Université de Neuchâtel
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HyperHelper – an application for improving the parameters in the MM+ Force Field. New parameters for some transition metal complexes of pyridine and pyrazine.

Thèse presentée à la Faculté des Sciences par

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IMPRIMATUR POUR LA THESE

Hyperhelper-an application for improving the parameters in the MM+Force Field. New parameters for some transition metal complexes of pyridine and pyrazine

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FACULTE DES SCIENCES

La Faculté des sciences de l'Université de Neuchâtel sur le rapport des membres du jury,

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Le doyen:

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Abbreviations

Å	Angstrom unit
ANG	Angle (file)
C	Character
CDK	Chemist's Developer Kit
CN	Coordination number
CSD, CCSD	Cambridge Crystallographic Structural Database
DDE	Dynamic Data Exchange
DFT	Density-Functional Theory
et al.	And others
HAPI	HyperChem Application Programming Interface
HIN	native HyperChem file type
HCL	HyperChem Command Language
HSV	HyperChem State Variables
hybr.	Hybridisation
LST	List of connections between atoms(file)
M	Metal
mac	Menu activation command
MB	Megabyte unit
M-DAT	Multiple Structure CSD DAT file
MM	Molecular mechanics
MM*	Modified (new) MM+ parameter set
MM+	MM+ HyperChem parameters set
MS	Microsoft
N	Number
MSI	Molecular Simulations Inc.
N.B.	Nota bene
OS	Operating System
OST	Oxidation state
PDB	Protein Database file format
PS	Preferred structure
py	Pyridine
pz	Pyrazine
QM	Quantum Mechanics
R	Remark
RAM	Random Access Memory
R^2	Coefficient of determination of linear regression
RMS	Root-mean-square
RO	Read-only
RW	Read/write
S-DAT	Single structure CSD DAT file
SP	Service pack
TOR	Torsion angle (file)
ULP	Unique labelling problem
V	Version
VB	Microsoft Visual Basic
VBA	Microsoft Visual Basic for Applications
vdW	van der Waals

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1. Introduction

In 1998 The Nobel Foundation Committee honored two scientist: Walter Kohn "for his development of density-functional theory" and John A. Pople "for his development of computational methods in quantum chemistry" **[1]**, ***Figure 1*** The two prizes showed that computational chemistry plays a very important role in modern chemistry.

There was another great Nobel Prize Winner Dorothy Crowfoot Hodgkin honored by the Foundation "for her determination by the X-ray techniques of the structures of important biochemical substances" (1964), ***Figure 1***. Professor Hägg in his presentation speech **[2]** said that "it is nearly always necessary to use electronic computers, and their arrival has made an enormous difference to the possibility of carrying out structure determinations. However, it is not usually possible to just feed in the experimental data, and get out the figures which give the final structure; the scientist's ability to handle the data is still of vital importance. It is in this respect that Mrs. Hodgkin has shown such exceptional skill".



Figure 1. Walter Kohn, John A. Pople and Dorothy Crowfoot Hodgkin

Now two different disciplines of science met together: computational chemistry and crystallography. At the beginning just to use the computer to analyze the X-ray diffraction data and more recently to assist in comparing the results of the measurements and the calculated (minimized) models in the case of powder X-ray diffraction data.

The Cambridge Crystallographic Structure Database (CCSD - **[3]**), where atomic parameters concerning all published crystal structure analyses are deposited, is

a mine of information for anyone interested in the analysis of molecule structure. By analysing selected groups of molecules it should be possible to obtain characteristic bond lengths and angles for a series of compounds. These parameters could then be used to improve the existing Force Field parameters in a Molecular Mechanics program in order to reproduce the crystal structure. Different methods (Molecular Mechanics, Quantum Mechanics) can be used to optimization the molecular geometry. Molecular Mechanics was chosen for this work, as this method is rapid, and does not require important computational resources.

The quality of Molecular Mechanics calculations depends on the accuracy of the force field parameters. Very often, it is necessary to change old parameters or to add new ones and to do this one has to perform calculations on a large number of compounds. A considerable amount of time is required to add the new parameters and to verify them.

There have been several publications on applying Molecular Mechanics to the calculations of coordination compounds **[4-8]**. For example, Rappé et al. **[9]** developed a Full Periodic Table Force Field, which was later used for metal complexes. They showed that the magnitudes of errors in the structures of metal compounds are larger than those for organic compounds but comparable to the errors for main group compounds.

In this work 139 structures, including pyridine and pyrazine transition metal complexes, from the CCSD were used. Ten further unpublished structures from work carried out within the Chemical Crystallography group at the *Instutut de Chimie*, were also included. Pyrazine and pyridine complexes of Chromium, Manganese, Iron, Cobalt, Nickel, Copper, Zinc, Ruthenium, Rhodium, Palladium, Silver and Platinum were chosen since they are of great interests in the formation of coordination polymers using substituted pyrazine ligands, and for their potential physical properties, such as electrical conductivity, magnetism and photochemical behaviour **[10-26]**.

HyperChem **[27]** was chosen for calculations and its MM+ force field was examined and updated.

The HyperHelper program has been written to rapidly prepare new bond stretching and bond angle force field parameters to be added to the existing MM+ force field in the HyperChem program. The program refines and improves these parameters in order to reproduce realistic structures of transition metal complexes of

substituted pyridine and pyrazine ligands. The results are illustrated by the net improvement in the structures found for some metal-pyrazine complexes when compared with the crystal structures obtained by single crystal X-ray analysis. The HyperHelper program also prepares the torsional parameters.

The thesis has been divided into chapters:

- Chapter 2 summarizes our present knowledge on Molecular Mechanics, computational and minimization options.
- Chapter 3 describes the application HyperHelper in detail
- Chapter 4 describes the methodology used.
- Chapter 5 describes the sources of the initial parameters used in Molecular Mechanics.
- Chapter 6 describes briefly how the calculations were performed.
- Chapter 7 summarizes the results of the calculations and gives the new parameters obtained for the various transition metal atoms.
- Chapter 8 discusses the overall results, conclusions and perspectives.

2. Theoretical part

2.1. Introduction to Molecular Mechanics computational methods

The complete mathematical description of a molecule can be expressed by the Schrödinger equation :

$$H\Psi(R,r) = E\Psi(R,r)$$

Equation 1. Schrödinger equation.

where H is the Hamiltonian for the system and Ψ is the wavefunction (a function of the coordinates of the nuclei (R) and the electrons (r)) and E is the energy.

In 1927 Born and Oppenheimer proposed the following approximation: the motion of the electrons can be decoupled from that of the nuclei, giving two separate equations, one describing electronic motion and the second describing the motion of the nuclei on a potential energy surface E(R). The direct solution of the second equation can be done by *ab initio* methods. However, the effort required to solve the equations is extremely large, so usually an empirical fit to the potential energy surface, commonly called a force field, is used. Since the nuclei are relatively heavy objects, quantum mechanical effects are often insignificant, so the equations describing the motion of the nuclei can be replaced by Newton's equation of motion:

$$-\frac{dV}{dR} = m\frac{d^2R}{dt^2}$$

Equation 2. Newton's equation of motion.

The solution of the above equation, using an empirical fit to the potential energy surface, is called Molecular Dynamics. In contrast Molecular Mechanics ignores the time evolution of the system and instead focuses on finding particular geometries and their associated energies. This includes finding equilibrium structures, relative energies and harmonic vibrational frequencies.

In general there are two main groups of methods of calculation: molecular mechanics (MM) and quantum mechanics (QM) (semi-empirical, DFT and ab initio techniques). The molecular mechanics methods are much faster than the ab initio methods, which are the slowest. Although nowadays scientists have very fast

computers not all calculations can be performed – the structures of certain compounds are still too large.

Zwaans **[28]** with the help of the program GAMESS-UK **[29]**, using a minimal STO3G basis set, optimized the geometry of a metallo-porphyrin (226 electrons divided over 185 basis functions). Several weeks of computer time (HP 750 & Silicon Graphics Power Challenge) were necessary to release all the symmetry restrictions (except those concerning the planarity of the porphyrin).

On the other hand, comparing the accuracy of MM and QM methods it is seen that the quantum methods are better than MM ones.

