Acid-catalysed Proton Exchange on Pyrrole and Alkylpyrroles

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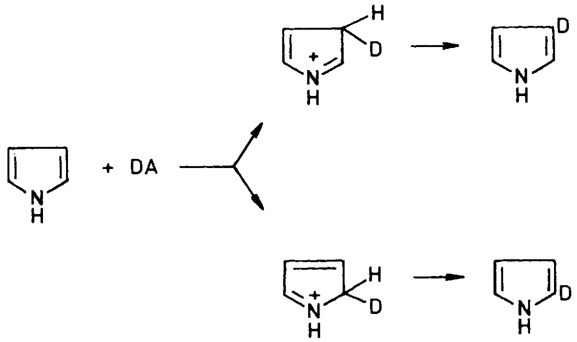
The rates of deuteriodeprotonation at the α- and β-positions of pyrrole have been determined as a function of acidity, concentration of deuterioacetic acid, and temperature in D_2O–dioxan solution. The reaction is subject to general acid catalysis. The rates of exchange on several alkylpyrroles were measured and relative positional reactivities found to agree with the predictions of Klopman's 'Polyelectron Perturbation' theory using orbital energies and wavefunctions obtained by the INDO MO method.

It has been demonstrated that acid-catalysed proton exchange occurs on those activated aromatic compounds such as trimethoxybenzene,[1] azulene,[2] and indole,[3] *via* the A–S_E2 mechanism in which there is general acid catalysis. We have previously reported[4] that the acid-catalysed deuteriodeprotonation in aqueous dioxan at the α- and β-positions of pyrrole and *N*-methylpyrrole exhibits general acid catalysis according to the Scheme.



Scheme

More recently Schwetlick and Unverferth[5] have determined the rate of overall protiodedeuteriation of pyrrole, along with furan, thiophen, and benzene, in aqueous methanol (61% w/w methanol) containing sulphuric acid whilst Muir and Whiting measured the rate of exchange on both the carbon and nitrogen atoms of a pyrrole and indole in aqueous (D_2O) acetonitrile (95% w/w acetonitrile).[6] We now report the specific rate constants for exchange of the α- and β-protons of pyrrole and of several alkylpyrroles along with the catalytic coefficients and activation parameters for exchange on pyrrole in D_2O–dioxan (1 : 1 w/w) containing deuterioacetic acid and buffered with potassium acetate.

EXPERIMENTAL

Materials.—Dioxan was purified according to Calvin and Wilson and distilled from sodium metal.[7] Pyrrole and *N*-methylpyrrole were obtained from Aldrich Chemical Company. The 2- and 3-t-butylpyrroles were prepared from pyrrolylmagnesium bromide and t-butyl chloride and were separated by preparative g.l.c.[8] Other pyrroles were prepared by known methods.[9] The pyrroles were freshly distilled under nitrogen before use. The deuterium oxide contained 99.8% D_2O. All solutions were made up and handled in a dry box under a dry nitrogen atmosphere. The ionic strength of all solutions was made 0.5 by the addition of the necessary amount of potassium chloride.

Acidity Measurements.—pH Measurements were made using an Orion 801 pH meter with a combination electrode calibrated with standard buffer solutions (in H_2O). The measured pH of water–dioxan (1 : 1 w/w) solutions which were 0.5M in KCl and to which varying amounts of toluene-*p*-sulphonic acid had been added were found to be 0.20 pH units higher than that calculated from the amount of acid added. For solutions in water–dioxan, but of lower ionic strength, VanUitert and Haas determined a correction of *ca.* 0.1.[10] Mikkelsen suggested a correction of 0.44 for pD when using a glass electrode calibrated in water.[11] Combining these corrections gave the relationship $\text{pD} = \text{pH}_{\text{obs.}} + 0.24$ which was used throughout this work.

