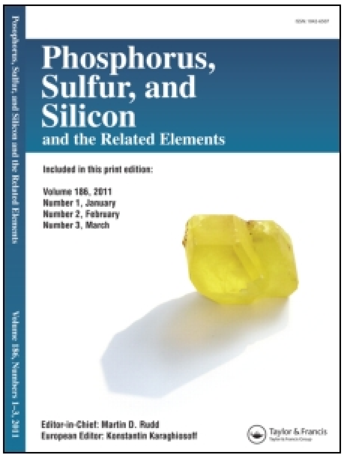

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CONFORMATIONAL ANALYSIS OF 1,1′-(METHYLPHOSPHINYLIDENE) BIS(METHANAMINE) AND ITS PLATINUM(II) COMPLEX

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The conformational behaviour of $H_3CP(O)(CH_2NH_2)_2$ (mpbm) and its N,N′-coordinated Pt(II) chelate chloro complex $[Pt(mpbm)Cl_2]$ has been studied by the Molecular Mechanics (MM) method. The calculation results for the complex have been compared with X-ray diffraction data. In the preferred mpbm conformations the C—N bonds were found to occupy *trans*, *gauche*-position with respect to C—CH_3 and C—CH_2 bonds. The *chair*-conformation with an equatorial methyl-group is the lowest energy conformation of $[Pt(mpbm)Cl_2]$ and the alternative *chair*-conformation is by 9 kJ mol^{-1} less stable. Three possible pathways for the ring inversion of the complex are considered. The energy difference between the two MM-calculated *chair*-conformations of $[Pt(mpbm)Cl_2]$ is confirmed by Extended Hückel calculations.

Keywords: Phosphine oxide derivatives; platinum complexes; conformational analysis; molecular mechanics; quantum-chemical calculations

INTRODUCTION

Due to the considerable success of the antitumor drugs cisplatin (*cis*-diamminedichloroplatinum(II)) and carboplatin (diammine (1,1-cyclobutanedicarboxylato) platinum(II)),[1] the search for new platinum-based cytostatics continues.[2] In order to overcome the low aqueous solubility of the parent compound, a number of platinum complexes with amine ligands modified with hydrophilic functional groups have been prepared and screened.[3] With the same goal in mind we synthesized and tested a series of platinum and palladium complexes of amino-substituted phosphine oxides.[4] These compounds have good solubility in water and some of them exhibited antitumor activity *in vivo*. The structure of one of these complexes, $[Pt(mpbm)Cl_2]\cdot(1/2)H_2O$, where mpbm is 1,1′-(methylphosphinylidene)bis(methanamine) was determined by single crystal X-ray diffraction analysis.[5] The structure of the complex is characterized by the presence of a six-membered chelate ring containing four different centers and offers an interesting conformational behaviour.

Among the computational methods for conformational analysis the most simple and less time-consuming is the method of Molecular Mechanics (MM),[6] enjoying remarkable success when applied to organic molecules.[7] In the last years, the interest in MM calculations of inorganic[8] and bioinorganic[9] systems has been also increasing. Quite large molecules as oligonucleotideplatinum(II) complexes were successfully treated by this approach.[10] The Extended Hückel Molecular Orbital (EHMO) method[11] is the most versatile quantum-chemical tool for treating the electronic structure of transition metal compounds.[12]

Here we report the conformational behaviour of mpbm and its cytostatically active complex $[Pt(mpbm)Cl_2]$ as studied by the MM method, and compare the results with i) the experimental X-ray data and ii) those obtained by the EHMO method.

COMPUTATIONAL DETAILS

MM calculations were performed with the PCMODEL programme[13] which utilizes the MMX parameter set, based on the Allinger's MM2 force field.[14] As previously noticed,[15] since the used force field does not account explicitly for the electronic factors, to obtain reliable geometry (square planar) for the Pt(II) coordination polyhedron, it is necessary to fix in one plane Pt and its four ligand donor atoms. The total MM energy was used as a measure of the relative stability of the conformations.