The accuracy of MM or semi-empirical quantum mechanics method depends on the database used to parameterize the method. Hence, these methods give the best results for a limited class of molecules. A disadvantage of these methods is that one must have parameters available before running a calculation, and developing parameters is extremely time-consuming **[30]**.

2.2. Molecular mechanics

Molecular mechanics consists of three main components:

- The force field, or function, which describes the analytic form of each of the terms in the potential equation.
- Atom types, which define the chemical environment of an atom: hybridization, formal charge, and immediate bonded neighbors. They are the fundamental basis for calculating interactions.
- The Parameter Sets

HyperChem **[27]** consists of four Force fields:

- MM+- the most general method for molecular mechanics calculations, developed principally for organic molecules as an extension of MM2 **[31]**. This is an all atom force field. It uses MM2 parameters (1991) and atom types with the 1977 functional form modified to incorporate nonbonded cutoffs, periodic boundary conditions, and the bond stretch term switched from a cubic form to a quadratic form at long range.

- AMBER (Assisted Model Building with Energy Refinement) **[32]**– developed for small organic molecules, nucleic acids and proteins. This force field provides both an all atom and a united atom representation.
- OPLS (Optimized Potentials for Liquid Simulations) **[33]**– used for calculations on proteins and nucleic acids.
- BIO+ - an implementation of CHARMM (Chemistry at Harvard Macromolecular Mechanics) **[34]** with usage similar to OPLS and AMBER.

2.3. Functional form of MM+ force field

Molecular Mechanics uses an analytical, differentiable, and relatively simple potential energy function, for describing the interactions between a set of atoms specified by their Cartesian coordinates.

The potential energy of a molecule in a force field is the sum of the individual components of the potential, such as bond stretch, angle bend, torsion bend, vdW potentials etc. **[30]**

$$E_{MM} = E_{bonds} + E_{angles} + E_{vdw} + E_{torsion} + E_{miscellaneus}$$

Equation 3. Energy components in MM.

The energies of the individual bonding components (bond angles, and dihedral angles) are functions of the deviations of a molecule from a hypothetical structure that has bonded interactions at a minimum energy value. The absolute energy of a molecule in MM has no intrinsic physical meaning; E_{TOTAL} values are useful only for comparison purposes between conformers.

The interaction potentials used by the MM+ force field uses the following terms:

- **Bond Stretching.**

We can consider that the bonds are springs connecting the atoms. A cubic form of Hook's Law is used to represent the spring:

$$E_{bond} = 144.88 \sum 0.5K_r(r - r_o)^2 \times$$

$$\times \left[1 + switch\left(r - r_o, -\tfrac{1}{3}\ CS, -\tfrac{4}{3}\ CS\right)\ CS\ (r - r_o)\right]$$

Equation 4. Bond stretching.

where 144.88 is the factor to convert original units [ergs] to[kcal/mol]. K_r is the force constant or spring "strength" and r_o is the ideal bond length or the length the spring at minimum energy. A larger value for stretch force constant K_r leads to a greater tendency for the bond to remain at its equilibrium distance r_o.

CS is the cubic stretch term factor (CS = -2.0). The switching function, s*witch*, is used to avoid the repulsive form of the above equation in cases when $r\text{-}r_o$ > 2/3 CS. The function takes the following values:

$$switch\left(r - r_o, -\tfrac{1}{3}\ CS, -\tfrac{4}{3}\ CS\right) = 1 \qquad r\text{-}r_o \le -1/3CS$$

$$switch\left(r - r_o, -\tfrac{1}{3}\ CS, -\tfrac{4}{3}\ CS\right) = 0 \qquad r\text{-}r_o \ge -4/3CS$$

$$switch\left(r - r_o, -\tfrac{1}{3}\ CS, -\tfrac{4}{3}\ CS\right) = \frac{\left(-\tfrac{4}{3}\ CS - (r - r_o)\right)^2 \left(-\tfrac{4}{3}\ CS + 2(r - r_o)\right)}{-CS^3} \qquad -1/3CS < r\text{-}r_o < -4/3CS$$

- **Bond dipoles**

The electrostatic contribution comes from defining a set of bond dipole moments associated with polar bonds (located in HyperChem in *mmpstr.txt* and *pgstr.txt* parameter set files). The center of the dipole is defined to be the midpoint of the bond and the two dipoles μ_i and μ_j , are separated by distance R_{ij} (***Figure 2***)

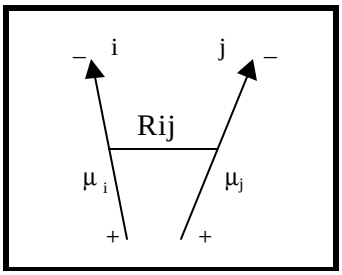


Figure 2. The center of the dipole.

The MM+ dipole interaction energy is given by:

$$E_{dipole} = 14.39418\ e \sum_{ij \in \text{polarbonds}} m_i m_j \left[\frac{\cos c - 3\cos a_i \cos a_i a_j}{R_{ij}^3} \right]$$

Equation 5. Dipole interaction energy.

where ε, the dielectric constant, is assumed to be greater than 1. The angle χ is the angle between the two dipole vectors, and α_I and α_j are the angles that the two dipole vectors make with the R_{ij} vector. The constant 14.39418 converts [erg/molecule] to [kcal/mol].

- **Bond Angle Bending.**

The following bending term is used:

$$E_{\text{bondangle}} = 0.043828 \sum_{\text{angles}} 0.5 K_\Theta \left(\Theta - \Theta_o\right)^2 \left[1 + SF\left(\Theta - \Theta_o\right)^4\right]$$

Equation 6.. Angle bending energy.

where θ_o – equilibrium angle, SF – scale factor SF=7E-8. The constant 0.043828 converts the MM+ bending constants expressed in [millidyne-A/ radian^2] to [kcal/mol per radian^2].

A larger value for the bending force constant K_θ leads to a greater tendency for the angle to remain at its equilibrium value θ_o.

- **Bond Stretch and Angle Bending Cross Term**

If the angle is defined to include atoms ***i***, ***j*** and ***k***, where ***k*** is the central atom, the MM+ couples the stretching of the ***ik*** and ***jk*** bonds with the angle:

$$E_{\text{stretch-bend}} = 2.51118 \sum_{angles} K_{sb}(\Theta - \Theta_o)_{ijk}[(r - r_o)_{ik} + (r - r_o)_{jk}]$$

Equation 7. Stretching-bending cross term.

If an atom ***i*** or atom ***j*** is a hydrogen, the deformation ($r-r_o$) is considered to be zero.

K_{sb} = 0.120 for XR_2, where X – atom in first long row

K_{sb} = 0.090 for XRH

or

K_{sb} = 0.250 for XR_2, where X – atom in second long row

K_{sb} = -0.400 for XRH

The stretch-bend force constants are incorporated into the program and cannot be modified. The constant 2.51118 converts [millidynes/radian] to [kcal/degree].

- **Out-of-Plane Bending.**

The program uses the same equation as for bond stretching. The parameters are taken from the *mmpoop.txt* or *pgoop.txt* files.

- **Dihedrals.**

Torsion angles or dihedral angles could not be modeled in the same manner since a periodic function is required **[5]**:

$$E_{dihedral} = \sum_{dihedral} \frac{V_n}{2}[1 + \cos(nq - q_0)]$$

Equation 8. Torsion periodic function.

For MM+ T_0=0 and n=1,2,3.

$$E_{dihedral} = \sum_{dihedrals} \frac{V_1}{2}(1+\cos q) + \frac{V_2}{2}(1-\cos 2q) + \frac{V_3}{2}(1+\cos 3q)$$

Equation 9. MM+ torsion periodic function.

The V_n parameters can be found in the *mmptor.txt* and *pgtor.txt* files.

- **Van der Waals.**

This term describes both the repulsive forces keeping two nonbonded atoms apart at close range and the attractive force drawing them together at long range.
In MM+, the vdW interactions combine an exponential repulsion with an attractive $1/R^6$ dispersion interaction. The vdW radius r_i^* for each atom type and a hardness parameter ε_i that determines the depths of the attractive well and how easy (or difficult) it is to push the atoms close together are the parameters in this type of interaction. There are interactions for each nonbonded ***ij*** pair, including 1-4 pairs. The parameters for each pair are obtained from individual atom parameters according to ***Equation 10*** *and* ***11***:

$$r_{ij}^* = \frac{r_i^* + r_j^*}{2}$$

Equation 10. Van der Waals radius.

$$e_{ij} \cong \sqrt{e_i e_j}$$

Equation 11. Hardness parameter.

