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Systematic investigation of 2,7-dihydroxy-1,8-naphthyridine dimerization – secondary interactions and tautomeric preferences calculations

Borys Osmialowski *

University of Technology and Life Sciences, Faculty of Chemical Technology and Engineering, Seminaryjna 3, PL-85-326 Bydgoszcz, Poland
University of Zürich, Organic Chemistry Institute (OCI), Winterthurestrasse 190, 8050 Zurich, Switzerland

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ABSTRACT

The tautomeric preferences and dimer formation of 2,7-dihydroxy-1,8-naphthyridine have been investigated using MP2/6-31G(2d,p), M05/6-311+G(2d,p) and B3LYP/6-311+G(2d,p) computational methods. Both geometrical parameters and energetic data are indicative of the presence of secondary interaction (SI) in the dimer formation. Weak hydrogen bonds (HB) form a cooperative network of SI, while stronger hydrogen bonds compete. The magnitude of the secondary interactions are compared across all dimers. The influence of dimerization on geometry, energy and relative molecules position is discussed.

1. Introduction

Intermolecular interactions are the subject of extensive research in many fields as chemistry, biochemistry, pharmacology, and material sciences among others. The most common intermolecular interaction is the hydrogen bond (HB), of A—H...B type, where A and B are electronegative elements. Tautomeric properties of organic compounds are important in self-organization, molecular recognition etc. Hydrogen bonding is the main driving force in dimer formation in case of most compounds involved in tautomerism. The hydrogen bonding and tautomeric equilibria are known to be responsible for a large number of molecular behaviors as, for example, DNA stabilization, peptide folding and relatively high water boiling point. As is well established, hydrogen bonds can serve to strongly stabilize structure. On the other hand, the number of HBs cannot describe the relative stabilization efficiently. The type of hydrogen bond acceptors (A) and donors (D) is another factor to be accounted for. For example, it is known that a dimer stabilized by a AAA/DDD pattern is in general more stable than a ADA/DAD pattern [1]. This is due to the existence of the network of secondary interactions (SI). In systems where two or more hydrogen bonds are close one to one another, secondary interactions play a role in overall structure stabilization. The concept of SIs was first introduced by Jorgensen [2], and has since been accepted as an important improvement of description of intermolecular interactions. There is, however, some skepticism of the extent that SIs can be useful in our understanding of structural stabilization in general [3]. Since the stabilizing or destabilizing factors met in, for example, dimer formation are not fully understand yet, the research effort should be taken to describe the interaction constituents efficiently and as accurate as possible. The field of intermolecular hydrogen bonding, secondary interactions, aromaticity, π-stacking, solvation effects need to be completely understood to be useful in, for example, non-covalent polymers synthesis and other fields of science where the intermolecular interaction theory should be applied. Thus, the heterocyclic compounds carrying acidic groups are of special importance in this topic, like hydroxyl/amino pyridine, quinoline, naphthyridine and other. Since naphthyridines contain two heterocyclic nitrogen atoms, these are most interesting among mentioned above. Naphthyridines are structures that can play a role in chemistry of ligands, for example 2,2′-bi-1,6-naphthyridines [4] or 2,7-disubstituted 1,8-naphthyridine derivatives [5]. Substituted naphthyridines have been shown to hold importance for their antiviral properties [6], and as potential antimalarials [7]. Substituted 1,8-naphthyridines show promise as potential antihypertensive agents. As such, it is of interest to better understand the basic structure and properties of these structures for better understanding of their pharmaceutical potential [8]. From the chemical point of view, naphthyridines have been the subject of research for over 30 years [9–11]. 2,7-Dihydroxy-1,8-naphthyridine, as a building block in supramolecular chemistry, has been synthesized and used as a substrate in macrocycle subunits [12]. 7-Amino-1,8-naphthyridine has been

* Address: University of Technology and Life Sciences, Faculty of Chemical Technology and Engineering, Seminaryjna 3, PL-85-326 Bydgoszcz, Poland. Tel.: +48 52 3749027; fax: +48 52 3749005.
E-mail address: borys.osmialowski@utp.edu.pl

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used as an analogue of thymine [13] and as a mimic of protonated cytosine [14,15]. These derivatives have also been recently used as a molecular sensors for monosaccharides [16] and effective binding agents for human telomerase [17].

