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Experimental and theoretical studies of the molecular structure of 1-(2-pyridinylmethyl)-2-methylbenzimidazole

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ABSTRACT

In this work, we report a combined experimental and theoretical study on the molecular structure and vibrational spectra of 1-(2-pyridinylmethyl)-2-methylbenzimidazole. The structure of the target compound has been proposed by elemental analysis and spectroscopic data, i.e., IR, Raman, UV, MS, ^{1}H and ^{13}C NMR. The experimental results were supported by performing DFT calculations for the ground state geometry, electronic structure and vibrational spectra using the B3LYP functional and the 6-311+G** basis set. The optimized geometric bond lengths and bond angles obtained by using DFT have been compared with X-ray diffraction values available in the literature for the precursors (2-methylbenzimidazole and 2-picoline), as a polycrystalline structure of this compound could not be obtained in this experiment. All the experimental vibrational bands have been discussed and assigned to normal mode on the basis of our calculations. Good linear correlation between the experimental ^{1}H and ^{13}C NMR chemical shifts in DMSO-d_6 solution and calculated GIAO shielding tensors were found.

1. Introduction

The benzimidazole scaffold is an accepted pharmacophore and represents an important synthetic precursor in new drug discovery [1–8]. It is also of considerable interest as a ligand towards transition metal ions in a variety of biological molecules [9,10]. At the same time, derivatives of picoline have potent hypolipidemic effects, antineoplastic and anti-inflammatory activities and show good activity against leukemia and human glioma cell growth [11]. In connection with our investigations in the field of N-substituted benzimidazoles, we extended our studies to the synthesis and characterization of potentially biological useful compounds from the reaction of 2-picolyl chloride hydrochloride with 2-methylbenzimidazole. Fig. 1 shows the numbering of the atoms in the structure of 1-(2-pyridinylmethyl)-2-methylbenzimidazole. Recently, we reported studies on the structural properties of two 1-alkyl-2-methylbenzimidazoles compounds [12], on the isomers of 1-propenyl-2-methylbenzimidazoles [13] and on the isomers of 1-(2-methylpropenyl)-2-methylbenzimidazole [14]. In the present work, 1-(2-pyridinylmethyl)-2-methylbenzimidazole was synthesized and then IR, UV, Raman and NMR spectroscopy techniques were used to validate its structure. In addition, the molecular geometry, absorption wavelengths and vibrational spectra of the title compound ($C_{14}H_{13}N_3$) were calculated by applying density functional theory computations using Becke's three-parameter hybrid functional method [15] with Lee, Yang and Parr's correlation functional [16] and the 6-311+G** basis set. The calculated geometric parameters and vibrational frequencies were analyzed theoretically and then compared with obtained experimental results. In addition, GIAO (gauge-independent atomic orbital) [17] ^{13}C and ^{1}H calculations of this derivative of 2-methylbenzimidazole have been calculated by using the B3LYP method with the 6-311+G** basis set. The solvent effects on NMR data were introduced by the Integral Equation Formulation-Polarizable Continuum Model (IEF-PCM) method [18] implemented in the GAUSSIAN 03 program [19]. These calculations were valuable for providing insight into molecular parameters, and vibrational and NMR spectra. In this article, we present basic experimental and theoretical information about the structure of a 1-(2-pyridinylmethyl)-2-methylbenzimidazole. To the best of our knowledge, no evidence of similar studies for this derivative of 2-methylbenzimidazole has been reported to date in the open chemical literature.

2. Experimental and calculations

2.1. Synthesis

All chemicals used for the preparation of the title compound were of reagent grade quality. The 1-(2-pyridinylmethyl)-2-methylbenzimidazole compound was prepared by a modified method that was used for N-alkylation of indoles and pyrroles [20]. Potassium hydroxide (KOH, 2.13 g, 37.9 mmol) was dissolved in 25.0 mL of

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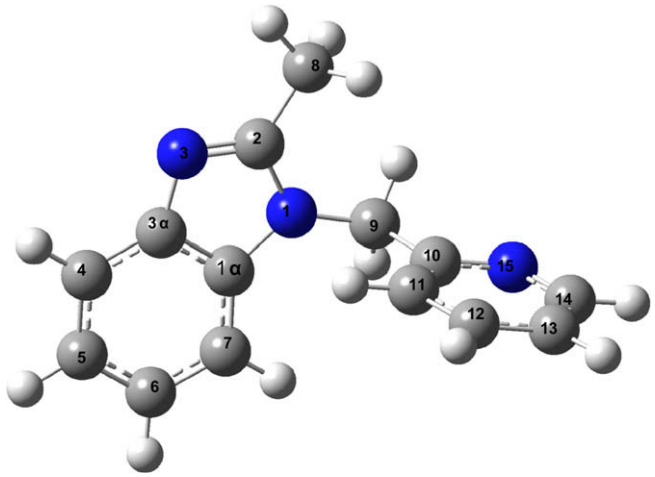

Fig. 1. Atom numberings and optimized structure of 1-(2-pyridinylmethyl)-2-methylbenzimidazole from B3LYP/6-311+G** calculations.

dimethylsulfoxide (352 mmol) with stirring in a 250 mL round-bottomed flask under a dry N_2 atmosphere. 2-Methylbenzimidazole (3.01 g, 22.8 mmol) was added and the mixture was stirred for 2 h. Upon transferring 2-picolyl chloride hydrochloride (3.80 g, 23.2 mmol), the solution turned violet after a few minutes. The reacting mixture was stirred at room temperature for 24 h under a dry N_2 atmosphere, and then products were diluted with dichloromethane and washed successively with water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed. The purified product was isolated and analyzed by GC–MS. The 1-(2-pyridinylmethyl)-2-methylbenzimidazole was obtained as a white solid. Yield 43%; mp 57–59 °C; mass spectrum produced by electron impact (EI) ionization showed *m/z*: 223($M^{+\cdot}$), 208, 145, 131, 118, 104, 93, 77, 65, 51, 39. Anal. Calc. for $C_{14}H_{13}N_3$: C, 75.34%; H, 5.83%; N, 18.83%. Found: C, 75.37%; H, 5.84; N, 18.81%.

