** levels. The conducted calculations, both in the gas phase (regardless of the computation level) and in solvents, revealed the barrier height increasing order as follows: **1** > **2** > **3** for the three reactions studied. The conformational behavior of the five-membered ring is discussed in the gas phase and in solvents. The fused dioxolane ring makes the furanoid ring less likely to undergo conformational changes. In the case of reaction **3**, the furanoid ring shape does not change either in the gas phase or in solvents. All conformers are close to $E_0$ or $^0E$.

## 1. Introduction

The quaternization reaction, first described by Menshutkin [1] more than one century ago, is the straightforward way of synthesizing of quaternary ammonium salts (QAS). The conceptual simplicity of this reaction, which is sometimes spurious, opens up the possibility for synthesis a wide variety of QAS from different classes of organic compounds, including derivatives of carbohydrates [2]. Although in the classic variant of the Menshutkin reaction (MR) halogen derivatives are used, the halide leaving group can be successfully replaced by a sulfonate ester [3–5].

Over the decades of experimental studies of the MR, scientists answered a number of questions regarding both the mechanics and the conditional aspects of this reaction. In particular, the nucleophile strength, the leaving group and the solvent polarity have been recognized as playing key roles. While the first two factors are important in all $S_N2$ reactions, the influence of the solvent polarity is of the greatest significance for the Menshutkin reaction because charged products are formed from neutral reactants.

Computational chemistry methods have delivered an alternative means of investigating the MR, which gives a deeper understanding of the problem under discussion. Many attempts have been undertaken to make a precise description of the MR with the use of theoretical chemistry methods [6–21].

Our aim is to extend the existing knowledge about the Menshutkin reaction in regard of structural features affecting its outcome. Previously, we carried out a series of studies focused on the formation of ammonium and pyridinium salts, starting from sulfonate esters of doubly substituted THF derivatives [22–26]. With the present work we continue our theoretical studies of the formation of QAS considering the reaction between pyridine and three mesylate ester derivatives (Fig. 1). The *O*-isopropylidene group is attached to the furanoid ring, which makes the THF ring with reduced freedom of motion; therefore, some of the conformations described by a pseudorotational circle seem to be inaccessible for the five-membered ring. We discuss the influence of branching both at the carbon atom next to the reaction center (the β carbon atom) and at the carbon atom three bonds distant from the reaction center (the methyl or methoxy group bounded to the furanoid ring is *cis*-oriented in relation to the reaction center carbon atom).

## 2. Methods

All the calculated structures were prepared in the MOLDEN program [27]. The ground state and the transition state

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1093-3263/

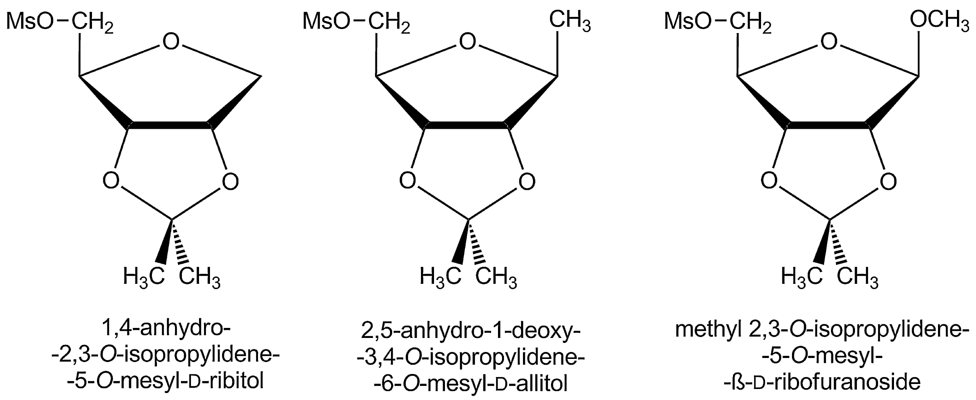


**Fig. 1.** Structures of mesylate derivatives converted into respective pyridinium salts.

geometries were fully optimized using density functional theory (DFT) based on Becke's three-parameter hybrid exchange [28] functional involving the gradient-corrected correlation functional of Lee, Yang and Parr [29] (B3LYP) with a 6-31+G$^{**}$ basis set [30,31]. The reactant complex and transition state geometries were also calculated at the B3LYP/6-311++G$^{**}$ level [32,33]. Reactant complexes and transition states were additionally optimized using the MPW1K (Pedrew–Wang 1-parameter model for kinetics) functional [34–36] and two basis sets: 6-31+G$^{**}$, 6-311++G$^{**}$.