Kinetics.—The rate of proton exchange was followed by measuring the integrated proton signal using a JEOL C-60HL n.m.r. spectrometer. The sample tubes were kept in a thermostatted water-bath between readings except when exchange was very rapid and it was necessary for the sample tubes to remain in the probe at a temperature of 32 °C. The exchange of the α- and β-protons were followed relative to *p*-dichlorobenzene which was used as an internal standard. Usually from 50 to 100 readings were taken during each kinetic run covering from 30 to 90% reaction. The pseudo-first-order rate constants were calculated using a somewhat modified version of the LSKIN1 computer program whilst the activation parameters were calculated by the ACTENG program.[12]

Molecular Orbital Calculations.—The CNINDO program of Pople and Beveridge was for the INDO calculations using

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[1] A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, 1961, **83**, 2877.

[2] J. Colapietro and F. A. Long, *Chem. and Ind.*, 1960, 1056.

[3] B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972, 1116.

[4] G. P. Bean, *Chem. Comm.*, 1971, 421.

[5] K. Schwetlick and K. Unverferth, *J. prakt. Chem.*, 1972, **314**, 603.

[6] D. M. Muir and M. C. Whiting, *J.C.S. Perkin II*, 1975, 1316; 1976, 388.

[7] M. Calvin and K. W. Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2003.

[8] P. S. Skell and G. P. Bean, *J. Amer. Chem. Soc.*, 1962, **84**, 4655.

[9] G. P. Bean, *J. Org. Chem.*, 1967, **32**, 228.

[10] L. G. VanUitert and C. G. Hass, *J. Amer. Chem. Soc.*, 1953, **75**, 451.

[11] K. Mikkelsen and S. O. Nielsen, *J. Phys. Chem.*, 1960, **64**, 632.

[12] D. F. DeTar, 'Computer Programs for Chemistry,' Benjamin, New York, 1968–69, vols. 1 and 2.

the standard geometry for pyrrole.[13,14] For the methylpyrroles, C–Me and N–Me distances of 1.52 and 1.43 Å were used.

RESULTS

The pseudo-first-order rate constants for proton exchange at the α- and β-positions of pyrrole in D_2O–dioxan (1 : 1 w/w) containing deuteriotrifluoroacetic acid and in a series of buffer solutions made with deuterioacetic acid and potassium acetate are given in Tables 1 and 2 respectively. The data in Table 2 were fitted by a least squares method to the equation $k_{obs.} = k_D + [D_3O^+] + k_{DOAc}[DOAc]$ and the resulting equations are (1) and (2). Rate constants for

$$k_{obs.}^{\alpha} = (3.9 \pm 0.7) \times 10^{-2}[D^+] + (3.9 \pm 0.2) \times 10^{-6}[DOAc] \quad (1)$$

$$k_{obs.}^{\beta} = (3.9 \pm 0.8) \times 10^{-2}[D^+] + (0.9 \pm 0.4) \times 10^{-6}[DOAc] \quad (2)$$

exchange on pyrrole and N-methylpyrrole in the same system but over a range of temperatures are given in Table 3 along with the activation parameters calculated for the exchange process. In Table 4 are the rate constants

TABLE 1

Rates of proton exchange on pyrrole in D_2O–dioxan (1 : 1 w/w) catalysed by deuteriotrifluoroacetic acid at 32° [a]

	Pseudo-first order rate constant (s^{-1})		Specific rate constant ($l\ mol^{-1}\ s^{-1}$)	
pD	10^6k^{α}	10^6k^{β}	10^2k^{α}	10^2k^{β}
1.20	4 970	4 820	7.88	7.64
1.33	3 350	3 510	7.16	7.50
1.39	2 710	2 350	6.65	5.81
1.44	2 110	2 130	5.82	5.87
1.44	2 090	2 170	5.75	5.98

[a] $\mu = 0.5$ in KCl.

