MNDO and MINDO/3 Study of the Reactivity of 3-Pyrrolin-2-one Tautomers and Derivatives

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MINDO/3 and MNDO methods have been applied to the study of the reactivity of 3-pyrrolin-2-one tautomers and derivatives. The different parameters that can influence the reactivity from the frontier molecular orbital point of view (atomic charge distribution, frontier orbital energy and frontier orbital reactivity indices) are compared and evaluated with respect to the experimental reactivity already known.

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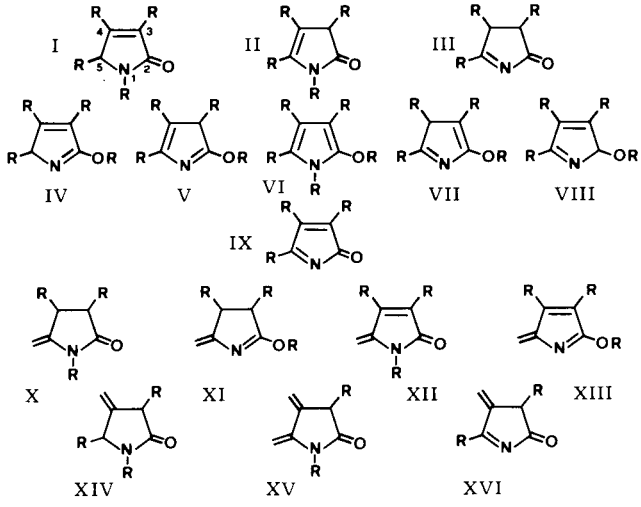
3-Pyrrolin-2-one tautomers and derivatives (see formula scheme) are models of the terminal rings of linear tetrapyrrolic pigments. In an earlier paper [1] we have already presented our MINDO/3 and MNDO results on the stability of such compounds.

Some differences between the MINDO/3 and MNDO calculated geometries (among which completely different dihedral angle for the hydroxylic hydrogen in 2-hydroxy-1*H*-pyrroles (**VI**) is the most remarkable) were also noticed. To our knowledge experimental geometries of the compounds studied in this paper are unknown, nevertheless at present there are enough X-ray data about pyrromethenones [2], 3,4-dihydropyrromethenones [3] and tetrapyrrolic pigments [4] that contain subunits very similar to the here described structures to allow us to make some new comments: MNDO always gives longer bond distnces (sometimes the difference between MINDO/3 and MNDO is as large as 0.07 Å) between carbons and nitrogens, or carbons and oxygens, nevertheless MINDO/3 seems to predict better values for bond distances between carbons and nitrogens, while MNDO seems to be better for carbons and oxygens. Bond distances between carbon atoms sometimes are larger by MNDO and sometimes larger by MINDO/3, the smaller values seems to be more similar to the known X-ray data. MINDO/3 predicts N-C2-O (numbering used in tables) and O-C2-C3 bond angles more in agreement with the X-ray data, while MNDO gives usually values 4-5° narrower and 4-6° wider, respectively, than MINDO/3 for the same bond angles. All 2-methoxy derivatives calculated (IV-VI, f and g) show 10-12° wider C2-O-C bond angles by MINDO/3 than by MNDO, nevertheless MNDO gives a value for this bond angle in 5-methoxy-2*H*-pyrrole derivatives (IV, R-O-C2 = CH_3) (only alkoxy stable tautomers that exist) more close to the X-ray datum (MNDO: 122.9°; X-ray [4c]: 117.0°). However both methods are equally good to calculate the inner bond angles of the rings.



	R-N	R-O-C2	R-C3	R-C4	R-C5	calculated
a	H	H	H	H	H	I-VIII
b	H	H	CH_3	CH_3	H	I-VI
c	H	H	CH_3	CH_3	CH_3	I-III, VI, IX
d	CH_3	H	H	H	H	I, II, VI
e	CH_3	H	CH_3	CH_3	H	I, II, VI
f	H	CH_3	H	H	H	IV-VI
g	H	CH_3	CH_3	CH_3	H	IV-VI
h	CHO	H	H	H	H	I, II, VI
i	H	H	H	CHO	H	I, II, VI
j	H	H	H	H	$=CH_2$	X, XII
k	H	H	CH_3	CH_3	$=CH_2$	X trans, cis, XI-XIII
l	H	H	CH_3	$=CH_2$	CH_3	XIV trans, cis, XVI
m	H	H	CH_3	$=CH_2$	$=CH_2$	XV

In spite of being rather rough, the geometrical parameters predicted by MINDO/3 and MNDO are good enough for many purposes. Nevertheless it must not be forgotten that semi-empirical methods of calculation predict geometries for isolated molecules, while X-ray data correspond to very compact structures, where interaction between molecules is very large.