The vdW interaction is then calculated as a Hill potential:

$$E_{vanderWaal} = \sum_{ij \in vdW} \varepsilon_{ij} (2.9 x 10^5 \exp(-12.5\, r_{ij}) - 2.25\, r_{ij}^{-6})$$

Equation 12. Van der Waals interaction energy.

where $r_{ij} = \frac{R_{ij}}{r_{ij}^*}$

At short distances, the above expression is replaced by ***Equation 13***:

$$E_{vanderWaal} = 336.176 \sum_{ij \in vdW} \varepsilon_{ij}\, r_{ij}^{-2}$$

Equation 13. Van der Waals energy for short distances.

For **C-H** interactions normal ε and r* values are replaced by ε=0.046 and r*=3.340. For **X-H** bonds (X is any heavy atom) the MM+ force field reduces the **X-H** bond length by a factor of 0.915 **[30]**.

- **Electrostatic term** describes the classical non-bonded electrostatic interactions of charge distributions:

$$E_{electrostatic} = \sum_{ij \in elctrostatic} \left[\frac{q_i q_j}{e\, R_{ij}} \right]$$

Equation 14. Electrostatic term.

The above potential describes the monopole-monopole interactions of atomic charges q_i and q_j at distance R_{ij} apart. ε – dielectric constant, sometimes scaled or made distance-dependent.

2.4. Atom types in MM+

Atoms in MM+ are described by introducing their atom types. Atom types recognized by HyperChem are included in the *mmtyp.txt* file. This file also consists the atomic masses of the elements.

If it is necessary to define a new atom type it must first be introduced into the *mmptyp.txt* file then certain conditions must be added to the *Chem.rul* file in the section dealing with the MM+ parameter set. The *Chem.rul* file must be compiled and then HyperChem must be restarted before it can be used for calculations.

Each time, when an ***Assign Type Atom*** or a ***Model Build*** command is chosen HyperChem will assign atom types for each atom, one by one, according to the conditions defined in *Chem.rul*. The search is hierarchical, that means that the most specific search conditions should be placed before the more general ones. In case HyperChem cannot determine the type of an atom, it assigns the symbol "**", meaning one unknown. The following example shows the structure of an entry for copper atom types.

Force field(mm+)
(…) ; other atom type definitions
; clauses and tests for copper
Cu:
; connected to pyrazine CN=6, 5, 4, 3
; clause 1
connected to N@1~C~C~N~C~C~N@1? ; test 1
connected to (-*)(-*)(-*)(-*)(-*)(-*)? ; test 2
=CU2.; numerical type 85 (mmptyp.txt)
; end clause 1
; clause 2
connected to N@1~C~C~N~C~C~N@1? ; test 1
connected to (-*)(-*)(-*)(-*)(-*)? ; test 2
=CU5.; numerical type 110
; end clause 2
; clause 3

connected to N@1~C~C~N~C~C~N@1? ; test 1

connected to (-*)(-*)(-*)(-*)? ; test2

=CU4.; numerical type 109

; end clause 3

; clause 4

connected to N@1~C~C~N~C~C~N@1? ; test1

connected to (-*)(-*)(-*)?; test2

=CU3.; numerical type 108

; end clause 4

; clause 5

;connected to pyridine

connected to N@1~C~C~C~C~C~N@1? ; test 1

=CU1.; numerical type 84

; end clause 5

; end definitions for copper

The first line indicates which type of force field is used. Then the element is introduced (Cu:) followed by tests grouped in the different clauses.

The first clause checks if copper is connected to a pyrazine ring (aromatic bonds are represented by tilde character "~", single ones as "-", double as "=") – test 1 - and if it is connected to 6 (any "*") atoms (coordination number 6) – test 2. If these two tests are true then the CU2 atom type is assign to copper.

Clauses 2 to 4 assign the atom types CU5 for CN=5, CU4 for CN=4, CU3 for CN=1.

Clause 5 defines CU1 atom type for copper connected to pyridine.

The new atom types and their condition definitions are added to the original set of atom types given in the sections describing each group of coordination compounds

2.5. MM+ parameter set

MM+ force field consisted originally of one parameter set, called MMPLUS

The second parameter set – PG – was created by copying all the necessary *mm*.txt* files into the *pg*.txt* files. All necessary changes will be done in *pg*.txt* files only.

One of the greatest advantages in HyperChem MM+ force field is its ability to generate missing parameters. If, during the initial phase of the typing procedure, it is not possible to find a suitable parameter then HyperChem uses a unique scheme to find a possible value for that parameter. **[30]**

First, the hybridization of the atoms is estimated. HyperChem uses five different hybridization states – ***null***, ***s***, ***p*** sp^2, $sp^{2.5}$ (for aromatic systems) and sp^3, based on the number of ***s*** and ***p*** valence electrons and the number of neighbouring atoms. This type of approximation is also used for transition metals (d orbitals are not considered).

The number of valence electrons assigned to certain elements is listed in ***Table 2***. ***Table 1*** summarizes the conditions used to determine a hybridization state for some chosen elements.

According to ***Equation 4*** one needs two bond stretching parameters. K_r depends on the bond order only. The equilibrium bond length is equivalent to the sum of the covalent radii of the two atoms involved in the bond. The covalent radii and K_r are listed in ***Table 2.***

For Boron HyperChem assigns different values of the covalent radius, depending on the hybridization. For sp^3 it takes 0.880 and for sp^2 – 0.790. Carbon takes the value of 0.770 for sp^3, 0.700 for $sp^{2.5}$, 0.670 for sp^2 and 0.602 for ***sp*** hybridization. For Nitrogen HyperChem gives 0.702 for sp^3, 0.650 for $sp^{2.5}$, 0.615 for sp^2 and 0.556 for ***sp*** hybridization. Oxygen is assigned 0.660 for sp^3, 0.660 for $sp^{2.5}$, 0.560 for sp^2 and 0.528 for ***sp.***

HyperChem assigns the value of 100 [kcal/mol/radian^2] for the default bending force constants.

The program does not generate the default parameters for stretch-bending or electrostatic interactions.

According to ***Equations 10 and 11*** one needs two parameters to calculate the van der Waals interactions. The default values are (radii r^* and ε), based on the atomic number only, are given in ***Table 2.*** The hardness parameters are the dissociation energies of the non-bonded interactions of two identical atoms divided by 1.125.

Table 1. Conditions for estimating the hybridization.

Number of valence electrons	Number of neighbors				Connected by	Hybr.
	1	2	3	4		
1						**s**
2 or 3				Ö		**sp^3**
			Ö			**sp^2**
	Ö	Ö				**sp**
4				Ö		**sp^3**
			Ö		at least one aromatic bond	**$sp^{2.5}$**
			Ö		double bond	**sp^2**
		Ö Ö			both single bonds one single bond	**sp^3** **sp^2**
		Ö			neither of the bonds is single	**sp**
	Ö				triple bond	**sp**
	Ö				0 aromatic bond	**$sp^{2.5}$**
	Ö				double bond	**sp^2**
	Ö				single bond	**sp^3**
5			Ö	Ö	double, aromatic or triple bond	**sp^2**
			Ö	Ö	single bond	**sp^3**
		Ö			aromatic bond	**$sp^{2.5}$**
		Ö				**sp^2**
	Ö				triple bond	**sp**
	Ö				aromatic bond	**$sp^{2.5}$**
	Ö				double bond	**sp^2**
	Ö				one single bond	**sp^3**
6		Ö Ö	Ö Ö	Ö Ö	double, aromatic or triple bond single bond	**sp^2** **sp^3**
	Ö				triple bond	**sp**
	Ö				double bond	**sp^2**
	Ö				aromatic bond	**$sp^{2.5}$**
	Ö				single bond	**sp^3**
7						**s**
8						**null**

Number of valence electrons – see ***Table 2.***

Table 2. Constants and default parameters in HyperChem MM+ force field (for some elements) [**30**].