TABLE 2

Rates of proton exchange on pyrrole in D_2O–dioxan (1 : 1 w/w) with deuterioacetic acid–KOAc buffer at 25° [a]

pD	[DOAc]/M	$10^6k^{\alpha}/s^{-1}$	$10^6k^{\beta}/s^{-1}$
3.87	0.174	4.86	4.90
4.06	0.174	4.41	3.93
4.41	0.174	2.05	1.67
4.77	0.174	1.08	0.524
5.08	0.174	0.852	0.472
5.27	0.174	0.808	0.361
3.53	0.344	12.9	12.8
3.84	0.344	7.78	8.55
3.87	0.344	6.77	6.87
4.12	0.344	4.69	3.55
4.69	0.344	1.92	1.01
5.02	0.344	1.59	0.637
5.09	0.344	1.58	0.509
5.18	0.344	1.474	0.383
5.72	0.344	1.264	0.0415
3.25	0.676	22.3	21.8
3.40	0.676	23.1	21.2
3.41	0.676	20.6	18.9
3.41	0.676	17.5	14.7
3.49	0.676	20.2	20.0
3.69	0.676	10.9	8.52
3.71	0.676	11.7	9.69
4.54	0.676	3.72	1.92
4.92	0.676	2.81	1.08
5.06	0.676	3.11	1.02
5.23	0.676	2.37	0.446
5.32	0.676	2.19	0.391
5.73	0.676	2.31	0.180
3.08	0.994	31.9	30.3
3.58	0.994	14.9	10.6
3.60	0.994	12.7	9.27
4.81	0.994	4.31	1.60
4.95	0.994	3.55	1.04
5.02	0.994	5.02	1.47
5.11	0.994	3.83	1.13

[a] $\mu = 0.5$ with KCl.

TABLE 3

Rate constants and activation parameters for proton exchange on pyrrole and N-methylpyrrole in D_2O–dioxan (1 : 1 w/w) with DOAc–KOAc buffer [a]

Compound		t/°C	$10^6k^{\alpha}/s^{-1}$	$10^6k^{\beta}/s^{-1}$
Pyrrole	pD 3.86	25	6.01	5.57
		30	13.03	12.17
		40	35.7	34.5
		50	90.6	89.9
		60	205	203
$\Delta H^{\ddagger}$ [b]			79 ± 4	81 ± 3
$\Delta S^{\ddagger}$ [b]			−78 ± 10	−73 ± 11
Pyrrole	pD 5.48	25	8.88	2.83
		35	23.1	10.40
		45	60.9	26.3
		55	144.8	76.1
		65	256	120.1
$\Delta H^{\ddagger}$			69 ± 3	73 ± 4
$\Delta S^{\ddagger}$			−109 ± 8	−105 ± 13
N-Methylpyrrole	pD 3.86	30	30.4	16.07
		40	87.3	50.4
		50	197.2	124.9
		60	454	358
$\Delta H^{\ddagger}$			72 ± 2	82 ± 2
$\Delta S^{\ddagger}$			−93 ± 7	−67 ± 7

[a] $\mu = 0.5$ with KCl. [b] Units of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are kJ mol^{-1} and J mol^{-1} K^{-1}, respectively.

TABLE 4

Rate constants for proton exchange on alkylpyrroles in D_2O–dioxan (1 : 1 w/w) with deuterioacetic acid (0.174M)–KOAc buffer [a,b]

		Rate of exchange $10^6k/s^{-1}$ at position			
	pD	2	3	4	5
2-Methylpyrrole	4.21		706	21.5	258
	4.22		639	23.7	241
	4.39		473	14.8	190
3-Methylpyrrole	3.89	804		160	42.1
	3.89	1 052		172	42.5
N-Methylpyrrole [c]	3.86	18.7	10.3	10.3	18.7
N,2-Dimethylpyrrole	3.88		1 339	81.9	1 296
2-Ethylpyrrole	4.57		97.3	9.26	136
	4.92		66.8	3.32	83.8
	4.92		82.0	1.50	99.6
3-Ethylpyrrole	4.18	317		44.1	114
	4.51	188		26.7	108
2-t-Butylpyrrole	3.70		[e]	108	343
3-t-Butylpyrrole	3.73	470		119	52.8
N-t-Butylpyrrole [d]	3.53	38.9	26.2	26.2	38.9
	3.56	34.4	29.2	29.2	34.4

[a] $\mu = 0.5$ with KCl. [b] At 32 °C unless otherwise indicated. [c] Calculated from activation parameters. [d] At 25 °C. [e] Rate not measurable due to solvent peak interference.