Refering to the stability, it is known that errors in ΔH_f°

calculated by MINDO/3 or MNDO can be very large [5-9], and the absolute value of the error, as well as its sign, depend very much on the particular structure studied (benzene: MINDO/3 [9] +37.7 kJ.mol^{-1}, MNDO [8] +5.9 kJ.mol^{-1}; pyridine: MINDO/3 [6] −2.1 kJ.mol^{-1}, MNDO [8] −24.7 kJ.mol^{-1}; phenol: MINDO/3 [6] −23.0 kJ.mol^{-1}, MNDO [8] -7.1 kJ.mol^{-1}). In the study of the tautomerism of 3-pyrrolin-2-one [1] it was seen that sometimes neither MINDO/3 nor MNDO were able to predict the experimental relative order of stability of the tautomers. Thus, 3,4,5-trimethyl-2-hydroxypyrrole (**VIc**) was expected to be more stable than 3,4,5-trimethyl-4-pyrrolin-2-one (**IIc**), and this one was predicted to be more stable than 3,4,5-trimethyl-3-pyrrolin-2-one (**Ic**) by both methods, just in the reverse order of the experimental evidence. Therefore the study of the reactivity of pyrrole derivatives by the approach of the reaction-coordinate is not suitable. Our aim in this work is to compare MINDO/3 and MNDO methods from the reactivity point of view of the frontier molecular orbital model.

Computational Procedure.

Standard MINDO/3 [5] and MNDO [7] semi-empirical SCF-MO methods have been used. Geometry optimizations were carried out without further assumptions than the restriction of equality of the CH bond lengths and HCH bond angles within each methyl group, and within each methylene group belonging to a planar five-membered ring. The geometry optimization procedure was found to be unable to change the methyl group conformations [1].

Reactivity indices have been calculated following the frontier orbital model [10] in its simplest version. That is, taking into consideration only the atomic coefficients in the frontier molecular orbitals (or frontier plus next-to-frontier, when degeneracy or nearly degeneracy occurs).

Results and Discussion.

MINDO/3 *vs.* MNDO Charge-Controlled Reactivity. Net Atomic Charge Distribution.

MINDO/3 net atomic charge distribution gives a much exaggerated charge separation than MNDO at the bondings between carbon and oxygen (C-O and C=O): at the carbon atom, the difference between MINDO/3 and MNDO values is larger than 0.20 (all carbon atoms studied here are also linked to nitrogen, but their net atomic charge shows the main influence of oxygen). This difference is usually larger than 0.30 (0.36 maximum value observed) when the carbon atom belongs to a C=C-*C*HO, C=N-*C*=O or N=*C*-O group. At the oxygen atom, the difference between MINDO/3 and MNDO values is bigger (0.24-0.26) also when it belongs to a C=N-C=O or N=C-O group. The difference is smaller (0.18-0.20) in the 2-hydroxy-1*H*-pyrrole structures (**VI**). These differences decrease when the oxygen belongs to a methoxy group. Thus, the 2-methoxy-1*H*-pyrrole structures (**VI**, R-O-C2 = CH_3) show the smaller difference (0.14) between MINDO/3 and MNDO values.

Carbons bonded to nitrogen behave in a different way depending on their nature (carbon atoms bonded also to oxygen have not been considered here). Carbon atoms belonging to an azomethine double bond, and sp^3 or sp^2 hybridized carbons at the α position of an azomethine nitrogen are expected to be more positive (by 0.08-0.19) by MINDO/3 than by MNDO. sp^3 or sp^2 hybridized carbons linked to nitrogen, but not belonging either to the former group or to an exocyclic double bond, are predicted to have a similar charge (differences observed are between 0.00-0.06) by MNDO and MINDO/3 methods. Moreover, sp^3 hybridized carbon atoms bonded to nitrogen have a quite similar charge by MINDO/3 (between +0.16 and +0.20), while by MNDO they are much more widely

Table 1

MINDO/3 and MNDO Reactivity Indices Towards Electrophiles and Net Atomic Charge Distribution for 3,4-Dimethyl-3-pyrrolin-2-one (**Ib**)

	E				Charges	
	MINDO3		MNDO		MINDO3	MNDO
Orbital energy (eV)	−9.56	−9.62	−9.63	−10.10	−10.40	
oribital hybridization	π	π	σ	π	π	
N	1.05	0.29	0.27	0.27	1.11	−0.23	−0.45
C2	0.01	0.00	0.14	0.00	0.00	+0.63	+0.39
O-C2	0.46	0.03	0.81	0.34	0.15	−0.55	−0.34
C3	0.07	0.68	0.38	0.56	0.27	−0.12	−0.13
C4	0.02	0.63	0.08	0.47	0.31	+0.01	−0.11
C5	0.06	0.01	0.04	0.04	0.01	+0.18	+0.20
H-N	0.00	0.00	0.04	0.00	0.00	+0.09	+0.21

spread (between +0.09 and +0.23).

Nitrogen atoms behave also in different way depending on their nature. Azomethine nitrogens show the same charge either by MINDO/3 or by MNDO (differences are between 0.00-0.04). R_2N-H or R_2N-CH_3 nitrogens show a much more negative charge by MNDO. The difference between MINDO/3 and MNDO values for nitrogens belonging to R_2N-H groups is 0.14-0.22. This difference is larger (0.25-0.26) for nitrogens of R_2N-CH_3 groups.

