Photoelectron spectroscopic study of *N*-aryl- and *N*-heteroaryl-pyrroles

B. Kovač,*[a] L. Klasinc,[a] J. Vorkapić-Furač,[b] M. Mintas[c] and J. V. Knop[d]

[a] *The Ruđer Bošković Institute, HR 10 001 Zagreb, Croatia*
[b] *Faculty of Food Technology and Biotechnology, University of Zagreb, HR 10 001 Zagreb, Croatia*
[c] *Department of Organic Chemistry, Faculty of Chemical Engineering and Technology, University of Zagreb, HR 10 001 Zagreb, Croatia*
[d] *Rechenzentrum der Universität Düsseldorf, Düsseldorf, Germany*

HeI photoelectron (PE) spectra of 13 *N*-aryl- and *N*-heteroaryl-pyrroles have been measured. The low energy region of the spectra has been analysed using semiempirical MNDO SCF MO calculations [assuming the validity of Koopmans' theorem (*Physica*, 1934, 1, 104)] and the composite molecule method (CMM) which has proven to be particularly useful for electronic structure elucidation of complex molecules. Electronic structure, especially in terms of the distribution of the outer valence electrons over the molecule, has been shown previously to be mostly responsible for their chemical properties.

Attention has been paid to the effect which particular constituents, *i.e.* either pyrrole or *N*-aryl- and *N*-heteroaryl-pyrrole, respectively, may play in the pharmacological activity of arylpyrroles. In all these compounds, the highest occupied MO is of pyrrole-type character, (a_2 symmetry, with a node on the N-atom). Consequently, the same ionisation process yields the lowest energy band in all PE spectra.

Introduction

N-Aryl- and *N*-heteroaryl-pyrroles (NAHAP) have been of manifold pharmacological interest. Thus, several 2,5-disubstituted derivatives of NAHAP have shown pronounced anti-spastic, anti-inflammatory and analgesic activities.[1–6] Furthermore, *N*-phenylpyrroles with diethylamino, ethyl and lipophylic ethyl ester groups have been found to possess anaesthetic activity,[7] while an anti-hypertensive activity was shown in the corresponding methylamine derivatives.[8] Patent literature indicates also that pyrrole aldehydes have found use as anti-psychotic drugs in treating brain disorders.[9] In all *N*-aryl or *N*-heteroaryl substituted pyrroles, it is the pyrrole moiety which seems to be essential for their pharmacological activity. Our interest in sterically hindered NAHAP has been concerned with their enantiomers and the barriers to restricted rotation about the C–N bond.[10,11] The PE spectra of several NAHAP (**1**, **2**, **7**, **10**, **12**) and the corresponding pyrrole aldehydes (**3**–**5** and **8**) are reported here.

Experimental

Low resolution (~25 meV FWHM) HeI PE spectra of compounds **1**–**13** [*N*-phenylpyrrole **1**,[13] *N*-phenyl-2,5-dimethylpyrrole **2**,[1] *N*-phenyl-2,5-dimethylpyrrole-3-carbaldehyde **3**,[12] *N*-(2-methylphenyl)-2,5-dimethylpyrrole-3-carbaldehyde **4**,[11] *N*-(2-fluorophenyl)-2,5-dimethylpyrrole-3-carbaldehyde **5**,[12] 2-aminopyridine **6**, *N*-(2-pyridyl)-2,5-dimethylpyrrole **7**,[12] *N*-(2-pyridyl)-2,5-dimethylpyrrole-3-carbaldehyde **8**,[12] 8-aminoquinoline **9**, *N*-(8-quinolyl)-2,5-dimethylpyrrole **10**,[12] thiazole **11**, *N*-(2-thiazolyl)-2,5-dimethylpyrrole **12**[12] and 2,5-dimethylpyrrole **13**[11]] were obtained on a Vacuum Generators UV-G3 instrument.[14] Spectra of less volatile compounds were obtained by raising the temperature of the sample inlet system (100–160 °C). The energy scale was calibrated by admitting some N_2 and Xe to the sample flow.

Electronic structure, deduced from PE spectra and quantum chemical calculations of molecules has been shown previously[15] to be mostly responsible for their chemical properties. Compounds **6**, **9** and **11** were purchased from Fluka.

The HeI PE spectra of compounds **1**–**13** are given in Figs. 1(*a*)–4(*a*). The vertical ionisation energies, $E_{i,v}$, or broad band maxima, are indicated above the corresponding band systems.

Standard semiempirical MNDO SCF MO calculations were performed for all compounds using the QCPE 464 (IBM MOPAC) program adapted for the Siemens 7580S (turbo version) at the Computing Centre of the University of Düsseldorf. The calculations were carried out for different conformations with a fixed (torsional) dihedral angle θ between the ring planes (θ ranging from 0 to 90° in increments of 15°) and for fully optimised geometries as well. Input geometries were optimised initially with a molecular mechanics (MM2) method. For all compounds discussed here calculations predict the structure with almost perpendicular ring systems (~85–91°) to be the most stable, *i.e.* with the lowest molar enthalpy of formation. (The total energies and molar enthalpy of formation may not always yield a correct prediction for the equilibrium dihedral angle.)[16] For comparison, in the X-ray crystal structure analysis of *N*-(4-fluorophenyl)-2,5-dimethylpyrrole-3-carbaldehyde (4-FPhPA),[17] the torsional angle between the two rings is −95.7°. However, crystal and gas phase structures are rarely found to be the same.

