TAUTOMERIC FORMS AND CONFORMERS OF RIFAMPICIN IN THE SOLID STATE

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Rifampicin (RIF), the key component in the anti-tuberculosis therapy, is a semisynthetic antibiotic with a broad spectrum of activity against bacterial pathogens [1]. The spectroscopic data indicate that RIF can be obtained in two polymorphic forms and in numerous solvated crystalline forms. Moreover, its molecule exhibits conformational flexibility that is strongly related to the generated system of intramolecular hydrogen bonds, which, in turn, depends on RIF ionization state that can be either neutral or zwitterionic [2]. The crystal structures of a few complexes of RIF with different proteins were determined [1,4,5] but, amazingly, up to day only one crystal structure of this important drug, namely that of RIF pentahydrate [3], has been reported. To fill this gap, we carried out crystallization works that resulted in single crystals of diverse RIF solvates that subsequently were subjected to X-ray structural analysis.

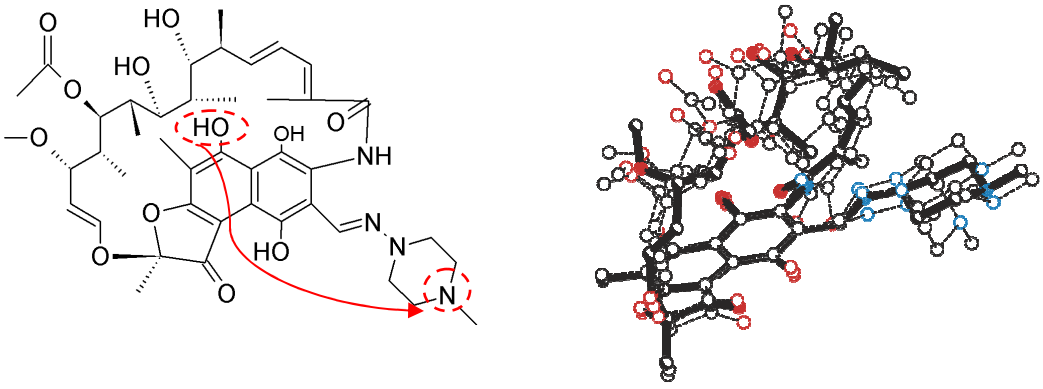

Figure 1: a) scheme of RIF b) superposition of RIF conformers

Indeed, as was suggested by the earlier spectroscopic studies, RIF crystallizes in the neutral and zwitterionic forms. When aprotic solvent, e.g. trichloroethane, m-xylene, chloroform, were used for crystallization, RIF crystallized in the neutral form, whereas from protic solvents (metanol, etanol, water) the zwittterionic form, with the protonated piperazine N-CH_3 unit and the phenolate group at C-8, was systematically obtained (Fig. 1a). This study has also revealed a pronounced conformational lability of RIF molecule (Fig. 1b), with conformational changes occuring mostly in the amide fragment and propagating along the *ansa* chain. Very significant conformational changes were also observed for the 4-methyl-piperazin-1-amine fragment. All these conformational changes were reflected in restructuring of the system of intramolecular hydrogen bonds (Fig. 2) and in the intermolecular interactions.

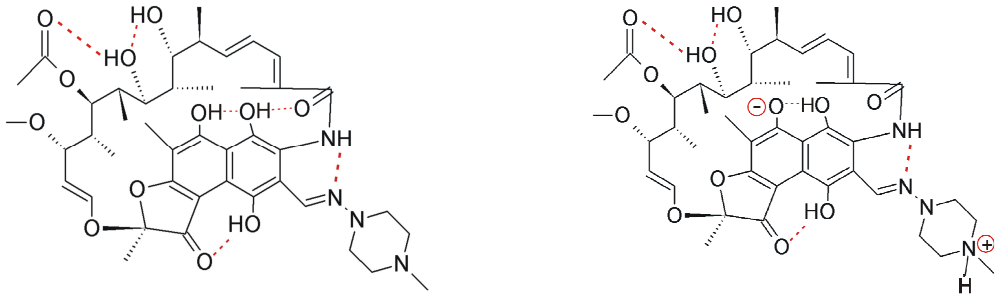

Figure 2: Possible intramolecular hydrogen bonds in a) neutral and b) zwitterionic form of RIF

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