Therefore, for the C-N bond between an sp^3 or sp^2 hybridized carbon and a nitrogen belonging to a R_2N-H or R_2N-CH_3 group, the charge separation is larger by MNDO. Thus, the charge separation between carbon and heteroatoms is not always larger by MINDO/3 than by MNDO. Oxygen and nitrogen behave in a different way.

3-Pyrrolin-2-ones (**I**) can be *O*-acetylated and *O*-methylated, by treatment, respectively, with acetic anhydride (even in the presence of sulphuric acid) and with dimethylsulphate or trimethyloxonium tetrafluoroborate [11]. According to the reactivity indices of the HOMO, MINDO/3 and MNDO do not predict for structures I a big reactivity towards electrophiles of their oxygen atom (see *e.g.* in Table 1 the case of 3,4-dimethyl-3-pyrrolin-2-one **Ib**). However, this characteristic behaviour can be explained through a charge-controlled process. Thus according to MINDO/3 atomic charge distribution, the highest negative net atomic charge is on the oxygen atom, in agreement with the experimental alkylation and acylation reactions, while MNDO places it on the nitrogen atom.

Hydrogen atoms bonded to heteroatoms behave in different way depending on the heteroatom. N-H hydrogens are calculated as more reactive towards bases by MNDO (their charge can be 0.16 more positive by MNDO than by MINDO/3), while O-H hydrogens are predicted to be more reactive towards bases by MINDO/3 (their charge can be 0.08 more positive by MINDO/3 than by MNDO). Thus in 2-hydroxy-1*H*-pyrrole structures (**VI**, R-O-C2 = H) the O-H hydrogen is predicted to react with bases much faster than the N-H hydrogen by MINDO/3 (N-H +0.05; O-H +0.25), while they are expected to react at a similar rate by MNDO (N-H +0.21; O-H +0.20). Table 2 shows that MINDO/3 net charges on hydrogen atoms bonded to heteroatoms (N, O) reflect their relative acidity, which is in accordance with the experimental pK_a order [12-14], when available. MNDO net charges for the same atoms do not agree with the experimental acidity order, nor with the acidity estimated from the differences of enthalpy of formation calculated by MNDO. The MNDO failure in predicting the acidity order is attributed mainly to an overestimation of the stability of the anion obtained by loss of the N-H hydrogen on the 1*H*-pyrrole structure (**VI**). Furthermore, for instance, the presence of methyl groups at positions 3 and 4 of the 3-pyrrolin-2-one ring (**I**) does not affect the N-H hydrogen charge by MINDO/3, while makes it 0.03 more positive by MNDO.

Thus, from the charge-controlled reactivity point of view, MINDO/3 is doubtless more in agreement with the experimental evidences than MNDO, for molecules containing both nitrogen and oxygen atoms.

Hydrogen atoms bonded to carbons are predicted to be less positive by MINDO/3 than by MNDO. MINDO/3 net atomic charge distribution gives usually negative charge on hydrogens at α position of a carbon atom belonging to a carbonyl or azomethine group, or at γ position of an α-β unsaturated carbonyl or azomethine double bond, in spite of their known experimental reactivity with bases [12]. Nevertheless it can be seen from the results of MINDO/3 calculations shown in Table 3, that when one of the hydrogens at a given position is substituted by a methyl group, the remaining hydrogen becomes more negative. Thus unsubstituted rings usually have positive C-H hydrogens even by MINDO/3, while alkyl substituted rings have negative charges on these hydrogens by MINDO/3. Therefore MINDO/3 seems to be too sensitive to the releasing effect of alkyl groups on their geminal substituents. It can then be deduced that with respect to MINDO/3 atomic charge distribution, methyl hydrogens can only be compared with other methyl hydrogens, methylene hydrogens with other methylene, ...When constraining to this rule, and in spite of their sometimes negative charge, MINDO/3 is able to predict, as well as MNDO does, which C-H hydrogen will be the more reactive. Compare for instance the charge on

Table 2

MINDO/3 and MNDO Estimated Acidities $\Delta(\Delta H_f^\circ)$ and Net Atomic Charge of Some Hydrogen Atoms Bonded to Heteroatoms. The Anion Considered is That Formed by Loss of the Hydrogen Atom in question

	q_H				ΔH_f° / (kJ/mol)						
	N-*H*		C2-O-*H*		neutral [1]		anion [12]		$\Delta(\Delta H_f^\circ)$		p*K*a for reference
	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO	
Ia	+0.09	+0.18			−140.8	−79.9	−117.2	−117.5	+23.6	−37.6	**Ib** [12] 17.1
IVa			+0.26	+0.22	−79.6	−63.1	−117.2	−117.5	−37.6	−54.4	
VIa			+0.25	+0.20	−125.4	−74.4	−158.3	−140.1	−32.9	−65.7	Phenol [13] 10.0
VIa	+0.05	+0.21			−125.4	−74.4	−71.6	−169.9	+53.8	−95.5	Pyrrole [14] 17.5

