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Structural characterisation of some vanillic Mannich bases: Experimental and theoretical study

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ABSTRACT

In this paper, synthesis and structural determination of 2-[1-(*N*-4-fluorophenylamino)-1-(4-hydroxy-3-methoxyphenyl)]methylcyclohexanone (**MB-F**) is presented. To determine the structure of this new compound, IR and NMR spectral characterisation was performed experimentally and theoretically. Simulation of spectral data was carried out using three functionals: B3LYP, B3LYP-D2, and M06-2X. The results obtained for **MB-F** were compared to those attained for similar, known compound 2-[1-(*N*-phenylamino)-1-(4-hydroxy-3-methoxyphenyl)]methylcyclohexanone (**MB-H**), whose crystal structure is presented here. Taking into account all experimental and theoretical findings, the structure of **MB-F** was proposed.

1. Introduction

Mannich-type reactions are of great importance in organic synthesis. The products of these reactions are β-amino-carbonyl compounds [1–5]. Many alkaloids, nucleotides, steroids, peptides, antibiotics and vitamins [6–10] comprise Mannich base fragments. Bioactivity, such as antioxidative [11], antifungal [12], anti-inflammatory [13], antimalarial [14], vasorelaxing [15], antitubercular [16], analgesic [17], anticancer [18–21], etc., is a common feature of this class of compounds. Recently, the details on the synthesis and biological activity of some Mannich bases were reported [22]. To elucidate physico-chemical properties of compounds various methods have been developed, such as analytical techniques X-ray, NMR, IR, ESI-MS, etc., as well as quantum chemical calculations.

In this study we report the synthesis of the new Mannich base, 2-[1-(*N*-4-fluorophenylamino)-1-(4-hydroxy-3-methoxyphenyl)] methylcyclohexanone (**MB-F**). In addition we present various results related to **MB-F** and 2-[1-(*N*-phenylamino)-1-(4-hydroxy-3-methoxyphenyl)]methylcyclohexanone (**MB-H**) [22]. This investigation includes the spectroscopic and crystallographic data, as well as the results of quantum chemical calculations, and is focused towards structural determination of both compounds. Our additional goal was to test the performance of different theoretical methods in determination of structural and spectroscopic properties of the investigated Mannich bases.

2. Experimental

2.1. Reagents

The compounds chloroacetic acid, vanillin, 4-fluoroaniline, cyclohexanone, were obtained from Aldrich Chemical Co. Diethanolamine (DEA) was purchased from Fluka. All common chemicals were of reagent grade.

2.2. Measurements

The ^{1}H NMR and ^{13}C NMR spectra were run in $CDCl_3$ on a Varian Gemini 200 MHz spectrometer. The IR spectra in the solid state were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer using KBr pellet technique. The resolution of the scanning was 400 cm^{-1} at 16 scans. Melting points were determined on a Mel-Temp capillary melting points apparatus, model 1001. Elemental microanalyses for carbon, hydrogen, and nitrogen were performed at the Faculty of Chemistry, University of Belgrade.

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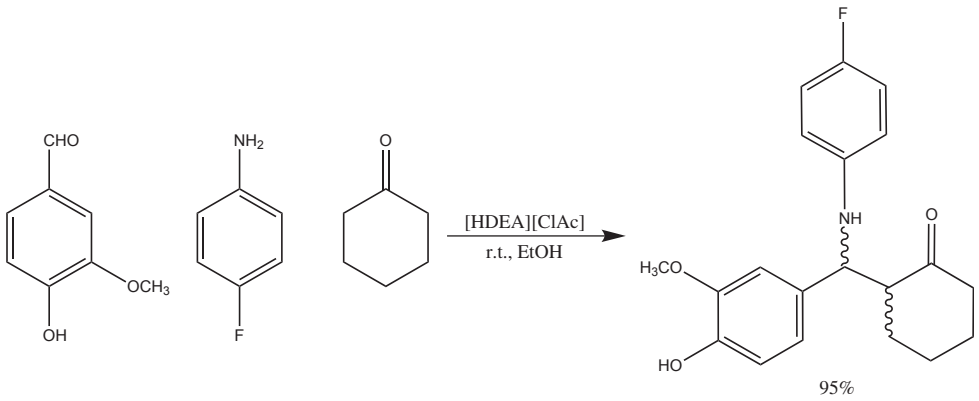


Scheme 1. Synthesis of **MB-F** with the yield indicated.

