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Theoretical Investigations (PM3) on the Coordinative Properties of Lumazine (Pteridine-2,4(1*H*,3*H*)-dione) and its Methylated Derivatives

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Abstract In order to study from a theoretical point of view the coordinative properties and explain the reported N5,O4-chelating behaviour in several oxopteridine derivatives, semiempirical molecular orbital calculations were carried out on lumazine (pteridine-2,4(1*H*,3*H*)-dione), its N- and C-methylated derivatives, as well as their deprotonated and protonated forms using the PM3 hamiltonian as implemented in the HYPERCHEM 4.0 package. The study of the partial charges over donor atoms does not allow us to justify the reported N5,O4-coordinating scheme, because some positive charge has been found on the N5 atom. Therefore, a more detailed analysis has been carried out taking into account the contributions of the AOs of each atom to the LCAO that defines each frontier MO. These calculations have confirmed the N5-O4 coordination mode of the neutral lumazine derivatives. The anionic forms could act as ligands in several ways, including the formation of either four- (N1-N8, N3-O4, N3-O2) or five-membered chelate rings (N5,O4). The experimental occurrence of only the latter coordination mode must be related to the higher stability of the five-membered chelate rings if it is compared with those of four and the possibility to establish π-M–N5 back-bonding.

Keywords Lumazine, Pteridine, PM3

Introduction

Pteridine derivatives are very interesting molecules because they play important roles in many biological systems, [1,2] especially those related to several metalloenzymes [3,4] and molybdopterins. [5-7] Since their biological significance is often associated with their coordinative properties, we are currently studying the molecular structure of several coordination compounds of lumazine (pteridine-2,4(1*H*,3*H*)-dione) derivatives.

Despite their having two oxygen and four nitrogen atoms, which may act as potential donor sites, both infrared and X-ray diffraction studies have shown that lumazine derivatives act as either neutral [8-14] or monodeprotonated [15,16] bidentate chelating ligands, but always through the N5 and O4 atoms. This paper is focused on justifying this non-versatile behaviour. The prediction and/or explanation of the coordination modes of a ligand from calculations of partial charges has been widely used, [17] but it has also been demonstrated in several papers that this method may be unsuccessful, [18-21] the present paper being a new example of this fact. Therefore, we have also tried to justify this coordination behaviour from molecular orbital calcula-

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tions, following a similar methodology to that used in previous papers for similar heterocycles. [18-21] The set of lumazine derivatives studied is summarised in the Figure 1.

Computational details

Semiempirical calculations were performed using the PM3 hamiltonian [22] as implemented in HYPERCHEM 4.0 package. [23] All calculations were carried out at the RHF level for the singlet lowest energy state with no configuration interaction. The molecular structures were generated with the molecular builder in HYPERCHEM and optimised *in vacuo* using the Polak-Ribiere algorithm until a rms gradient less than 30 cal·Å^{-1}·mol^{-1}, was attained. In order to check the nature of the resulting structures, the vibrational frequencies have been calculated, the lack of imaginary frequencies being unequivocal evidence that each structure represents a potential energy minimum and not a transition state.

Results and discussion

From the above-cited calculations, optimised structures for lumazine (pteridine-2,4(1*H*, 3*H*)-dione), its N- and C-methylated derivatives and the corresponding anions, in their dicarbonylic tautomeric form, were obtained. All of them are virtually planar. The bond lengths and angles are similar to those observed by X-ray diffraction for the coordinated species, [8-16] the small differences being attributable to either packing or coordination effects. This means that coordination does not imply dramatic changes in the electronic densities, as has been proposed from NMR data. [12-14]
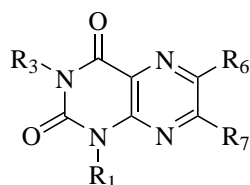
	R$_1$	R$_3$	R$_6$	R$_7$
LM	H	H	H	H
1MLM	Me	H	H	H
3MLM	H	Me	H	H
DLM	Me	Me	H	H
LMD	H	H	Me	Me
1MLMD	Me	H	Me	Me
3MLMD	H	Me	Me	Me
DLMD	Me	Me	Me	Me

Figure 1 *Molecular structure of the studied compounds*

Table 1 *Mean values (standard deviation in parentheses) of the calculated net atomic charge (e.u.) of the heteroatoms for the neutral and deprotonated forms of the lumazine methylated derivatives*

	Neutral	Anion-N1	Anion-N3	Dianion
N1	0.108(9)	-0.323(9)	0.027(9)	-0.357(4)
N3	-0.033(7)	-0.100(9)	-0.444(1)	-0.530(4)
N5	0.078(1)	0.087(4)	0.059(3)	0.057(6)
N8	-0.097(1)	-0.124(2)	-0.176(5)	-0.232(3)
O2	-0.375(2)	-0.446(5)	-0.474(4)	-0.535(3)
O4	-0.312(3)	-0.431(4)	-0.416(1)	-0.530(4)

