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Journal of Molecular Structure 831 (2007) 174–179

Journal of MOLECULAR STRUCTURE

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Solid state structure by X-ray and ^{13}C CP/MAS NMR of new 5,5′-diethoxy-3,3′-methanediyl-*bis*-indole

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Received 6 April 2006; received in revised form 31 July 2006; accepted 2 August 2006
Available online 14 September 2006

Abstract

5,5′-Diethoxy-3,3′-methanediyl-*bis*-indole **1** was synthesized by novel protocol and its solid state structure was analyzed using X-ray diffraction and ^{13}C CP/MAS NMR methods. Double resonances were observed in the spectrum of **1**, and different structure of both indole systems in one molecule (shown by X-ray studies) is responsible for this spectral pattern. In the crystal only one intermolecular hydrogen bond (N1–H1···O11′) was revealed, which is uncommon among *bis*-indole derivatives.

Keywords: 5,5′-Diethoxy-3,3′-methanediyl-*bis*-indole; X-ray data; ^{13}C CP/MAS NMR analysis

1. Introduction

In the course of our studies on *bis*-indoles [1,2] we are interested in optimization of the synthetic procedure leading to substituted indoles and subsequently to new 3,3′-diindolylmethanes, which could inhibit human breast cancer cell growth [3,4]. For 5,5′-disubstituted-3,3′-methanediyl-*bis*-indoles, we observed a diversified resonance pattern in solid state ^{13}C CP/MAS NMR spectra and various intermolecular interactions detected by X-ray analysis, which could be responsible for their biological function [5]. Moreover, X-ray studies revealed a butterfly-like shape for several of those *bis*-indoles, which is analogous to the one proposed for inhibitors of HIV-1 reverse transcriptase [6]. The different structure in solid state was dependent on the nature of substituents at C5, C5′ atoms of indole rings. Then we decided to continue studies on this class of compounds, and for new 5,5′-diethoxy-3,3′-methanediyl-*bis*-indole **1** (Scheme 1) we observed double signals with intensity ratios of 1:1 in the ^{13}C CP/MAS NMR spectrum (Fig. 1) for the majority of C atoms. This could have been caused by the presence of two energetically similar conformers of **1** in solid state, or by a different packing mode of both indole rings in one conformer as we defined it previously for 5,5′-dimethoxy-3,3′-methanediyl-*bis*-indole **2** [1].

In the present paper, we report our novel protocol of the synthesis of alkoxy indoles and *bis*-indoles, spectral data for new intermediate (*E*)-5-ethoxy-2-nitro-β-morpholinostyrene **1a** as well as the single crystal X-ray diffraction analysis, and fully resolved ^{13}C CP/MAS spectra of new 5,5′-diethoxy-3,3′-methanediyl-*bis*-indole **1** in the temperature range 298–358 K.

2. Experimental

2.1. Syntheses

All chemicals were purchased from major chemical suppliers as high or highest purity grade and used without further purification. Melting points were determined with a Digital Melting Point Apparatus 9001 and are uncorrected. All reported elemental analyses were averaged from two

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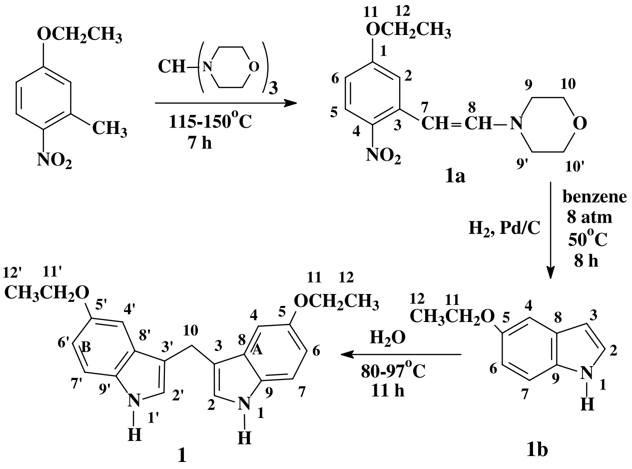
doi:10.1016/j.molstruc.2006.08.003



Scheme 1. Reagents and conditions for preparation of 5,5′-diethoxy-3,3′-methanediyl-*bis*-indole **1** with atom numbering of product **1** and intermediates **1a** and **1b**.