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[13] J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970.

[14] B. Bak, D. Christensen, L. Hansen, and J. Rastrup-Andersen, *J. Chem. Phys.*, 1956, **24**, 720.

determined in a similar manner for exchange on several alkylpyrroles. Under the conditions used, no proton exchange could be detected at the α- or β-positions of either 2-formyl- or 2-nitro-pyrrole.

It is possible to estimate the reactivity of the various positions on these alkylpyrroles relative to the equivalent position of pyrrole from the data in Table 4 and the rate of proton exchange calculated for the same pD and temperature by means of equation (1) or (2) and the activation parameters in Table 3. These relative reactivities for proton exchange are given in Figure 1.

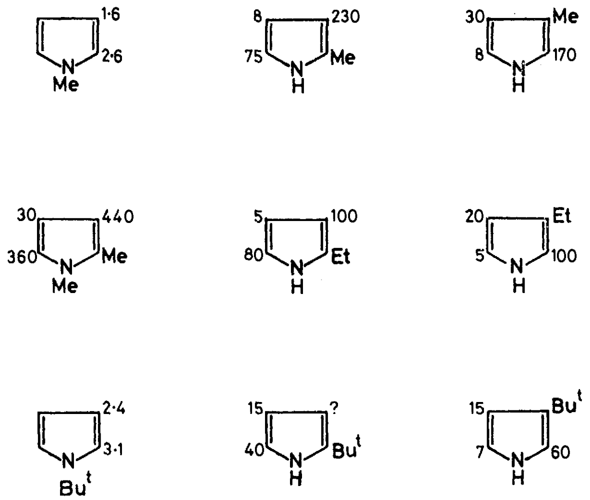

FIGURE 1 Relative reactivity of alkylpyrroles for proton exchange relative to exchange at corresponding position of pyrrole

DISCUSSION

Electrophilic substitution on the aromatic pyrrole ring is particularly facile and is generally considered to occur exclusively at the α-position with the exception of nitration where *ca.* 7% of the β-isomer is also produced.[15] Chiang and Whipple have reported that in 16M-deuteriosulphuric acid α-protonation of *N*-methylpyrrole is thermodynamically favoured; for α-protonation, $pK_a = -3.1$ whilst for protonation at the β-position the pK_a is -5.1.[16]

However they also noted that deuterium exchange occurred more rapidly at the β-position (k_β/k_α 2.3). In deuteriotrifluoroacetic acid exchange was found to be slightly more rapid at the α-position. The rate constants given in Table 1 for exchange in dilute solutions of deuteriotrifluoroacetic acid and the catalytic coefficients [from equations (1) and (2)] for that portion of proton exchange catalysed by D_3O^+ in deuterioacetic acid solutions indicate that exchange is equally rapid at both positions of pyrrole whilst proton transfer from weaker acids (*e.g.* DOAc) more selectively protonates the α-position.

Schwetlick and Unverferth have reported a Brönsted coefficient of 0.8 for the overall rate of protiodedeuteriation for 2,3,4,5-tetradeuteriopyrrole in aqueous methanol when several different weak acids were used as the catalyst.[5] It might be tempting to compare this value with that of *ca.* 0.6 found for general acid catalysed proton exchange on trimethoxybenzene, azulene, or the β-position of indole which have been ascribed to a symmetrical transition state.[1,3,17] This would suggest that the transition state for proton exchange on pyrrole occurs later and would thus resemble the intermediate conjugate acid. However these data were determined for exchange in water and any comparison with the data obtained in a mixed solvent system is questionable.[18] Rather we may assume that the transition state for exchange on pyrrole is similar to that for the analogous reaction at the β-position of indole and whose pK_a of -3.6 is close to that of the α-position of pyrrole (-3.8). Bell and Goodall have suggested the quantity $pK_{\text{substrate}} - pK_{\text{catalyst}}$ as an index of transition state symmetry.[19] For a symmetrical transition state, ΔpK is 0. In the case of exchange either at the β-position of indole or the α-position of pyrrole $\Delta pK = -2$ for catalysis by D_3O^+, close to a symmetrical transition state, whilst for that portion catalysed by DOAc, $\Delta pK = -8$ and indicates a much later transition state. For the β-position of pyrrole (pK_α -5.9) the corresponding ΔpK values of -4 and -11 suggest that both transition states are even later.[3]

