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Formyl- and acetylindols: Vibrational spectroscopy of an expectably pharmacologically active compound family

Ferenc Billes[a,d], Paula Veronica Podea[b], Ildikó Mohammed-Ziegler[c,*],
Monica Toşa[b], Hans Mikosch[d], Dan-Florin Irimie[b]

[a] Department of Physical Chemistry and Material Science, Budapest University of Technology and Economics, H-1521 Budapest, Budafoki út 8, Hungary
[b] Department of Biochemistry and Biochemical Technology, Babeş-Bolyai University, Cluj, Romania
[c] Gedeon Richter Plc, H-2510 Dorog, Esztergomi út 27, Hungary
[d] Institute for Chemical Technologies and Analysis, Vienna University of Technology, A-1060 Wien, Getreidemarkt 9, Austria

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ABSTRACT

In the peresent paper, indole and its seven derivatives were compared, namely 3-formylindole, 1-methyl-3-formylindole, 1-ethyl-3-formylindole, 3-acetylindole, 1-methyl-3-acetylindole, 1-ethyl-3-acetylindole and 1,3-diacetylindole. The substitution of indole in position 3 with aldehydes and with alkyl groups cause only minor changes in the molecular geometry, however, substantially larger alterations are found in the charge distribution and in the vibrational force constants. The appearance of the aldhyde groups increased the degree of association as it was observable on the shape of infrared NH stretching band and its shifts. The alkyl substitution shifts the aldehyde carbonyl stretch band frequencies to somewhat higher values. The effect of the second acetyl group in position 1 is not comparable with those of the 1-alkyl groups. The latter effect is observable in the molecular geometry, however, it is more pronounced in the changes of the net charge distribution, the vibrational force constants and the infrared spectra.

1. Introduction

Indole derivatives are present in both animals and plants. The most important compound of this group is tryptophan, an essential amino acid in the human diet, that is a 3-substituted indole. Important alkaloids, like serotonin and tryptamin are also indols substituted in position 3. Indole-3-carbinol can be found in some vegetables (like cabbage) and its anticarcinogenic and antioxidant effects are subjects of research [1]. An other important indole derivative is the indole-3-acetic acid, a phytohormone, coordinateing several growing processes of plants [2]. It seems that the biological activity of the indole derivatives is in connection with the nature of substituent in position 3, on the pyrrole ring.

Similarly, some highly selective drugs contain indole structure, like Sumatriptan and Ondansetron. The first one is for treatment of migraine, the latter one is used for the suppression of the nausea and vomiting, caused by cancer chemotherapy and radiotherapy [3]. Some other drugs also have indole structure, e.g. indomethacin used for the treatment of rheumatoid arthritis and LSD with high hallucinogenic activity.

This was the reason of our interest in 3-formyl and 3-acetyl derivatives of indole.

The vibrational spectra of the parent molecule, the *indole*, were several times discussed during the last 50 years. Here we mention some of them. Millich and Becker [4] synthesized several indole derivatives and measured their infrared spectra in the CH, NH and C=O stretching regions and compared them to that of indole. Lautié et al. [5] studied both infrared and Raman spectra of indole and its deuterated derivatives. They also gave curves approximate assignments of the observed spectral bands. In 1986, two articles delt with the vibrational spectroscopy of indole in the same journal issue. Suwaiyan and Zwarich [6] presented the infrared and Raman spectra with approximate assignment but only for the parent compound. Takeuchi and Harada [7] carried out normal coordinate analysis of the indole molecule already in 1986, vibrational force constants were presented and the calculated vibrational frequencies were compared with the experimental ones of Lautié et al. [5]. In 1988, Collier [8] already applied semiempirical (AM1) calculations for the assignment of the indole spectra and compared them with his experimental results. In the 90s, ab initio frequency calculations were also used for the interpretation of the indole spectra. Majoub and Vergoten [9] applied the HF model with 3-21G basis set and obtained the optimized geometry, the complete force constant matrix, the assignment (potential energy distribution) of the vibrational spectra, even for some deuterated derivatives of

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* Corresponding author. Tel.: +36 203824958.
E-mail addresses: fbilles@mail.bme.hu (F. Billes), mohazihu@yahoo.com (I. Mohammed-Ziegler), hans.mikosch@tuwien.ac.at (H. Mikosch).

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indole. Barstis et al. [10] observed the applicability of modern spectroscopic methods in the studies of the excited state vibrational spectra of indole. In this work, the jet-cooled resonant two-photon ionization (R2PI) was used with time-of-flight (TOF) mass spectrometric detection. Klots and Collier [11] studied in detail the experimental infrared and Raman spectra of indole both in vapour and liquid phase. Walden and Wheeler [12] already applied DFT calculations with B3LYP functional and 6-311G(d) basis set for the frequency calculations of the indole molecule. Collier et al. [13] calculated vibrational frequencies of some bicylic molecules, including those of indole. However, in this article benzofuran was in the focus. El-Azhary [14] used DFT method, the B3LYP functional with 6-31G** basis set for the calculation of vibrational frequencies of seven heterocyclic molecules, including indole. The quantum chemically calculated force field was scaled to experimental frequencies taken from the literature. Xue et al. [15] carried out DFT calculations for computing the vibrational frequencies of indole, applying different functionals, e.g. B3LYP, B3PW91, all of them with 6-31G** basis set. Sundaraganesan et al. [16] calculated molecular geometric parameters and vibrational frequencies of indole, 7-azaindole and 5-aminoindole with HF and B3LYP functionals and 6-311++G(d,p) basis set. They also presented the interpretation of the calculated normal frequencies.