2.3. Reaction procedure

The synthesis of the Mannich product **MB-F** was performed using diethanolammonium chloroacetate [HDEA][ClAc] as catalyst (Scheme 1), whose preparation has been earlier described [22]. All components (4-fluoroaniline and vanillin (1 mmol), cyclohexanone (1.5 mmol), and ionic liquid as catalyst (15 mol%)) were stirred at room temperature for 24 h, in 1 ml of ethanol. The precipitated product was filtrated and washed with ethanol. Recrystallization from dichloromethane and propanol (2:1) yielded **MB-F**, which was analysed by ^{1}H NMR, ^{13}C NMR (Tables 2 and 3), and IR spectroscopy (Fig. 3). White compound: Mp 153–155 °C; $C_{20}H_{22}FNO_3$ (FW = 343.39): C, 69.95; N, 4.08; H, 6.46%; found: C, 70.09; N, 4.07; H, 6.20%. The synthesis of **MB-H** has been carried out using very similar procedure [22]. Possible *anti* and *syn* diastereoisomers of **MB-H** and **MB-F** are depicted in Scheme 2.

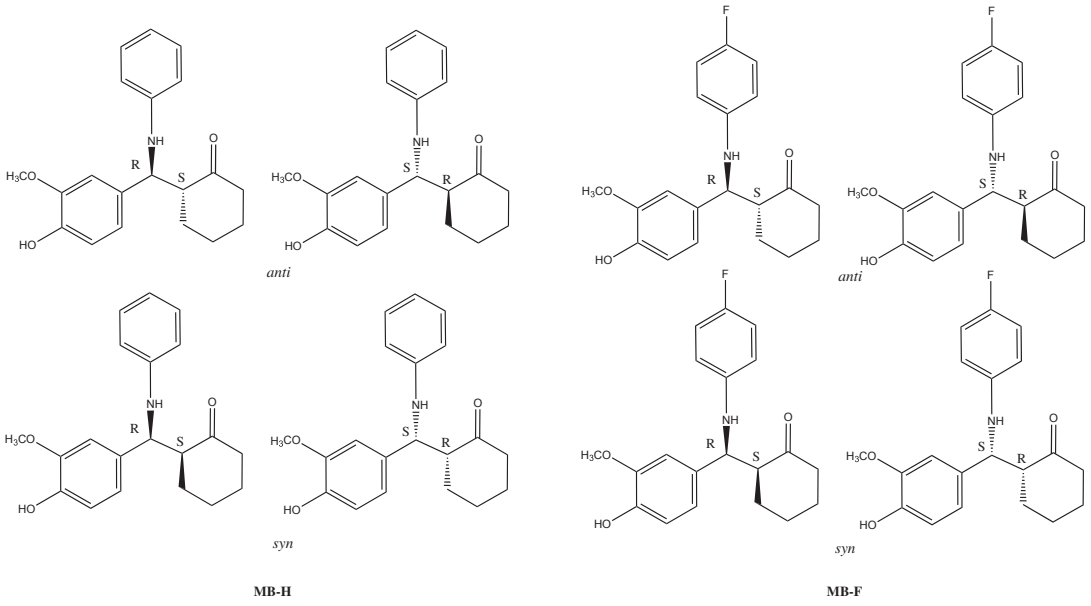
2.4. X-ray experiment

Single-crystal diffraction data for **MB-H** were collected on an Oxford Diffraction Xcalibur Sapphire3 Gemini diffractometer equipped with Cu Kα radiation (λ = 1.5418 Å) at room temperature. Data were processed with CrysAlis software [23] with multi-scan absorption corrections applied using SCALE3 ABSPACK [23]. The crystal structure was solved with SHELXS [24] and refined using SHELXL [24].

All non-H atoms were refined anisotropically to convergence. The H atoms attached to O1 and N1 were located from the difference map and were refined with isotropic displacement parameters. All H attached to C atoms were placed at geometrically calculated positions with the C–H distances fixed to 0.93 Å from C(sp^2); 0.96, 0.97 and 0.98 Å from methyl, methylene and methine C(sp^3), respectively. The positions of these H atoms were geometrically idealized and allowed to ride on their parents atoms with U_{iso}(H) = 1.2 U_{eq}(C). Methyl-group H atoms were located from Δ F map, then geometrically idealized and refined as a rigid groups with U_{iso}(H) = 1.5 U_{eq}(C).

Figures were produced using ORTEP-3 [25] and MERCURY, Version 2.4 [26]. The software used for the preparation of the materials for publication: WinGX, PLATON, PARST [27–29].

Crystallographic data for the structural analysis were deposited with the Cambridge Crystallographic Data Centre, CCDC No. 935220 for **MB-H**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.



Scheme 2. Possible *RS* and *SR* enantiomers of the **MB-H** and **MB-F** diastereoisomers (*anti* and *syn*).