	1																	18
	H																	**He**
1	1																	8
	0.32																	0.93
	3.20																	2.80
	0.015	2											13	14	15	16	17	0.01
	Li	**Be**											**B**	**C**	**N**	**O**	**F**	**Ne**
	1	2											3	4	5	6	7	8
2	1.23	0.90											0.82*	0.77*	0.75*	0.73*	0.72	0.71
	3.64	1.66											4.02	3.90	3.66	3.40	3.47	3.12
	0.015	0.1											0.095	0.095	0.077	0.096	0.073	0.069
	Na	**Mg**											**Al**	**Si**	**P**	**S**	**Cl**	**Ar**
	1	2											3	4	5	6	7	8
3	1.54	1.36											1.18	1.11	1.06	1.02	0.99	0.98
	3.14	3.46											4.39	4.27	4.15	4.03	3.95	3.82
	0.50	0.1	3	4	5	6	7	8	9	10	11	12	0.31	0.31	0.32	0.344	0.283	0.238
	K	**Ca**	**Sc**	**Ti**	**V**	**Cr**	**Mn**	**Fe**	**Co**	**Ni**	**Cu**	**Zn**	**Ga**	**Ge**	**As**	**Se**	**Br**	**Kr**
	1	2	3	4	5	3	2	3	2	2	2	2	3	4	5	6	7	8
4	2.03	1.74	1.44	1.32	1.22	1.18	1.17	1.17	1.16	1.15	1.17	1.25	1.26	1.22	1.20	1.16	1.14	1.12
	5.5	3.47	2.2	2.08	1.98	1.94	1.93	4.54	1.92	3.26	2.8	4.54	4.39	4.27	4.15	4.03	3.95	4.04
	0.1	0.05	0.1	0.1	0.1	0.1	0.1	0.055	0.1	0.1	0.1	0.055	0.40	0.40	0.41	0.43	0.37	0.340

Bond stretching parameters

Bond order	K_r: [kcal/mol/ Å^2]
Single	700
Double, aromatic	1400
Triple	2100

Angle bending

K_θ = 100 [kcal/mol/rad]

Atom symbol	**B**	
Valence electrons assigned	3	
Covalent radii	0.82*	* - see text
van der Waals r^* param.	4.02	[Å]
van der Waals e param.	0.095	[kcal/mol]

Table cont.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	Rb	**Sr**	**Y**	**Zr**	**Nb**	**Mo**	**Tc**	**Ru**	**Rh**	**Pd**	**Ag**	**Cd**	**In**	**Sn**	**Sb**	**Te**	**I**	**Xe**
5	1	2	3	4	5	2	7	3	3	2	1	2	3	4	5	6	7	8
	2.16	1.91	1.62	1.45	1.34	1.30	1.27	1.25	1.25	1.28	1.34	1.48	1.44	1.41	1.40	1.36	1.33	1.31
	2.92	2.67	2.38	2.21	2.1	2.06	2.03	2.01	2.01	2.04	3.44	3.16	4.59	4.47	4.35	4.23	4.15	4.60
	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.55	0.55	0.55	0.57	0.51	0.439
	Cs	**Ba**	**La**	**Hf**	**Ta**	**W**	**Re**	**Os**	**Ir**	**Pt**	**Au**	**Hg**	**Tl**	**Pb**	**Bi**	**Po**	**At**	**Rn**
6	1	2	3	4	5	6	7	4	4	4	3	2	3	4	5	6	7	8
	2.35	1.98	1.69	1.44	1.34	1.30	1.28	1.26	1.27	1.30	1.34	1.49	1.48	1.47	1.46	1.46	1.45	1.45
	3.11	2.74	2.45	2.2	2.1	2.06	2.04	2.02	2.03	3.5	3.32	3.1	3.92	4.04	2.23	2.23	2.22	2.22
	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

As mentioned before HyperChem uses ***Equation 9*** to calculate the torsion interactions. It contains three parameters V_1, V_2 and V_3, which, in case they have not been defined, are generated on the basis of the bond order and hybridization of the relevant atoms. The rules used to determine the above parameters are summarized in ***Table 3.***

Table 3. **Estimation of the torsion parameters.**

Atom 1	Atom 2	Bond type	barrier [kcal/mol]		
			V_1	V_2	V_3
sp^3	sp^3	single			2.0
group 6 sp^3	group 6 sp^3	single		-2.0	
group 6 sp^3	sp^2 or $sp^{2.5}$	single		2.0	
sp^3	sp^2 or $sp^{2.5}$ connected to sp^2 or $sp^{2.5}$	single	-01.67		-0.1
sp^3	sp^2 or $sp^{2.5}$ not connected to sp^2 or $sp^{2.5}$	single			2.0
sp^2	sp^2 or $sp^{2.5}$	single		5.0	
$sp^{2.5}$	$sp^{2.5}$	single		10.0	
sp^2	sp^2	double		45	
$sp^{2.5}$	$sp^{2.5}$	double		25	

2.6. Computational options

Single Point determines the total energy of a molecular system or a selection of atoms. It is used to describe the static properties of a molecule. The molecular symmetries (point group) are reported, in Semi-empirical and *Ab Initio* quantum mechanical calculations. For Semi-Empirical or *Ab Initio* calculation methods, the Single Point calculation also determines the distribution of the electrons and the charges.

Geometry Optimization calculates and displays the structure of a molecule or a selection of atoms with the minimum energy and minimal atomic forces. The main concept of geometry optimization is to start the process with a set of molecular coordinates and to find a new set of coordinates with a minimum potential energy. It is possible to use Molecular Mechanics, Semi-empirical or *Ab Initio* methods.

Molecular Dynamics simulates molecular movement so one can observe equilibrium properties and the kinetic behaviour of a molecular system.

2.7. Minimization options

Molecular Modeling programs provide calculations that explore molecular potential energy surfaces. For a diatomic molecule (***Figure 3***) the energy is a function of the configuration, that is, the intermolecular distance.

A single point calculation will give the values of the energies at any point A, B, C or D of the surface. The energies here being $E_a > E_b = E_d > E_c$.

If (X_A, Y_A, Z_A) are the Cartesian coordinates of atom A, then the gradient or the force on atom A has the components: $(\partial E/\partial X_A, \partial E/\partial Y_A, \partial E/\partial Z_A)$. The gradient is large at position A compared to the gradient at position B.

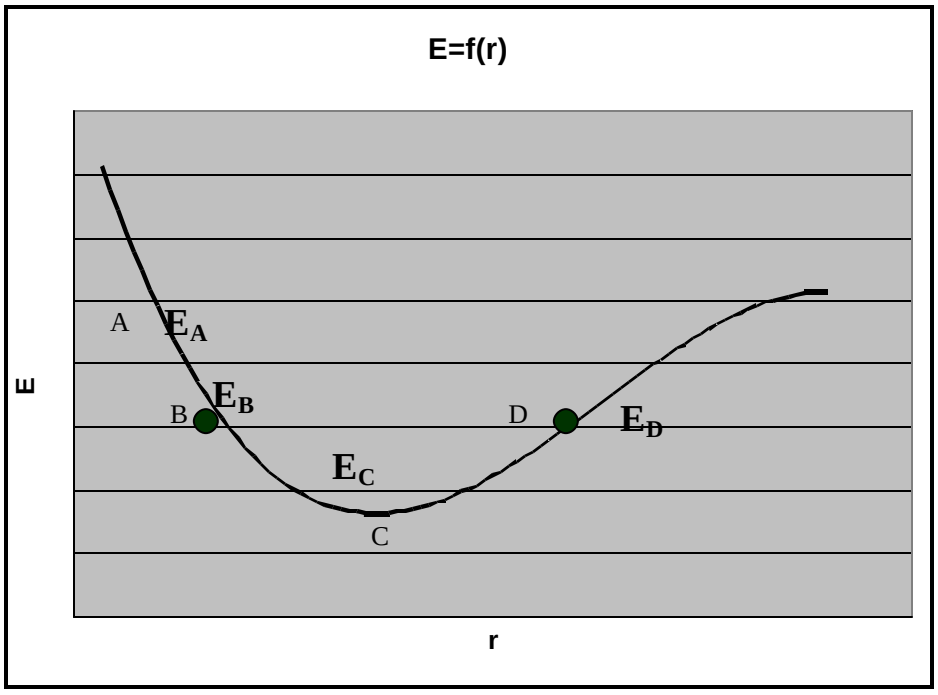


Figure 3. Energy versus bond distance for diatomic molecule.