Elguero et al. have recently confirmed that hydrogen bonding plays a crucial role in 2,7-dihydroxy-1,8-naphthyridine dimerization, although information regarding the magnitude and extent of secondary interactions has not been investigated systematically from one dimer to another [18]. 2,7-Dihydroxy-1,8-naphthyridine has a similar hydrogen bonding pattern as the heterodimer of 2-pyridone/2-hydroxypyridine [19–25]. The more combinations of hydrogen bond acceptors (A) and donors (D) possible in the molecule, the larger the number of "hydrogen bonding patterns", and therefore the more possibilities for dimer formation [26,27]. Interestingly, some compounds designed to form AADD patterns in dimerization, actually dimerize in ADDA patterns [28,29]. This would imply that tautomerism/rotamerism, together with SI effects, are very important, and can have implications in, for example, self-assembly in the building of supramolecular polymers [30]. There is a number of publications related to the homo- or heterocomplex formation where constituents are held together by hydrogen bonding. Works by Sijbesma, Meijer, Murray, Zimmerman and others shows the importance of this topic [31,32]. Murray and Zimmerman [33] have shown that relative dimer stability can not be predicted with accuracy by only taking into an account the number of hydrogen bonds. Thus, the cooperativity effects are responsible for stabilization of complexes. These effects were studied by DFT and *ab initio* methods for water and H_2O_2/H_2O systems as the simplest systems where cooperativity may be observed [34,35]. Moreover, the cooperativity effects were present only in the global minimum structure of the water trimer. Based on these results the flexible, triple-ζ basis set was suggested for hydrogen-bonded system calculations [36,37]. The improved density functional methods (DFT-D) methods were successfully applied for systems there non-covalent interactions are essential [38]. On the other hand the DFT methods are still used in describing the intermolecular interactions [39].

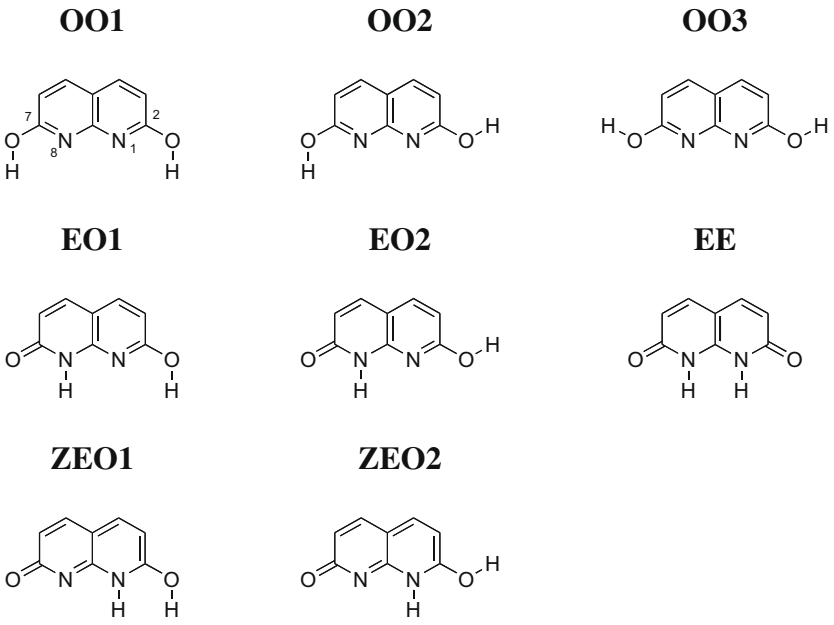
The aim of this work is to (a) investigate and verify if a secondary interaction (SI) model is useful in understanding of hydrogen-bonded dimer systems, (b) investigate how the type of interaction (attractive vs. repulsive) affects the geometry of complex and, finally, (c) determine if the subjected naphthyridine derivatives exist in homo- or heterodimeric form (or if a simultaneous four proton transfer (PT) is possible in certain cases).

2. Methodology

All calculations have been made with the use of GAMESS [40] and Gaussian [41] programs. First, the basis set study was ran to investigate the effect of double vs. triple split valence and the effect of diffuse functions on the dimerization energy in the case of dimer **D1**. Since the basis set study showed very little change in dimerization energies at all levels, the 6-31G(2d,p) basis set at MP2 level was chosen to not touse a lot of computational effort with 6-311+G(2d,p) one. Thus, the geometry was optimized at the B3LYP/6-311+G(2d,p), M05/6-311+G(2d,p) and MP2/6-31G(2d,p) level for monomers and dimers. The frequency calculations were performed for checking if the optimized geometry is in the energy minimum for all monomers and dimers at B3LYP and M05 level and for all monomers and the four hydrogen-bonded dimers (**D1** and **D2**) at MP2 level. The B3LYP optimized geometry has been used as a starting point in MP2 and M05 optimizations. Dimerization energies have been calculated as a difference in energy between two monomers and one dimer including the BSSE error correction. The single point MP2/6-31G(2d,p) calculations on the geometry obtained at the B3LYP/6-311+G(2d,p) and M05/6-311+G(2d,p) level gave very similar (within 0.4 kcal/mol) energy results as MP2/6-31G(2d,p) optimizations. Taking into account those tautomers, where the energy relative to the lowest one is below 10 kcal/mol, four tautomers/rotamers have been selected for further investigations (dimer formation). Those were **EO1**, **EE**, **EO2** (rotamer of **EO1**) and **OO1**. The **EO2** was excluded from dimer calculations because it is very low probable that this rotamer would exist in any dimeric form.

3. Results and discussion

The calculations made during this study allowed comparisons of few molecular properties as bond lengths and angles, intermo-



Scheme 1. The tautomers and rotamers possible for studied molecule.