Table 3

Effect of a Geminal Methyl Group on the Net Atomic Charge on Hydrogen Atoms Bonded to Carbons

	H-C5		H-C3		H-C3		H-C4		H-C3		H-C4	
	Ib	**Ic**	**IIa**	**IIb**	**IIIa**	**IIIb**	**IIIa**	**IIIb**	**Xj**	**Xk**	**Xj**	**Xk**
MINDO/3	−0.04	−0.06	+0.01	−0.01	+0.02	−0.01	−0.01	−0.03	+0.02	−0.01	−0.02	−0.04
MNDO	+0.01	+0.02	+0.04	+0.05	+0.05	+0.05	+0.04	+0.04	+0.04	+0.05	+0.02	+0.03

Table 4

Comparison of the Net Atomic Charge on the Hydrogen Atoms of the Methyl Groups at Carbons 3 and 4

	H-C-C3		H-C-C4	
	Ib	**Ie**	**Ib**	**Ie**
MINDO/3	−0.03	−0.03	−0.01	−0.01
MNDO	0.00	0.00	+0.01	+0.01

the methyl hydrogens at positions 4 and 3 of 3,4-dimethyl-3-pyrrolin-2-one (**Ib**) and 1,3,4-trimethyl-3-pyrrolin-2-one (**Ie**), where the hydrogens of the methyl group at position 4 (see Table 4) are always predicted to be more reactive with base, in agreement with deuteration experiments in alkaline medium [12]. In the same way the hydrogen at position 3 of 3,4-dimethyl-5-methylene-pyrrolidin-2-one (**Xk**-*trans*, **Xk**-*cis* and also **Xj**) is expected to be more reactive with bases than that at position 4 (see Table 3), in agreement with experiments on 5-arylcyanomethylene derivatives [15].

MINDO/3 *vs.* MNDO Frontier Orbital Energy and Hybridization.

MNDO predicts a lower energy for the frontier molecular orbitals than MINDO/3 does (except for 2-methoxy-1*H*-pyrrole structures **VIf** and **g**, where the MNDO LUMO is 0.1 eV less stable than the MINDO/3 LUMO). The larger difference between MINDO/3 and MNDO values (0.6-1.6 eV) is found in structures having an azomethine nitrogen. For structures not having an azomethine nitrogen, the difference between MINDO/3 and MNDO energies is 0.4-0.8 eV.

The effect of substituents follows the same general trends by both MINDO/3 and MNDO, but quantitatively the effect is not always the same.

The presence of methyl groups at positions 3 and 4 decreases the stability of the HOMO and increases that of the LUMO (see Table 5). The only exceptions are molecules without participation of atoms 3 and 4 in the corresponding frontier orbital, *i.e.* when either C3 and C4 are sp^3, and 2-hydroxy (or alkoxy)-1*H*-pyrrole structures (**VI**) where the ring is already very electron-rich (enamine and enol). Nevertheless, the presence of methyl groups at positions 3 and 4 always decreases the energy gap between HOMO and LUMO, either by MINDO/3 or by MNDO; the only exception being 5-methylene-pyrrolidin-2-one (**Xj**) by MNDO, where the effect is very small (0.02-0.04 eV) but in the opposite direction.

Table 5

Effect of the Presence of Methyl Groups at Positions 3 and 4 on the Energy (eV) of HOMO and LUMO

	ϵHOMO		ϵLUMO	
	MINDO3	MNDO	MINDO3	MNDO
Ia	−9.63	−10.34	0.54	−0.18
Ib	−9.56	−10.10	0.23	−0.28
IIa	−8.74	−9.19	1.09	0.46
IIb	−8.52	−9.15	0.97	0.36
VIa	−7.72	−8.47	1.57	0.97
VIb	−7.73	−8.50	1.39	0.89

The quantitative effect of the presence of methyl groups at positions 3 and 4 on the stability of the frontier orbital parallels the effect on the stability of the molecule (ΔH_f° [1]). Both MINDO/3 and MNDO slightly stabilize (0.01-0.04 eV) the HOMO of the dialkylsubstituted 2-hydroxy (or alkoxy)-1*H*-pyrrole forms (**VIb**, *e.g*) (see Table 5). Nevertheless the methyl groups at positions 3 and 4 decrease the stability of the HOMO of 4-pyrrolin-2-ones (**II**) or 2-hydroxy (or alkoxy)-3*H*-pyrroles (**V**), this effect being always more pronounced by MINDO/3 than by MNDO, and being the more accentuated case that of 4-pyrrolin-2-one itself ($\Delta\epsilon_{HOMO}$ MINDO/3 = 0.22 eV; $\Delta\epsilon_{HOMO}$ MNDO = 0.04 eV). While the decrease in stability of the HOMO of 3-pyrrolin-2-ones (**I**) or 5-hydroxy (or alkoxy)-2*H*-pyrroles (**IV**) due to the presence of methyl groups at positions 3 and 4 is more pronounced by MNDO than by MINDO/3, being the more accentuated case that of 3-pyrrolin-2-one itself ($\Delta\epsilon_{HOMO}$ MINDO/3 = 0.07 eV; $\Delta\epsilon_{HOMO}$ MNDO = 0.24 eV). Thus, MINDO/3 seems to match more closely the experimental fact of the big increase in stability of the 3-pyrrolin-2-one form (**I**) when alkyl groups are present at positions 3 and 4.