For multi-dimensional potential energy surfaces HyperChem uses root-mean-square (RMS) gradients:

$$RMS = (3N)^{-1}\left(\sum_{A} \left(\frac{\partial E}{\partial XA}\right)^2 + \left(\frac{\partial E}{\partial YA}\right)^2 + \left(\frac{\partial E}{\partial ZA}\right)^2 \right)^{1/2}$$

Equation 15. RMS.

The optimizers attempt to find *extrema* on a potential surface. This means that they find the points where all the components of the gradient vector tend to zero. In the case of diatomic molecules (***Figure 3***) the optimizers would find the stable equilibrium configuration, the only minimum on the surface (point C).

For more complicated cases the surface may contain more than one minima. Normally the optimizers start at some initial guess. If it starts at point B it may reach the global minima. If it starts at F it may not, since minimization calculations cannot cross or penetrate potential energy barriers (***Figure 4*** – point *D*)

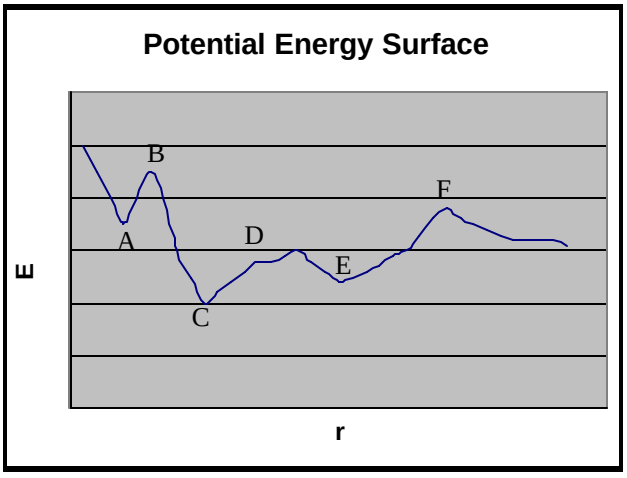


Figure 4. Multiple minimum problem.

There are several optimization methods available.

- **Steepest Descent**.

The direction of Steepest Descent, G, is just the negative of the gradient vector:

$$G = -(\frac{\partial E}{\partial X_1}, \frac{\partial E}{\partial Y_1}, \frac{\partial E}{\partial Z_1}, \frac{\partial E}{\partial X_2}, \frac{\partial E}{\partial Y_2}, \ldots \frac{\partial E}{\partial Zn})$$

Equation 16. Direction of minimization.

New points are found by:

$$X_{i+1} = X_i + n_i \frac{G_i}{|G_i|}$$

Equation 17. Calculations of the new points.

where, n_i is the step size.

The main advantage of the steepest descent method is that each cycle requires little computational time. This method is good for the initial optimization of very distorted geometries.

- **Conjugate Gradient Methods.**

In the steepest decent method the gradient is calculated after each iteration. This means that the search direction can be changed at each step if the molecule is moved through the minimum at each step. This may be avoided if the history of gradient is stored and used to modify the subsequent steps. An important difference of conjugate gradient methods from the steepest descent algorithm is that each step is one-dimensional, i.e. the minimization occurs along a line, and from each lower-energy point found on the surface the search direction is changed. Therefore the method is more time-consuming, but convergence is in general more rapid.

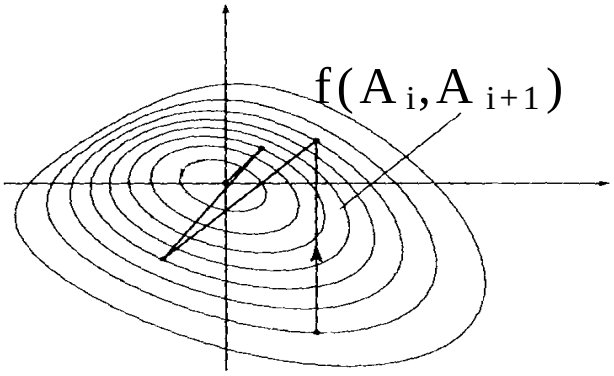


Figure 5. Conjugate gradient method.

In conjugate gradients, h_{i+1}, the new direction vector leading from point ***i+1***, is computed by adding the gradient at point ***i+1***, G_{i+1}, to the previous direction h, scaled by a constant γ_i:

$$h_{i+1} = G_{i+1} + g_i h_i$$

Equation 18. New direction vector in conjugate method.

where γ_i is a scalar that is defined in two ways:

- in the Polak-Ribiere method, according to ***Equation19***:

$$g_i = \frac{(G_{i+1} - G_i)G_{i+1}}{G_i G_i}$$

Equation 19. Constant γ_i in Polak-Ribiere method.

- and in the Fletcher-Reeves method, according to ***Equation20***:

$$g_i = \frac{G_{i+1} G_{i+1}}{G_i G_i}$$

Equation 20. Constant γ_i in Fletcher-Reeves method.

Fletcher-Reeves chooses a descent direction to lower energy by taking into account the current gradient and that of the previous step. For each descent direction, a one-dimensional search attempts to locate the minimum.

Polak-Ribiere – is similar to Fletcher-Reeves but it improves it by considering the previous conjugate direction. It is more computer intensive but converges more quickly.

The Newton-Raphson Method

The full Newton-Raphson method computes the full Hessian A matrix of second derivatives and then computes a new guess at the 3N coordinate vector **x** according to ***Equation 21***:

$$x_{i+1} = x_i + A^{-1} \bullet G_i$$

Equation 21. New points in Newton-Raphson method.

The Newton-Raphson method converges very efficiently for molecules close to the optimum structures. The method should be used for systems containing not more than 200 atoms (due to fact that the Hessian matrix has the size of $(3N)^2$ a very large amount of computer memory is required for large molecules).

For MM+ the block-diagonal Newton-Raphson method is used. The method considers only one atom at a time, computing 3x3 Hessian matrix associated with that atom and the 3 components of the gradient for that atom and then inverts the 3x3 matrix and obtains new coordinates for the atom according to Newton-Raphson formula. It then goes on to the next atom and moves it in the same way, using first and second derivatives for the second atom that include any previous motions of atoms.

Smart Minimizer.

An interesting method was used in the Cerius^2 program **[35]**. Minimization procedures start with the Steepest Decent algorithm followed by Adapted Basic Newton-Raphson (a

first derivative method) and Quasi Newton (simulates second derivatives) methods and ends with the Truncated Newton method (combines strengths of conjugate gradient and Newton-Raphson method).

3. HyperHelper

3.1. Introduction to HyperHelper

HyperHelper is the program to help drive calculations in HyperChem and to collect the results of such calculations. The main aim of this program is to prepare and test new stretching, bending and torsional parameters.

Hypercube includes the Chemist's Developer Kit (CDK) as a part of the general release of HyperChem (starting from version 5) for Windows 95 and NT. This is a direct interface for programs written in Microsoft® Visual Basic, C++ or Fortran. CDK enables the control of HyperChem from outside the program, and allows reading and writing to HyperChem's data structures via external messages **[36]**. This means it is possible to write either a front-end or a back-end application. HyperHelper is a front-end application for HyperChem. *Dynamic Data Exchange* (DDE) is used to communicate between HyperChem and HyperHelper. This method was chosen because it is widely used within Windows programs.

The program is divided into two main parts. The first part has been compiled as an MS Windows executable file, the second part is included in Microsoft® Excel as a set of macros. Both parts are written in Microsoft® Visual Basic (the final version has been compiled under version 6 Service Pack 5 of Visual Basic).

The main functions of the HyperHelper program are:

1) Dividing the multiple structure M-FDAT file(M-DAT), obtained from CSD (SAVE-FDAT command), into single structure S-DAT files (***Figure 6***).
2) Preparing and executing the batch files for transforming S-DAT files into two formats: Protein Database (**.ent*) and HyperChem HIN (**.hin*) files. Babel **[37]** program carries out the transformations.
3) The program prepares the files LST (list of connections between atoms), ANG (list of angles) and TOR (list of torsion angles). The list of connections (bonds) is made automatically. All of the non H-X (where X is any atom) bonds are included. The ANG and TOR files are prepared with the help of a graphical interface (***Figure 7***).