Results and discussion

Figs. 1–4 show the HeI PE spectra with the corresponding correlation diagrams of compounds **1**–**5** [Fig. 1(*a*) and (*b*)], **6**–**8** [Fig. 2(*a*) and (*b*)], **9** and **10** [Fig. 3(*a*) and (*b*)] and **11**–**13** [Fig. 4(*a*) and (*b*)]. Only π- and n-type orbitals will be discussed here, because σ-ionisation appears in the higher energy region (E_i > 12 eV).

The proposed assignment of the low energy region (up to ⩽12 eV) of the spectra, as shown in the correlation diagrams [Figs. 1(*b*)–4(*b*)] is based primarily on the calculations and when necessary, on the composite molecule method (CMM method), which was crucial for the interpretation of some spectra [see Fig. 4(*a*) and (*b*)].

The interpretation of the electronic structure of compounds **1**–**5** on the basis of their PE spectra, and the results of MNDO quantum chemical calculations is rather straightforward [see Fig. 1(*a*) and (*b*)].

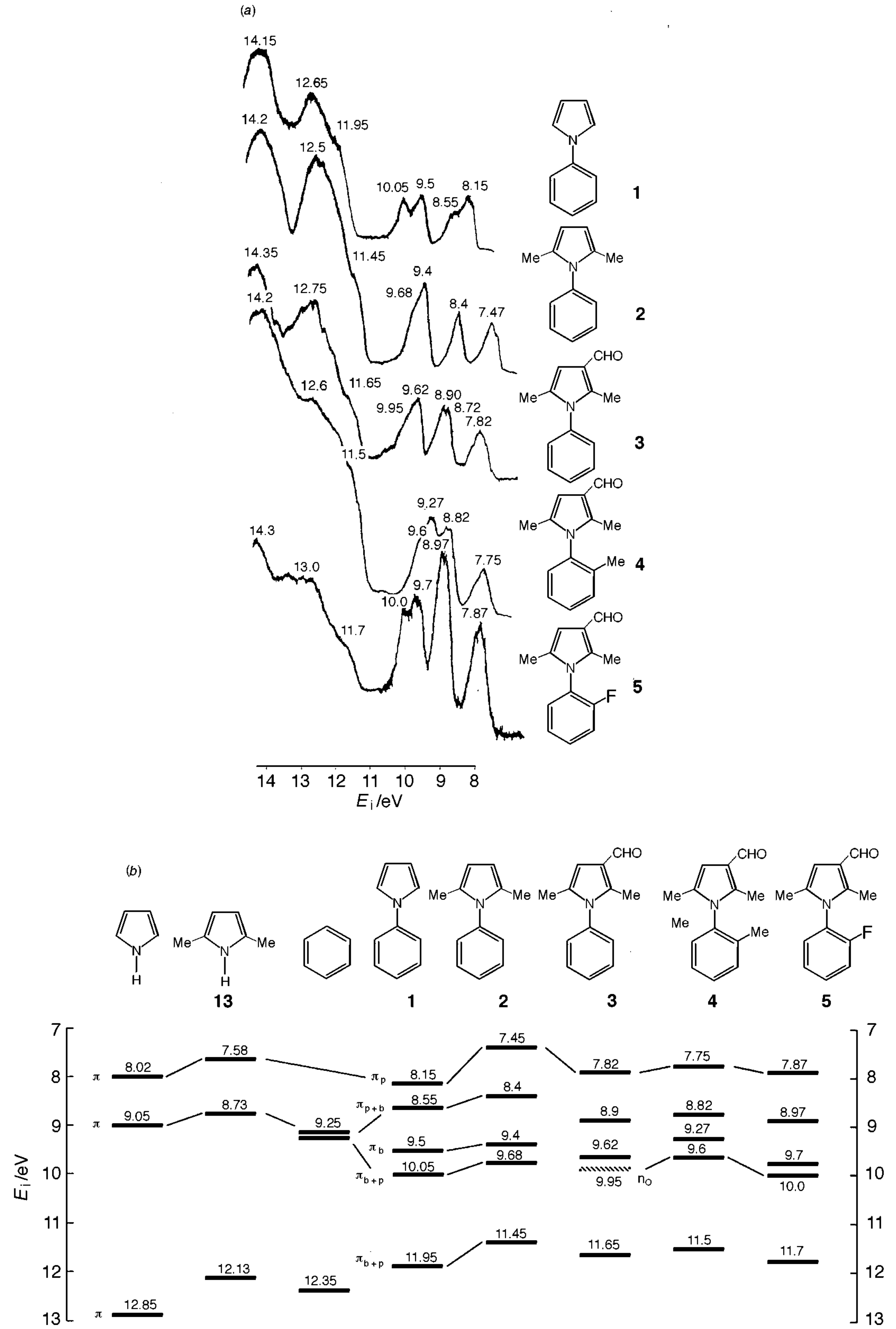
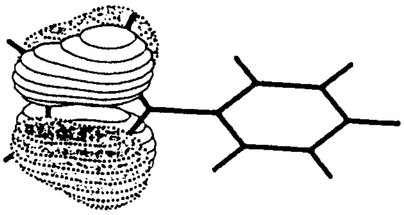