2.2. Physical methods

GC–MS analyses were performed using a Hewlett Packard 5890 series II Gas Chromatograph coupled with a Hewlett Packard model 5970 mass selective detector. A Supelco SPB-5 capillary column (length: 30 m × 0.25 mm i.d.) was used for the chromatographic separation and the helium carrier gas was set to a flow rate of 0.9 mL/min. The oven temperature was initially at 70 °C (held for 10 min) and then increased to 250 °C at a rate of 10 °C/min. The mass spectrometer was operated in electron impact mode with ionization energy of 70 eV. The ion source temperature was maintained at 280 °C.

The room temperature Fourier transform infrared spectrum of the title compound was measured on a Perkin Elmer System 2000 FT-IR spectrometer in the 4000–400 cm^{-1} region with 4 cm^{-1} resolution. FT-Raman spectra were recorded on a Bruker Optics RFS-100 Fourier Transform Raman spectrometer (excitation source: Nd:YAG, 1064 nm). The measurements of the spectra were performed in the range of 100–3600 cm^{-1}, the Stokes region, with 1 cm^{-1} spectral resolution. The ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 FT-NMR spectrometer. The internal lock was provided by a deuterated DMSO solvent (δ = 39.51 ppm) and both proton and carbon signals were referenced to TMS. All spectra were measured at room temperature.

2.3. Computational methods

The molecular structure of the 1-(2-pyridinylmethyl)-2-methylbenzimidazole in the ground state was optimized by a DFT method with B3LYP functional and a 6-311+G** basis set. UV absorption energies and vibrational frequencies were calculated using the Configuration Interaction Singles (CIS) method [21]. The entire set of calculations was performed using the GAUSSIAN 03 W™ software (Gaussian Inc., Wallingford, CT) for Windows™ operating system (Microsoft Corp.,) and the assignment of the calculated wavenumbers was aided by the animation option of the GaussView 3.0™ graphical interface [22]. The overestimation (known systematic errors) of computed wavenumbers was compensated for by applying a wavenumber-linear scaling method (WLS) [23]. NMR calculations were performed using the GIAO method. NMR shifts were computed at the B3LYP/6-311+G** level of theory and the values for the ^1H and ^{13}C isotropic chemical shifts were referenced to the corresponding values for TMS, which was calculated at the same level of theory. The effect of solvent on the theoretical NMR parameters was included using the default IEF-PCM model provided by GAUSSIAN 03. Dimethylsulfoxide (DMSO), which has a dielectric constant (ε) of 46.7, was used as the solvent.

3. Results and discussion

3.1. Geometry optimization

The calculated molecular structure of 1-(2-pyridinylmethyl)-2-methylbenzimidazole and its numbering scheme are shown in Fig. 1. The global energy minimum obtained by DFT of the structure optimization for the title compound was −705.7897021 Hartree (-4.43×10^5 kcal mol^{-1}). The optimization studies of the picolyl derivative showed that the molecule belongs in a C_1 symmetry point group. The experimental and optimized structural parameters of 1-(2-pyridinylmethyl)-2-methylbenzimidazole calculated at the B3LYP level of theory with a 6-311+G** basis set are listed in Table 1 in accordance with the atom numbering given in Fig. 1. These values were then compared with X-ray diffraction values available in the literature for 2-methylbenzimidazole and 2-picoline [24,25]. As expected, most of the calculated C—C bond lengths for 2-methylbenzimidazole and 2-picoline were larger than the experimental values. The optimized geometry of 2-methylbenzimidazole in the ground state corresponded to C_S symmetry and the calculated bond lengths and bond angles with the computational method yielded 0.04 Å and 3° discrepancies relative to the X-ray values, respectively. For 2-picoline, the optimized geometry showed a maximum difference in bond lengths and bond angles of 0.03 Å and 0.6° between non-hydrogen atoms from the experimental values. These deviations may be attributed to the solid-state inter-molecular interactions related to the strong hydrogen bonding and crystal packing effects. Interesting, the crystal packing of 2-picoline is a $C_{(aromatic)}$—H···Π inter-molecular contact with a short H···X distance of 2.64 Å, which brought about the peculiar packing motif of 2-picoline (X is the center of the aromatic ring) [25]. Direct attachment of 2-picoline to the 2-methylbenzimidazole ring produces a small expansion in imidazole interatomic distances and all bond lengths in the pyridine ring are slightly shorter than those of the 2-picoline molecule. Significant changes, with respect to experimental and calculated values of 2-methylbenzimidazole, occur in the length of the N_1—C_2 and $C_{3\alpha}$—$C_{1\alpha}$ bonds in the imidazole ring. Also, the $C_{3\alpha}$—$C_{1\alpha}$—N_1 angle in the imidazole ring has been reduced by five degrees as a result of this substitution. In addition, it is well known that, due to low scattering factors of hydrogen atoms in X-ray diffraction, the experimental bond lengths of X—H bonds are expected to be shorter than the estimated bond lengths. The optimized C—C bond lengths in the pyridine ring fall in the range of 1.388–1.392 Å for the B3LYP/6-311+G** method, which are in good agreement with those in the crystal structure of 2-picoline (1.367–1.390 Å). The pyridine ring was found to be off-plane from