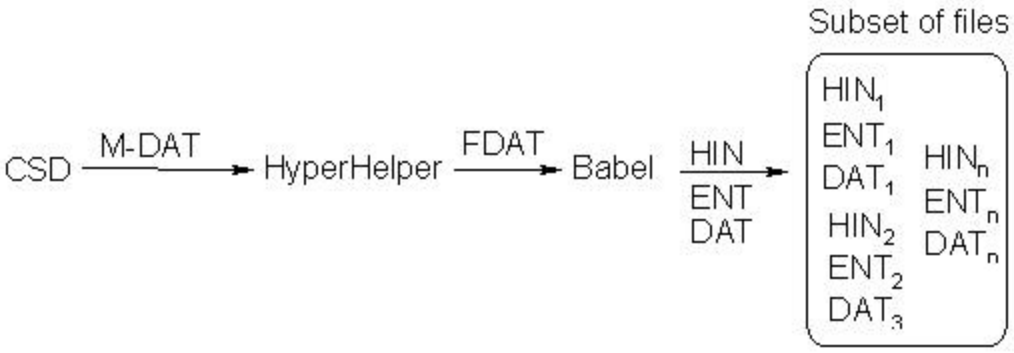


Figure 6. Treatment of the CSD multi structure M-DAT files.

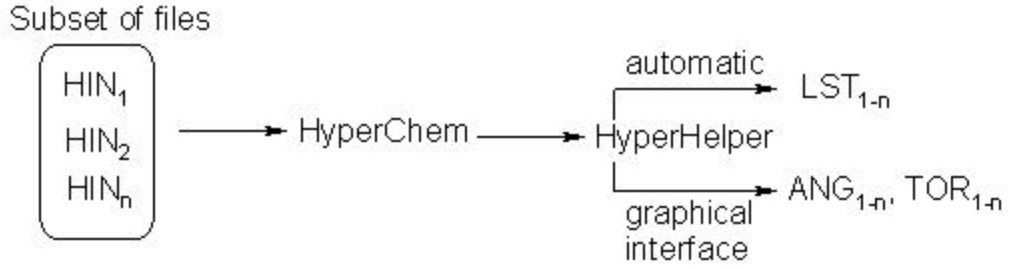


Figure 7. Preparation of the files containing list of bonds (LST), angles (ANG) and torsion angles (TOR).

4) The calculations in HyperChem are then carried out. First, the program sets up the initial conditions for the calculations (termination criteria, etc. taken from *helper.ini* file). Secondly, the program reads all of the HIN files belonging to the subset. With the help of the LST, the ANG and the TOR files, HyperChem calculates the initial geometry of the CSD crystal model and carries out a single point calculation, for each member of the subset. Geometry optimization with the original MM+ force field is then carried out followed by the recalculation of the geometry. HyperChem is then instructed to carry out a geometry optimization using the new MM* force field parameters and again it calculates the new geometry.

5) HyperHelper extracts the results of the calculations and passes them to the MS Excel worksheets.

6) It then creates the HIN files after each step of the calculation (**mm.hin* after MM+, **pg.hin* after MM*) (***Figure 8***)

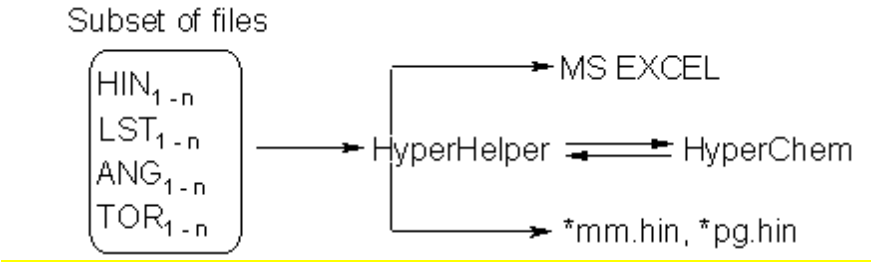


Figure 8. Flow of information between HyperHelper, HyperChem and OS.

7) The application then restarts the calculations and passes the results to MS Excel.
8) It then organizes the pictures of the various compounds which will help the user to compare the geometrical arrangements of the CSD model and those calculated after the MM+ and the MM* calculations.

There are nineteen macros included in HyperHelper (second part of the application), which are listed in ***Table 8*** They are responsible for the calculations carried out in the MS Excel calculation workbook.

3.2. HyperHelper – detailed description of the program

The program has been constructed of ten forms and two modules listed in ***Figure 9.***. The *hapi.bas* and *hsv.bas* are two standard modules included with HyperChem installation (the modules has been added for future use of HyperChem Application Programming Interface – HAPI -, which probably will replace DDE interface). The structure of the application is saved in *Helper.vbp* file. Each form is saved in their own files *(1.frm, 2.frm* etc.). These files contain the information of the property of the form itself (graphical interface), objects and the code provided to run the program.

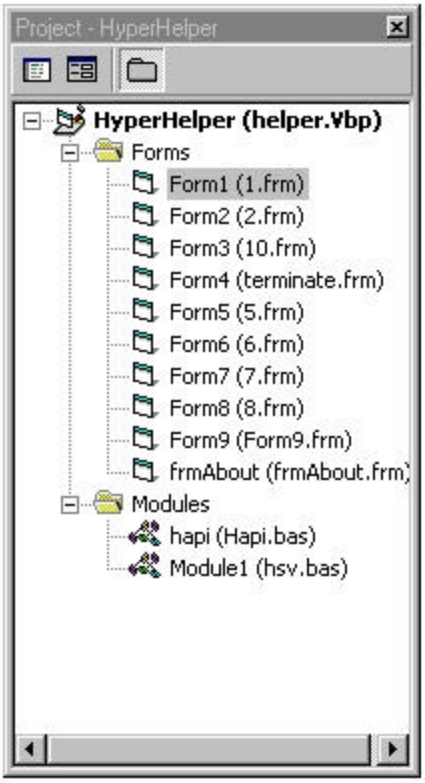


Figure 9. Forms and modules of HyperHelper.

The HyperChem State Variables (HSV) are used to read and write the data, menu activations as well as direct commands to drive the calculations and maintain the files in HyperChem. These form HyperChem Command Language (Hcl). Also the standard VB and VBA dialects of programming languages are used. The code of the program is provided with the installation so one can develop the code easily. In ***Table 4*** the direct script commands, HSVs and menu activation commands (starting with **menu**-*item*) that were implemented into the program are presented.

Table 4. HSVs, direct Commands and MACs used in HyperHelper.

1	2	3
Command/Varible	**Type**	**Description**
allow-ions	v	Allows excessing the valence on atoms. (RW-YES/NO)
atom-count	v	Number of atoms in the j^{th} molecule(RO)
atom-labels	v	Type of labels displayed on the screen identical to ones available from menu: Display/Labels…(RW)
atom-type	v	type of i^{th} atom in j^{th} molecule (RW)
bend-energy	v	Bending energy obtained after calculations(RO)
calculation-method	v	In HyperHelper only "molecular mechanics" is used(RW)
dipole-moment	v	Dipole moment (RO)
do-optimization	c	Does molecular mechanics structure optimization
do-single-point	c	Does single point calculations
estatic-energy	v	Results after calculations (RO)
explicit-hydrogens	v	In HyperHelper set to YES (RW-YES/NO)
file-format	v	In HyperHelper only "hin" format is used (RW)
hbond-energy	v	Energy results after calculations (RO)
image-destination-clipboard	v	Forces HyperChem to use Widows clipboard for storing images (RW- YES/NO)
image-source-window	v	In HyperHelper only "workspace" is a source of the images (RW)
mechanics-mmp-electrostatics	v	The type of electrostatic interactions for MM+ calculations. "Bonddipoles" is used only
mechanics-print-level	v	Level of details taken during logging to chem.log (RW)
menu-build-calculate-types	mac	Clculates the atom types for the system
menu-build-model-build	mac	Forces internal model builder to rebuild the system
menu-display-scale-to-fit	mac	Scales the entire molecular system to fit to the size of the window
menu-edit-copy-image	mac	Places the image of the molecule into the clipboard
menu-file-new	mac	Clears the workspace
menu-file-save	mac	Saves the current model
menu-select-atoms	mac	Single atoms can be selected
molecular-mechanics-method	v	In HyperHelper only "mm+" is used
multiple-selections	v	Allows multiple selections (RW-YES/NO)
named-selection-value	v	The value of named selection (RO)
name-selection	c	Give the name(string)to the selection
neighbors	v	The list of neighbors for the i^{th} atom of j^{th} molecule(RO)
nonbond-energy	v	Energy obtained after the calculations (RO)
open-file	c	Opens the file in HyperChem (full path and the name as the argument)
optim-algorithm	v	In HyperHelper optimization algorithm is taken from helper.ini. The possible choice is: SteepestDescents, FletcherReeves, PolakRibiere, Newtonraphson and EigenVectorFollow) (RW)
optim-converged	v	Informs if the optimization has converged (RO)
optim-convergence	v	Optimization gradient convergence (RW)
optim-max-cycles	v	Maximum number of optimization steps (RW)
query-response-has-tag	v	if "NO" no identifying tags are returned with Text1.LinkRequest (RW-YES/NO)
render-method	V	Rendering method (RW)
rms-gradient	v	RMS obtained after calculations(RO)
select-atom	c	Selects i^{th} atom of j^{th} molecule
selection-value	v	The value of current selection (RO)