Although measurable proton exchange on benzene occurs only under much more acidic conditions, Katritzky estimated the partial rate factor for proton exchange at the α-position of *N*-methylpyrrole as 4×10^{10}.[20] This was based upon an extrapolated value of 10^{-11} s^{-1} as the rate constant for exchange on benzene at pH 0 and our earlier data.[4] From the data presented here we revise this to 1×10^{10} and similarly calculate the partial rate factor for pyrrole as 4×10^9. The rate data of Challis and Millar for exchange at the β-position of indole gives a partial rate factor of 10^9 which is comparable with that for pyrrole.[3] These values are considerably less than the 10^{15} for pyrrole and the corresponding value of 10^7 for thiophen and furan which were reported by Schwetlick and Unverferth for exchange catalysed by sulphuric acid in aqueous methanol.[5]

Examination of the activation parameters indicates that the somewhat slower rates of exchange observed in less acidic solutions for the β-positions of pyrrole and *N*-methylpyrrole are the result of two opposing effects. Although α-exchange for both compounds is favoured by a lower enthalpy of activation it is almost cancelled in the case of pyrrole by an unfavourable negative entropy

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[15] A. R. Cooksey, K. J. Morgan, and D. P. Morrey, *Tetrahedron*, 1970, **26**, 5101.

[16] Y. Chiang and E. B. Whipple, *J. Amer. Chem. Soc.*, 1963, **85**, 2763.

[17] R. J. Thomas and F. A. Long, *J. Amer. Chem. Soc.*, 1964, **86**, 4770.

[18] J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, p. 242.

[19] R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, **A294**, 273.

[20] S. Clementi, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1675.

of activation due, at least in part, to the solvation of the adjacent N–H group. In *N*-methylpyrrole, the inductive effect of the methyl group causes an expected lowering of $\Delta H^{\ddagger}$ for α-proton exchange but this is offset by an even greater negative $\Delta S^{\ddagger}$ produced by the bulkiness of the *N*-methyl group. $\Delta S^{\ddagger}$ for exchange at the β-positions of pyrrole and *N*-methylpyrrole are approximately equal (*ca.* −70 J mol^{-1} K^{-1}). Muir and Whiting's reported values of −32 and −33 J mol^{-1} K^{-1} for $\Delta S^{\ddagger}$ for exchange at the α- and β-positions of pyrrole in 10 mole % D_2O–acetonitrile suggests (not unexpectedly) that less water is ' frozen ' into the transition state for exchange in this much less aqueous system.[6]

As anticipated, the inductive effect of an alkyl group activates the adjacent position(s) of the ring toward proton exchange (Figure 1), but the influence of a methyl group attached to the ring nitrogen atom is considerably less than if attached to carbon. This effect has also been noted in trifluoroacetylation where an *N*-methyl group increases the reactivity by a factor of only 1.9 whilst a 2-methyl group produced a 24-fold increase in the rate of attack at the 5-position. In contrast, 2-methylfuran and 2-methylthiophen are 1 700 and 380 times more reactive than their parent heterocycles and it has been suggested that the lower selectivity of pyrrole supports the hypothesis that the transition state for electrophilic substitution on pyrrole is quite early.[21]