The effect of a formyl group in increasing the stability of HOMO and LUMO is very similar either by MINDO/3 or by MNDO (much greater in the LUMO than in the HOMO [16]).

Either MINDO/3 and MNDO predict degenerate or nearly degenerate frontier orbitals, but MINDO/3 predicts

more degenerate or nearly degenerate unoccupied frontier orbitals. The limit for nearly degeneracy has been taken here as 0.40 eV. Sixteen different structures (see formula scheme, 48 compounds) have been studied, but only 5 of them show no degeneracy (either in the HOMO or in the LUMO) either by MINDO/3 or MNDO. Among the 11 structures that show degeneracy, some of them appear as degenerate by both MINDO/3 and MNDO methods, and some only by one of the methods (MINDO/3 or MNDO). Among these 11 structures, 5 show degeneracy in their HOMO by MINDO/3, and 5 by MNDO (not necessarily the same 5 structures); 8 show degeneracy in their LUMO by MINDO/3 and only one by MNDO.

Among the 9 differently substituted 2-hydroxy (or alkoxy)-1*H*-pyrroles (**VI**) calculated, that are the aromatic structures studied, only one shows degeneracy, and only in the LUMO, and by MINDO/3 only.

Degeneracy in the HOMO (**I, IV, IX, XIII, XVI**) seems to be associated with Δ^3 double bonds, and degeneracy in the LUMO (**II, V, X**) associated with Δ^4 double bonds, while degeneracy in both orbitals (**XI, XIV**) seems to be associated with exocyclic double bonds at positions 4 or 5, but the rule is not always followed.

Either MINDO/3 and MNDO predict σ frontier or next-to-frontier orbitals, but MINDO/3 predicts more of them. Among the 16 different structures that have been studied, only 3 have no σ frontier or next-to-frontier orbitals, either by MINDO/3 or MNDO. Among the 13 structures that have σ frontier orbitals, 4 have σ frontier orbitals by both MINDO/3 and MNDO, and 9 only by MINDO/3. No one has σ frontier orbitals only by MNDO. Among these 13 structures, 9 show σ occupied frontier orbitals by MINDO/3, and 4 of these 9 also by MNDO. 8 of these 13 structures have unoccupied σ frontier orbitals by MINDO/3, but no one by MNDO.

All 9 differently substituted 2-hydroxy (or alkoxy)-1*H*-pyrroles calculated have σ unoccupied frontier orbitals by MINDO/3.

The existence of σ occupied frontier orbitals (**I, III, IV, VIII, IX, XIII, XVI**) seems to be associated with Δ^3 or Δ^5 double bonds, and the existence of σ unoccupied frontier orbitals (**IV-VI, X**) seems to be related to the presence of Δ^4 double bonds, while the presence of σ occupied and unoccupied frontier orbitals (**XI, XIV**) seems to be related to exocyclic double bonds at positions 4 or 5, but the rule is not always true.

Degeneracy and the existence of σ frontier orbitals seem to be associated, but the rule is not always followed, thus *e.g.* 5-pyrrolin-2-ones (**III**) have single HOMO that are σ by both MINDO/3 and MNDO, 2-hydroxy (or alkoxy)-1*H*-pyrroles (**VI**) have single LUMO that are σ by MINDO/3.

MINDO/3 *vs.* MNDO Orbital-Controlled Reactivity.

MINDO/3 and MNDO do not always agree in their predictions.

2-Hydroxy (or alkoxy)-1*H*-pyrroles (**VI**) are the tautomers with higher HOMO and LUMO either by MINDO/3 or by MNDO (with the exception of the LUMO of 1-formyl-2-hydroxy-1*H*-pyrrole (**VIh**) by MNDO).

3-Pyrrolin-2-one (**I**) tautomers have the lower HOMO and LUMO by MINDO/3 [17], but the lower HOMO and LUMO by MNDO correspond to 5-pyrrolin-2-one tautomers (**III**).

Of the 48 compounds presented in this work, only 4 show the same relative order of reactivity indices by MINDO/3 and by MNDO. In 16 compounds the reactivity indices towards nucleophiles, or towards electrophiles, or both, are different enough to give a different first reactive centre by each method.

Important changes in relative reactivity order between MINDO/3 and MNDO are more often found among 5-methylene-pyrrolidin-2-ones (**X**), 5-pyrrolin-2-ones (**III**), structures containing an α,β-unsaturated azomethine double bond (C=C-C=N) (**IV, VIII, IX** and **XIII**) and *N*-methyl compounds. When experimental reactivity is known, it is in agreement with MINDO/3.