Fig. 1 (*a*) HeI PE spectra of compounds **1**–**5**; (*b*) proposed assignment of the low energy region of the HeI PE spectra of compounds **1**–**5**

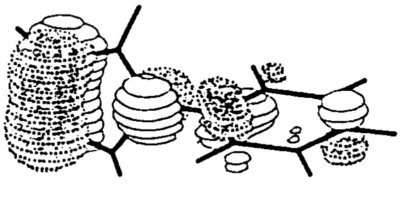
N-Phenylpyrrole (1)

The compound **1**, at least formally, consists of two entities, pyrrole and benzene, and the quantum chemical picture for the whole molecule can be generated from the orbitals of the separate fragments. Were the two pyrrole and benzene moieties strictly orthogonal, no π-interaction between them would be expected. For such a configuration MNDO calculations predict two pure pyrrole and two pure benzene MOs, as the four outermost orbitals of **1**. But the PE spectrum [Fig. 1(*a*)] and the correlation diagram [Fig. 1(*b*)] clearly show that some mixing occurs and that probably $\theta \neq 90°$.

In the PE spectrum of **1**, there are two electronic systems in the energy region 8–9 eV, which are assigned to two, mainly pyrrole-type orbitals. The highest energy orbital (HOMO) has significant orbital coefficients in the 2- and 5-positions and a nodal plane through the N-atom. Therefore, irrespective of the torsional angle an interaction with the benzene ring π-orbitals is not expected. This is confirmed by MNDO calculations for



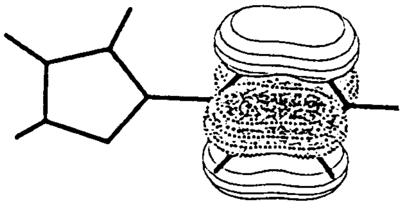
1 HOMO
$-E^{\mathrm{MNDO}} = 8.53$ eV



1 SHOMO
$-E^{\mathrm{MNDO}} = 9.16$ eV

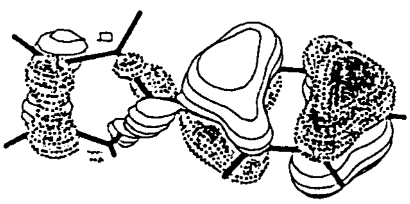
different conformations. The second orbital, SHOMO, has a nodal plane through the 2,5-positions of the pyrrole ring, and a significant contribution from the N atomic orbital. This orbital is subject to more or less pronounced interaction with benzene type π-orbitals, depending on the dihedral angle between the two moieties. The best results are achieved for the almost perpendicular (80–90°) conformation of rings, because the difference in the eigenvalues, ΔE^{MNDO}, best reflects the observed band splitting in the PE spectrum.

Two systems appear in the energy region of 9–10.5 eV. The one of lower energy (at 9.5 eV) is ascribed to the benzene orbital with the nodal plane through the 1,4-positions, thus excluding interaction with the pyrrole system at any torsional angle. Therefore, one should expect this system to have almost the same ionisation energy in **2**, **3** and **5**, although there will be some difference due to the inductive effect of 2,5-di-Me and/or 3-CHO group.



1 3rd MO
$-E^{\mathrm{MNDO}} = 9.66$ eV

The system at 10.05 eV, however, corresponds to electron ejection from an orbital with significant contribution of both rings. The higher energy region (with ionisation energies >11.5 eV) corresponds to electron ejection from the mixed benzene–pyrrole π- and σ-orbitals.

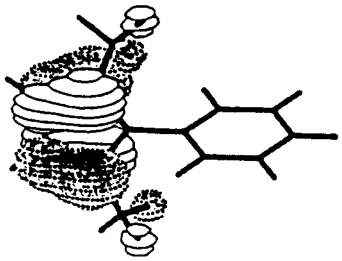


1 4th MO
$-E^{\mathrm{MNDO}} = 9.73$ eV

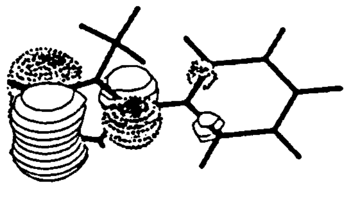
N-Phenyl-2,5-dimethylpyrrole (2)

In the PE spectrum of **2** [Fig. 1(*a*)], the effect of the two Me groups substituted in the 2- and 5-positions of the pyrrole ring is predominant.

