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Synthesis, spectroscopic and computational characterization of the tautomerism of pyrazoline derivatives from chalcones

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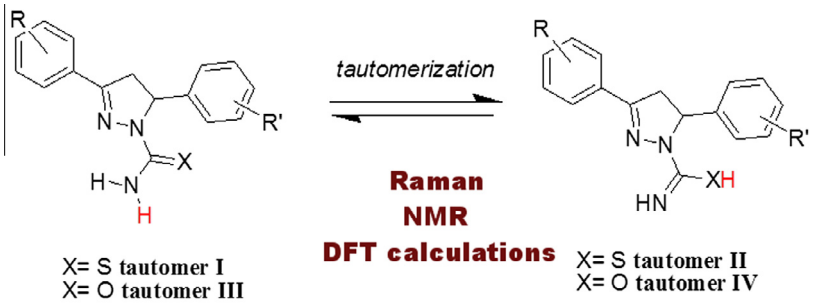
HIGHLIGHTS

- Synthesis of a series of new pyrazolines derived from chalcones is described.
- NMR and Raman spectroscopy study on the tautomerization equilibrium in the series of compounds.
- Energy and vibrational computational DFT calculations allowed understanding the tautomerization equilibrium.

GRAPHICAL ABSTRACT



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ABSTRACT

In the present study a series of novel pyrazolines derivatives has been synthesized, and their structures assigned on the basis of FT-Raman, ^{1}H and ^{13}C NMR spectral data and computational DFT calculations. A joint computational study using B3LYP/6-311G(2d,2p) density functional theory and FT-Raman investigation on the tautomerism of 3-(4-substituted-phenyl)-4,5-dihydro-5-(4-substituted-phenyl)pyrazole-1-carbothioamide and 3-(4-substituted-phenyl)-4,5-dihydro-5-(4-substituted-phenyl)pyrazole-1-carboxamide are presented. The structures were characterized as a minimum in the potential energy surface using DFT. The calculated Raman and NMR spectra were of such remarkable agreement to the experimental results that the equilibrium between tautomeric forms has been discussed in detail. Our study suggests the existence of tautomers, the carboxamide/carbothioamide group may tautomerize, in the solid state or in solution. Thermodynamic data calculated suggests that the $R(C{=}S)NH_2$ and $R(C{=}O)NH_2$ species are more stable than the R(C=NH)SH and R(C=NH)OH species. Additionally, results found for the ^{1}H NMR shifting, pointed out to which structure is present.

1. Introduction

The interest in obtaining chalcones and their pyrazolines analogs has grown in the past 10 years because of numerous pharmacological properties have been discovered, namely: antimicrobial [1–6], anti-tubercular [1,7,8], anticancer [8,9], anti-inflammatory [8] and antioxidant [5] activities. The wide range of pharmacological activities of these compounds shows the importance of this family of heterocyclic compounds in the area of medicinal chemistry. Consequently, the use of known

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methods for the synthesis and characterization of this class of compounds constitutes an important field of synthetic organic chemistry [2,10,11].

In general, 2-pyrazolines derivatives are obtained by condensation between α,β-unsaturated carbonyl compound and hydrazine derivatives [10,12,13]. In the case of compounds having a large number of unsaturations, an effect known as tautomerism may occur. The study of the tautomerism may contribute to the understanding of the structural/biological activity of this family of compounds [14,15]. Among the available spectroscopic tools, Raman spectroscopy has been suggested as a powerful technique to identify tautomers. The possibility of understanding the substances fingerprints in a Raman spectrum, which may be assigned to characteristics frequencies for each tautomeric form, has led to the development of this spectroscopic technique as an important tool for the characterization of tautomeric forms [16–19].

On the other hand, nuclear magnetic resonance (NMR) spectroscopy was introduced into organic chemistry to determine carbon skeleton of the organic compounds, plays an enormously important role in studying various chemical interactions, tautomeric rearrangement, purity and authenticity of molecules. In this context, NMR is a widely used and very powerful tool for the characterization of tautomeric equilibrium for some important compounds such as histidine and D-fructose, among others [20,21]. The use of NMR techniques for the description of tautomeric equilibrium relies on chemical systems that present slow enough proton exchange for both systems to be measured in solution [22,23]. Additionally, the support from quantum chemistry predictions is usually essential for the interpretation of NMR results [22,24]. Molecular structure, conformational stability and vibrational frequencies have been studied by ab initio and DFT methods [22,25–28]. The support of quantum chemistry methods, mostly based on density functional theory (DFT), has been essential for the interpretation of both NMR and Raman spectroscopy results for the assignment of spectra from both techniques, as well as on the calculation of total energy changes between different tautomeric species. Recently, Hadda's research group has published a benchmark paper featuring the tautomerism of some curcumin derivatives which have several biological significance [29].