TABLE 5

Experimental and theoretical quantities for pyrrole and methylpyrroles

	p*K* [a]	ΔG [b]	Localization energy [b–d]	$\Delta G^{\ddagger}$ [b,e]	Charge densities [d,f,g] q_σ	q_π	q_{total}	c_{HOMO}	Substituent chemical shift
Pyrrole									
2-Position	−3.8	21.7	47.6	104.8	155	−98	57	0.596	
3-Position	−5.9	33.7	60.0	105.0	59	−94	−36	0.386	
N-Methylpyrrole									
2-Position	−3.1	17.7	35.3	102.4	154 (−1)	−105 (−7)	49 (−8)	0.596	3.8 [h]
3-Position	−5.1	29.1	39.5	103.9	55 (−4)	−91 (+4)	−36 (0)	0.381	0.2
2-Methylpyrrole									
3-Position	−2.3	13.1	11.7	91.2	60 (+2)	−111 (−17)	−51 (−15)	0.393	2.3
4-Position	−4.5	25.7	48.0	99.8	55 (−3)	−90 (+4)	−35 (+1)	0.357	0.1
5-Position	−0.2	1.1	4.8	93.9	154 (−1)	−99 (−1)	55 (−2)	0.565	1.2
3-Methylpyrrole									
2-Position	−1.0	5.7	3.6	91.8	158 (+3)	−115 (−17)	43 (−14)	0.580	
4-Position	−4.7	26.9	43.7	96.2	58 (−1)	−105 (−11)	−47 (−12)	0.185	
5-Position	−2.1	12.0	40.3	99.6	151 (−4)	−90 (+8)	61 (+4)	0.531	

[a] Ref. 16. [b] In kJ mol^{-1}. [c] Adjusted to arbitrary value of 60 kJ mol^{-1} for 3-pyrrole ion. [d] INDO Calculations. [e] Calculated at 32 °C and pD = 3.88. [f] $\times 10^{-3}$. [g] Figures in parentheses are differences in charge from corresponding position on pyrrole. [h] R. J. Abraham, R. D. Lapper, and K. M. Smith, *J.C.S. Perkin II*, 1974, 1004. [i] T. F. Page, T. Alger, and D. M. Grant, *J. Amer. Chem. Soc.*, 1965, **87**, 5333.

The effect of alkyl substituents on the ground state electronic distribution in the pyrrole ring can be estimated either by ^{13}C n.m.r. or by molecular orbital calculations. In Table 5 are the σ, π, and total electronic charges calculated by the INDO method and the ^{13}C substituent chemical shifts for pyrrole and the isomeric methylpyrroles. In the ^{13}C substituent chemical shifts, the *N*-methyl group produces a greater effect whilst the calculated electron densities are more affected by a substituent attached to a ring carbon atom, possibly due to the hyperconjugative effect not operating through nitrogen. The limited transmission of electronic effects through the N–H group of pyrrole has been noted by Tirouflet and by Marino; *e.g.* the pK_a values of 4- and 5-substituted pyrrole-2-carboxylic acids correlate with the corresponding σ_m and σ_p substituent constants.[22-24] The inequality of the C–C bond lengths suggests partial bond fixation in pyrrole and attachment of substituents at either the 2- or 3-position produces an effect expected for a ' butadiene-like ' system, *i.e.* the effect produced by a substituent is most pronounced at the same end of the system.

The rate determining step in aromatic electrophilic substitution is usually the formation of the intermediate σ-complex which in the case of proton exchange is the conjugate acid of the substrate. Prior formation of a π-complex can neither be proven nor rejected from kinetic data but the possible existence of such a complex for pyrrole has been investigated by Heidrich using the semi-empirical CNDO2 and MINDO2 MO methods.[25] These calculations indicate the existence of an energy minimum above the plane of the ring lying between the α- and β-positions. This suggests that there is no

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[21] S. Clementi and G. Marino, *J.C.S. Perkin II*, 1972, 71.

[22] P. Fournari, Dissertation, Dyon, 1961.

[23] F. Fringuelli, G. Marino, and G. Savelli, *Tetrahedron*, 1969, **25**, 5815.

[24] H. H. Jaffe and H. L. Jones, *Adv. Heterocyclic Chem.*, 1964, **3**, 209.

[25] D. Heidrich and M. Grimmer, *Z. Chem.*, 1972, **12**, 67; 1974, **14**, 481.