The ICONC programme of Calzaferri's group[16] was used in the EHMO calculations. In this programme diagonal Hamiltonian matrix elements are calculated using a self-consistent charge iteration procedure, and a weighted distance-dependent Wolfsberg-Helmholz formula is used to calculate the off-diagonal elements.[17] The Fitzpatrick and Murphy's consistent set of parameters for the atomic radial functions, single exponent Slater-type functions[18] for s- and p-orbitals, and Double-Dzeta functions[19]—for platinum d-orbitals were used. Valence state ionization potentials were taken from Ref.[16]. Molecular geometries produced by MM calculations were utilized as input for EHMO computations.

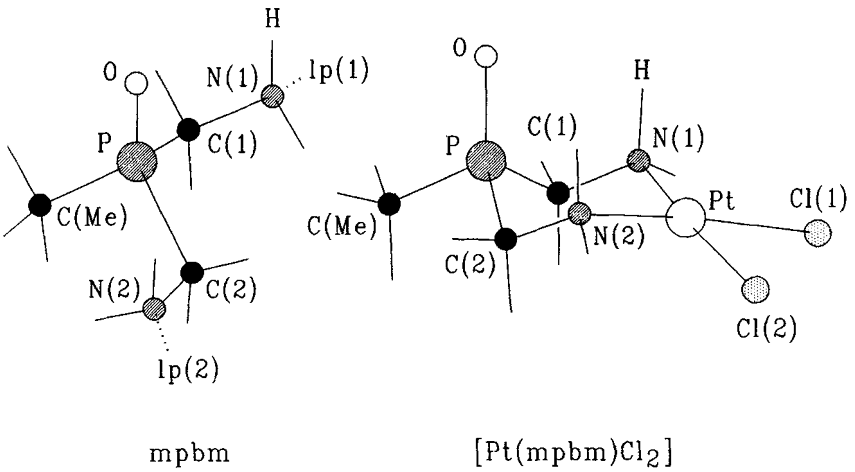


FIGURE 1 PCMODEL obtained structures of the lowest-energy conformations of mpbm and $[Pt(mpbm)Cl_2]$ with the atom numbering scheme. Lone electron pairs on N atoms are denoted with lp.

RESULTS AND DISCUSSION

MM Calculations

Comparison of calculated and experimental geometric parameters for $[Pt(mpbm)Cl_2]$

Data from the X-ray diffraction analysis of the complex $[Pt(mpbm)Cl_2]\cdot(1/2)H_2O$[5] can serve as a basis for an overall estimation of the reliability of our MM computational results. However, total reproduction can not be expected since the MM results refer to an isolated molecule.

PCMODEL drawings of the free mpbm ligand and the $[Pt(mpbm)Cl_2]$ complex in their lowest-energy conformations are presented in Figure 1. The calculated geometric parameters, together with those for $[Pt(mpbm)Cl_2]\cdot(1/2)H_2O$, found by X-ray analysis, are summarized in Table I. Agreement between the calculated parameters of the complex in its lowest-energy conformation, and the parameters experimentally found is satisfactory, as indicated by the root-mean-square value of the relative differences, 0.04. The hydrogen bond network existing in the crystal of $[Pt(mpbm)Cl_2]\cdot(1/2)H_2O$[5] causes weak distortions of the structure of the complex molecule with respect to the isolated molecule with its C_s point group symmetry. The most important features of the experimental and calculated structures are qualitatively comparable. Thus, in the planar co-

TABLE I MM calculated geometric parameters for the lowest-energy conformations of mpbm and [Pt(mpbm)Cl_2], compared with those experimentally found for [Pt(mpbm)Cl_2]·(1/2)H_2O. Atom labelling scheme according to Figure 1.