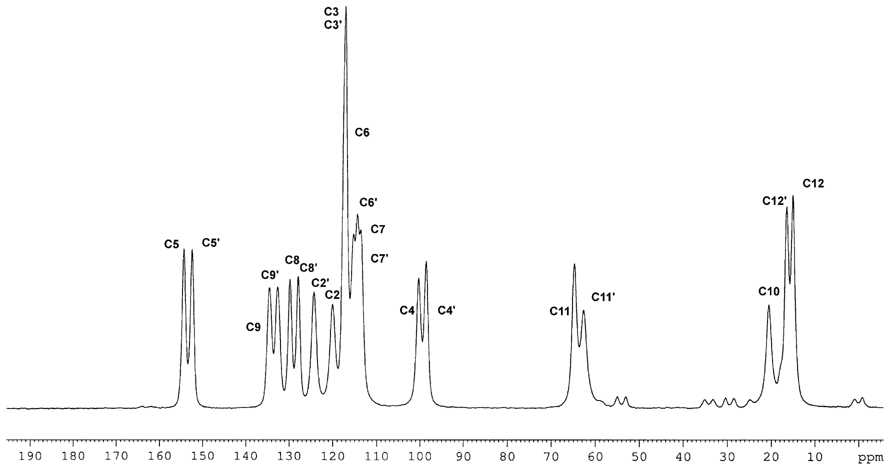
independent determinations. Prefabricated silica gel sheets (Merck Kieselgel 60 F_{254}) were used for TLC.

2.1.1. (E)-5-Ethoxy-2-nitro-β-morpholinostyrene *1a*

A mixture of morpholine (7.49 g, 0.105 mol) and triethyl orthoformate (7.41 g, 0.050 mol) with 0.2 ml CH_3COOH was stirred at 122 °C for 4 h. The ethanol forming during the reaction and excess of orthoformate were evaporated. The residue, white precipitate of trimorpholylmethane was mixed at 115 °C with 3-methyl-4-nitroethoxybenzene (2.97 g, 0.016 mol) (obtained from 3-methyl-4-nitrophenol and ethyl iodide [7]). Next the mixture was heated at 150 °C for 7 h and then cooled to 70 °C. The ethanol (2.5 ml) was added and the dark red solution was then allowed to cool to room temperature. After nearly 24 h at 4 °C orange crystals were formed. After filtration and recrystallization from ethanol the obtained yield was 1.62 g (36.5% yield) of orange crystals with m.p. 121.8–122.0 °C. Found: C, 60.29; H, 6.67; N, 10.03%. Calcd for $C_{14}H_{18}N_2O_4$ 278.14: C, 60.42; H, 6.52; N, 10.07%. ^1H NMR (400 MHz, $CDCl_3$): 1.44 (t, $J = 7.0$ Hz, 3H, 12-CH_3), 3.17 (t, $J = 4.6$ Hz, 4H, 9-CH_2, 9′-CH_2), 3.75 (t, $J = 4.6$ Hz, 4H, 10-CH_2, 10′-CH_2), 4.09 (q, $J = 7.0$ Hz, 2H, 11-CH_2), 6.26 (d, $J = 13.6$ Hz, 1H, 7-H), 6.60 (dd, $J_1 = 2.4$ Hz, $J_2 = 9.2$ Hz, 1H, 4-H), 6.73 (d, $J = 13.6$ Hz, 1H, 8-H), 6.84 (d, $J = 2.4$ Hz, 1H, 6-H), 7.97 (d, $J = 9.2$ Hz, 1H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 14.84 (C-12), 48.90 (C-9, C-9′), 64.15 (C-11), 66.43 (C-10, C-10′), 95.65 (C-7), 109.80 (C-6), 110.55 (C-4), 128.32 (C-3), 138.05 (C-1), 139.40 (C-2), 143.98 (C-8), 162.45 (C-5) ppm. IR (nujol): $\tilde{\nu}$ 3100–3000, 3000–2800, 1630, 1620, 1610, 1460, 1570 (NO_2), 1450, 1330 (NO_2), 1320, 1230, 1170, 1030, 870, 850, 760 cm^{-1}.