The experimental reactivity of 5-methylene-pyrrolidin-2-ones (**X**) and 5-methylene-3-pyrrolin-2-ones (**XII**), and their derivatives, is well known. The nucleophilic attack by CN^- on 3,4-dimethyl-5-methylene-3-pyrrolin-2-one (**XIIk**) is to the exocyclic methylene carbon [18], in agreement with both MINDO/3 and MNDO predictions (see Table 6), while in 4,4-dimethyl-5-methylene-pyrrolidin-2-one the nucleophilic attack by $NO_2CH_2^-$ is to position 5 of the ring [19], in agreement with MINDO/3 (in spite of giving two degenerate orbitals with some σ character, separated by 0.07 eV), but not with MNDO (which gives a unique π LUMO that is 0.66 eV more stable than the MINDO/3 one) which predicts a preferent nucleophilic attack at the exocyclic methylene carbon (see Table 6). MINDO/3 and MNDO do not predict a larger reactivity towards bases of the N-H hydrogen of the saturated ring, according to the charge distribution, however the MINDO/3 reactivity indices towards nucleophiles of the N-H hydrogens allow to expect a big increase in reactivity in the saturated ring (see Table 6).

3,4,5-Trimethyl-2*H*-pyrrol-2-one (**IXc**) is reasonably predicted to have by MINDO/3 a HOMO (σ, -8.78 eV) with the highest coefficient on the nitrogen, but MNDO predicts for it two high occupied MO (π, -10.36 eV; σ, -10.68 eV) having both of them the highest coefficient on atom 3. The comparison with 3,4-dimethyl-5-methylene-3-pyrrolin-2-one (**XIIk**) shows that MINDO/3 again reasonably gives as more reactive towards electrophiles the former, while it is the latter the more reactive according to MNDO (see

Table 6).

Similarly, 5-hydroxy and 5-methoxy-3,4-dimethyl-2*H*-pyrrole (**IVb** and **IVg**) are reasonable calculated by MINDO/3 as having a HOMO (σ, -8.78 eV for **IVg**) with the highest coefficient on the nitrogen, that is nearly degenerate with a π orbital (-8.93 eV for **IVg**) which has also the highest coefficient on the nitrogen, while MNDO predicts in both cases a unique π HOMO (-9.80 eV for **IVg**) which has the highest coefficient on atom 4 (numbering used in the tables, see Table 6).

Table 6

MINDO/3 and MNDO Reactiviy Indices Towards Electrophiles (E) and Nucleophiles (N), and Net Atomic Charges for *trans*-3,4-Dimethyl-5-methylene-pyrrolidin-2-one (**Xk**-*trans*), 3,4-Dimethyl-5-methylene-3-pyrrolin-2-one (**XIIk**), 3,4,5-Trimethyl-5-pyrrolin-2-one (**IIIc**), 3,4,5-Trimethyl-2*H*-pyrrol-2-one (**IXc**), 3,4-Dimethyl-5-methoxy-2*H*-pyrrole (**IVg**), 3,4-Dimethyl-5-hydroxy-2-methylene-2*H*-pyrrole (**XIIIk**), 3-Methyl-4,5-dimethylene-pyrrolidin-2-one (**XVm**) and 3,5-Dimethyl-4-methylene-5-pyrrolin-2-one (**XVII**).

Compound	**Xk**-*trans*						**XIIk**					
	E		N		Charges		E		N		Charges	
	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO
Orbital engery (eV)	-8.81	-9.21	1.27	1.34	0.61		-8.81	-9.21	-0.11	-0.79		
orbital hybridization	π	π	$\pi\sigma$	$\pi\sigma$	π		π	π	π	π		
N	0.72	0.58	0.28	0.13	0.00	-0.20	-0.36	0.54	0.35	0.01	0.00	-0.21	-0.35
C2	0.02	0.01	0.41	0.43	0.42	+0.61	+0.35	0.02	0.01	0.17	0.16	+0.62	+0.37
O-C2	0.16	0.13	0.17	0.16	0.23	-0.54	-0.33	0.26	0.20	0.10	0.14	-0.55	-0.32
C3	0.00	0.00	0.15	0.08	0.00	-0.05	-0.06	0.15	0.26	0.51	0.53	-0.13	-0.14
C4	0.01	0.01	0.06	0.05	0.01	+0.06	-0.01	0.03	0.09	0.58	0.58	+0.02	-0.03
C5	0.26	0.40	0.38	0.47	0.61	+0.13	+0.03	0.25	0.34	0.13	0.14	+0.13	+0.04
C-C5	0.78	0.84	0.24	0.42	0.67	-0.15	-0.12	0.72	0.72	0.35	0.40	-0.11	-0.07
H-N	0.00	0.00	0.12	0.07	0.00	+0.09	+0.20	0.00	0.00	0.00	0.00	+0.09	+0.19

