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## A Charge Density Study of Arylacetylene Substituted Cytochrome P450 Inhibitors

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Cytochrome P450 enzymes belong to the super family of proteins containing the heme cofactor, and are involved in the metabolism of endogenous and exogenous compounds including drugs, sterols, fatty acids, carcinogens, vitamins and steroids. It has been shown that arylacetylenes can function as mechanism-based inhibitors of P450 enzymes involved in carcinogenesis and possibly prevent the initiation of cancer. Previous studies of the docked inhibitor-protein complexes revealed a direct relationship between the inhibition potency and the proximity of the inhibitor's triple bond to the prosthetic heme Fe of the enzyme. 7-(4-trifluoromethyl)coumarin propargyl ether,  $\alpha$ -naphthoflavone 2'-propargyl ether, and 2-phenylflavone-7-propargyl ether were synthesized as potential therapeutics for inhibiting P450 metabolism because each docks in the heme active site and is substituted with an arylacetylene group. Extensive high resolution data sets were collected on a Bruker Kappa APEX II CCD X-ray diffractometer at 150(2) K. Conventional, radial, and multipole refinements were performed on the data using the Shelx and the XD software packages. Deformation density maps of the propargyl ether groups show a buildup of density in the triple bonds. Electrostatic potential maps have been calculated and show negative potential associated with regions of reactivity near the trifluoromethyl substituent and the ketone groups. Net atomic charges calculated in the radial refinement allow differentiation of the acetylene carbon atoms. Critical points show the presence of C-H...F and C-H...O hydrogen bonds. NIH/MBRS-CORE (SC1GM084722) and NIH/RCMI (1G12RR026260) support is gratefully acknowledged.

**Keywords:** charge density, P450 inhibitor

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## Conformation of half-sandwich Mn(I) O-alkyl and O-aryl Fischer carbene complexes: a joined experimental-theoretical study

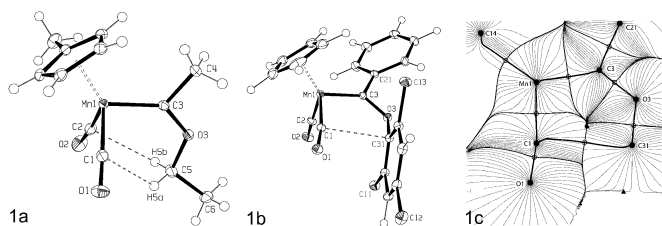
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Seminal MO calculations by Hoffman *et al.*<sup>[1]</sup> predicted that carbene ligands in half-sandwich complexes of the type Cp(CO)<sub>2</sub>M=C(R)R' should adopt a so-called 'vertical coordination mode',<sup>[2]</sup> whereby the carbene plane sits in the symmetry plane of the Cp(CO)<sub>2</sub>M unit (see Fig. 1a for an example). Such a coordination mode gives rise to two different rotamers, differing in the orientation of the R/R' groups relative to the Cp ligand. Early theoretical<sup>[3]</sup> and structural<sup>[4]</sup> studies of the half-sandwich Mn(I) O-alkyl carbene complexes Cp(CO)<sub>2</sub>Mn=C(OR)Ph (R = Me, Et) have nevertheless revealed some discrepancies between their predicted and observed conformation.

For our part, we have investigated the structure and conformation of a series of half sandwich Mn(I) O-alkyl- and O-aryl Fischer carbene complexes by mean of a joined experimental-theoretical study based on

the experimental X-ray charge density analysis of two representative examples of such complexes, namely Cp'(CO)<sub>2</sub>Mn=C(Me)OEt (Fig. 1a) and Cp(CO)<sub>2</sub>Mn=C(Ph)O(2,4,6-C<sub>6</sub>H<sub>2</sub>Cl<sub>3</sub>) (Fig. 1b) ( $S < 1.1 \text{ \AA}^{-1}$  (MoK $\alpha$ ), 100K), and DFT calculations.

Both the topological analysis of the experimental electron density within Bader's AIM theory, and the DFT calculations, through the Second-Order Perturbation Theory (SOPT) of the NBO method, clearly revealed that hitherto unsuspected weak intramolecular interligand interactions including C...H interactions between the O-alkyl group and the carbonyl ligands (Fig. 1a)<sup>[5]</sup> or C...C interactions between the O-aryl group and the carbonyl ligands (Fig. 1b and 1c)<sup>[6]</sup> play a key role regarding the conformation of those complexes.



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## Electronic structure of Bis{bis(methoxycarbimido)aminato}-copper(II) complex

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The bonding properties of transition metals in coordination compounds are of great importance for inorganic as well as bio-inorganic chemistry. Recently, we have found that in tetrakis( $\mu_2$ -Acetato)-diaqua-di-copper(II) complex (I) for Cu central atom only Cu-O bonds in the equatorial plane are actual the coordination bonds [1,2]. Contrary to very small apical Cu-O bond distance of 2.1443(1) Å, this interaction is not a coordination bond. The lone electron pair of water oxygen atom is faced directly to the fully populated Cu  $d_z^2$  orbital. To compare the distribution of electrons in 3d-orbitals in different geometries we have chosen the compound Bis{bis(methoxycarbimido)aminato}-copper(II) complex (II) [3,4]. Central atom in this complex is square-planar coordinated with Cu atom in the centre of symmetry. In axial direction the closest interaction is on the distance of 3.7 Å. The aim of this study is to compare the bonding properties of Cu central atom in the compounds (I) and (II).

The GEMINI R diffraction data at 100K will be used for electronic structure study. To guarantee a high redundancy the whole diffraction sphere was measured also for a monoclinic space group (P 2<sub>1</sub>/n) up to resolution of 0.39 Å. In 63 omega runs 120163 diffractions were collected with the average redundancy of 10.3. The multipole refinement and the results of both experimental and theoretical topological analysis for both coordination polyhedra will be discussed.