TABLE 6

Test of polyatomic perturbation approach to electrophilic substitution

		Hard, charge controlled			Soft, frontier orbital controlled		
	π-Electron density (10^{-3})	log $\Delta E/E_0$ [a] E_n^* 8.0	$\Delta G^\ddagger$/kJ mol^{-1} for proton exchange	c_{HOMO}	log $\Delta E/\Delta E_0$ [a] E_n^* 1.5	Nitration ratio [b-d]	Formylation ratio [e,f]
Pyrrole							
2-Position	−98	0.0	104.8	0.596	0.0	4.3	199
3-Position	−94	−25.1	105.0	0.386	−44.1	1	1
N-Methylpyrrole							
2-Position	−105	1.2	102.4	0.596	5.7	1.8	16
3-Position	−91	−3.5	103.9	0.381	−11.0	1	1
2-Methylpyrrole							
3-Position	−111	3.8	91.2	0.393	−3.8	1	
4-Position	−90	−3.5	99.8	0.357	−12.7	0	
5-Position	−99	0.3	93.9	0.565	−1.0	5.7	
3-Methylpyrrole							
2-Position	−115	2.6	91.8	0.580	2.3		4
4-Position	−105	−1.5	96.2	0.185	−8.8		0
5-Position	−90	−6.2	99.6	0.531	−6.3		1

[a] × 10^{-3}. [b] A. R. Cooksey, K. L. Morgan, and D. P. Morrey, *Tetrahedron*, 1970, **26**, 5101. [c] H. J. Anderson, *Canad. J. Chem.*, 1957, **35**, 21. [d] P. E. Sonnet, *J. Heterocyclic Chem.*, 1970, **7**, 399. [e] H. J. Anderson and H. Nagy, *Canad. J. Chem.*, 1972, **50**, 1961. [f] R. L. Hinman and S. Theodoropulos, *J. Org. Chem.*, 1963, **28**, 3052; J. Elguero, R. Jacquier, and B. Shimizu, *Bull. Soc. chim. France*, 1969, 2823.

preference for α- or β-substitution at this stage of the reaction and may, at least in part, explain the low selectivity of pyrrole toward protonation by strong acids.

Attempts to apply molecular orbital theory to electrophilic substitution which use either the intermediate or the reactants as a model for the transition state (*i.e.* the isolated molecule or localization approach) have had only limited success with heterocyclic systems. The localization energies given in Table 5 were calculated by the INDO method and are the energy for protonation. The results are in relatively good agreement with the pK_a (ΔG) for protonation. Comparison of $\Delta G^\ddagger$ with the localization energies (and ΔG) indicate a poor correlation. The equilibrium and kinetic energy differences do not follow the same effect of substituents and thus the conjugate acid is not a satisfactory model for the transition state. The π-electron density gives a better correlation with $\Delta G^\ddagger$.

As suggested by Pearson's HSAB approach, Klopman has derived the ' Polyatomic Perturbation Theory ' which considers the hardness (polarizability) of the electrophile.[26] As the electrophile approaches the aromatic ring, a mutual polarization of the molecular orbitals (MOs) of both species occurs. The total perturbation [equation(3)] is produced by two distinct effects; a

$$\Delta E = -q_r q_s \frac{\Gamma}{\varepsilon} + \Delta\text{Solv} + \sum_{\substack{m \\ \text{occ}}} \sum_{\substack{n \\ \text{unocc}}} \frac{2(c_r^{m})^2(c_s^{n})^2\beta^2}{E_m^* - E_n^*} \quad (3)$$

coulombic interaction (ionic) which depends upon the charges and solvation of the species, and an electron transfer effect produced by the overlapping of the MOs to give covalent bonding. The most significant term is the difference in energy, $E_m^* - E_n^*$, between the MOs of

