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NMR STUDIES ON THE RESTRICTED ROTATION OF 1-[2-(1-PHENYL)PROPYL]-2,5-DIMETHYLPYRROLE DERIVATIVES

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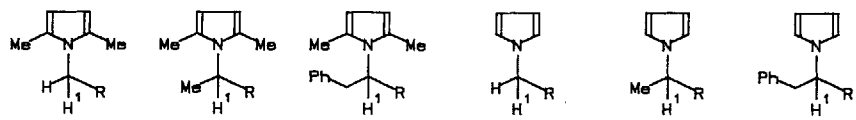
ABSTRACT

From the ^{1}H-NMR spectra of the various pyrrole compounds, 1- substituted 2,5-dimethylpyrroles having two substituent groups on the carbon adjacent to the nitrogen atom were found to be very much hindered compounds. 1-[(1-Substituted)-2-phenylethyl]-2,5-dimethylpyrroles showed the restricted rotation, and the phenyl group of the most stable conformer was in close proximity to the pyrrole group due to dipole interaction. These NMR observations were supported by force field conformational analysis.

Previously, we have investigated the utility of the pyrrole ring as a protecting group of N-terminals in peptide synthesis.[1] In the course of these investigations, we prepared a large number of pyrrole compounds, especially 1-substituted pyrroles. When the NMR spectra were measured in order to ascertain their structures, some unexpected phenomena were incidentally observed in the ^{1}H-NMR spectra of 1-substituted 2,5-dimethylpyrroles (**1**, **2**, and **3**) compared with those of 1-substituted pyrroles (**4**, **5**, and **6**).



(1) (2) (3) (4) (5) (6)

a: R=H b: R=Me c: R=CH_2Ph d: R=CH_2OH
e: R=CH_2OMe f: R=CO_2H g: R=CO_2Me h: R=CHO

First of all, the methine proton adjacent to pyrrole nitrogen (H-1) of 1-substituted 2,5-dimethylpyrroles (**2**) appeared at about 0·1 ppm lower field than those of analogous pyrroles (**5**) as summarized in Table 1. On the contrary, the methylene signals of **1** appeared at 0·1 ppm higher field than those of pyrrole analogues **4**. Namely, the larger anisotropic effect of dimethylpyrrole ring was observed in the case of **2** compared with the case of **1**. This fact indicated that the H-1 proton and the pyrrole ring should be coplanar in the case of **2**. Since

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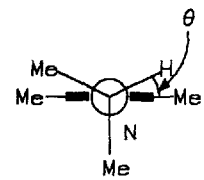
Table 1. ^{1}H-NMR Signals of H-1 for **1**, **2**, **4**, and **5**

R	4	1	4 − 1	5	2	5 − 2
H	3·63	3·35	0·28			
Me	3·90	3·77	0·13	4·23	4·39	−0·16
$PhCH_2$	4·07	3·89	0·18	4·22	4·35	−0·13
CO_2H	4·61	4·51	0·10	4·77	4·88	−0·11
CO_2Me	4·60	4·47	0·13	4·75	4·84	−0·09

Table 2. The potential energy and the rotational angle (θ) in **2b** by force field calculation



Rotational Angle (°)	Potential Energy (kcal/mol)
0	0
30	9·8
60	16·0
90	330·5

this was expected to be caused by the steric interaction between the two α-methyl groups on the pyrrole ring and the two substituent groups on the carbon (C-1) adjacent to nitrogen atom, the conformational analysis of 1-(2-propyl)-2,5-dimethylpyrrole (**2b**) was undertaken using force field calculation. The results in Table 2 supported that the methine proton of **2b** was located on the plane of the pyrrole ring in the most stable conformation.

Secondly, an unexpected ^{1}H-NMR spectrum was observed in the case of 1-[2-(1-phenyl)propyl]-2,5-dimethylpyrrole (**3b**), compared with that of 1-(2-propyl)-2,5-dimethylpyrrole (**2b**). Compound **3b** is the phenyl substituted analog of **2b** on the terminal methyl group. The α-methyl signal of **3b** appeared at δ 2·16 ppm, while that of **2b** appeared at δ 2·27 ppm. Since the α-methyl group was separated by 4 atoms, the inductive effect of the phenyl group should be negligible at the α-methyl group. Therefore, this higher field shift indicated that the methyl groups on the pyrrole ring were susceptible to the anisotropic effect of the phenyl group through space.