Parameter	*mpbm (calculated)*	*[Pt(mpbm)Cl_2] (calculated)*	*[P(mpbm)Cl_2]·(1/2)H_2O (experimental[a])*
Bond lengths, Å			
P—O	1.47	1.47	1.49
P—C(Me)	1.84	1.84	1.76
P—C(1)	1.84	1.84	1.79
P—C(2)	1.84	1.84	1.81
C(1)—N(1)	1.44	1.44	1.49
C(2)—N(2)	1.44	1.44	1.50
Pt—N(1)		2.12	2.05
Pt—N(2)		2.12	2.04
Pt—Cl(1)		2.45	2.31
Pt—Cl(2)		2.45	2.30
Valence angles, deg			
O—P—C(Me)	116	116	115
O—P—C(1)	116	116	113
O—P—C(2)	116	116	109
C(Me)—P—C(1)	102	102	107
C(Me)—P—C(2)	103	102	107
C(1)—P—C(2)	103	104	106
P—C(1)—N(1)	110	111	112
P—C(2)—N(2)	110	111	109
C(1)—N(1)—Pt		111	120
C(2)—N(2)—Pt		111	118
N(1)—Pt—N(2)		103	94
N(1)—Pt—Cl(1)		85	88
N(1)—Pt—Cl(2)		172	179
N(2)—Pt—Cl(1)		172	177
N(2)—Pt—Cl(2)		85	87
Cl(1)—Pt—Cl(2)		87	92
Torsional angles, deg			
P—C(1)—N(1)—Pt		63	61
P—C(2)—N(2)—Pt		−63	−69
C(1)—N(1)—Pt—N(2)		−43	−47
C(2)—N(2)—Pt—N(1)		43	51
C(1)—P—C(2)—N(2)	−176.5	77	68
C(2)—P—C(1)—N(1)	−72.1	−77	−64
Dihedral angles between planes, deg			
ρ(Cl(1),Cl(2),Pt,N(1),N(2))			
σ(N(1),N(2),C(1),C(2))			
τ(C(1),C(2),P)			
ρ-σ		141	140
σ-τ		113	120
ρ-τ		152	160

[a] X-ray diffraction data [5].

ordination polyhedron the Pt—Cl bond lengths are greater than Pt—N, and the Cl—Pt—Cl bond angle is smaller than N—Pt—N; the conformation of the six-membered chelate ring is a slightly distorted *chair* with a methyl group in equatorial position. The bond lengths and bond angles given in Table I are also representative for the remaining mpbm and [Pt(mpbm) Cl_2] conformations discussed, since they vary insignificantly from one conformation to another.

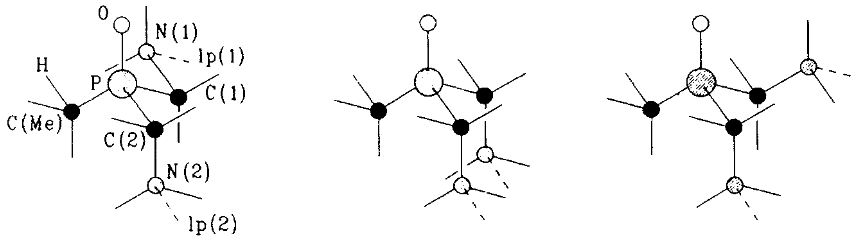
mpbm Conformations

For the rotations around the H_2C—P bonds, nine conformations corresponding to minima on the energy hypersurface (minimum-energy conformations, MECs) are expected. Further, taking into account the rotations around the N—C bonds, nine MECs are possible for each of the nine MECs with respect to the H_2C—P rotations. From each of these 9 groups out of 9 conformations, we will consider only the lowest-energy conformation. Six of the nine mentioned MESc are presented in Figure 2. The remaining three conformations, (g^-, g^-; *t, t*), (g^-, *t; t, t*) and (g^+, *t; t, t*), are enantiomers of **1**, **3** and **5** respectively (see Figure 2). The **4**, **5** and **6** MECs have very similar energies. In these conformations, each of the N—C bonds is in *trans, gauche*-position towards the P—Me and P—CH_2 bonds, thus occupying possibly the most favourable orientation with respect to the bulkiest groups bound to phosphorus. Inbetween in energy are the **1** and **3** forms, in which one of the N—C bonds is in *gauche*-orientation with respect to both P—Me and P—CH_2 bonds, and the other is *trans, gauche*-positioned towards them. Of highest energy is conformation **2**, where both N—C bonds are *gauche, gauche*-oriented with respect to the P—Me and P—CH_2 bonds. Similar six conformers have been discussed for methylphosphinylidenebis(chloromethane),[20] where the NH_2 groups are replaced by chlorine atoms. The authors, however, claim that the most stable conformer is that with Cl—C bonds *gauche, gauche*-oriented towards the P—Me and P—CH_2 groups.[20,21]