The HOMO is again of the pyrrole type, shifted from 8.15 eV in **1** to 7.47 eV in **2**, due to the hyperconjugative effect of the two methyl groups on the large electron density in the 2- and 5-positions of pyrrole. Compared with the HOMO of 2,5-dimethylpyrrole (**13**) the system is destabilised by only 0.1 eV (7.58 eV in **13** *vs.* 7.47 eV in **2**). The systems at 8.4 and 9.4 eV in **2** remain almost unperturbed in comparison to their position in **1** and are assigned to pyrrole and benzene π-orbitals, with the zero orbital coefficient in the 1- and 1,4-positions, respectively. The system occurring at 10.05 eV in **1** is shifted to 9.68 eV in **2**, on account of the mixing of benzene with 2,5-dimethyl pyrrole orbitals.



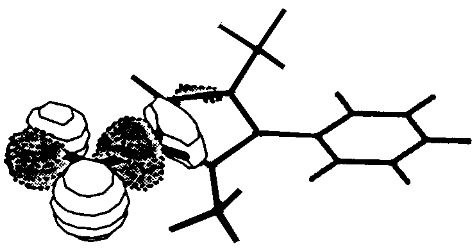
2 HOMO
$-E^{\mathrm{MNDO}} = 8.38$ eV



2 SHOMO
$-E^{\mathrm{MNDO}} = 9.26$ eV

N-Phenyl-2,5-dimethylpyrrole-3-carbaldehyde (3)

In the case of **3**, the overall feature of the spectrum resembles the PE spectrum of **2**, but shifted to a higher energy region, due to the inductive effect of the -CHO group in the 3-position. However, one more band system is expected in the low energy region, which may be assigned to the oxygen lone pair ionisation. MNDO calculations and empirical arguments indicate[18,19] that the shoulder of the band system at 9.95 eV is due to the oxygen lone pair ionisation.