In Table 1, the mean values of the partial charges of the potential donor atoms in each of these species are shown. Net atomic charges have been calculated as the difference between the number of valence electrons and the sum of the diagonal elements in the density matrix for the atom under consideration. In the four cases, both oxygen atoms exhibit a substantial negative charge, which increases with the dissociation level. The N1 and N3 nitrogen atoms display a close-to-zero net charge when the corresponding N-H is not ionised, but it becomes *ca.* -0.4 when the corresponding proton is lost. The N8 atom, with a small negative charge in the neutral form (*ca.* -0.1), undergoes on ionisation a slight increase to *ca.* -0.2 in the dianionic forms. Finally, the N5 atom displays a sligthly positive charge of +0.08 in the neutral forms and in N1 monoanions and +0.05 in N3 monoanions and in dianions.

Therefore, if the metal-ligand bond is considered from a strict electrostatic point of view, it is clear that the most commonly reported coordination mode for the lumazine derivatives -bidentate through the O4 and N5 atoms- cannot be explained, because there are other atoms more negatively charged and, consequently, more suitable to be attracted by the positive metal ions. The bidentate coordination mode must be due to the strong covalent character of the M-L bonds. Thus, the Racah's parameters measured from the electronic spectra of DLM and DLMD metal complexes with the first-row metal ions indicate the existence of covalent character, since they are about half of the value corresponding to the free ions. [12-14] Therefore, in order to draw more concise conclusions, the question relative to the potential donor sites must be closely analysed from other points of view. Taking into account the covalent contribution to the M-L bond, an alternative approach could be the study of the situation of the frontier molecular orbitals able to form σ-donor bonds with the metal.

A list of selected MOs for the neutral and dissociated forms of the lumazine (LM) is given in Table 2. The conclusions drawn from these data may be applied to the other lumazine derivatives studied. In this table, the contribution of the atomic orbitals of the heteroatoms to the LUMO (π), HOMO (π), the following occupied π-MO and the three higher occupied σ-MOs are given. More internal orbitals are unlikely to play an important role in either protonation or metallation.

Table 2 *Contributions of atomic orbitals of the heteroatoms to selected MOs for the neutral and dissociated forms of lumazine (LM)*

	MO [a]	[b]	E(eV)	Contributions to LCAO [c]					
				N1	N3	N5	N8	O2	O4
LM	HOMO-5	σ	-11.952	0.004	0.004	0.268	0.583	0.008	0.013
	HOMO-3[d]	σ	-11.539	0.031	0.090	0.061	0.010	0.315	0.405
	HOMO-2	σ	-10.699	0.008	0.011	0.447	0.199	0.009	0.076
	HOMO-1	π	-10.686	0.000	0.679	0.000	0.000	0.172	0.140
	HOMO	π	-9.782	0.389	0.007	0.008	0.062	0.060	0.041
	LUMO	π	-1.375	0.027	0.020	0.091	0.051	0.001	0.053
LM(a1) [e]	HOMO-5	σ	-7.368	0.230	0.030	0.043	0.121	0.239	0.176
	HOMO-3	σ	-6.521	0.139	0.070	0.154	0.128	0.210	0.165
	HOMO-2	π	-6.314	0.003	0.681	0.002	0.002	0.143	0.157
	HOMO-1	σ	-5.726	0.420	0.039	0.133	0.167	0.036	0.005
	HOMO	π	-4.500	0.352	0.000	0.003	0.098	0.079	0.041
	LUMO	π	3.194	0.024	0.024	0.181	0.000	0.000	0.000
LM(a3) [f]	HOMO-4	σ	-7.000	0.015	0.057	0.414	0.143	0.145	0.012
	HOMO-3	σ	-6.239	0.057	0.130	0.042	0.024	0.270	0.390
	HOMO-2	π	-5.438	0.385	0.013	0.000	0.097	0.102	0.011
	HOMO-1	σ	-5.323	0.054	0.586	0.022	0.008	0.020	0.134
	HOMO	π	-4.825	0.024	0.602	0.001	0.007	0.147	0.187
	LUMO	π	2.782	0.004	0.009	0.174	0.179	0.002	0.026
LM(d) [g]	HOMO-4	σ	-2.123	0.155	0.174	0.189	0.208	0.056	0.004
	HOMO-3	σ	-1.176	0.097	0.119	0.009	0.001	0.272	0.405
	HOMO-2	σ	-0.659	0.225	0.420	0.032	0.034	0.084	0.054
	HOMO-1	π	-0.475	0.000	0.617	0.002	0.000	0.169	0.178
	HOMO	π	-0.167	0.321	0.002	0.002	0.157	0.047	0.037
	LUMO	π	7.489	0.001	0.012	0.223	0.233	0.004	0.028

[a] The orbital labelled HOMO-1 is the MO which lies immediately below the HOMO; that labelled HOMO-2 lies immediately below and so on
[b] The molecular plane is a symmetry plane for a σ MO and a nodal plane for a π MO
[c] The contribution of one atom is calculated as the sum of the squared coefficients of that atom AOs in the LCAO that defines the MO

[d] For 6,7-dimethyl derivatives (LMD-DLMD), the MO which displays similar contributions is the HOMO-4
[e] Monoanion with N1 deprotonated
[f] Monoanion with N3 deprotonated
[g] Dianion with both N1 and N3 deprotonated.

