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β-SILYLATION OF N-ALKYLPYRROLES, EXPERIMENTAL SUPPORT OF THEORETICAL CALCULATIONS

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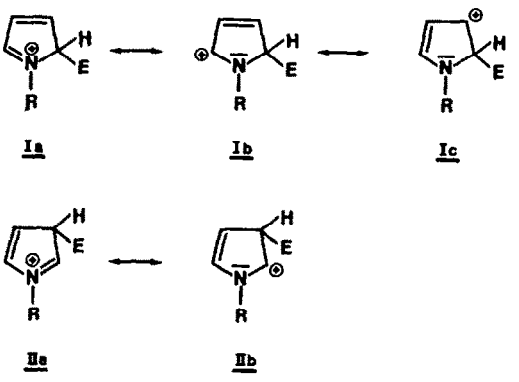
Abstract - The β-substitution of N-alkylpyrroles which is "unusual" but predicted by theoretical calculations, was supported by the ^{1}H-NMR and GC/MS analysis of the reaction products of 1-methylpyrrole-2,5-d_2 (1a) with trimethylsilyl trifluoromethanesulfonate (2) in triethylamine (3). Thus, 1a gives with 2 in 3 predominantly the β-isomer 5b (two deuteriums) and small amounts of the α-isomer 4a (one deuterium). The formation of these products of such a deuterium distribution evidently supports the results of theoretical calculations which indicate that the electron density is the major factor controlling the electrophilic substitution of N-alkylpyrroles with hard electrophiles. The thermodynamic stability of the α-substituted form I (Scheme 1) is assumed to be the second factor governing this reaction, since the α ⇌ β isomerization was conclusively ruled out.

Electrophilic substitution of the pyrrole ring remains a challenging problem, which still is not completely answered. Almost all experimental evidences of these reactions carried out in solution[2] have shown that pyrrole and its N-alkyl derivatives are substituted at the α-carbon[3]. This has been explained by resonance stabilization or delocalisation of the positive charge in the intermediate cation (Scheme 1)[4]. On the other hand, theoretical calculations of several kinds such as: semiempirical, "ab initio"[5] or molecular electrostatic potentials[6] indicate greater electronic charge at the β-carbon than at the α-carbon. Very recent calculations carried out by Yanez and Catalan[7] in which the linear correlations between gas-phase proton affinities and 1s "ab initio" orbital energy computations were compared (a procedure which gives the intrinsic basicities), have shown that the β-position in pyrrole from the kinetic point of view is the preferred site of protonation.

According to these calculations, the α-protonated form should be thermodynamically more stable. The experimental evidence for the preferred formation of the α-isomers was explained by a subsequent $C_\beta \rightarrow C_\alpha$ isomerization.

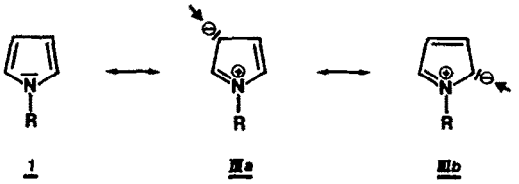
In the electrophilic substitution of 1 two canonical forms I and II can be considered as potential sites of attack.

According to the above mentioned calculations, the greater negative charge is located on the β-carbon, i.e. at the hard center, and with hard electrophiles at this center the attack should take place. The α-position on the other hand is the softer position. Additionally, after substitution, the formed adduct is better stabilized by resonance, i.e. it is thermodynamically more stable (see scheme 1).



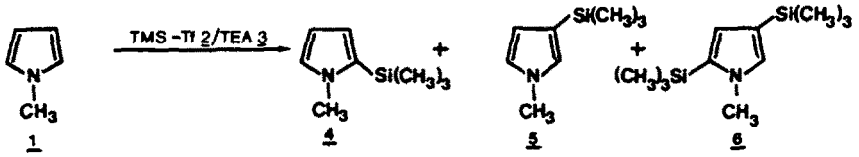
R = H, alkyl

Scheme 1



Scheme 2

The assumption finds support in the gas-phase alkylation of pyrroles 1. The formation of the less abundant α-isomer was explained by subsequent isomerization of the β-substituted intermediate of type II to the thermodynamically more stable α-analogue of type I (Scheme 1)[8]. In the chemical literature, there are also some examples of α to β isomerizations catalyzed by acids[9]. In the course of our studies in the silylation of heteroaromatics with trimethylsilyl trifluoromethanesulfonate (2), we have found that this reagent with 1-methylpyrrole (1) in triethylamine (3), gives predominantly 1-methyl-3-trimethylsilylpyrrole (5) (83% GC), 1-methyl-2-trimethylsilylpyrrole (4) (8% GC), and 1-methyl-2,4-bis-trimethylsilylpyrrole (6) (8% GC) (10).



