THE ATROPOISOMERISM OF HIGHLY SUBSTITUTED 1-PHENYLPYRROLES. CASE STUDY

Marcel Mirel POPA[1*], Constantin DRĂGHICI[2], Florea DUMITRAŞCU[3], Emilian GEORGESCU[4], Florentina GEORGESCU[5], Florin BADEA[6]

Atropoisomerism of 1-phenylpyrroles is an interesting property and could be of interest regarding chirality and applications of such compounds. Herein is synthesized and studied a highly substituted 1-pehnylpyrrole with the aim to study both experimentally and by computational method the rotation energy barrier about the C-N bond. The hindered rotation around the C-N bond is due to the bulky susbtituents on the pyrrole or the phenyl ring. The value of the rotation energy barrier is important for further optical resolution of such kind of compounds.

Keywords: 1-phenylpyrrole, energy barrier, hindered rotation, NMR, atropisomerism

1. Introduction

Pyrroles are building blocks of many natural compounds of high relevance being porphirins which are found in two of the most important structural motifs of life: chlorophyll and hemoglobin. Among the class of pyrroles are of particularity the 1-phenylsubstituted pyrroles (Fig. 1**)** which present very interesting physicochemical properties being known as belonging to the class of twisted intramolecular charge transfer (TICT) molecules [1].

The degree of substitution of such kind of compounds could provide a useful strategy towards compounds with enhanced biological activity as for example antimicrobial and antifungal properties [2-4], anti-HIV [5,6] and anti-cancer cell lines activity [7].

[1]PhD Student, Faculty of Applied Chemistry and Materials Science, University POLITEHNICA of Bucharest/Center of Organic Chemistry "C. D. Nenitzescu", Romanian Academy, Bucharest, Romania, e-mail: mirelupb@gmail.com
[2] Senior Researcher, Center of Organic Chemistry "C. D. Nenitzescu", Romanian Academy, Bucharest, Romania
[3] Senior Researcher, Center of Organic Chemistry "C. D. Nenitzescu", Romanian Academy, Bucharest, Romania
[4] Senior Researcher, Oltchim Research Center, str. Uzinei, Ramnicu-Valcea, Romania
[5] Senior Researcher, Oltchim Research Center, str. Uzinei, Ramnicu-Valcea, Romania
[6] Professor, Department of Organic Chemistry, Faculty of Applied Chemistry and Materials Science, University POLITEHNICA, Bucharest, Romania

Due to increasing importance of the chiral ligands in the domain of medicinal chemistry the atropoisomerism of 1-phenylpyrroles could be of great importance and was intensively studied [8-12]. The atropoisomerism of 1-phenylpyrroles is a cause of the hindered rotation around the C-N bond due to the bulky substituents which may be grafted on the phenyl or pyrrole ring (Fig. 1).

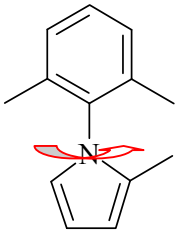


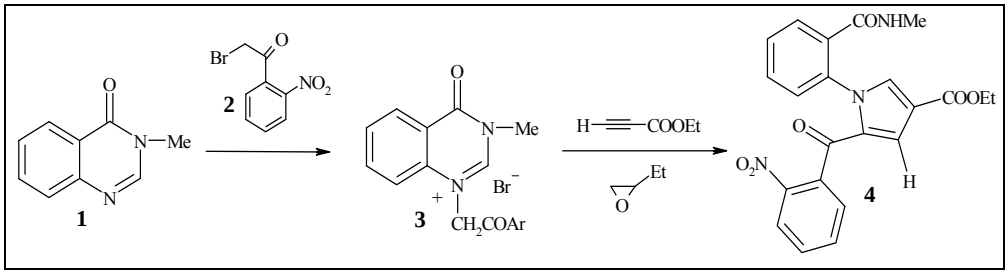
Fig. 1. The hindered rotation along the C-N bond caused by bulky substituents

Herein is synthesized and studied a highly substituted 1-phenylpyrrole by two step method we already developed [13,14]. The atropoisomerism of this compound will be studied both by experimental and computational methods calculating the rotation barrier around the C-N bond.