2.1.2. 5-Ethoxyindole *1b* [7]

(*E*)-5-Ethoxy-2-nitro-β-morpholinostyrene **1a** (5.56 g, 0.02 mol) was dissolved in 170 ml of benzene and then 2 g of 10% Pd/C was added. The mixture was kept for 8 h at 50 °C and at a pressure of 8 atm in an autoclave. Finally, the catalyst was removed from light green solution by filtration. After solvent evaporation, the residue was separated chromatographically on silica gel with toluene. The oily residue of **1b** was crystallized from hexane. The obtained yield was 1.16 g (36.0 %) of white crystal with m.p. 39.2–39.8 °C (35 °C [7]). ^1H NMR (400 MHz, $CDCl_3$): 1.43 (t, $J = 7.0$ Hz, 3H, 12-CH_3), 4.07 (q,



chemical shifts of ^{13}C in solid state δ [ppm]										
C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
120.1	117.3	100.4	154.4	115.3	114.4	129.8	134.6	20.5	64.7	15.0
C2’	C3’	C4’	C5’	C6’	C7’	C8’	C9’	-	C11’	C12’
124.3	117.3	98.6	152.5	114.4	113.6	127.9	132.7	-	62.6	16.4

Fig. 1. The ^{13}C CP/MAS NMR spectrum of 5,5′-diethoxy-3,3′-methanediyl-*bis*-indole **1** in solid state at 298 K. Assignment of resonances is shown in table.

$J = 7$ Hz, 2H, 11-CH_2), 6.47 (d, $J = 2.4$ Hz, 1H, 4-H), 6.86 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz, 1H, 6-H), 7.10 (d, $J = 2$ Hz, 1H, 3-H),7.16 (t, $J = 2.8$ Hz, 1H, 2-H), 7.26 (d, $J = 8.8$ Hz, 1H, 7-H), 8.04 (br s, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 15.28 (C-12), 64.37 (C-11), 102.58 (C-4), 103.70 (C-3), 111.84 (C-7), 113.16 (C-6), 124.99 (C-2), 128.51 (C-8), 131.18 (C-9), 153.64 (C-5) ppm.

2.1.3. 5,5′-Diethoxy-3,3′-methanediyl-bis-indole **1**

5-Ethoxyindole **1b** (1.80 g, 0.005 mol) was dissolved in water (25 ml) with formalin (0.185 ml, 0.20 g, 0.0025 mol) and one drop of concentrated H_2SO_4 acid was added. The mixture was kept out of light and stirred at 80–97 °C for 11 h and then allowed to cool to room temperature. The water phase was extracted three times with diethyl ether (10 ml each). The organic phase was dried with $MgSO_4$. The solvent was evaporated in vacuum. The oily residue was recrystallized from ethanol three times under the conditions without light. Th obtained yield was 0.68 g (81.34%) of white crystals with m.p. 139.7–140.0 °C. Found: C, 75.41; H, 6.61; N, 8.37%. Calcd for $C_{21}H_{20}N_2O_2$ 334.40: C, 75.42; H, 6.63; N, 8.38%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.40 (t, $J = 7.0$ Hz, 6H, 12-CH_3, 12′-CH_3), 4.03 (q, $J = 7.0$ Hz, 4H, 11-CH_2, 11′-CH_2), 4.14 (s, 2H, 10-CH_2), 6.85 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, 2H, 6-H, 6′-H), 6.88 (br s, 2H, 2-H, 2′-H), 7.06 (d, $J = 2.4$ Hz, 2H, 4-H, 4′-H), 7.22 (d, $J = 8.8$ Hz, 2H, 7-H, 7′-H), 7.77 (br s, 2H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 15.25 (C-12, C-12′), 21.49 (C-10), 64.43 (C-11, C-11′), 102.47 (C-4, C-4′), 111.89 (C-7, C-7′), 112.78 (C-6, C-6′), 115.45 (C-3, C-3′), 123.21 (C-2, C-2′), 128.17 (C-8, C-8′), 131.84 (C-9, C-9′), 153.25 (C-5, C-5′) ppm. IR (nujol): $\tilde{\nu}$ 3450, 3360 (NH), 3100–3000, 3000–2800, 1630, 1590, 1480, 1450, 1370, 1220, 1190, 1050, 950, 870, 790 cm^{-1}.