Table cont.		
1	2	3
select-none	c	Unselects any selected atoms in the system
select-target	v	In HyperHelper "Molecules" and "Atoms" are selected (RW)
set-bond-torsion	c	For selected atoms sets the torsion angle
show-hydrogen-bonds	v	(RQ-YES/NO)
show-hydrogens	c	(RQ-YES/NO)
show-multiple-bonds	c	(RQ-YES/NO)
start-logging	c	Starts recording the results of calculations
stop-logging	c	Stops recording results of calculations
stretch-energy	v	Energy results obtained after calculations (RO)
torsion-energy	v	Energy results obtained after calculations (RO)
total-energy	v	Energy results obtained after calculations (RO)
use-parameter-set	c	In HyperHelper two parameters are used "mmplus" or "PG"
window-color	c	The color of the background in HyperChem window
windows-height	v	Height of HyperChem window (pixels) (RW)
window-width	v	Width of HyperChem window (pixels) (RW)
write-file		Saves the file to the dis (The full path and the name of the file as the argument)

c – direct script command, v – variable, mac – menu activation command, RO- read only, RW – read/write.

3.3. Start of the program

When the application is started the control is taken by the procedure FORM_LOAD().

First it reads the helper.ini file (the contest of helper.ini file is explained in the manual of the program) and checks if the location of certain files is correct. In case the executables of HyperChem (*chem.exe*), Babel (*babel.exe*) and MS Excel are not located in the directories listed in initialization file program edits helper.ini and closes itself. It also loads the path to the executables and loads some starting parameters for running HyperChem. It loads FORM2 in invisible mode. When this portion of the program is finished the ***FDAT***, ***FC***, ***C***, ***TS*** and ***P*** buttons are visible enabling the user choosing the option to run (***Figure 10***). At the end the DISABLE_MICROSOFT_EXCEL_-MACROS() procedure is called to check which commands should be enabled in *Excel macros* menu. This is done by checking the state of the cell "A9" in the sheet "Sheet1" of the currently opened workbook. In case the length of the string taken from the "A9" cell is shorter than 14 characters the *Prepare workbook* menu command is enabled. When chosen, will execute the macro responsible for preparing the workbook for calculations.

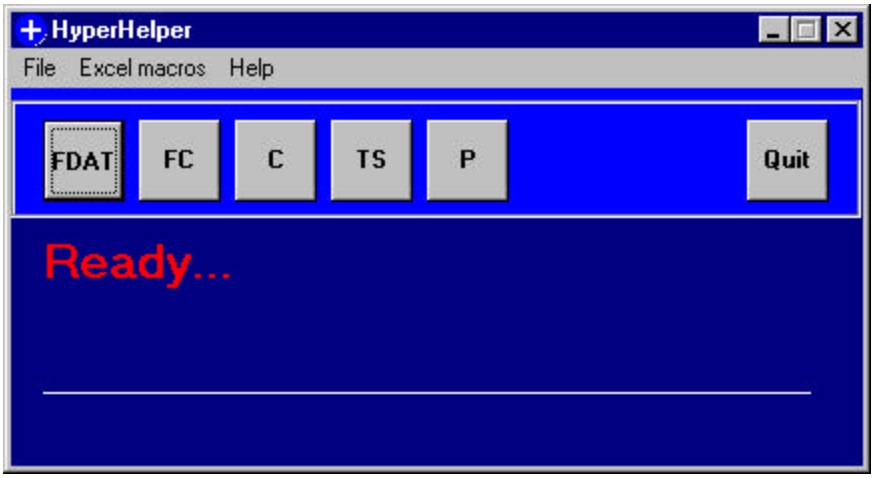


Figure 10. HyperHelper – starting page.

3.4. FDAT – preparation of the DAT, HIN and PDB files from CSD FDAT file

The procedure is called by pressing ***FDAT*** button (FORM1.COMMAND1). First it disables the command buttons and passes by to USERDIR_CLICK(), which enables to choose the directory where the FDAT files is located. When the directory is chosen the sub ONE() is called. This is the main procedure, which is responsible for preparing the files.

After searching the CSD one obtains one FDAT file containing all found structures (we call this: multi structure FDAT or M-DAT for short). The M-DAT is constructed in the following manner:

```
#JAHRAL  23891010       18  9  0  0  0  4  4 33  0  0 4713220000000000000000088
 16484  7725 17100    90 11667    90333020 5 2 2 0 2 0  0182  9Cc        440
R=0.0280
211 0121 0112 0211 6121 6112 0211 0101 0112 6211 6101 6112 6
C  68AG159N  68O  54
AG1        0   1730  25000 N1     19040 -14610  58860 C1     22860  -5760  55130
C2     18730  -1510  46320 N2     10060  -5410  41200 C3      6030 -13790  44910
C4     -3700 -18010  39660 N3     -8220 -13330  31350 C5    -16390 -17470  27030
C6    -21330 -27390  30810 N4    -17000 -31820  39100 C7     -8480 -27290  43710
```

```
C8     -3580 -32270  52760 C9      5110 -28030  57610 C10     9943 -18320  53630
N5    -18700 -14350  -8840 C11   -23180  -6070  -5050 C12   -18580   -680   3820
N6    -10230  -4860   8900 C13    -5270 -13900   5210 C14     3900 -18280  10140
N7      8180 -12980  18900 C15    17120 -17800  23330 C16    21050 -26780  19190
N8     17370 -31960  10900 C17     8160 -27350   6300 C18     3710 -31590  -2790
C19    -5150 -27480  -7510 C20   -10140 -18850  -3870 N9       -20  40610  24950
O1      7260  31560  28420 O2     -7030  33350  21280 O3     -1660  55690  21340
 5 3 4 5 6 7 8 1 8 910 71213 2171819 11920 12223242126271631 03030 6151112141520
29212225262829
# HAHRAK (…)
```

Each new structure starts with a hash "#" and then the code of the structure follows. This information is used in the program to create new single DAT file whenever # sign shows up. First of all user chooses the directory where the multiple M-DAT file is located. Then the program automatically:

1. creates DATS subdirectory, and HIN directory under DATS,
2. reads the first line of M-DAT,
3. creates log.txt file where the code names and current names (without extensions) are stored,
4. creates new single structure DAT file (S-DAT). The name of the file is an integer and ".dat" extension (*1.dat*, *2.dat*, etc.),
5. reads M-DAT and writes lines in S-DAT till new "#" sign is reached,
6. closes S-DAT file,
7. creates two batch files to run Babel.