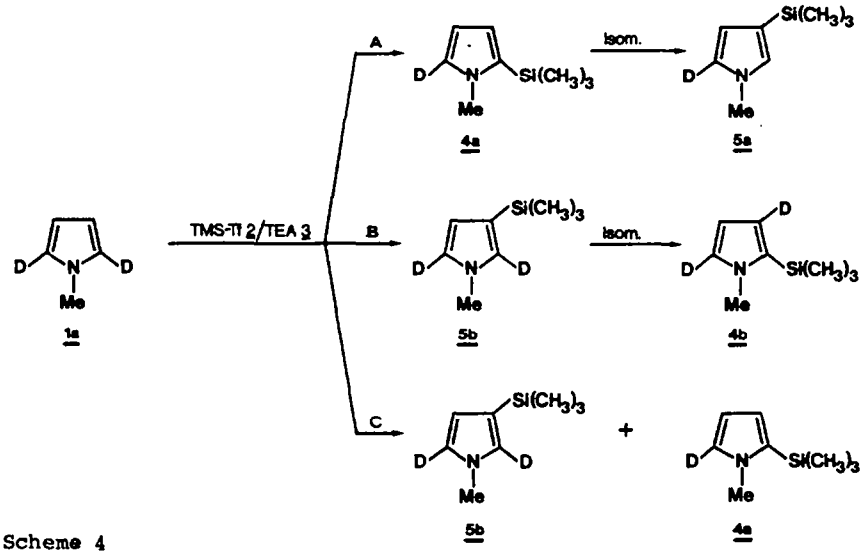
Scheme 3

In order to shed new light on the mechanism of the electrophilic substitution of N-alkyl pyrroles, we carried out the same reaction with 1-methylpyrrole-2,5-d_2 1a. By using the nondeuteriated methylpyrrole 1, we were able to show that electrophilic substitution takes place predominantly on the β-carbon in agreement with theoretical calculations. Nevertheless, the following question remained open:

A. Does the electrophilic attack take place at the α-position with the β-substituted product 5 being formed as a result of intramolecular isomerization (Scheme 4),

B. does the electrophilic attack take place directly on the β-carbon with the mi-

nor α-product 4 resulting from partial rearrangement
C.or is there "independent" electrophilic substitution at both centers predominantly on the β-carbon via electron density control and to a lesser extent on the α-carbon via transition state control.



Scheme 4

If the β-isomer 5a is formed according to path A, then the ^{1}HNMR spectrum should have shown two different kinds of protons (two doublets) of equal intensity, similar to the α-isomer 4a . The total intensity of the two doublets should have been two thirds of the N-methyl singlet. In contrast, the β-isomers formed by path B and C 5b should have given rise to only one singlet of one third intensity as compared to the N-Me singlet. However, the α-isomers 4a,4b should have differed significantly giving rise to a singlet for 4b and two doublets for 4a. The relative intensities of these protons should have been different as well.
The ^{1}HNMR spectrum of the starting dideuteriopyrrole 1a shows almost complete exchange of the α-protons by deuteriums. The β-protons give rise to one singlet (δ,6.13) with intensity approximately two thirds that of the N-Me singlet (δ,3.63). The residual α-protons are seen as a very small triplet at 6.60 ppm.
The ^{1}HNMR spectrum of the main fraction (65-67°/12 mm Hg) consisting of 90% of the β-isomer 5 and 10% of the α-isomer 4 exhibits two sets of signals corresponding to isomers 4 and 5.
Isomer 5 gives rise to one singlet (δ,6.20) whose intensity is only one third of the N-Me singlet at 3.60 ppm, and one singlet at 0.19 ppm for the TMS group.
The ring protons of the α-isomer 4 give rise to two doublets at 6.35 and 6.13 ppm (J=3.8 Hz). Their summed integral corresponds approximately to two thirds of the 3.69 ppm N-Me singlet. The TMS group resonants as a singlet at 0.28 ppm. Due to the decrease of the intensity of the largest peak at δ = 6.20 (β-protons), the relative intensity of the undeuteriated species at 6.60 ppm doubles. These spectral changes rule out mechanism A, since when the intensity ratio of the ring protons in 5 (singlet at 6.20 ppm) is twice reduced, no new signal of comparable intensity in the aromatic region appears. Although path B (Scheme 4) leads to the same isomer 5 as path C, these two paths differ when isomers 4 are compared. The presence of two small doublets at 6.35 and 6.13 ppm in the ^{1}HNMR spectrum clearly indicates that only isomer 4a is present. This allows us to rule out mechanism B, in which subsequent isomerization (proton transfer) takes place.
Isomers 4 differ by one in their molecular masses. The GC/MS analysis gives mole-