2.2. Crystallography

Crystals of **1** suitable for X-ray analysis were grown by slow evaporation from acetone solution. All details of the measurements, crystal data and structure refinement are given in Table 1. The data were collected on an Oxford Diffraction KM4CCD diffractometer [8] at 293 K, using graphite-monochromated MoK_α radiation. A total of 1072 frames were measured in six separate runs. The ω-scan was used with a step of 0.75°, two reference frames were measured after every 50 frames, they did not show any systematic changes either in peaks positions or in their intensities. The unit cell parameters were determined by least-squares treatment of setting angles of 3143 highest-intensity reflections selected from the whole experiment. Intensity data were corrected for the Lorentz and polarization effects [9]. The structures were solved by direct methods with the SHELXS97 program [10] and refined by the full-matrix least-squares method with the SHELXL97 program [11]. The function $\sum w(|F_o|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma^2(F_o)^2 + (0.0663P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. The coordinates of hydrogen atoms were calculated from the geometry and refined as a riding model with their thermal parameters calculated as 1.2 (1.5 for methyl group) times U_{eq} of the respective carrier carbon atom. The CCDC 619208 contain supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Table 1
Crystal data, data collection and structure refinement for **1**

Compound	**1**
Empirical formula	$C_{21}H_{22}N_2O_2$
Formula weight	334.41
T (K)	293(2)
Wavelength (Å)	0.71073
Crystal system, space group	Triclinic, $P-1$
Unit cell dimensions	
a (Å)	8.0728 (9)
b (Å)	10.995 (1)
c (Å)	11.697 (1)
α (°)	64.95 (1)
β (°)	71.31 (1)
γ (°)	80.80 (1)
Volume (Å^3)	890.6 (2)
Z, D_x (Mg/m^3)	2, 1.247
μ (mm^{-1})	0.081
F(000)	356
θ range for data collection (°)	3.31–26.50
hkl range	$-10 \leqslant h \leqslant 10$
	$-11 \leqslant k \leqslant 13$
	$-14 \leqslant l \leqslant 14$
Reflections:	
Collected	10,825
Unique (R_{int})	3672 (0.034)
Observed ($I > 2\sigma(I)$)	2468
Data/restraints/parameters	3672/0/226
Goodness-of-fit on F^2	1.050
$R(F)$ ($I > 2\sigma(I)$)	0.0470
$wR(F^2)$ (all data)	0.1293
Max/min. $\Delta\rho$ (e/Å^3)	0.155/−0.193

2.3. NMR spectra

^{1}H NMR and ^{13}C NMR spectra in solution were recorded with a Bruker Avance DMX 400, and standard Bruker software was employed. The solid state ^{13}C CP/MAS NMR spectra were measured using a Bruker Avance DMX 400. A powdered sample was spun at 10 kHz. Contact time of 2 ms, repetition time of 20 s, and spectral width of 24 kHz were used for accumulation of 3000 scans. Non-protonated carbons were selectively observed by dipolar-dephasing experiment with delay time 50 μs Temperature measurement was made with a Bruker B-VT 1000E unit. Chemical shifts δ [ppm] were referenced to TMS. The notation used in detailed description of NMR resonances is given in Scheme 1.

2.4. Molecular modeling details

Crystallographic atom coordinates were used for computation of shielding constants σ [ppm] of ^{13}C atoms to assign the double resonances in solid-state NMR spectrum. Conformation corresponding to a local minimum was also analyzed as most adequate in the analysis of solution spectra. We have employed DFT method with B3LYP/6-311** hybrid functional for calculations of geometries, and CHF-GIAO approach for shielding constants calculations [12].

3. Results and discussion

3.1. Chemistry

New 5,5′-diethoxy-3,3′-methanediyl-*bis*-indole **1** was prepared according to the procedure given by us in [1] and shown in Scheme 1. For unknown (*E*)-5-ethoxy-2-nitro-β-morpholinostyrene **1a** more detailed data are given. High purity 5-ethoxyindole **1b** was obtained in reductive cyclization process from **1a** with a higher, sharp melting point as compared with that obtained by previously published procedure [7]. Its structure was proved by spectroscopic methods.

3.2. ^{13}C CP/MAS NMR spectra of 1

The ^{13}C CP/MAS NMR spectrum of 5,5′-diethoxy-3,3′-methanediyl-*bis*-indole **1** in solid state at 298 K is shown in Fig. 1 together with the assignment of resonances. The single resonance observed for C10 atom is most consistent with an interpretation demanding the presence of only one molecule in the crystallographic independent unit, and double resonances of the remaining C atoms could be accounted for by the structurally distinct both indole systems of A and B in one molecule.