Moreover, the α-methyl signals on the pyrrole ring of **3b** were found to be very short in their peak height and rather broad. A lowering of the temperature caused the splitting of this signal and two sharp singlet signals at δ 2·50 and 1·93 ppm were observed at −50 °C. Also the singlet signal of the β-protons on the pyrrole ring appeared at δ 5·71 ppm at room temperature, while a pair of doublets of β-protons were observed at δ 5·84 and 5·69 ppm at −50 °C. The signals other than those of the α-methyl groups and β-protons on the pyrrole ring were not changed by

Table 3. ^{1}H-NMR Data on the pyrrole ring of **2**, **3**, **5** and **6**

Compound	R	δ_α (ppm)	δ_β (ppm)	Coalescent Temperature (K)	$\Delta G^{\ddagger}$ (kcal/mol)
2a	H	2·20	5·74	**	—
2b	Me	2·27	5·72	**	—
2d	CH_2OH	2·25	5·73	**	—
2f	CO_2H	2·20	5·78	**	—
2g	CO_2Me	2·17	5·77	**	—
2h	CHO	2·16	5·83	**	—
3a	H	2·09	5·75	*	—
3b	Me	2·17	5·71	273	15·8
3d	CH_2OH	2·14	5·71	288	16·8
3e	CH_2OMe	2·09	5·68	298	17·2
3f	CO_2H	2·00	5·74	243	13·9
3g	CO_2Me	1·95	5·72	233	13·4
3h	CHO	1·91	5·79	**	—
5a	H	6·64	6·12	**	—
5b	Me	6·71	6·13	**	—
5f	CO_2H	6·72	6·19	**	—
5g	CO_2Me	6·73	6·17	**	—
5h	CHO	6·70	6·26	**	—
6a	H	6·57	6·11	*	—
6b	Me	6·62	6·10	*	—
6d	CH_2OH	6·67	6·14	*	—
6f	CO_2H	6·67	6·14	**	—
6g	CO_2Me	6·70	6·13	**	—

* No coalescent point was observed.
** Not measured.

the temperature reduction. From these phenomena, the two isomers should reach equilibrium rather slowly when compared with the NMR time scale. Thus the activation free energy $\Delta G^{\ddagger}$ of this conversion was evaluated to be 15·8 kcal/mol from the coalescent temperature of 0 °C. Similarly 1-[(1-substituted)-2-phenylethyl]-2,5-dimethylpyrroles (**3**), the analogs of **3b**, showed the α-methyl peaks at higher field. Also, the coalescent temperatures were observed in the cases of **3c–3h** by the ^{1}H-NMR measurement at various temperatures, summarized in Table 3. Table 3 indicates that substrates possessing a bulky substituent group on the carbon (C-1) adjacent to the pyrrole nitrogen showed a higher $\Delta G^{\ddagger}$. On the other hand, neither the corresponding 2,5-unsubstituted pyrroles (**6**) nor 1-(2-phenylethyl)-2,5-dimethylpyrrole (**3a**) showed any change in their ^{1}H-NMR spectra, even at an extremely low temperature of −90 °C. In addition, **3b** did not possess any C=C or C=O double bond functionality, or more than two asymmetric carbons. From these facts, the structural conversions were not based on stereoisomerism, tautomerism or geometrical isomerism, but on the restricted rotational isomerism. Since the H-1 proton signal of **3b** appeared at δ 4·35 ppm without any change of the signal shape and chemical shift by the temperature reduction, the bond-rotation along the C-1 and N bond was suggested to be frozen even at room temperature with the C-1 and H-1 bond coplanar with the pyrrole ring. Furthermore, from the fact that α-methyl protons on the pyrrole ring appeared at higher field by the anisotropic effect of the phenyl group and that the methylene protons adjacent to the phenyl group appeared as a double AB quartet with J= 13·2 Hz, these conversions could arise from the restricted rotation along the bond between C-1

and C-2 on the 1-substituent group, and the pyrrole ring should be spatially close to the phenyl plane in the most stable conformer of 1-[(1-substituted)-2-phenylethyl]-2,5-dimethylpyrroles (**3**).

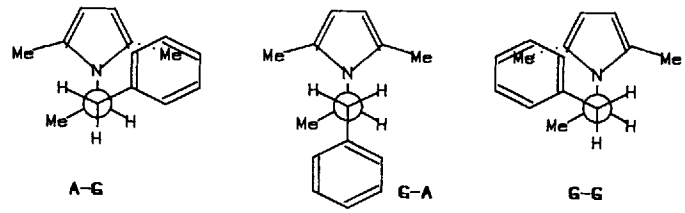


Figure 1

Here, three conformers **A–G**, **G–A** and **G–G** in Figure 1 were speculated to be the most stable ones. Since the phenyl group had one pyrrole on the *anti* position and one methyl on the *gauche* position, the **G–A** conformer should include a small *gauche* repulsion. In the case of the **A–G** conformer, the phenyl group is located on the *gauche* position from the pyrrole group and on the *anti* position from the methyl group. Therefore, the interaction between the pyrrole and phenyl groups should be the main contributors. However, Barton reported that pyrrole interacted with benzene due to dipole interaction.[2] This interaction was similarly observed in the case of 1,2,5-trimethylpyrrole (**1a**) from the fact that the ^{1}H-NMR signals in $CDCl_3$ were remarkably shifted in C_6D_6. Although both the pyrrole and phenyl group were bulky, the approach of the two groups should cause energy stabilization by dipole interaction.