2. Discussion

2.1 Synthesis of the title compound

The synthesis of the compound for study was achieved efficiently by two-step synthesis presented in Scheme 1. This synthesis proved to be very efficient in obtaining of large libraries of 1-phenylpyrroles [13]. Thus by reacting the bromide salt, obtained previously from quinazolinone **1** and bromoacetophenone **2**, with ethyl propiolate in 1,2-epoxybutane the highly substituted pyrrole **4** was obtained in yield of 70%. The use of the ethyl propiolate is explained by the fact that in our previous reports we observed that in NMR spectra of some pyrroles the methylenic protons in the ethyl groups were characterized by unusual splitting of the signals which are a cause of the magnetic non-equivalence of these protons due to the hindered rotation around the C-N bond. Thus the presence of the ethyl group is necessary.



Scheme 1

The structure of the pyrrole was assigned by NMR spectroscopy. Thus the characteristic doublets corresponding to the hydrogen in the pyrrole ring appear in expected ranges with J = 1.6 Hz. The aromatic protons appear superimposed and could be assigned by COSY and HETCOR experiments. Also the methyl group appears as a doublet while the NH proton appears as a quartet at 6 ppm, with J = 4.9 Hz. All the ^{13}C signals appear as expected and confirm the proposed structure.

2.2 Calculation of the energy barrier of rotation

In the first case the energy barrier of rotation was computed for a similar structure previously reported by our group [13], by using Gaussian03 software [15] and using the X-ray structure as starting structure for the geometrical optimization. The .cif file deposited at the Cambridge database was used and first geometrical optimization was made in Hyperchem [16] at AM1 empirical method. This structure was exported to Gaussian03 and both the geometrical optimization and further calculation were made using the PM3 method.

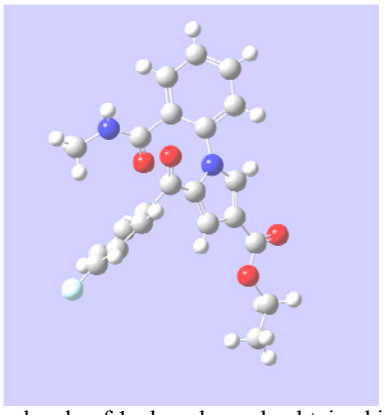


Fig. 2. The optimized molecule of 1-phenylpyrrole obtained in a previous work [13]

The energy barrier was calculated in relaxed coordinates varying the angle between 0 and 360°. In this preliminary study the computed energy barrier was evaluated at a value of ~17 kcal/mol.

It was interesting to see what will happen if the aroyl moiety grafted at position 2 on the pyrrole ring will be substituted in *ortho* position with a relatively bulky instead of the *para* susbtituent as the previous case. Thus the pyrrole **4** was synthesized and its NMR spectrum was recorded at different temperatures with the aim to experimentally determine the rotational energetic barrier around the C-N bond. Below is presented the NMR at 300 MHz spectra of pyrrole **4** recorded at 26.5°C.

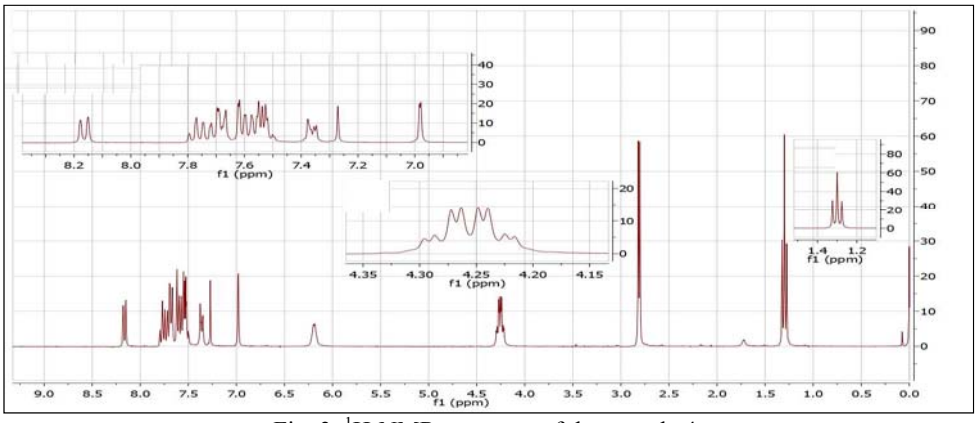
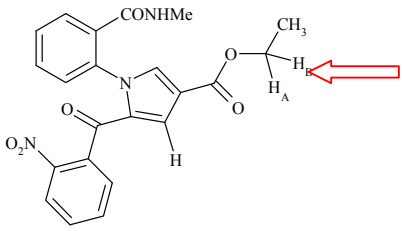


Fig. 3. ^{1}H-NMR spectrum of the pyrrole 4.