In all the mpbm MECs, except **2** and **6**, the lone electron pairs on nitrogen atoms are *trans*-oriented with respect to the P—CH_2 bond. In **2** and **6** one of the lone pairs is *trans*- and the other is *gauche*-positioned toward P—CH_2 bond, thus making these conformations asymmetric. The corresponding symmetric MECs have a considerably higher energy, *e. g.* (*t, t;* g^+, g^-) and (g^-, g^+; g^-, g^+) (see notations in Figure 2) are of -5 and $+1$ kJ mol^{-1}, respectively.

Conformational behaviour of [Pt(mpbm)Cl_2]

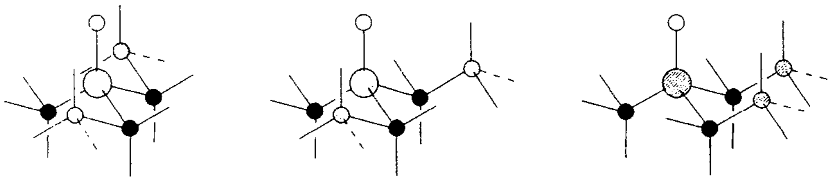
The ring inversion of cyclohexane can serve as a model to understand the conformational changes in other six-membered ring systems. Two possible pathways for the conversion of one *chair*-form, through the *twist*-, into another *chair*-



1 *(g⁺, g⁺; t, t)*
$\eta_1 = 75°$, $\eta_2 = 57°$
$\theta_1 = 180°$, $\theta_2 = 180°$
E = −10 kJ mol^{-1}

2 *(g⁻, g⁺; g⁻, t)*
$\eta_1 = -40°$, $\eta_2 = 52°$
$\theta_1 = -59°$, $\theta_2 = 180°$
E = −7 kJ mol^{-1}

3 *(t, g⁺; t, t)*
$\eta_1 = -175°$, $\eta_2 = 54°$
$\theta_1 = 180°$, $\theta_2 = 180°$
E = −12 kJ mol^{-1}



4 *(g⁺, g⁻; t, t)*
$\eta_1 = 71°$, $\eta_2 = -71°$
$\theta_1 = 180°$, $\theta_2 = 180°$
E = −14 kJ mol^{-1}

5 *(t, g⁻; t, t)*
$\eta_1 = -178°$, $\eta_2 = -71°$
$\theta_1 = 180°$, $\theta_2 = 180°$
E = −15 kJ mol^{-1}

6 *(t, t; t, g⁻)*
$\eta_1 = -177°$, $\eta_2 = -179°$
$\theta_1 = -179°$, $\theta_2 = -60°$
E = −14 kJ mol^{-1}

FIGURE 2 Selected minimum-energy conformations of mpbm. Letters *g* and *t* denote *gauche* and *trans*, respectively. The first couple of letters in brackets corresponds to the torsional angles $\eta_1 \equiv$ N(1)C(1)PC(Me) and $\eta_2 \equiv$ N(2)C(2)PC(Me), respectively, and the second—to the torsional angles $\theta_1 \equiv$ lp(1)N(1)C(1)P and $\theta_2 \equiv$ lp(2)N(2)C(2)P, respectively. Signs + and − correspond to the sign of torsional angle. The torsional angle ijkl has positive sign if viewing along the jk bond with j nearer to the observer, the angle from the projection of ji to the projection of kl is traced in clockwise sense.

form, differing in the geometry of the transition state, have been discussed.[22] The first way involves a transition state with five atoms lying in a plane (C_s symmetry), and the second—a four-coplanar atom transition state (C_2 symmetry). The later transition state has been found to be of lower energy than the former and it is considered to correspond to a saddle point on the pathway from *chair*- into *twist*-conformation. The *boat*-conformation is a transition state of the interconversion of the *twist*-forms. Similar considerations have been applied by Gollogly and Hawkins in studying the ring inversion of model metal-1,3-diaminopropane six-membered chelates.[23]