For the neutral forms, the two highest occupied σ-MOs are HOMO-2 and HOMO-3 (LM-DLM) or HOMO-4 (LMD-DLMD), which mainly reside on the N5 and O4 atoms, displaying also lower contribution of AOs of N8 and O2, respectively. These results corroborate the observed tendency of lumazine derivatives to bind as N5,O4-bidentate chelators because the coordination-to-metal through either N8 or O2 does not allow the formation of any chelate ring. These atoms could probably act as secondary binding sites once the main N5 and O4 sites were occupied. On the other hand, analysis of the AOs that define the LUMO and the two highest occupied π-MOs indicates that these compounds must neither be good π-acceptor nor π-donor ligands, since the MOs available to make π bonds have no contribution from

the AOs of atoms that act as main metal binding sites (N5 and O4).

The data corresponding to the N1-monoanion clearly indicate that the MO more likely to make a σ M–L bond is the HOMO-1 which mainly lies on N1 and also shows a small contribution of N8 and N5, being possible the establishment of either N1-N8 four membered chelate rings or two independent M-N1 and/or M-N8. These monoanionic forms could also be π-donors through the HOMO, which resides on the N1 atom. However, there is no reported example of these coordination modes. It is clear that the formation of a N5,O4-five membered chelate ring through HOMO-3 and HOMO-1 is favoured, because the formation of a π M–L back bond is

also possible through the N5 atom, whose AOs contribute about 18% to the LUMO.

The location of the molecular orbitals does not depend on the situation of the formal negative charge in the structure of the monoanion because, during the process of the structure optimisation, this charge is delocalized. However, in order to be sure of this fact we have carried out the same calculations assuming as starting point for the optimisation process structures in which the negative charge formally resides in the O2 and O4 atoms, these oxygens passing from carbonylic to phenolic type. These calculations showed that, in each case, the optimised structure obtained does not depend on the limiting form assumed as starting point. It is nearer to the dicarbonylic form than the phenolic ones, but the phenolic character of both exocyclic oxygens is slightly enhanced on increasing deprotonation, as indicated by the changes and the calculated C-O bond lengths which increase from *ca.* 1.21 Å in the neutral structures to *ca.* 1.24 Å in the deprotonated ones.

Similar comments can be made for the N3-mono-deprotonated forms, with the only difference being that the highest occupied σ-MO (HOMO-1) is mainly concentrated over the N3 atom, the O4 atom being also involved to a little extent. The following σ-MO (HOMO-3) shows main contributions from O4, O2 and N3. These data permit us to predict four-membered chelating behaviour through the N3-O4 or N3-O2 atoms for these forms. Moreover, a π M–L bond is possible through the HOMO, which mainly resides on N3, O4 and O2 atoms. However, N5-O4 five-membered chelating behaviour is also possible through the HOMO-3 and HOMO-4, this coordination mode being stabilised by π M–L back-bonding through the N5 atom (*ca.* 18% in LUMO) as well as the more favourable geometry of the five-membered rings if compared with those of four.

For the N1,N3-dianionic forms, a great coordination versatility may be predicted. Thus, the highest occupied σ-MO is HOMO-2, with the main contribution of N3 and N1 AOs. The HOMO-3 lies mainly on O4 and, to a lesser extent, O2 and N3, whereas in the HOMO-4 the AOs of the four nitrogens are involved. The π M–L back-bonding may be established through N8 and N5 (*ca.* 22% in LUMO). In addition, mainly N1 and N3 atoms are available to give π bonds, through the HOMO and HOMO-1.

Conclusions

Although the semiempirical employed method confirms the N5-O4 coordination mode displayed by the lumazine derivatives, other coordination modes can be proposed from the theoretical point of view, but unfortunately, there are no reported examples of them. Their anionic forms could act as ligands in several patterns, which include the formation of either four- (N1-N8, N3-O4, N3-O2) or five-membered chelate rings (N5,O4). The experimental occurrence of only the last coordination mode may be related to the higher stability of the five-membered chelate rings if compared with that of the four-membered rings and the possibility to estab-

lish π-M–N5 back-bonding. On the other hand, for the neutral, N1-monoanionic and dianionic forms, the HOMO (π symmetry) could be involved in the formation of organometallic π-donor compounds through the C4a and C6 atoms, especially with metals of the second and third transition series.

Supplementary material available A complete list (27 pages) of net charges, atomic coordinates and LCAOs (LUMO to HOMO-11), as well as the 3D coordinates of the calculated structures (MOL2 format, file-list with a brief description in the supplementary materials file) for the compounds studied is available.

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