

Structural evidence of an intramolecular proton transfer leading to keto-amine tautomer in the crystals of Schiff bases derived from tyrosine and histidine esters



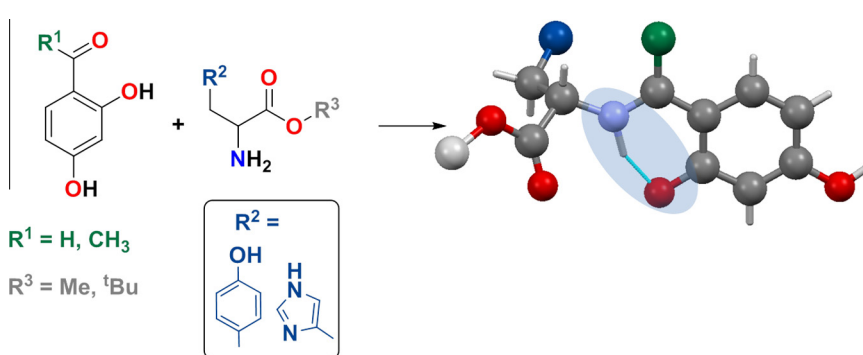
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HIGHLIGHTS

- We synthesized three Schiff bases derived from resorcinol and tyrosine and histidine a.a. esters.
- The single crystal X-ray studies show the structures dominated by N–H···O interactions.
- The H-atom in the intramolecular interaction bonds to the nitrogen.
- IR studies confirm the predominance of the keto-amine tautomer and agree with the X-ray results.
- H NMR solution studies suggest the predominance of phenol-imine tautomer and N···H–O interaction.

GRAPHICAL ABSTRACT



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ABSTRACT

Three Schiff bases derived from 2,4-dihydroxybenzaldehyde or 2,4-dihydroxyacetophenone and esters of tyrosine and histidine have been synthesized and the crystal and molecular structures determined by single crystal X-ray diffraction. The molecular structures of the three compounds are dominated by short intramolecular hydrogen bonds with distances N···O ranging from 2.536(2) to 2.588(2) Å and the hydrogen atom is bonded to the nitrogen. In the solid state, the structures are characterized by the keto-amine tautomer, whereas in the solution the phenol-imine form was detected by ¹H NMR spectroscopy. Inter-molecular interactions influencing crystal packing are discussed.

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1. Introduction

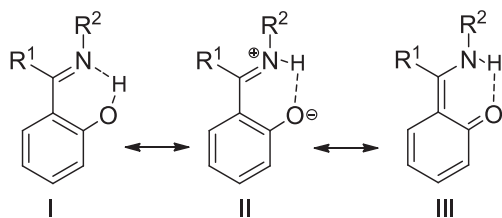
Schiff base compounds have attracted considerable attention in both theoretical and experimental studies. The investigation of these compounds is of interest for several reasons: they have shown biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and

antipyretic properties [1]. They have shown to be useful for analytical [2] and catalytic applications [3].

The *ortho*-hydroxy aromatic Schiff-base compounds present an electron-rich centre (O) with a hydrogen atom covalently bonded, providing the possibility of forming different type of intra- and intermolecular hydrogen bonds. The presence of this *ortho*-hydroxyl group in a Schiff base allows the formation of an intramolecular hydrogen bond with the imine nitrogen and an intramolecular proton transfer. Thus, tautomerism between the phenol-imine (O–H···N) and keto-amine (O···H–N) forms (forms I and III in

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Scheme 1.

(Scheme 1) can occur both in solution and in the crystalline state. This tautomeric reaction can be induced either by light or by heat or the solvent nature [5] and is even encountered in biological media [4]. The NH tautomer can also exist in a zwitterionic form (II) characterized by the presence of ionic $N^+ \cdots H \cdots O^-$ hydrogen bond [6,7].

Several experimental studies have been reported about the tautomeric equilibrium and the intramolecular $O \cdots H-N$ hydrogen bond in small Schiff bases. X-ray structural analysis of Schiff bases suggest that the enol form is the dominant configuration [6,8] whereas there is a small number of examples with the bridging hydrogen located on the imino nitrogen [6,9].

On the other hand, Schiff bases prepared from chiral α -amino acids are known to promote racemization of the chiral center [10a,b]. The efficiency of the process depends on the nature of aldehyde or ketone but it seems to be notably enhanced when salicylaldehyde derivatives are used [10b,c]. This fact was attributed to the stabilizing role of the intramolecular hydrogen bonding on the imine intermediary and, consequently, enhancing the protonation-deprotonation sequence of the α -hydrogen atom at the chiral center [10c].