As stated above, the lowest energy conformation of [Pt(mpbm)Cl_2] is the *chair*-form with an equatorial Me group. Ring inversion leading to the alternative

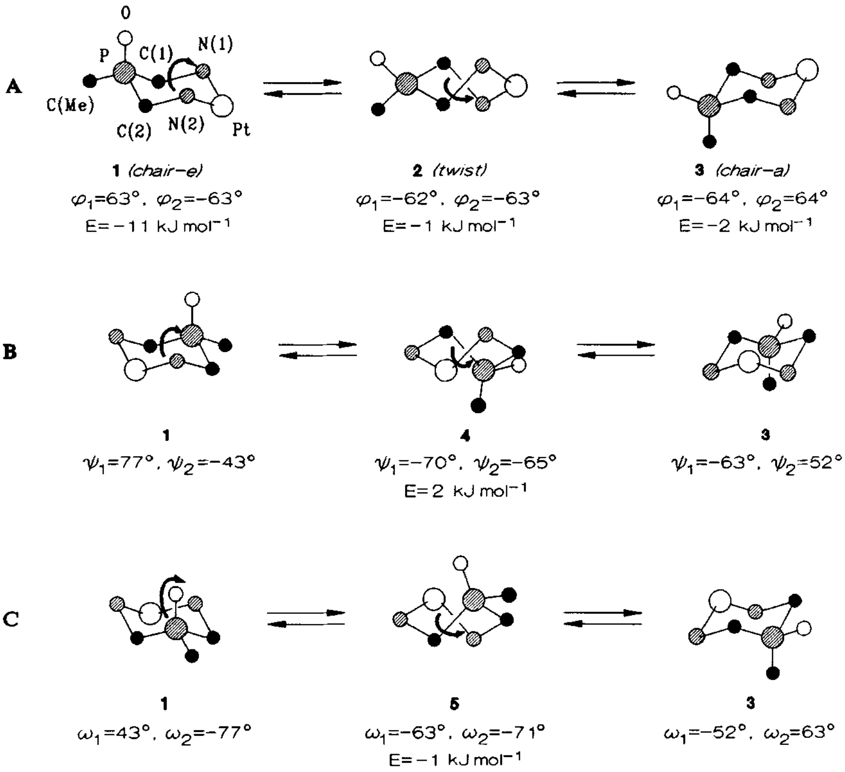


FIGURE 3 Ring inversion of $[Pt(mpbm)Cl_2]$ proceeding *via* subsequent rotations around the corresponding couple of bonds: the two N—C bonds (A), P—C and N—Pt bonds (B) and N—Pt and P—C bonds (C). H and Cl atoms are omitted. Letters *e* and *a* stand for *equatorial* and *axial*, respectively and refer to the position of Me group in *chair*-conformations. ϕ_1, ϕ_2, ψ_1, ψ_2, ω_1 and ω_2 denote the torsional angles PtN(1)C(1)P, PtN(2)C(2)P, C(1)PC(2)N(2), C(1)N(1)PtN(2), C(2)N(2)PtN(1) and C(2)PC(1)N(1), respectively.

chair-form may take three pathways with four-coplanar transition states, differing in the bonds around which the subsequent rotations occur: A) C—N, C—N, B) P—C, N—Pt and C) N—Pt, P—C Figure 3. The first stage of each of these inversion modes is a rotation around a bond, leading to a minimum energy intermediate with *twist*-geometry. In the second stage, rotation occurs around the bond in 1,3-position with respect to the first one, and the intermediate passes into the alternative *chair*-conformation with an axial Me group. The inversion route A includes transition states where the eclipsed atoms are Pt and P with greatest radii and is less probable than pathways B and C. The MM energy difference between the two *chair*-forms is 9 kJ mol^{-1} in favour of this one having the bulkier phosphorus substituent, namely the Me group, in an equatorial position.