3 n_O
$-E^{\mathrm{MNDO}} = 10.57$ eV

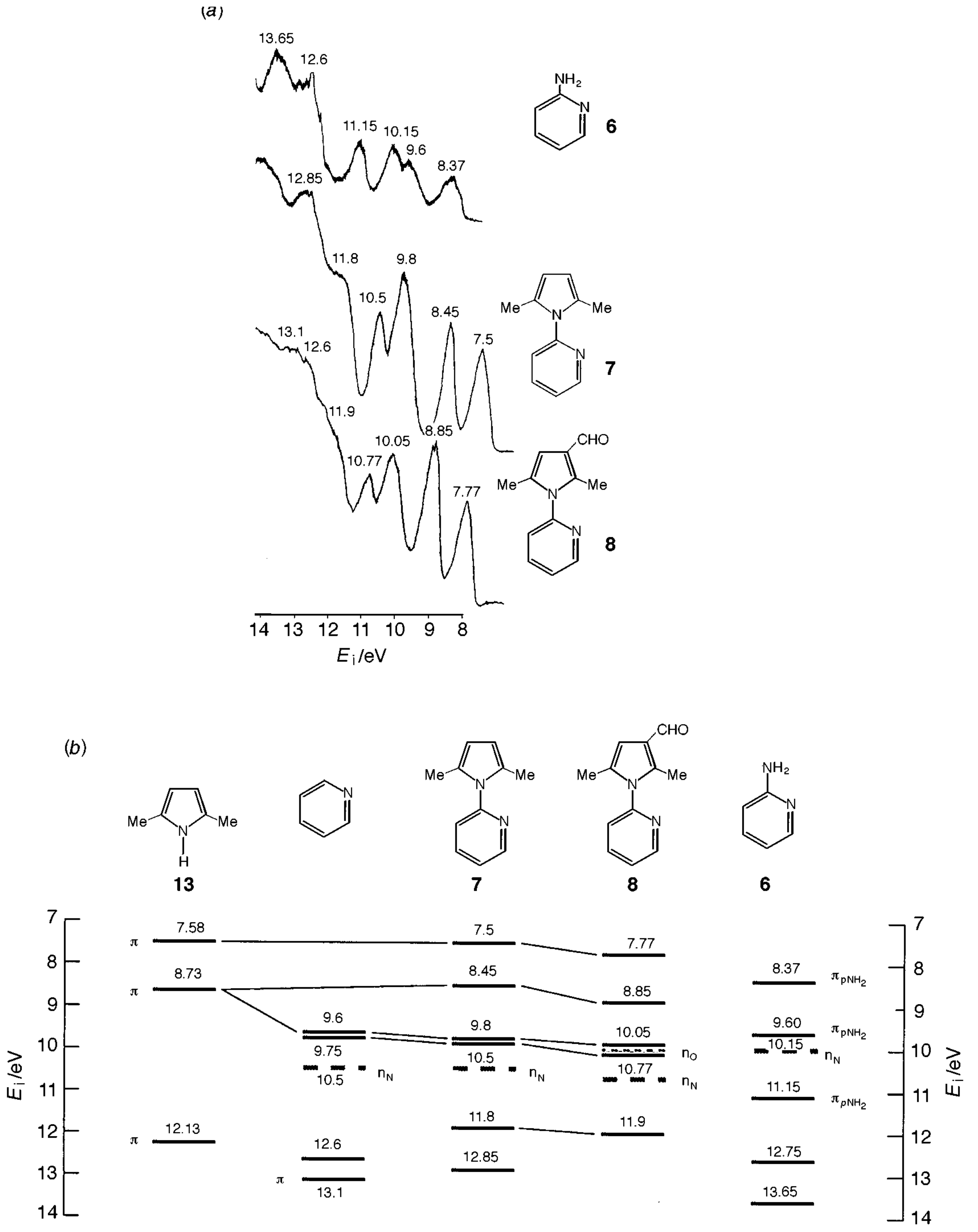


Fig. 2 (*a*) HeI PE spectra of compounds **6**–**8**; (*b*) proposed assignment of the low energy region of the HeI PE spectra of compounds **6**–**8**

N-(2-Methylphenyl)-2,5-dimethylpyrrole-3-carbaldehyde (4) and *N*-(2-fluorophenyl)-2,5-dimethylpyrrole-3-carbaldehyde (5)

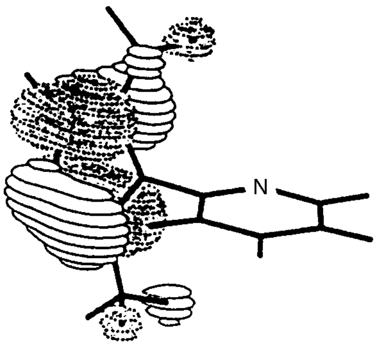
Compounds **4** and **5** differ from **3** by the presence of one substituent (-Me in **4**, -F in **5**) in the benzene moiety and exert, in comparison to **3**, a slight inductive destabilisation and stabilisation, respectively, of all systems in their spectra. The effect is most prominent in the system at 9.27 eV for **4** (9.62 eV in **3**). In the MO picture (results of MNDO calculations) this electronic system results from electron ejection from the predominantly benzene-type orbital which has a 1,4-nodal plane, *i.e.* high electron density at the Me substituent position and a strong hyperconjugative effect, shown by the Me group.

N-Phenyl-2,5-dimethylpyrrole-2-aminopyridine (6), *N*-(2-pyridyl)-2,5-dimethylpyrrole (7), *N*-(2-pyridyl)-2,5-dimethylpyrrole-3-carbaldehyde (8)

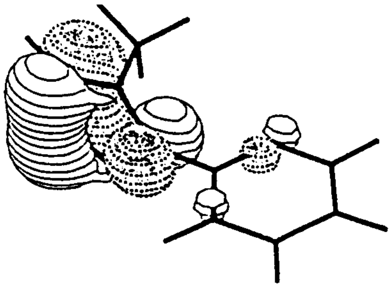
The PE spectra of **6**–**8** are shown in Fig. 2(*a*), and their interpretation is supported by the correlation diagram in Fig. 2(*b*). The low energy region *i.e.* up to <14 eV, is ascribed to π and lone pair (n_O, n_N) ionisations.

The overall feature of the PE spectrum of **7** shows all the main characteristics of the 2,5-dimethylpyrrole (**13**) and pyridine PE spectra.[20,21] Thus, first ionisation potentials in **7** and **13** (7.5 and 7.58 eV, respectively) are almost identical. No interaction with pyridine ring orbitals is expected according to the MNDO calculations (see pictures below). The loss of vibrational structure indicates some mixing, though. The second ionisation potential is shifted from 8.73 eV in **13** to 8.45 eV in **7**. The explanation for this is given on the basis of MNDO calculations: mixing of pyrrole orbitals with pyridine orbitals has taken place. The loss of vibrational structure is also evident [see Fig. 2(*a*)].

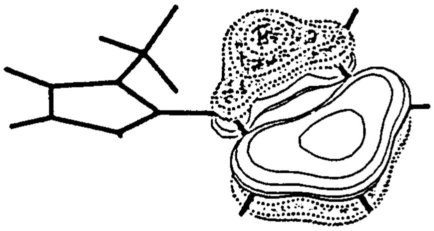
The energy region from 9–11 eV represents the electronic systems arising from ionisations from pyridine-type orbitals. The band maximum at 9.8 eV is assigned to two nearly degenerate systems, as its relative intensity suggests. According