Some papers report on the indole *ions*. Unterberg et al. [17] studied experimentally the indole cation and the indole + water cation using IR/PIRI and IR photodissociation spectroscopy and also theoretically with ab initio calculations. Jalbout et al. [18] calculated the Rydberg electron transfer of an indole–water dimer anion.

Other articles present *reactions* of indole. Zhou and Liu [19] investigated the role of tautomerism of indole in the thermal degradation of the compound with DFT B3LYP/6-31G** method. Yurtsever and Yurtsever [20] applied a similar DFT method for simulation of the polymerisation of indole. Smith and Liu [21] studied the indole tautomers (2H- and 3H-indole) in the same manner.

Several articles dealt with the vibrational spectroscopy of indole derivatives. Barstis et al. [22] studied 4-, 5- and 6-*fluoroindols* in detail. Their excitation spectra were measured using jet-cooled one-color resonant two-photon ionization (IC R2PI) time-of-flight mass spectrometry, and the ground state infrared and Raman spectra were also recorded. HF/3-21G calculations were also carried out for assignment of the fundamental vibrational frequencies. Results of indole derivatives were compared with those of the parent compound [10].

Arjunan et al. [23] recorded the infrared and Raman spectra of 5-*aminoindole*. The assignment of the normal frequencies was achieved without quantum chemical calculations using normal coordinate analysis. Later, Sundaraganesan et al. [16] also dealt in their aforementioned article with the vibrational spectroscopy of 5-aminoindole basing the assignment of vibrational fundamentals on high level quantum chemical calculations.

Carney and Zwier [24] applied modern experimental methods to characterize the hydrogen-bonding topologies of indole–(water)$_{1,2}$, 1-*methylindole*–(water)$_{1-3}$, and 3-methylindole––(water)$_1$ clusters. A combination of resonant two-photon ionization (R2PI), resonant ion-dip infrared spectroscopy (RIDIRS), and infrared-ultraviolet (IR-UV) hole-burning spectroscopy were used. Besides, the vibrational frequencies and band intensities were computed with the Becke3LYP/6-31+G* functional and basis set.

Suwayan and Morsy [25] recorded polarized infrared spectra and Raman spectra of melt cryatalline 5-*methoxyindole*, and calculated their vibrational spectroscopic properties by HF/3-21G.

Morzyk-Ociepa et al. [26] determined the crystal structure and recorded the infrared spectrum of indole-2-*carboxylic acid*.

In the peresent work, indole and its seven derivatives were *studied*, i.e. 3-formylindole, 1-methyl-3-formylindole, 1-ethyl-3-formylindole, 3-acetylindole, 1-methyl-3-acetylindole, 1-ethyl-3-acetylindole and 1,3-diacetylindole (see Fig. 1). Thus, one can observe different substituent effects. Beside the simple substituent effect on indole, the change from formyl to acetyl substitent in position 3 gives the possibility to study the effect of the additional methyl group on different properties of the molecular skeleton. With the change of the substituent in position 1 from hydrogen to ethyl group one can follow the stepwise change of the molecular properties. Finally, a radical change in position 1 can cause some peculiar results.

2. Experimental

2.1. Preparation of the studied indole derivatives

3-Formylindole (indole-3-carboxyaldehyde) was prepared with the help of the complex, formed between phosphorus oxychloride and dimethylformamide. Phosphorus oxychloride (10 mL) was added drop by drop to ice-cooled dimethylformamide (30 mL), followed by addition of indole (100 mmol). This mixture was stirred at 100 °C for 2 h and then poured onto 500 g of ice. The pH value of the mixture was set to 6 by addition of saturated aqueous NaOAc solution and it was extracted with toluene (200 mL, four times). The combined toluene solutions were dried over anhydrous Na_2SO_4, and then concentrated to a volume of 50 mL by distillation under reduced pressure. Chromatography on silica gel using toluene as eluent followed by recrystallization from ethanol or hexane yielded the desired compound (Scheme 1).

Synthesis of the *intermediers* 1-(1H-indol-3-yl)ethanone and 1-(5-bromo-1H-indol-3yl)ethanone, respectively [27]. $SnCl_4$ was added (1.44 mL, 12 mmol) in a single portion via syringe to a stirred solution of indole (1.17 g, 10 mmol) in CH_2Cl_2 (20 mL) under argon at 0 °C. After the ice bath was removed, the mixture was stirred at room temperature for 30 min, and then acetyl chloride (10 mmol) was added in small portions to the suspension, followed by nitromethane (15 mL). The mixture was stirred for 2 h at room temperature under argon atmosphere, after quenching it with ice and water (30 mL) (Scheme 2).

The N-alkyl derivatives were synthesized through alkylation of both derivatives with alkyl iodide in presence of a strong base (Scheme 3).

2.2. Recording of the spectra

The infrared spectra were recorded on a Nicolet Magna 75 IR spectrometer at 2 cm^{-1} resolution and with the coadditon of 250 individual spectra in the 4000–400 cm^{-1} region in KBr discs.

The Raman spectra were measured on Bruker RFS 100/S FT-Raman spectrometer at 4 cm^{-1} resolution and with the coaddition of 2000 single spectral scans in the 3500–200 cm^{-1} region. The spectra were excited using the 1064 nm band of a Nd–YAG laser with 400 mW output power. The germanium detector was cooled with liquid nitrogen.

The overlapping frequencies were resolved by the PCCP software [28].

3. Calculations

For the quantum chemical calculations, the Gaussian 03 program package [29] was used with the DFT B3LYP functional and the 6-311G** basis set. By the first step of the calculations, the optimized molecular geometries, the NBO charges, the Mulliken, and the atomic net charges were obtained. The second step of the computations gave the vibrational force constants of the molecules, the calculated fundamental frequencies, the corresponding infrared and Raman intensities, and the depolarization ratios of the Raman bands.