cular mass 155 for the more abundant isomer 5 and 154 for the lesser abundant isomer 4. Isomers 4a and 5b can only be present together if the reaction follows the path C (Scheme 4). Such a product distribution undoubtedly indicates that electrophilic substitution of N-methylpyrrole takes place predominantly at the β-carbon and to a lesser extend at the α-carbon. Our experiments clearly prove that isomerization can be ruled out as a possible way of formation of either β- or α-isomers. This is further checked by stirring pure isomer 4[11] or "enriched" isomer 5[12] with TMS-Tf 2, $CF_3SO_3^{\ominus}HN^{\oplus}(Et)_3$ 7 in 3 or methylene chloride, where no isomerization is observed (GC).

The products formed with their deuterium distributions 4 and 5 indicate that electron density is the major factor governing this reaction, i.e. the reaction is kinetically controlled. In other words, since "trimethylsilyl cation" is a very hard electrophile[13, 14], the β-substitution results from the hard-hard interaction. The formation of the α-isomer is governed by the transition state stability (I in Scheme 1). In order to prove this, we carried out a similar reaction of N-methylpyrrole (1) where trimethylsilyliodide (8) was used in place of 2 and similar excess of 5 (90% GC) was obtained[15].

The steric effects should not play significant role in the trimethylsilylation of 1-methylpyrrole (1), since methyl group is too "small" to exert a β-directing effect[16].

The benzyl group appears to be of greater sterical demand and exclusive formation of the β-isomer is observed, what is in agreement with the Anderson's studies[17].

In summary, by the reaction of 1-methylpyrrole-2,5-d_2 (1a) with a hard electrophile such as trimethylsilyl trifluoromethanesulfonate (2), we showed for the first time that the electrophilic substitution of pyrrole is governed to great extend by electron density factors and takes place predominantly at the β-ring carbon as has been predicted by theoretical calculations. We also ruled out isomerization as a possible way of formation of the α-isomer, whose formation must be controlled by the stability of the transition state, which seems to play a significant role in the electrophilic substitution with softer electrophiles, where almost exclusively the α-isomers are formed.

Acknowledgement

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EXPERIMENTAL

GC-analysis were performed on Carlo-Erba Gas Chromatography SE 54 with dimethylsilicone column, helium as carrier gas, FID and temp. programming from 50 to 250°C. NMR spectra were recorded on Bruker WP 80 (80 MHz) and CXP 300 (300 MHz) in $CDCl_3$/TMS. GC/MS was performed using the W. Blum and W.J. Richter modified Finigan GC/MS system with Incos Data System 2300 directly coupled with Carlo Erba Fractovap 2151 AC-Special Gas Chromatograph[18]. All reactions were carried out under dry nitrogen. The glass ware were flame dried in nitrogen atmosphere.

I. 1-Methylpyrrole-2,5-d_2 (1a)

127 ml 1.6 molar butyllithium in hexane was evaporated in vacuum at 40 °C, and absolute diethyl ether (100 ml) was slowly added at -80°C. The methanol/liquid nitrogen bath was removed and stirring was continued for another 0.5 h. Then 16.5 g (0.203 mol) of 1-methylpyrrole was added via syringe and the reaction mixture heated to reflux for 5 h, cooled to -80°C and deuterium oxide 2.0 g (0.4 mol) was carefully added. Stirring at this temperature was continued for 2 h, then at 0°C for 1 h and finally at room temperature overnight.