The chemical shift of the signals for the two protons H_A and H_B was made directly on the NMR spectrum with assistance of a simulated spectrum by using



Spinworks [17]. It is noteworthy to mention that some degree of approximation was made for the calculation of K_c (the rate constant at coalescence) and subsequently $\Delta G^{\#}$ was obtained by using the equations (1), (2) and (3) [18].

$$K = k_B \cdot \frac{T}{h} \cdot e^{\frac{(\Delta G^{\#})}{(RT)}} \quad (1)$$

$$\Delta G^{\#} = 4.576 \cdot T \cdot \left(10.319 + \log\frac{T}{K}\right) \quad (2)$$

$$K_c = \pi \cdot \frac{\sqrt{(\Delta\nu^2 + J^2)}}{\sqrt{2}} \quad (3)$$

K-rate constant
$K_b = 1{,}381*10^{-23}$ J/°C Boltzmann constant
T-temperature in Kelvin
$h = 6{,}6261*10^{-34}$ J*s Plank constant
R = 1.986 cal/K Gas constant
K_c-rate constant at coalescence (s^{-1})
J – coupling constant of the geminal AB system (Hz)

Usually such kinds of calculations are made by using simulated spectra at different rate constants and compare them with the experimental spectra. Below can be seen the experimental spectra of the pyrrole **4** at different temperatures. The coalescence temperature is usually calculated by linear regression from the experimental values but in this case was observed directly on the NMR spectra. The multiplet generated by the vicinal coupling (J_{HAHB} ~ 10 Hz) coalesces at 50 °C into a quartet with coupling constant of 7.1 Hz corresponding to a normal multiplicity for a methylene in the ethyl group (quartet-CH_2, triplet-CH_3).

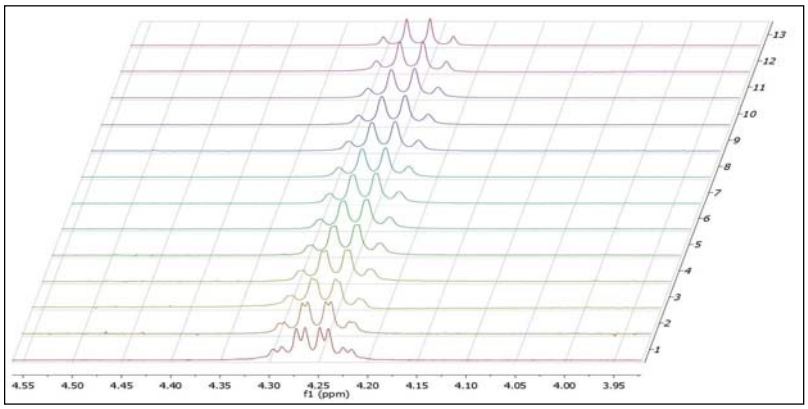


Fig. 4. The spectra of **4** at different temperatures-the signal of the methylene protons. **1**:26.5 °C; **2**:30 °C; **3**:38 °C; **4**:40 °C; **5**:41 °C; **6**:42 °C; **7**: 43 °C; **8**:43.5 °C; **9**: 46 °C; **10**: 47 °C; **11**:48 °C; **12**:50 °C; **13**:62.5 °C.

The value of $\Delta G^{\#}$ = 17 kcal/mol was determined from the experimental study for a rate constant of 29.9 s^{-1} and $\Delta\nu^2$ of ~9 Hz. Experimentally $\Delta G^{\#}$ represents the best estimate of the energy barrier of hindered rotation.

The value of the rotation energy barrier was computed also using Gaussian03. The molecule geometric optimization was made at PM3 level.

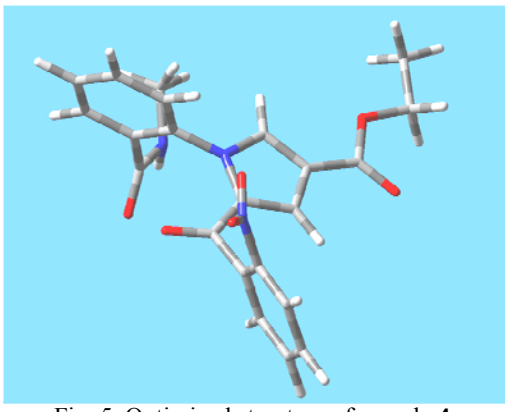


Fig. 5. Optimized structure of pyrrole **4**

The calculation of the rotational barrier was made by scanning the energy of the conformers when the dihedral angle between the pyrrole ring and the phenyl ring was incremented with 10 degrees between 0^o and 360^o in relaxed coordinates. The rotational barrier was calculated by difference between the energies of the highest energy conformer and the lowest one.