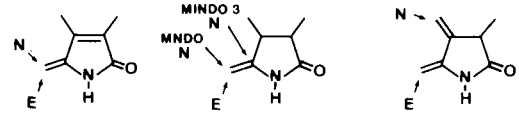
Compound	**IIIc**						**IXc**						
	E		N		Charges		E			N		Charges	
	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO		MINDO3	MNDO	MINDO3	MNDO
Oribital energy (eV)	-8.78	-10.46	0.39	-0.38			-8.78	-10.36	-10.68	-0.38	-1.31		
orbital hybridization	σ	σ	π	π			σ	π	σ	π	π		
N	0.93	0.63	0.37	0.38	-0.28	-0.25	0.93	0.29	0.67	0.22	0.22	-0.28	-0.25
C2	0.14	0.10	0.35	0.36	+0.61	+0.27	0.15	0.00	0.10	0.26	0.23	+0.62	+0.29
O-C2	0.26	0.74	0.20	0.30	-0.50	-0.25	0.27	0.01	0.72	0.22	0.28	-0.48	-0.22
C3	0.32	0.30	0.00	0.00	-0.07	-0.09	0.31	0.75	0.28	0.39	0.45	-0.13	-0.13
C4	0.17	0.10	0.01	0.00	+0.01	-0.06	0.17	0.67	0.09	0.37	0.39	-0.04	-0.11
C5	0.04	0.03	0.82	0.85	+0.19	+0.05	0.03	0.06	0.02	0.37	0.35	+0.20	+0.07

Compound	**IVg**								**XIIIk**								
	E			N			Charges		E				N			Charges	
	MINDO3		MNDO	MINDO3		MNDO	MINDO3	MNDO	MINDO3			MNDO	MINDO3		MNDO	MINDO3	MNDO
Orbital energy (eV)	-8.78	-8.93	-9.80	0.61	0.90	-0.20			-8.67	-8.72	-8.96	-9.31	-9.71	0.21	-0.82		
orbital hybridization	σ	π	π	π	σ	π			π	σ	π	π	π	π	π		
N	1.16	0.76	0.55	0.16	0.11	0.23	-0.33	-0.34	0.65	1.20	0.15	0.27	0.39	0.10	0.13	-0.34	-0.30
C2	0.16	0.12	0.09	0.18	0.42	0.19	+0.50	+0.22	0.29	0.14	0.00	0.28	0.03	0.21	0.24	+0.50	+0.20
O-C2	0.04	0.10	0.07	0.02	0.38	0.03	-0.43	-0.27	0.18	0.01	0.00	0.21	0.02	0.03	0.04	-0.45	-0.23
C3	0.26	0.34	0.50	0.51	0.20	0.54	-0.10	-0.11	0.00	0.22	0.73	0.12	0.68	0.42	0.35	-0.11	-0.12
C4	0.14	0.46	0.61	0.73	0.04	0.79	-0.02	-0.13	0.08	0.17	0.53	0.00	0.68	0.54	0.46	0.00	-0.06
C5	0.09	0.00	0.00	0.02	0.06	0.00	+0.18	+0.10	0.25	0.12	0.12	0.44	0.01	0.12	0.13	+0.13	-0.05
C-C5									0.53	0.00	0.19	0.65	0.01	0.44	0.61	-0.06	+0.05
H-O-C2									0.00	0.01	0.00	0.00	0.00	0.00	0.00	+0.26	+0.22
C-O-C2	0.02	0.00	0.00	0.00	0.43	0.00	+0.44	+0.22									

Table 6 (continued)

Compound	XVm						XVII						
	E		N		Charges		E			N		Charges	
	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO	MINDO3	MNDO		MINDO3	MNDO	MINDO3	MNDO
Orbital energy (eV)	−8.71	−9.07	0.77	−0.02			−8.71	−10.40	−10.46	0.16	−0.74		
orbital hybridization	π	π	π	π			σ	σ	π	π	π		
N	0.60	0.41	0.02	0.01	−0.20	−0.36	0.92	0.62	0.37	0.38	0.36	−0.28	−0.25
C2	0.02	0.01	0.05	0.04	+0.60	+0.35	0.14	0.10	0.00	0.22	0.17	+0.61	+0.27
O-C2	0.12	0.08	0.02	0.02	−0.54	−0.33	0.26	0.75	0.13	0.14	0.16	−0.50	−0.25
C3	0.00	0.00	0.01	0.00	−0.03	−0.01	0.33	0.30	0.03	0.00	0.00	−0.05	−0.05
C4	0.05	0.09	0.44	0.42	−0.01	−0.11	0.16	0.08	0.61	0.14	0.20	−0.06	−0.17
C5	0.25	0.36	0.29	0.28	+0.15	+0.08	0.04	0.02	0.10	0.65	0.56	+0.21	+0.09
C-C4	0.14	0.21	0.71	0.72	−0.01	0.00	0.01	0.01	0.68	0.37	0.50	+0.01	+0.03
C-C5	0.79	0.82	0.44	0.49	−0.15	−0.11	0.03	0.04	0.00	0.01	0.00	+0.04	+0.07
H-N	0.00	0.00	0.00	0.00	+0.09	+0.20							