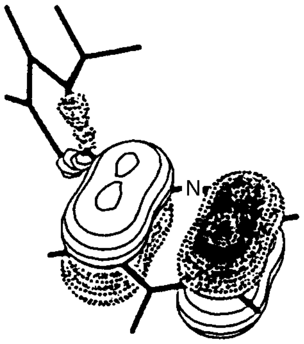
7 HOMO
-E^{MNDO} = 8.37 eV



7 SHOMO
-E^{MNDO} = 9.29 eV

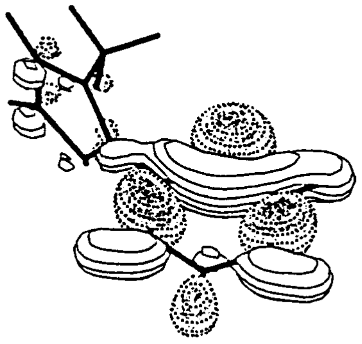


7 3rd MO
-E^{MNDO} = 9.94 eV



7 4th MO
-E^{MNDO} = 10.80 eV

to the MNDO calculations, both systems are assigned to ionisations from the orbitals with considerable electron density on the pyridine ring. Comparison with the PE spectrum of pyridine[20,21] supports this explanation. Therefore, the PE spectrum of **7** confirms the presumption that the torsion (dihedral) angle between the pyrrole and pyridine rings is nearly 90° (−90.2°). The electronic systems corresponding to the same type of ionisation can be found at almost the same energy as other compounds: 9.6 eV in **6**, nearly 9.6 eV in pyridine, 9.8 eV in **7** and 10.05 eV in **8**. The system at 10.5 eV is assigned, as in pyridine, to ionisation from the predominantly n_N lone-pair orbital.

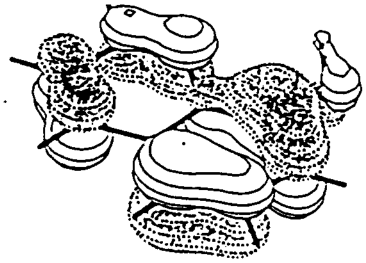


7 n_N
-E^{MNDO} = 11.26 eV

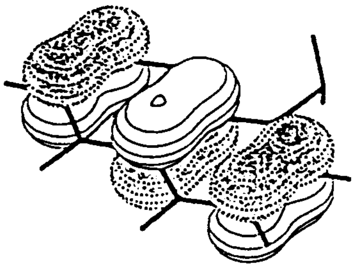
Substitution by the -CHO group as in **8**, stabilises all the systems and an additional oxygen lone-pair orbital ionisation is found in the energy region at 10 eV.

8-Aminoquinoline (9) and *N*-(8-quinolyl)-2,5-dimethylpyrrole (10)

The perturbation caused by an amino group, as in **9**, or 2,5-dimethylpyrrole substitution, as in **10**, on the quinoline ring electronic structure, is clearly shown in Figs. 3(*a*) and (*b*).



9 HOMO
-E^{MNDO} = 9.02 eV



9 SHOMO
-E^{MNDO} = 9.41 eV

The HOMO in **9** results from mixing of the -NH_2 group orbital with the quinoline π-orbital (electronic system at 7.65 eV). According to quantum chemical calculations the nodal plane passes through the substitution position (-NH_2) in the SHOMO. Thus no change in electron ionisation from this orbital is expected in comparison to the same system in quinoline (9.01 and 9.16 eV, respectively). Ionisation from mainly the nitrogen lone-pair orbital, n_N is assigned to the system at 9.45 eV. The first ionisation system (7.12 eV) in **10**, as calcul-

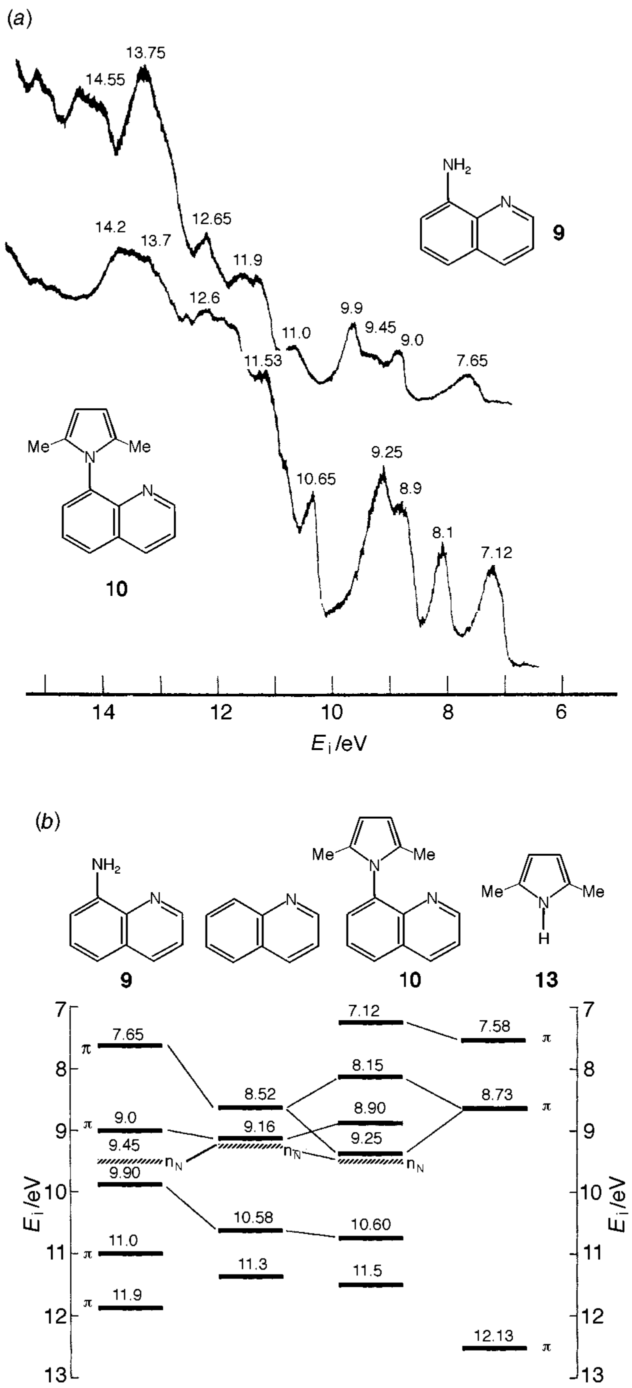
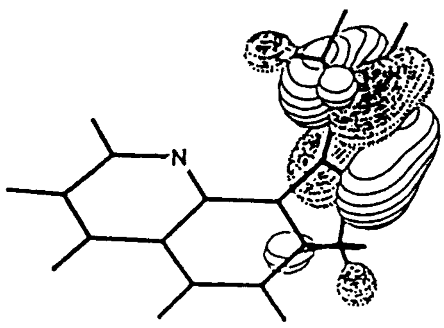