The etheral phase was decanted, the residue washed with ether (2x20 ml), dissolved in water (20 ml) and extracted with ether (2x30 ml). Combined etheral extracts were washed with brine (2x10 ml), dried, filtered, evaporated and distilled. B.p. 108-111°C/760 mm Hg, 8.45 g, 50% yield. This procedure was repeated three times, yielding 2 g of >95% (NMR) 1-methylpyrrole-2,5-d_2 (1a).

II. 1-Methyl-3-trimethylsilylpyrrole-2,5-d_2 (5b); 1-Methyl-2-trimethylsilylpyrrole-5-d_1 (4a)

2 g (0.024 mol) of 1a were dissolved in triethylamine (3) (15 ml) and 5.34 g (0.024 mol , 4.35 ml) of 2 were added and stirring was continued overnight. The lower phase was separated, washed with absolute ethyl ether, mixed with solid sodium hydroxide (0.5 h), filtered, concentrated and distilled. A fraction 65-67°C/12 mm Hg was collected. 2.6 g, 70% yield. As determined by GC, the ratio of 4 to 5 was not affected by distillation. ^{1}H-NMR spectra see text.

III. Attempted isomerization of 5 and 4.

Equimolar amounts (0.01 mol) of 2 and 5 (or 4) in triethylamine (3) (20 ml) or methylene chloride were stirred overnight and worked up as above. In another experiment triethylammonium trifluoromethanesulfonate (7) instead of 2 was used.

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5: 6.82-6.65 (m,2H,$C_{2,5}$H), 6.30 (t,J=2.2Hz,1H,C_4H), 3.60 (s,3H,N-Me), 0.19 (s,9H,Si-Me), b.p. 65-67°C/12 mm Hg.
4: 6.85 (t,J=2Hz,1H,C_5H), 6.45 (d of d,J=2,J=4Hz,1H, C_4H), 6.20 (d of d,J=2 and J=4Hz,1H,C_3H), 3.70 (s,3H,N-Me), 0.28 (s,9H,Si-Me), b.p. 65-67°C/12 mm Hg.
6: 6.85 (d,J=1.5Hz,1H,C_3H), 6.47 (d,J=1.5Hz,1H,C_5H), 3.75 (s,3H,N-Me), 0.27 (s,9H,C_2-SiMe), 0.22 (s,9H,C_4-SiMe), b.p. 107-109°C/12 mm Hg, m.p. 30-31°C (ethanol).
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12) Equimolar amount of TMS-Tf 2 and the 65-67/12 mm Hg fraction (90% of 5) in TEA 3 after 16 h stirring give the same fraction (95% of 5).
13) Trimethylsilyl trifluoromethanesulfonate 2 in triethylamine 3 forms a complex which is slightly soluble and disappears as the reaction proceeds. It can be sublimed, but during distillation it decomposes to 2 and 3. Conductivity measurements indicate that in this complex at room temp. the ionic 2A form remains in equilibrium with the pentacovalent form 2B, i.e.

$$CF_3SO_3Si(CH_3)_3 + Et_3N \rightleftharpoons CF_3SO_3^{\ominus}/Et_3\overset{\oplus}{N}\text{-}Si(CH_3)_3 \rightleftharpoons (Et)_3N\ldots\overset{|}{\underset{/\backslash}{Si}}\ldots SO_3CF_3$$

2 3 2A 2B

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15) See experimental section, point II, where 0.024 mol of 1 and trimethylsilyliodide(8) in place of 1a and 2 respectively were used.

16) Detailed studies carried out by Anderson et al. indicate that only tert-butyl- and triphenylmethyl group on nitrogen exert great β-directing effect in the electrophilic substitution of pyrroles. Unexpectedly, the β-directing effect of the 1-isopropyl group appears to be very small.
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17) See experimental section, point II, where 0.024 mol or 1-benzylpyrrole 11 in place of 1a were used.

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