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PROTONATION OF 3-AMINOPYRROLES[1]

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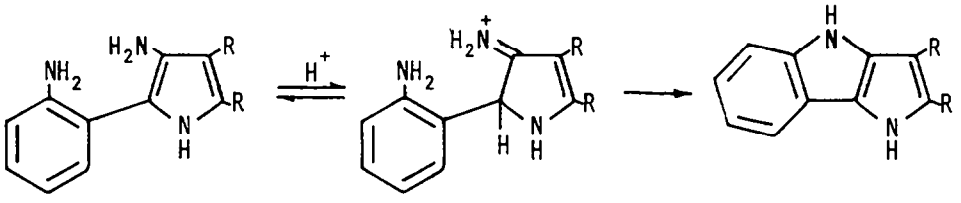
Abstract - The protonation of 3-aminopyrroles has been investigated using ^{1}H and ^{13}C n.m.r. spectroscopy. The spectral data are compatible with predominant protonation of the amino group with no evidence for protonation of the pyrrole ring.

In an earlier publication,[3] we reported the acid-catalysed synthesis of pyrrolo[3,2-b]indoles (3) from 3-aminopyrroles (1) and we proposed a mechanism, which required the intermediate formation of the ring protonated species (2).[4] The generation of such an intermediate is in accord with the the reported behaviour of 2-aminopyrroles in trifluoroacetic acid, which has been interpreted as being compatible with protonation of the 5-position of the pyrrole ring.[5] No record has



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appeared in the literature which defines the site of protonation of 3-aminopyrroles. We have, therefore, prepared a series of 3-aminopyrroles (4) - (8) by standard procedures[6] and examined the ^{1}H and ^{13}C n.m.r. spectra of the free bases and of their protonated forms.

	R^1	R^2	R^3	R^4	R^5
4	H	Ph	NH_2	H	Me
5	H	Ph	NH_2	COMe	Me
6	H	Ph	NH_2	CO_2Et	Me
7	Me	Ph	NH_2	CO_2Et	Me
8	H	Ph	NH_2	H	Ph

The n.m.r spectra of the free bases were measured in DMSO-d_6. Comparison of the spectral data with those of other 3-substituted pyrroles,[7] shows the spectra to be compatible with the amino tautomeric form, and not with an alternative imino structure.[8] The protonated species were generated by the addition of a two-fold

excess of trifluoroacetic acid to the solutions in DMSO-$\underline{d}_6$.

The ^{1}H n.m.r. spectral data for the free bases and their protonated forms (Tables 1 and 2) were strongly indicative of protonation of the amino group, but broadening of the signals upon protonation of the aminopyrroles did not allow the conclusion to be totally unambiguous. All of the ^{1}H resonance signals showed downfield shifts with no change in multiplicity and, significantly, there was no evidence for upfield signals expected for the ring protonated species. The broad signals attributable to the 3-amino group showed a downfield shift of ca. 5 p.p.m. upon protonation and the integration of the signals increased from two to three protons. The resonance signal for the pyrrolic NH showed only a ca. 1.2 p.p.m. shift downfield.

Table 1. ^{1}H N.m.r. Data for 3-Aminopyrroles (4) - (8)

Subst. \ Pyrrole	(4)	(5)	(6)	(7)	(8)
R^1	9.98(bs,1H)	10.94(bs,1H)	10.97(bs,1H)	3.36 (s,3H)	10.40(bs,1H)
R^2	6.94 (t,1H) 7.26 (t,2H) 7.45 (d,2H)	7.06 (t,1H) 7.34 (t,2H) 7.51 (d,2H)	7.05 (t,1H) 7.34 (t,2H) 7.52 (d,2H)	7.28 (m,3H) 7.44 (t,2H)	7.08 (t,1H) 7.35 (m,2H) 7.67 (m,2H)
R^3	3.91(bs,2H)	5.30(bs,2H)	4.84(bs,2H)	4.41(bs,2H)	4.11(bs,2H)
R^4	5.40 (d,1H)	2.50 (s,3H)	1.28 (t,3H) 4.20 (q,2H)	1.29 (s,3H) 4.21 (q,2H)	6.14 (d,1H)
R^5	2.13 (s,3H)	2.34 (s,3H)	2.41 (s,3H)	2.47 (s,3H)	7.14 (t,1H) 7.35 (m,2H) 7.67 (m,2H)