In this paper, we report the synthesis of three 2-hydroxy Schiff bases resulting from the condensation of 2,4-dihydroxybenzaldehyde with *L*-tyrosine methyl ester (**TyrL**¹) or *L*-histidine methyl ester (**HisL**¹) and 2,4-dihydroxyacetophenone with *L*-tyrosine tert-butyl ester (**TyrL**²) (Scheme 2). These new compounds were characterized by spectroscopic methods including IR, ¹H NMR and mass spectrometry. The tautomeric forms in crystalline solid state and in solution are investigated by spectroscopic methods and X-ray structure analysis.

2. Experimental section

2.1. Materials and methods

L-tyrosine methyl ester, *L*-tyrosine tert-butyl ester, *L*-histidine methyl ester, 2,4-dihydroxybenzaldehyde and 2,4-dihydroxyaceto-

phenone were purchased from Aldrich and used without further purification.

All solvents used for synthesis were dried over appropriate drying agents, degassed using a vacuum line and distilled under an Ar atmosphere [11]. Elemental analyses were carried out on a Fisons EA-1108. Melting points (Mp) were determined on a Gallenkamp MFB-595 and they are uncorrected. Mass spectra were recorded on a Bruker FTMS APEXIII spectrometer operating under ESI conditions. Infrared spectra were recorded from KBr pellets on a Jasco FT/IR-6100 spectrometer. The ¹H NMR spectra were obtained on a Bruker ARX-400 spectrometer from DMSO-*d*₆ solutions.

CD spectra were obtained on a Jasco J815 from ethanol solutions (10^{-4} – 10^{-5} M range).

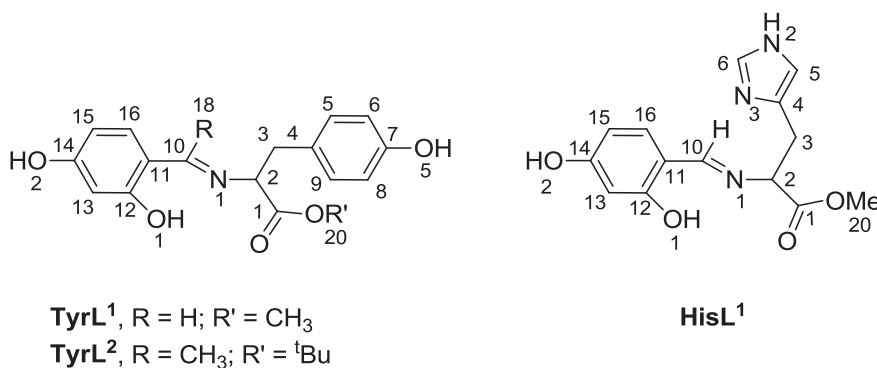
2.2. X-ray data collection, structure determination and refinement

Crystallographic data were collected on a Bruker SMART CCD-1000 (**TyrL**¹ and **HisL**¹) or a Bruker CCD Smart 6000 (**TyrL**²) diffractometers at r.t. using graphite monochromated Mo K α radiation ($\lambda = 0.71073$ Å) or Cu K α radiation ($\lambda = 1.54178$ Å), and were corrected for Lorentz, polarization and absorption effects [12a,b]. The structures were solved by direct methods using the program SHELXS97 [12c]. All non-hydrogen atoms were refined on F^2 with anisotropic thermal parameters using SHELXL97 [12c]. Hydrogen atoms were inserted at calculated positions and refined as riders except those belonging to O–H and N–H groups what were refined on positions determined from Fourier difference maps.

The Flack parameter was refined in the structures of the tyrosine derivatives though its reliability is questionable, given the poor anomalous effect expected. Consequently, we further tried to determine the absolute structure using likelihood methods [13a] with PLATON program [13b]. The absolute structure parameter γ for **TyrL**² was 0.09(4) indicating that the absolute structure has probably been determined correctly and is in agreement with the Flack parameter. This analysis for **TyrL**¹, based on the Bayesian approach with the value γ of $-0.1(7)$ has not been conclusive. Graphics were produced with PLATON [13b] and MERCURY [14]. Crystallographic data collection and refinement parameters are listed in Table 1.

2.3. Synthesis of **TyrL**¹

2,4-Dihydroxybenzaldehyde (116 mg, 0.84 mmol) was suspended in 20 mL of dry CH₂Cl₂ with molecular sieves (4 Å) and *L*-tyrosine methyl ester (156 mg, 0.84 mmol) was added. The reaction mixture was heated under reflux for 2 h which resulted in the formation of a clear yellow solution. A yellow precipitate was deposited within a few minutes, filtered off and vacuum dried.



Scheme 2.

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