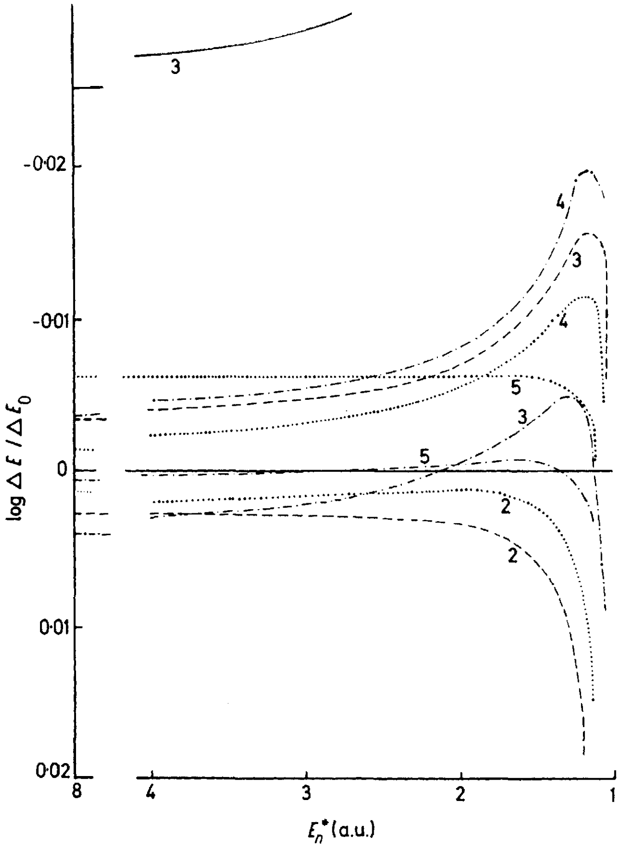

FIGURE 2 Plot of log $\Delta E/\Delta E_0$ against E_n^*: pyrrole (—); *N*-methylpyrrole (– – – –); 2-methylpyrrole (— · — · —); 3-methylpyrrole (· · · ·)

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[26] G. Klopman, *J. Amer. Chem. Soc.*, 1968, **90**, 223; see also M. V. Basilevsky, *Adv. Chem. Phys.*, 1975, **33**, 345.

the electron donor (the aromatic ring) and acceptor (the electrophile). When this difference is large electron transfer becomes negligible and the perturbation energy is primarily determined by the charge density at the various positions on the atomatic ring, *i.e.* ' charge-controlled '. This situation arises when the electrophile is difficult to polarize (hard) and is small and thus strongly solvated, *e.g.* the proton. At the other extreme, when $E_m^* - E_n^*$ is small, the interaction between the orbitals dominates as electron transfer occurs. Under these conditions the reaction becomes ' frontier-controlled ' and orientation is determined by the frontier electron density, $(c_{\text{HOMO}})^2$. It is enhanced by high polarizability (softness) of the electrophile and low solvation.[27] The quantity $\Delta E_k = \sum_{j=1}^{\text{occ}} 2c_{jk}^2/(E_j - E_n^*)$ has been calculated for the α- and β-positions of pyrrole and the isomeric methylpyrroles. Although orbital energies and wavefunctions derived from Hückel molecular orbital calculations have been used by others we have chosen to use the energies and wavefunctions for the π-orbitals obtained from calculations using the INDO method so as to avoid the problem of deciding which empirical parameter to use for the methyl group. In Figure 2 the quantity log $\Delta E_k/\Delta E_0$ is plotted against E_n^* where ΔE_0 is for the 2-position of pyrrole. When E_n^* is large, and thus indicating a hard electrophile such as the proton, the order of reactivity for each compound agrees with that found for proton exchange (Table 6).

The nitration and Vilsmeier–Haack formylation of pyrrole and the methylpyrroles involves electrophiles which are softer (more polarizable) than the proton and provide a test for the validity of this approach. As indicated by the data in Table 6, the order of positional reactivity for the 2- and 3-methylpyrroles differs from that observed for protonation but is correctly predicted by log $\Delta E_k/\Delta E_0$ when E_n^* is *ca.* 1.5. Extension of this method to other heterocycles is under investigation.

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[27] A somewhat similar approach to that of Klopman has been devised by Chalvet and his co-workers and in which the transition state is modelled after the σ complex but examines the effect of varying the coulomb integral for the attacking species. See J. Bertran, O. Chalet, R. Daudel, T. F. W. McKillop, and G. H. Schmid, *Tetrahedron*, 1970, **26**, 339 and later papers.