TABLE II EHMO calculation data for the lowest energy conformation of mpbm, the two *chair*-conformations of [Pt(mpbm)Cl_2] and *cis*-[Pt$(NH_3)_2Cl_2$].

Quantity	*mpbm* *($t,g^-;t,t$)*	*[Pt(mpbm)Cl_2]* *(chair-e)*	*[Pt(mpbm)Cl_2]* *(chair-a)*	*cis-[Pt$(NH_3)_2Cl_2$]*
TE[a], kJ mol^{-1}	−7178	−8007	−7996	−3769
OSE[b], kJ mol^{-1}	−11395	−12342	−12332	−5839
RE[c], kJ mol^{-1}	4217	4335	4336	2070
Pt		0.63	0.63	0.45
Cl		−0.79	−0.79	−0.66
Atomic N	−0.66	−0.33	−0.32	−0.26
charges H (NH_2, NH_3)	0.23–0.24	0.22	0.22	0.23
P	0.50	0.58	0.58	
O	−0.59	−0.43	−0.44	

[a] Total energy, TE = OSE + RE.

[b] Orbital stabilization energy, OSE = Σsubform $a_i\epsilon_i - \sum_{\mu} b_\mu I_\mu$, where a_i and ϵ_i are the occupation number and energy, respectively for the i-th molecular orbital, and b_μ and I_μ are the occupation number and valence orbital ionization potential, respectively for the μ-th atomic orbital.

[c] Repulsion energy, RE = $\sum\sum_{\alpha<\beta} q_\alpha q_\beta / r_{\alpha\beta}$, where q_α, q_β are the calculated atomic charges and $r_{\alpha\beta}$ is the distance between centers α and β.

EHMO calculations

Some EHMO results for the free mpbm ligand in its lowest-energy conformation and for the complex [Pt(mpbm)Cl_2] in the two *chair*-conformations, as well as for cisplatin, are summarized in Table II. The difference obtained for the total EH energies of the two *chair*-conformations of the complex is 11 kJ mol^{-1}, which is in satisfactory agreement with MM energy difference of 9 kJ mol^{-1}. The charge distribution picture indicates considerable charges on Cl, O and N (negative) and on Pt, P and H (NH_2, NH_3) (positive). Coordination of mpbm to Pt(II) reduces the negative charges on the N and O atoms. The charges on C and H(CH_3, CH_2) are slightly affected by complex formation, being in the −0.24 to −0.27, 0.08 to 0.12, 0.10 to 0.11 and 0.07 to 0.08 ranges for C(CH_3), C(CH_2), H(CH_3) and H(CH_2), respectively. Charges on Pt, Cl and N are higher for [Pt(mpbm)Cl_2] than for *cis*-[Pt$(NH_3)_2Cl_2$].

CONCLUSIONS

1. MM calculations (MMX force field) are successfully applicable to the phosphoryl-containig chelate amine complex [Pt(mpbm)Cl_2], the results being in good agreement with X-ray diffraction data.
2. The lowest-energy (−15 and −14 kJ mol^{-1}) conformations of the mpbm ligand are those with N—C bonds in *trans*, *gauche*-position with respect to C—Me and C—CH_2 bonds.

3. The lowest energy (-11 kJ mol^{-1}) conformation of the complex [Pt(mpbm)Cl_2] has *chair*-geometry with an equatorial Me group. This conformation corresponds to the experimentally found in the solid state.
4. The second in energy MEC of [Pt(mpbm)Cl_2] is a *chair*-conformation with an axial methyl group. The MM energy difference between the two *chair*-forms is 9 kJ mol^{-1}.
5. The remaining MECs of [Pt(mpbm)Cl_2] are three enantiomeric couples with *twist*-geometry. They correspond to the intermediates in the interconversion of the *chair*-forms.
6. The energy difference between the two *chair*-forms of [Pt(mpbm)Cl_2], calculated by the EHMO method is 11 kJ mol^{-1} in favour of the conformation with an equatorial Me group, and is in satisfactory agreement with the value obtained by the MM method.

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