The spectra in the range of 298–358 K did not show any changes consistent with significant solid-state motions. As the temperature is increased the aromatic signals between 113.6 and 115.3 ppm assigned to C6, C6′ and C7, C7′ pairs of atoms merge becoming almost a singlet at 114.2 ppm, and two signals of C12, C12′ methyl carbons come closer. This could be indicative of small motions of ethoxy groups, and slight changes of the packing motif in the proximity of C6, C6′ and C7, C7′ atoms.

A comparison of solid state spectrum of **1** with the solid state spectrum of 5,5′-dimethoxy derivative **2** [1] reveals twofold multiplicity of resonances associated with C6, C6′ and C7, C7′ atoms in **1** which were not observed for **2**. This suggests crystallographic asymmetry contrasting with the structure of **2**.

The local minimum geometry computed at DFT level (with B3LYP/6-311G** functional) showed a symmetrical molecule with only a single set of calculated shielding constants for both indole rings and both ethoxy substituents. These data imply that the asymmetric intermolecular interactions in solid state differentiate the structure of even symmetrically substituted indole rings. The calculated shielding constants for optimized structure of **1** help us to assign of ^{1}H and ^{13}C resonances in solution spectra.

In order to properly assign the C atom resonances to A and B indole rings, DFT calculations (B3LYP/6-311** and CHF with GIAO approach) of ^{13}C shielding constants were carried out basing on the crystallographic atomic coordinates. Then the linear correlation between the computed shielding constants σ [ppm] and the experimental chemical shifts δ [ppm] was found with correlation coefficient $r^2 = 0.992$, and the resultant assignment is given in Fig. 1.

3.3. X-ray structure of 1

The molecular and crystal structure of **1** in solid state was analyzed by single crystal X-ray diffraction. Crystallographic data, together with data collection and structure refinement details are listed in Table 1. Selected bond lengths, bond angles and torsion angles are listed in Table 2. The displacement ellipsoid representation of the molecule, together with the atomic numbering scheme, is shown in Fig. 2 (the drawings were performed with a Stereochemical Workstation [13]).

The molecular structure of **1** is very similar to **2** [1]. Two ethoxyindole systems (A and B, see Fig. 2) are connected through a common C atom. Both indole moieties are quite planar and their planes make an angle of 68.92(4)°. The small tilts between the planes of the five-membered and six-membered rings are 4.38(8)° and 1.14(7)° in indoles A and B, respectively. The C10 atom is displaced from the mean plane of indole fragments by 0.089(2) and 0.052 Å for indole A and B, respectively. We have observed different conformations of the ethoxy groups. The disposition of these groups with respect to indole fragments can be described by the torsion angles C4–C5–O11–C11 of 12.1(2)° and C4′–C5′–O11′–C11′ of -1.7(2)°. In consequence the ethyl carbon atom C11 is found to be 0.364(3) and C12 0.571(3) Å out of the

Table 2
Selected bond lengths [Å] and angles [deg] and selected torsional angles [deg]

C3–C10	1.492 (2)
C3′–C10	1.508 (2)
C5–O11	1.379 (2)
C5′–O11′	1.382 (2)
O11–C11	1.419 (2)
O11′–C11′	1.421 (2)
C3–C10–C3′	115.5 (1)
C4–C5–O11	124.3 (1)
C4′–C5′–O11′	124.8 (2)
C2–C3–C10–C3′	−114.3 (2)
C4–C5–O11–C11	12.1 (2)
C3–C10–C3′–C2′	−4.8 (3)
C4′–C5′–O11′–C11′	−1.7 (3)

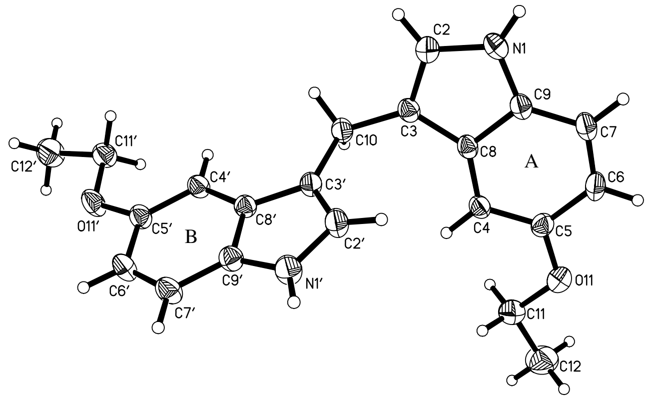


Fig. 2. The molecular structure of **1** with 30% probability displacement ellipsoids and the atom-numbering scheme.

indole A plane, the other ethyl carbon atom C11′ is found to be only 0.023(3) and C12′-0.001 Å out of the indole B plane. So, the results show a different structure of both ethoxyindole fragments of the molecule. We have also observed such differences of the configuration of methoxyindole systems for **2**, and in both cases those different packing modes of both indole systems could be the reason for double resonances in the solid-state NMR spectra.