On the other hand, the phenyl group of the **G–G** conformer is located at the *gauche* position from either the pyrrole or methyl group, and affected either the *gauche* repulsion from the methyl group or the interaction from the pyrrole group. As mentioned before, the plane of the pyrrole ring was fixed on the plane consisting of the H–1, C–1 and nitrogen atoms in the cases of 1-substituted 2,5-dimethylpyrroles having the two substituent groups on C–1. Thereby, in

Table 4. The potential energy with the rotational angle between C-1 and C-2 in **3b** by force field calculation

Rotational Angle* (°)		Potential Energy (kcal/mol)
30		2.5
45		0
60	**(A–G)**	0·6
75		3·2
90		4·2
105		4·3
120	(Eclipsed)	4·3
150		2·3
165		1·9
180	**(G–A)**	4·1
300	**(G–G)**	1165

*For the energy minimization, the rotational angle between C-2 and the phenyl group was approximately given in the range of 45° to 135°.

the **G–G** conformer of **3**, the α-methyl group on the pyrrole ring was in close proximity to the phenyl group, and a large non-bonding repulsion should be additionally expected.

After all, the most stable conformer could be the **A–G** form, where the phenyl group caused a higher field shift of ^{1}H–NMR signals on the pyrrole ring by the anisotropic effect of the benzene ring. In order to support the above speculations, the energies of each conformer of **3b** were evaluated by force field calculations. The results are summarized in Table 4, in which the **A–G** conformer was the most stable and the **G–A** conformer was 2 kcal/mol less stable. The **G–G** conformer showed an extremely large steric hindrance between the α-methyl and phenyl groups, and would be impossible to exist. Furthermore, the rotational barrier between **A–G** and **G–A** conformers was evaluated to be more than 4 kcal/mol in the eclipsed form. Although the rotational barrier was underestimated by force field calculation, the detection of the conformers by restricted rotation was suggested to be possible.

In conclusion, the 1-[(1-substituted)-2-phenylethyl]-2,5-dimethylpyrroles (**3**) were very hindered compounds, and the bond rotation between C–1 and C–2 was observed to be restricted by means of ^{1}H–NMR. Further, the ^{1}H–NMR spectra gave the conclusion that the phenyl group of the most stable conformer was in close proximity to pyrrole group due to dipole interaction.

EXPERIMENTAL

The ^{1}H–NMR spectra were taken on JEOL-100 spectrometer, in deuteriochloroform solution using TMS as an internal standard. In the case of the measurement below −60 °C, deuterated methanol was used as a solvent. Since the CAMSEQ-II program was about two orders of magnitude faster including the parameters of hetero atoms,[3] the force field conformational analyses of the pyrrole compounds were calculated based on the coordinated of the pyrrole ring[4] using the MFO program[5] which was a modified program from CAMSEQ-II.

Materials.

The 2,5-dimethylpyrrole compounds were prepared mainly by the condensation of the corresponding amino compounds with 2,5-hexanedione, and the 2,5-unsubstituted pyrrole compounds were prepared by the reaction of the corresponding amino compounds with 2,5-dimethoxytetrahydrofuran.[1] Since the use of the restorative 1-phenyl-2-propylamine is restrained, 1-[2-(1-phenylpropyl)]pyrroles (**3b** and **6b**) were prepared from the corresponding 1-[2-(1-phenyl-3-hydroxypropyl)]pyrroles (**3d** and **6d**) by tosylation and lithium aluminium hydride reduction.

1-[2-(1-Phenyl)propyl]-2,5-dimethylpyrrole (**3b**). Bp 70 °C (4mmHg); IR ($CHCl_3$) 1500, 1450, 1400, 1300, and 700 cm^{-1}. Analyses calculated for $C_{15}H_{19}N$: C, 84·45; H, 8·97; N, 6·56. Found: C, 84·30; H, 9·04; N, 6·54 %.

1-[2-(1-Phenyl)propyl]pyrrole (**6b**). Bp 60 °C (4mmHg); IR ($CHCl_3$) 1490, 1450, 1270, 1090, and 700 cm^{-1}. Analyses calculated for $C_{13}H_{15}N$: C, 84·27; H, 8·16; N, 7·56. Found: C, 84·28; H, 8·19; N, 7·48 %.

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