In this report, a series of pyrazolines derivatives was synthesized and the structures assigned on the basis of FT-Raman, ^{1}H and ^{13}C NMR spectral data and computational DFT calculations. Furthermore, theoretical calculations were also used to check on the stability of such compounds. Here, the spectroscopic techniques have been used along with computational calculation for the evaluation of the tautomerism. Based on the spectroscopic data experimentally obtained, full quantum mechanical calculations have been applied to pyrazoline derivatives (Fig. 1).

2. Material and methods

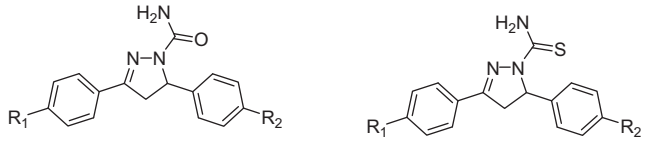

Fig. 1. Chemical structure of the pyrazolines analogs.

All procedures for the synthesis of pyrazoline derivatives **18**–**47** are presented in Supporting information as well as the structural data collected. NMR spectra and other details about some procedures related to computational details are also presented.

2.1. Synthesis

In order to synthesize *O*-alkylated chalcone derivatives **1**–**17**, 4-hydroxybenzaldehyde was initially alkylated (79–99% yield), using a Williamson ether synthesis [38–40], with K_2CO_3 and butyl, hexyl, octyl, nonyl, decyl, dodecyl or tetradecyl bromide in DMF. Commercial aldehydes 4-bromobenzaldehyde, 4-methoxybenzaldehyde, 4-(dimethylamino)benzaldehyde, 4-methylbenzaldehyde, 4-chlorobenzaldehyde, benzaldehyde and *O*-alkylated aldehydes were then treated with equimolar quantities of the acetophenone or 1-(4-fluorophenyl)ethanone and NaOH (1.5 eq.) in ethanol (Scheme 1), using Claisen–Schmidt reaction [40–43]. All the compounds were purified by recrystallization using a suitable solvent and the assignment of the structures is fully supported by their characteristic chemical shift values.

The pyrazolines **18**–**47** were prepared by treatment of chalcone derivatives in ethanol, hydrazine derivatives under basic conditions (Scheme 2). All the compounds were purified by recrystallization using a suitable solvent. After purification procedures, pyrazolines **18**–**47** were characterized by ^{1}H NMR, ^{13}C NMR spectral data.

NMR results suggests that only the R(C═S)NH_2 and R(C═O)NH_2 species, more stable, are present. The ^{1}H NMR spectra of the compounds showed three doublet of doublets in the regions of δ 3.0 and δ 6.0 ppm with $J_{a,b} \sim 17.7$ Hz, $J_{a,x} \sim 4.8$ Hz, and $J_{b,x} \sim 12.0$ Hz, confirming the nonequivalence of hydrogen at Hx (ABX system). NH_2 protons were observed at δ 6.51 ppm (compound 32) or δ 7.92–8.03 ppm (compound **46**) as singlet. In the ^{13}C NMR spectra signals in the δ 43.0 and δ 59.0 ppm corresponding to C4 and C5 carbons (for details see Supporting information).

2.2. Spectroscopy techniques

The Raman spectra were recorded in the 50–3500 cm^{-1} region at a resolution of 4 cm^{-1} using a FT-Raman Bruker RFS-100 spectrometer. The Nd:YAG laser line at 1064 nm wavelength has been used as exciting radiation for the Raman measurements. The laser power has been kept at 20 mW, and 1000 or 2000 scans have been averaged for each solid sample. The hydrogen (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker Advance DRX300 (300 MHz) spectrometer. The chemical shifts values (δ) have been reported in parts per million (ppm) with reference to tetramethylsilane (TMS) as internal reference. NMR experiments have been carried out in deuterochloroform ($CDCl_3$) or deuterodimethylsulfoxide (DMSO-d_6). The following abbreviations are used for the multiplicities for proton spectra: s (singlet); d (doublet); dd (double doublet); m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz).

2.3. Computational methodology

In order to get a full comparison with the spectroscopic data experimentally obtained, full quantum mechanical calculations have been applied to compounds **21**, **29**, **30**, **31**, **32**, **37**, **45** and **46**.

Firstly, the compounds were fully unconstrained optimized to a global minimum point at the potential energy surface using B3LYP functional [30,31] with 6-311G(2d,2p) basis set [32] in the polarizable continuum method IEFPCM [33] as implemented in Gaussian 09 program package [34]. The solvent used was the DMSO since the synthesized compounds are soluble in this solvent. Vibrational harmonic frequencies calculations were performed