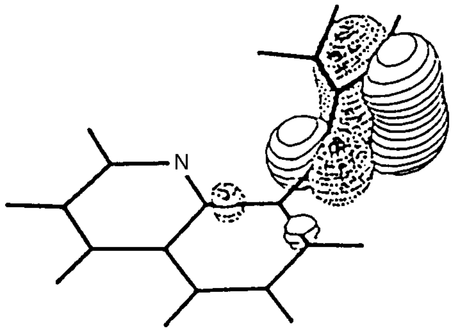
Fig. 3 (*a*) HeI PE spectra of compounds **9** and **10**; (*b*) proposed assignment of the low energy region of the HeI PE spectra of compounds **9** and **10**

ations suggest, is ascribed to the HOMO with pure pyrrole character, as in all the aforementioned compounds. The second (8.15 eV) and the fourth systems (9.25 eV) result from ionisation events from anti-symmetric and symmetric linear combinations of quinoline and pyrrole orbitals, respectively. The third system at 8.90 eV results from ionisation from the pure quinoline orbital with a nodal plane through the substitution position. The same type of ionisation in quinoline and **9** are found at nearly the same energy (9.16 and 9.01 eV, respectively).

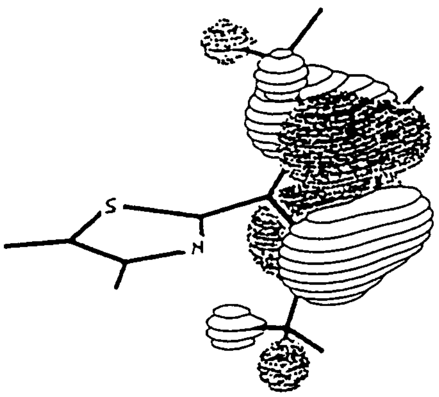
The energy region at 9.25 eV reveals the presence of two electronic systems as supported by the relative intensity. Besides the one (already mentioned) due to electron ejection from the molecular orbital described as symmetric linear combination of quinoline and pyrrole orbitals, the other one originates from the lone-pair orbital predominantly located on nitrogen.