The calculated value of the barrier energy of rotation is 20 kcal/mol.

The calculated energy barrier value is slightly greater than expected and calculated for the pyrrole previously obtained [13] but in accordance with reported data from literature [12]. Maybe the presence of the nitro group in *ortho* position induces a higher degree of steric hinderance. To test that the dihedral was incremented in 10^o steps, kept frozen and the rest of the molecule was optimized. For angles between 120 and 180^o the geometric optimization failed and it was visually observed that the nitro group in the ortho position on the benzoyl moiety and the amide group are sterically congested. It can be also observed that the ethyl group lies in the plane of the pyrole ring, fact which was observed also in the X-ray data for such types of compounds [13].

It is noteworthy that energy of activation E_a of the free rotation was not computed due to the lack of spectral simulations for obtaining accurate rate constants values to be used in the Arrhenius Plot. $\Delta G^{\#}$ is a good approximation but must keep in mind that is not equal E_a. The present study gives an overview of such calculations and measurements and opens the way for more detailed and insightful studies regarding the atropoisomerism of these 1-pehylpyrroles.

3. Experimental

General

Melting point was determined on a Boëtius hot plate and is uncorrected. The IR spectrum was recorded on FT-IR Bruker Vertex 70. The NMR spectrum was recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C.

*General procedure for obtaining the compounds **3** and **4***

Bromide salt **3**: The quinazolinone **1** and bromoacetophenone **2** were stirred under reflux in ethanol for 2 hours. The precipitate obtained was removed by filtration and used further without purification

Pyrrole **4**: 5 Mmol of quinazolinium salt **3**, 7 Mmol of ethyl propiolate were kept under stirring at reflux for 24 hours in 10 mL 1,2-epoxybutane. After the solvent was partly removed by evaporation, 10 mL of ethanol were added and the mixture was left over night at room temperature. The solid was filtered, washed with a small quantity of cold ethanol and was crystallized from a suitable solvent.

Ethyl 1-(2-methylaminocarbonylphenyl)-2-(2-nitrobenzoyl)pyrrole-4-carboxylate (**4**). Colorless crystals with mp 149-151 ºC were crystallized from ethanol; Yield 87%. Anal. Calc. $C_{22}H_{19}N_3O_6$: C 62.70, H 4.54 N 9.97. Found: C 63.01, H 4.82 N 9.76. IR (ATR, cm^{-1}): 1256, 1524, 1649, 1704, 2935, 3086, 3286; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.30 (t, 3H, *J* = 7.1 Hz, $MeCH_2$); 2.81 (d, 1H, *J* = 4.9 Hz, MeNH); 4.26 (sext, 2H, *J* = 9.5, 7.1 Hz, CH_2); 6.20 (q, 1H, *J* = 4.9 Hz, NH); 6.98 (d, 1H, *J* = 1.6, H-5); 7.34-7.37(m, 1H, H-6"); 7.49-7.55 (m, 5H, H-4", H-5"); 7.57-7.60 (m, 1H, H-5'); 7.61 (d, 1H, *J* = 1.6, H-3); 7.66-7.69 (m, 1H, H-3"); 7.74-7.79 (m, 2H, H-4', H-5'); 8.15-8.18 (m, 1H, H-3'); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.4 ($MeCH_2$); 26.8 (MeNH); 60.6 (CH_2O); 117.7 (C-4); 123.1 (C-3); 124.9 (C-3'); 127.8, 128.6, 129.4, 129.7, 130.6 (C-6', C-3", C-4", C-5", C-6"); 132.1, 134.0, 136.1 (C-2, C-1", C-2",); 133.8 (C-4'); 130.8, 135.1 (C-1', C-5'); 136.4 (C-5); 147.2 (C-2'); 163.2 (COO); 167.6 (CONH); 183.1 (COAr).

4. Conclusions

In summary, the synthesis of a new N-arylpyrrole was performed with the special aim to study both experimentally and theoretically the energy barrier of rotation around the C-N bond. This is a tipical case of atropoisomerism caused by a hindered rotation. The obtained value for the rotation energy could assume that the two rotation stereoizomers could not be separated by ordinary methods.

Acknowledgements

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