3,4-Dimethyl-5-hydroxy-2-methylene-2*H*-pyrrole (**XIIIk**) has never been detected, however one of its derivatives *Z*-3,4-dimethyl-5-methoxy-2-(4-methylphenyl)methylene-2*H*-pyrrole has been studied. It has been seen that on this compound sodium cyanide gives the nucleophilic attack to the exocyclic methylene carbon [18], but with more difficulty than on the corresponding *Z*-3,4-dimethyl-5-(4-methylphenyl)methylene-3-pyrrolin-2-one. This behaviour is in agreement with both the MINDO/3 energy of the LUMO of the monocyclic model **XIIIk** (less stable than that of 3,4-dimethyl-5-methylene-3-pyrrolin-2-one (**XIIk**), see Table 6) and its distribution on the molecule (very similar reactivity indices for both compounds), while MNDO predicts for **XIIIk** a reactivity too high towards nucleophiles. It has been found for the same *Z*-3,4-dimethyl-5-methoxy-2-(4-methylphenyl)methylene-2*H*-pyrrole that in d_1-TFA at 60°, deuterium exchange takes place at the exocyclic methylene hydrogen with the same rate as in the corresponding 5-methylene-3-pyrrolin-2-one derivative [20]. MINDO/3 predicts reasonably for **XIIIk** a nearly degenerate HOMO (π, -8.67 eV; σ, -8.72 eV) having both orbitals the highest coefficient on the nitrogen, and being the exocyclic methylene carbon the second reactive place, and a third high occupied MO (π, -8.96 eV) with the higher coefficients on atoms 3 and 4. That is, one HOMO with higher energy, but with a smaller coefficient at the meso carbon (see Table 6) than that of **XIIk**. On the other hand, MNDO predicts for **XIIIk** two high occupied MO (π, -9.31 eV; π, -9.71 eV), having the first orbital the highest coefficient on the exocyclic methylene carbon, and the second orbital having the higher coefficients on atoms 3 and 4. That is, one HOMO more stable, and with a smaller coefficient at the meso carbon than that of **XIIk**, and which unreasonably has a small participation of the nitrogen atom.



XIIk Xk XVm

Figure 1. MINDO/3 and MNDO predictions of attack by nucleophiles (N) and electrophiles (E) to the monopyrrolic models of the terminal ring A of linear tetrapyrrolic pigments.

In spite of the differences noticed above, MINDO/3 and MNDO usually give a quite good prediction of reactivity, being that from MINDO/3 more in agreement with the experimental evidences. As an example, Figure 1 summarizes the calculated orbital-controlled reactivity of the models of the terminal rings of linear tetrapyrrolic pigments. Compound **Xk** is the model of the terminal ring A of the pigments from plants when linked to the protein, and **XVm** is the model of the same ring in the isolated chromophores. MINDO/3 and MNDO agree in predicting for all of them the same most reactive position towards electrophiles, the meso carbon, and both methods agree again in calculating as the more reactive the HOMO of **XVm** (see Table 6). Nevertheless the reactivity towards nucleophiles, according to MINDO/3 is different for each kind of terminal ring. For structure **XVm**, either by MINDO/3 or by MNDO, the nucleophilic attack is predicted to go to the methylene carbon bonded to position 4, in agreement with the addition of methanol to phycocyanobilin [21]. These results would justify the bonding of linear tetrapyrrolic pigments from plants to a sulphur from a cysteine of the apoprotein chain in nature, without having to imagine an intermediate with the terminal ring A as in structure **XVI**, as it was suggested in [21].

3,4,5-Trimethyl-5-pyrrolin-2-one (**IIIc**) could be the model of the terminal ring A in the P_{fr} form of phyto-

chrome [22], MINDO/3 predicts for it a fast electrophilic attack on the azomethine nitrogen, which can also be justified for a charge-controlled process (see Table 6).

Summary.

Charge-controlled reactivity: the charge separation between carbon and hetero atoms is not always larger by MINDO/3 than by MNDO. Oxygen and nitrogen behave in a different way. Hydrogen atoms bonded to heteroatoms behave in different way depending on the heteroatom. While MNDO is maybe better for atoms bonded to oxygen, MINDO/3 is doubtless better for nitrogen, and nitrogen and oxygen containing molecules. MINDO/3 atomic charge distribution, if maybe sometimes exaggerated, reproduces slightly better the characteristic features of each structure.

Orbital-controlled reactivity: MNDO predicts lower frontier orbital energies than MINDO/3 does. MINDO/3 predicts more degenerate or nearly degenerate frontier orbitals. MINDO/3 predicts more σ frontier or next-to-frontier orbitals. MINDO/3 and MNDO do not always agree in predicting the relative order of stability of HOMO and LUMO between different tautomers or different compounds. MINDO/3 and MNDO do not always agree in predicting the distribution of the frontier orbitals on the molecule. Nevertheless experimental reactivity favours MINDO/3 σ frontier orbitals (when they have been predicted), degeneracy (<0.3 eV), relative stability order of frontier orbitals between different compounds, and distribution of the frontier orbitals on the molecule.

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