Table 2. ^{1}H N.m.r. Data for Protonated 3-Aminopyrroles

Subst. \ Pyrrole	(4)	(5)	(6)	(7)	(8)
R^1	11.28(bs,1H)	12.03(bs,1H)	112.03bs,1H)	3.37 (s,3H)	11.43(bs,1H)
R^2	7.29 (t,1H) 7.45 (t,2H) 7.50 (d,2H)	7.40 (t,1H) 7.52 (m,4H)	7.40 (t,1H) 7.51 (m,4H)	7.44 (t,2H) 7.53 (m,3H)	7.14 (t,1H) 7.25 (t,2H) 7.48 (t,2H)
R^3	9.81(bs,3H)	10.20(bs,3H)	9.80(vb,3H)	9.60(vb,3H)	9.74(vb,3H)
R^4	5.93 (d,1H)	2.59 (s,3H)	1.33 (t,3H) 4.28 (q,2H)	1.32 (t,3H) 4.28 (q,2H)	6.38 (d,1H)
R^5	2.22 (s,3H)	2.48 (s,3H)	2.47 (s,3H)	2.53 (s,3H)	6.98 (t,1H) 7.14 (t,2H) 7.39 (d,2H)

Examination of the ^{13}C n.m.r. data (Tables 3 and 4) is more conclusive. It is to be expected that protonation of either the amino group, or of the pyrrole ring, would lead to distinct changes in the ^{13}C chemical shifts of the ipso carbon and the "ortho" carbon resonance, respectively. signals. Thus, the ^{13}C n.m.r. spectra of aniline, 3-aminothiophenes, and 4-aminopyrazoles[9] all show upfield shifts of the ipso carbon resonance signals upon protonation of the amino groups. In contrast, 2H-pyrroles exhibit downfield shifts of the ipso carbon resonance signals and upfield shifts of the "ortho" carbon resonance signals[10,11] and comparison of the ^{13}C n.m.r data for 3-methoxy-1-phenylpyrrole and its 2-protonated form shows upfield shifts of 42.6 and 1.7 p.p.m. for 2-C and 4-C, respectively, and downfield shifts of 37.5 and 51.1 p.p.m. for 3-C and 5-C, respectively,[12] upon protonation of the ring.

A completely unambiguous assignment of the ^{13}C chemical shifts for the free base and protonated forms of compounds (4) - (8) was achieved by recording

Table 3. ^{13}C N.m.r. Data for 3-Aminopyrroles

Subst. \ Pyrrole		(4)	(5)	(6)	(7)	(8)
C-2		112.35 (s)	110.11 (s)	110.86 (s)	114.61 (s)	116.22 (s)
C-3		131.29 (s)	133.57 (s)	132.76 (s)	131.74 (s)	132.52 (s)
C-4		100.99 (d)	112.74 (s)	101.79 (s)	100.64 (s)	100.17 (d)
C-5		126.63 (s)	133.57 (s)	133.54 (s)	133.31 (s)	129.92 (s)
R^1					31.63 (q)	
R^2	C-1'	134.34 (s)	132.83 (s)	132.99 (s)	131.46 (s)	132.58 (s)
	C-2'/6'	122.47 (d)	123.04 (d)	123.06 (d)	128.57 (d)	123.57 (d)
	C-3'/5'	128.30 (d)	128.51 (d)	128.47 (d)	128.95 (d)	128.32 (d)
	C-4'	122.47 (d)	123.40 (d)	123.42 (d)	125.85 (d)	125.35 (d)
R^4			30.16 (q)	14.37 (q)	14.36 (q)	
			194.42 (s)	58.44 (t)	58.48 (t)	
				165.86 (s)	165.47 (s)	
R^5		12.89 (q)	15.03 (q)	13.78 (q)	11.38 (q)	133.54 (s)
						124.07 (d)
						128.44 (d)
						125.35 (d)

Table 4. ^{13}C N.m.r. Data for Protonated 3-Aminopyrroles

Subst. \ Pyrrole		(4)	(5)	(6)	(7)	(8)
C-2		122.29 (s)	123.57 (s)	123.77 (s)	125.81 (s)	125.59 (s)
C-3		110.82 (s)	112.41 (s)	111.53 (s)	113.78 (s)	112.67 (s)
C-4		103.24 (d)	114.95 (s)	105.60 (s)	104.42 (s)	102.84 (d)
C-5		127.77 (s)	135.76 (s)	135.37 (s)	135.52 (s)	131.18 (s)
R^1					31.63 (q)	
R^2	C-1'	130.61 (s)	128.94 (s)	129.06 (s)	128.98 (s)	129.93 (s)
	C-2'/6'	125.73 (d)	126.84 (d)	127.11 (d)	128.82 (d)	124.21 (d)
	C-3'/5'	128.73 (d)	128.79 (d)	128.78 (d)	130.46 (d)	128.68 (d)
	C-4'	126.40 (d)	127.72 (d)	127.73 (d)	128.65 (d)	126.64 (d)
R^4			29.97 (q)	14.11 (q)	14.12 (q)	
			195.73 (s)	59.68 (t)	59.61 (t)	
				164.21 (s)	165.89 (s)	
R^5		12.46 (q)	14.26 (q)	12.89 (q)	11.34 (q)	131.38 (s)
						127.01 (d)
						128.68 (d)
						127.29 (d)