As opposed to the above findings, the crystal structure of **1** is quite different as compared with **2**. In the case of derivative **1**, we have not observed any interaction between NH or CH groups and π-electron systems of indole rings, which are present in **2** and other *bis*-indole derivatives [1,2,5]. Only intermolecular hydrogen bonds N–H···O determine the crystal packing of the molecules. They form infinite chains (Fig. 3) parallel to the [−1 0 1] direction *via* intermolecular hydrogen bonds N1–H1···O11′ ($x-1, y, z+1$). The geometric parameters are: the N1···O11′ distance is 2.976(1) Å, H1···O11′ 2.17 Å and the angle N1–H1···O11′ is 156°.

4. Conclusions

Small changes in composition of the studied *bis*-indoles, an exchange methoxy group to ethoxy one, introduced more significant differences in the crystal arrangement. The longer ether chains prevent the formation of

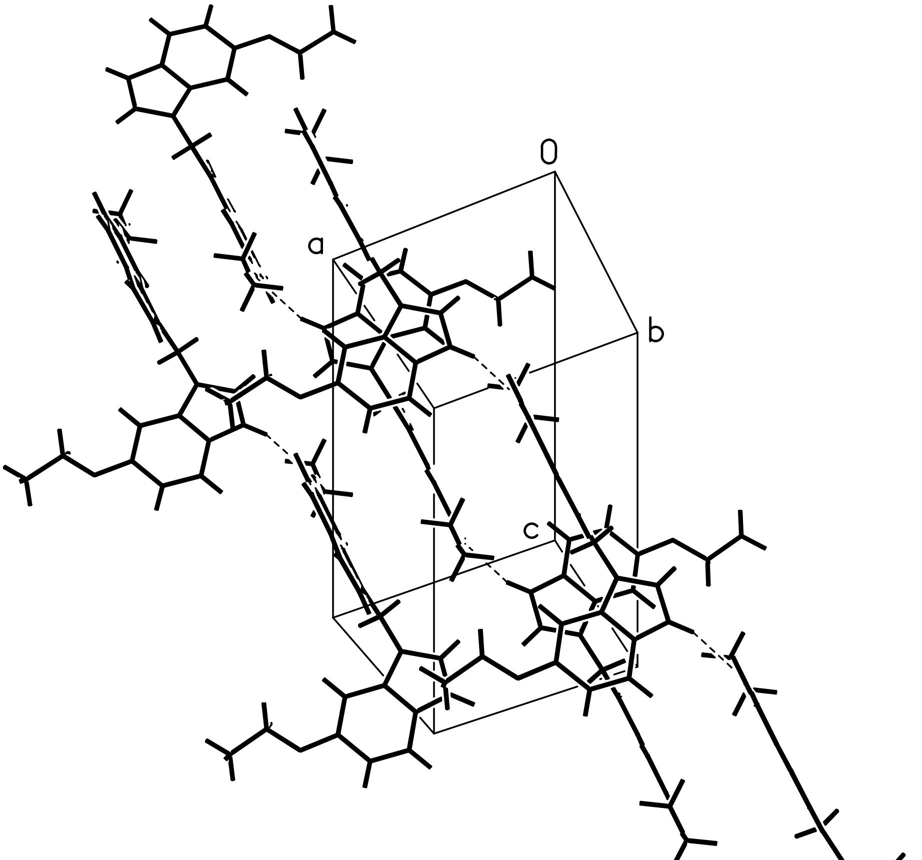


Fig. 3. Infinite chains of the molecules of **1**.

N–H···π impact, which could alter their interactions with biological target. Only a single chain of intermolecular hydrogen bonds between N1–H1···O11′ was revealed in the crystal.

Double resonances in ^{13}C CP/MAS NMR spectrum of **1** do not arise from the presence of two conformers in solid state, but from a different packing mode of both indole systems.

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