The optimization was considered satisfactory if the energy difference between optimization cycles was less than $1 \times 10^{-6}$ Hartree and a gradient of $<1 \times 10^{-4}$ a.u. was achieved. The convergence of all the systems studied was checked by harmonic vibrational analysis. No imaginary frequencies were observed for the ground state, and there was only one for the transition state. The vibrational analysis also enabled molecular entropies and thermal energy contributions for each conformer to be determined, according to statistical thermodynamics formulae.

Solvent effects were included in the calculations employing the self-consistent reaction field SCRF-PCM solvation model.[37] The reactions were studied in chloroform ($\epsilon = 4.9$) and water ($\epsilon = 78.39$) at the B3LYP/6-31+G$^{**}$ level. This continuum model, although not directly, accounts for the specific solvent/solute interactions (like hydrogen bonds) in some way, because the main component of such interactions has an electrostatic nature. In the PCM method the solute is placed inside a cavity generated by a series of interlocking atomic spheres. Implicit solvent calculations imply the generation of a vacuum cavity inside a continuous and homogeneous dielectric field. We used UA0 with scale factor alpha = 1.2 for water and 1.4 for chloroform [17]. The NBO analysis was carried out at the B3LYP/6-311++G$^{**}$ level. All calculations were done with the aid of the Gaussian 03 program [38].

## 3. Results and discussion

The studied reactions together with atom numbering order used in this paper are shown in Scheme 1. The steps of the reactions under consideration are as follows: two separated reactants approach one another (denoted as **R**, electrophile – mesylated derivative, and nucleophile – pyridine) which leads to the creation of the van der Waals reactant complex (**RC**) followed by its conversion into an intimate ion pair (**IP**), passing through the $S_N2$ saddle point structure (**TS**). Finally, the ion pair constituents are moved to an infinitely great distance (**P**) from one another.

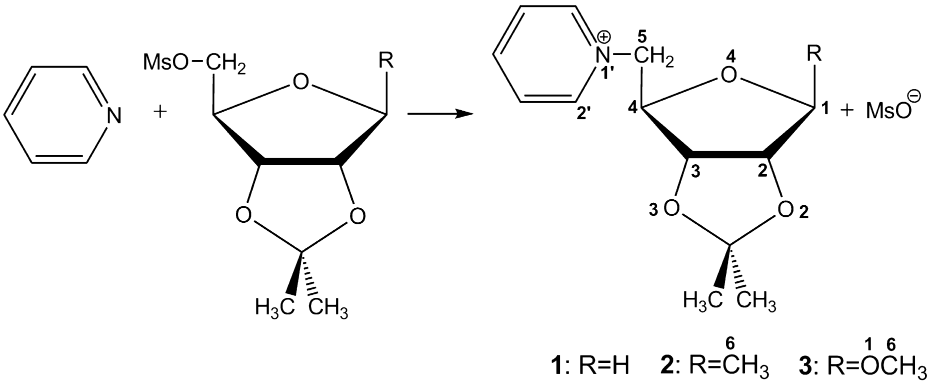
### 3.1. Gas phase calculations

### 3.1.1. Starting geometries of the exocyclic groups

Based on our previous experience we chose the −*sc* orientation of the mesyloxy group, with respect to C3 carbon atom, as a starting geometry for the subsequent calculations (Fig. 2a). In reaction **3** we set the $OCH_3$ group in the −*sc* orientation, with respect to the O4 oxygen atom, in starting geometries (Fig. 2b). This geometry is preferred because of the *exo*-anomeric effect stabilization and negligible steric strains.

### 3.1.2. Starting geometries of the fused furanoid and dioxolane rings

Attention is continuously focused on the conformational behavior of the furanoid ring due to natural occurrence of this structural motif in biopolymers, such as DNA and RNA, and oligosaccharides



**Scheme 1.** Reactions of pyridinium mesylates formation.