two-dimensional heterocorrelated ^{13}C spectra in which the heterocorrelation was optimised for $J_{H,C}$ = 6 Hz. For compounds (4) - (7), the 1'-C signal displays a three bond coupling to the phenyl 3'- and 5'-protons, and the pyrrolyl 5-C signal shows coupling with the methyl substituent; the pyrrolyl 2-C atom is coupled with the phenyl 2'- and 6'-protons and also, in the case of compound (4), with the pyrrolyl 3-proton, whilst, with the exception of compound (7), the pyrrolyl 3-C signal shows strong coupling with the pyrrolyl NH proton.

Comparison of the data in Tables 3 and 4 shows that there is a marked upfield shift in the ipso carbon resonance and a smaller, but distinct, downfield shift in the "ortho" resonance signal. The magnitudes and directions of these shifts are similar to those observed upon N-protonation of aniline and the 4-aminopyrazoles,[9] and distinctly different from those observed upon protonation of the ring of 3-methoxy-1-phenylpyrrole.

The spectral data provides overwhelming evidence for the predominant protonation of the amino group of the 3-aminopyrroles, but does not totally

preclude the possiblity of a very low equilibrium concentration of the 2-protonated species, as required for the postulated nucleophilic ring-closure reaction leading to the pyrrolo[3,2-b]indoles.

EXPERIMENTAL

All melting points were taken using a Buchi-Tottoli capillary apparatus. Mass spectra were recorded with a JEOL LMS-01 SG-2 double focussing mass spectrometer operating at 70 eV.
^{1}H and ^{13}C N.m.r. spectra were recorded using a Varian XL300, FT n.m.r. spectrometer, operating at 299.943 and 75.429 MHz, respectively. For ^{1}H spectral measurements 0.05 mmol of the aminopyrrole was dissolved in DMSO-d_6 (0.5 ml) and for measurement of the ^{13}C spectra 0.5 mmol was used. Protonation was achieved by adding two equivalents of trifluoroacetic acid to the solutions.

The following acquisition and processing parameters were used.
For ^{1}H spectra: spectral window 4000 Hz, acquisition time 2000 s, pulse width 5 μs, number of points 16000.
For ^{13}C spectra: spectral window 16501.7 Hz, acquisition time 0.979 s, pulse width 5 μs, number of points 32000, exponential line broadening factor 1000.
For HETCOR: 90° pulse width 17 μs, duration of the 90° pulse from decoupler coils 47.9 μs, spectral window in the evolution domain 2853.1 Hz, spectral window in the detection domain 2637.8 Hz, acquisition time 0.179 s, number of points 1024, number of transients 80, number of increments 256, exponential line broadening factor in the first domain lb = 1.000, exponential line broadening factor in the second domain lb2 = 0.318, final size of data matrix (1024 x 1024).

3-Amino-5-methyl-2-phenylpyrrole (4) (78%), m.p. 166°C (from benzene) was obtained by catalytic reduction (10% Pd-C) of the corresponding nitro compound[13] in methanol at room temperature under 3 atmos. of hydrogen using a Parr hydrogenator. (Found: C, 76.7; H, 7.1; N, 16.2 $C_{11}H_{12}N_2$ requires C, 76.7; H, 7.0; N, 16.3%) m/z = 172.
4-Acetyl-3-amino-5-methyl-2-phenylpyrrole (5) (55%), m.p. 223°C (lit.,[14] m.p. 218 - 220 °C) and 3-amino-4-ethoxycarbonyl-5-methyl-2-phenylpyrrole (6) (41%), m.p. 105°C (lit.,[10] m.p. 105°C) were prepared from 2-amino-2-phenylacetonitrile and the appropriate 1,3-dicarbonyl compound, according to the procedure described in the literature.[14]
3-Amino-1,5-dimethyl-4-ethoxycarbonyl-2-phenylpyrrole (7) (99%), m.p. 65°C was prepared from the corresponding nitropyrrole[15] by a procedure analogous to that used for compound (4). (Found: C, 69.6; H, 7.0; N, 10.7 $C_{15}H_{18}N_2O_2$ requires C, 69.6; H, 7.0; N, 10.85%) m/z = 258.
3-Amino-2,5-diphenylpyrrole (8) (93%), m.p. 187°C (lit.[16] m.p.[17] 187°C) was prepared by catalytic reduction of the corresponding nitroso compound[17] using a procedure analogous to that described for the reduction of the nitropyrroles.

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