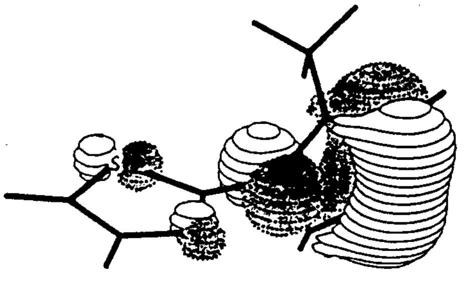
10 HOMO
$-E^{\mathrm{MNDO}} = 8.17$ eV



10 SHOMO
$-E^{\mathrm{MNDO}} = 9.06$ eV



12 HOMO
$-E^{\mathrm{MNDO}} = 8.62$ eV



12 SHOMO
$-E^{\mathrm{MNDO}} = 9.54$ eV

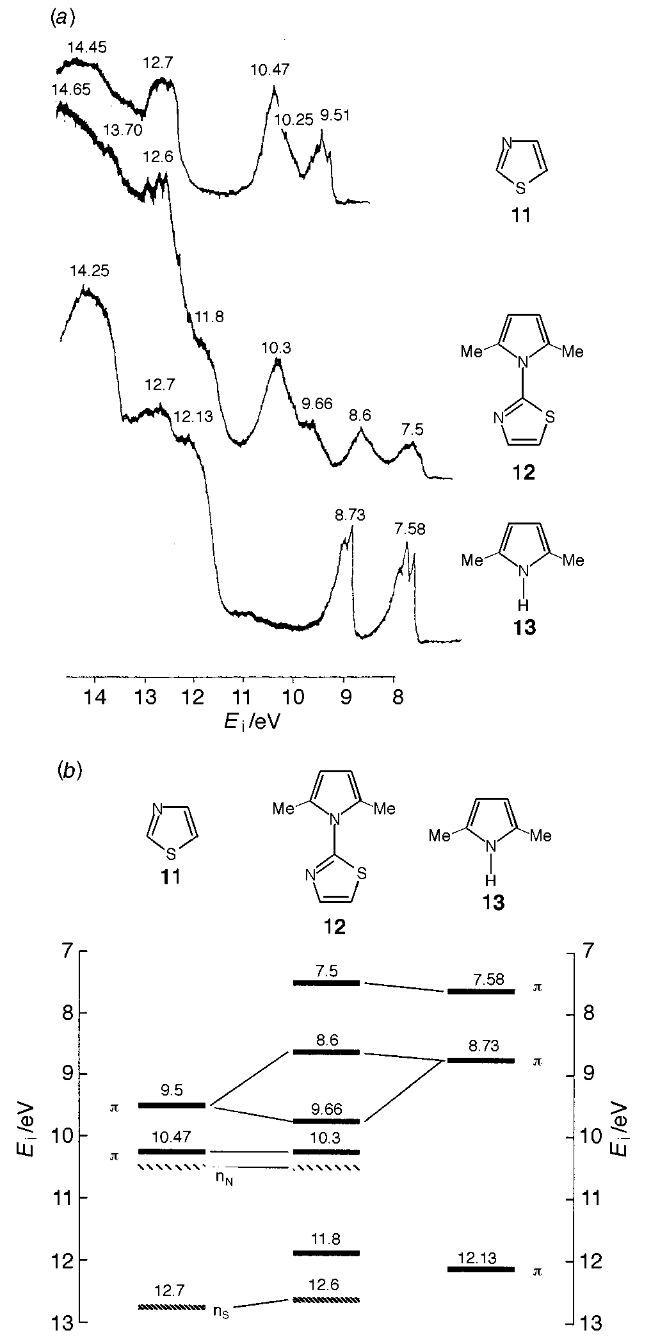
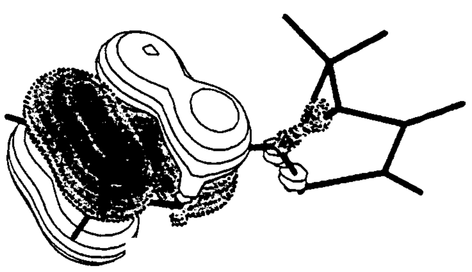


Fig. 4 (*a*) HeI PE spectra of compounds **11**–**13**; (*b*) proposed assignment of the low energy region of the HeI PE spectra of compounds **11**–**13**

Thiazole (11), *N*-(thiazol-2-yl)-2,5-dimethylpyrrole (12) and 2,5-dimethylpyrrole (13)

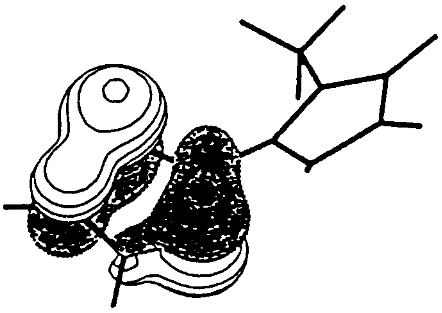
Figs. 4(*a*) and 4(*b*) show the PE spectra and the corresponding correlation diagram for compounds **11**–**13**. The overall feature of the PE spectrum of **12** looks like superposition of the PE spectra of **11** and **13**, but some perturbation is evidently taking place. The first system is almost the same as the one in **13**, but with less pronounced vibrational structure, and should be assigned to electron ejection from the pyrrole-type[22] orbital. Calculations strongly support such an interpretation (see the orbital picture below). The broadening of the second system with only slightly destabilised band maximum (8.6 eV in **12** compared to 8.73 eV in **13**) suggests some mixing of the two rings. But the character of this MO is predominantly pyrrole-type. Some mixing is evident from the broadness of the third system at 9.66 eV, but the thiazole[23] character predominates (at 9.5 eV in **11**). The band maximum at 10.3 eV, just as the one at 10.47 eV in **11**, is assigned to two overlapping electronic systems. Namely, ionisations from the purely thiazole π-orbital and the nitrogen lone pair orbital, n_N, are nearly degenerate.

Electron ejection from the sulfur lone-pair orbital (n_S) is found at 12.2 and 12.7 eV in the PE spectra of **12** and **11**, respectively, in agreement with results on thiazole[23a] and the HeI/HeII intensity dependence of the PE spectrum of thiophene.[23b]



12 3rd MO

$-E^{\text{MNDO}} = 10.02$ eV



12 4th MO

$-E^{\text{MNDO}} = 10.98$ eV

Conclusions

This study shows that spectroscopic and quantum chemical results in combination with composite molecule arguments can yield a reliable assignment of electronic structure. Since most pharmacologically interesting molecules are built from already biologically active constituents such an approach allows a systematic investigation of increasingly complex molecules of biological interest.

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