First batch file will prepare the HIN file. It consists of the following lines (after ' character – comment):

`C:` ' Babel program disk defined in *Helper.ini*

`Cd BABELDIR` ' go to the directory of the Babel program. BABELDIR defined in *Helper.ini*

`Babel –fdat FULL_PATHTO_S_DAT_FILE –ohin –FULL_PATH_TO_HIN_FILE`

' executes the command line

Second batch file is similar to the previous one where **–ohin** is changed to **–oent** and **–FULL_PATH_TO_HIN_FILE** is changed to **–FULL_PATH_TO_ENT_FILE**

Since Babel uses 8.3 file names when the name (path & name) is invalid then DATS directory will be empty. The program will inform the user of the fact by displaying the warning:

The path name contains characters not allowed by DOS.
Please copy your DAT file into c:\TEMP and restart the program
Then open c:\temp\dats and copy the results to the target directory.

Babel will convert S-DAT into HyperChem HIN and ENT files. Two formatted files, accepted by HyperChem are created, because there have been rare problems reading HIN files after the conversion. In that case the ENT file can be read instead.

8. closes and executes (in a hidden window) batch files and afterwards, deletes them.

The time needed for execution of the batch file is located in *helper.ini* file in [FdatTimer] section. For slower computer 5 seconds should be enough. For faster ones 1 second should be the choice.

Steps 4 to 8 are repeated until the end of M-DAT file is reached. Then the M-DAT file is removed from the disk and the program quits.

3.5. FC – file creator

The program can be run in two manners, either it can treat one, chosen file or treat the subset of files (procedure Q11()). First it loads FORM6 (visible) - ***Figure 11***- from which one can choose the type of the file to be created.

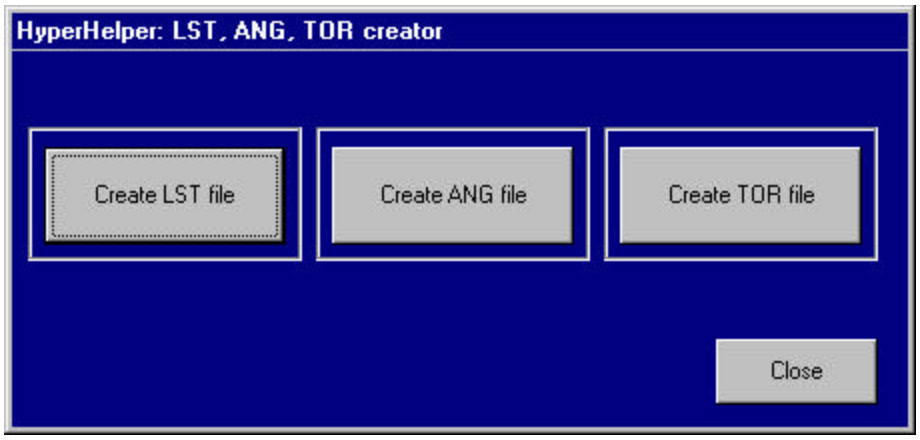


Figure 11. Form6 – LST, ANG, TOR creator.

- **LST – List of connections (FORM6.LST())**

The procedure reads each of the HIN files and recalculates the atom types. It reads all the atoms into the array. Then using the variable ***neighbors*** the connections between atoms are found by choosing each of the atoms separately and comparing with remaining ones. Any connections between of the type ANY_ATOM_TYPE-HYDROGEN are rejected from the list of connections. The list is saved to the file, which name is constructed of the root name of HIN file and the extension *.LST*.

This procedure is fully automatic and does not need any user's action.

The format of the output file is:

Number_of_connections CHR(13)
First_Atom CHR(13)
Second_Atom CHR(13)
First_Atom CHR(13)
Second_Atom CHR(13)
(..)

where CHR(13) is the representation of *Return* key.

- **ANG – list of chosen angles (FORM6.COMMAND2, FORM8.COMMAND1)**

The procedure is a graphical interface for choosing the angles (***Figure 12***).

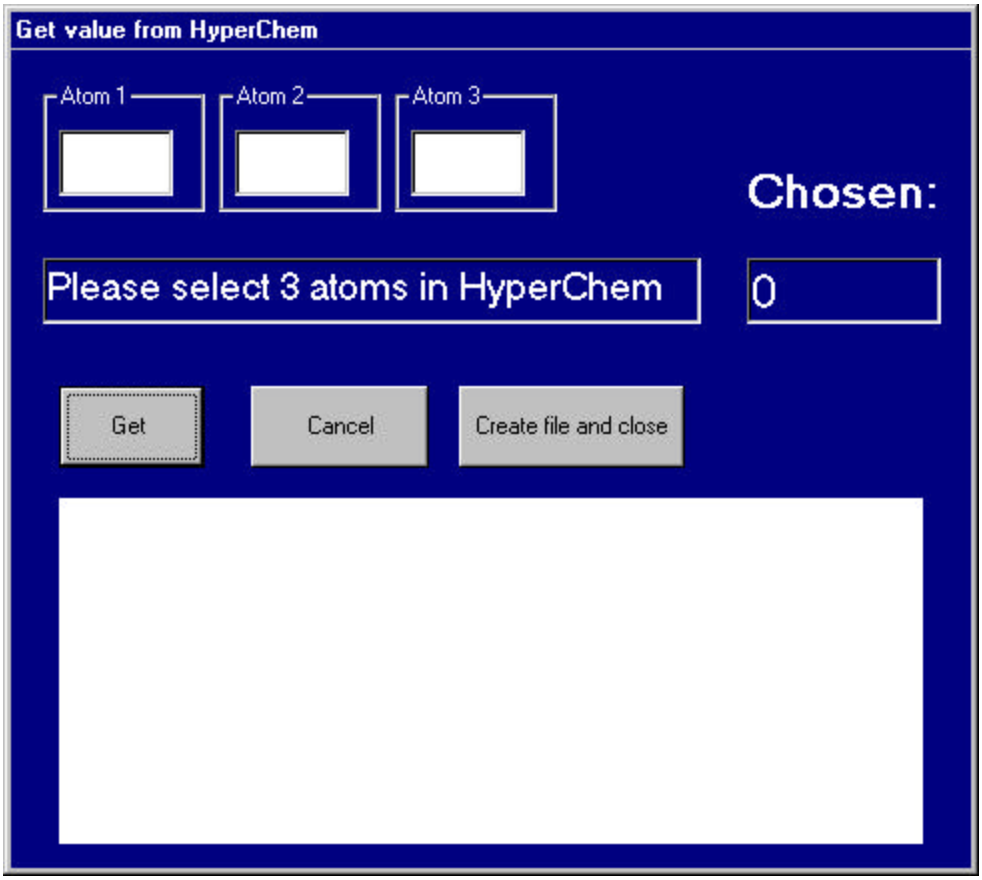


Figure 12. Graphical interface to choose the angles.

The user has to choose the angles, one by one, in the window of HyperChem and then, by clicking on Get button the numbers of chosen angle are stored in the array. The current choice is displayed in ***Atom 1***, ***Atom 2*** and ***Atom 3*** **TextBoxes.** The full list is displayed in the white area of the window. When the ***Create file and close*** button is hit the file with .ANG extension is created and the program terminates.

The procedure can be used to choose either proper or improper angles. The proper angles are defined when all three atoms are connected with bonds one to each other.

Improper angles are taken in the case where the atoms are not connected one to each other by bonds. The program does not allow combinations of too less, or too many atoms selected.

The format of the output file is:

NUMBER_OF_ANGLES
First_atom CHR(13)
Second_Atom CHR(13)
Third_Atom CHR(13)
First_atom CHR(13)
Second_Atom CHR(13)
Third_Atom CHR(13)
(…)

- **TOR – list of torsional angles (FORM6.COMMAND3, FORM8.COMMAND1)**

This procedure is also a graphical interface to choose either proper or improper torsion angles from the model opened in HyperChem window. User's choice is displayed in ***Atom 1***, ***Atom 2***, ***Atom 3*** and ***Atom 4*** **TextBoxes.** The full list is displayed in the white area of the window (***Figure 12***). When the ***Create file and close*** button is hit the file with .TOR extension is created and the program terminates.

The format of the file is:

NUMBER_OF_ANGLES
First_atom CHR(13)
Second_Atom CHR(13)
Third_Atom CHR(13)
Fourth_Atom CHR(13)
First_atom CHR(13)
Second_Atom CHR(13)
Third_Atom CHR(13)
Fourth_Atom CHR(13)
(…)

3.6. C- calculations (FORM1.COMMAND4)

- **New (first) calculations.**

This option is used at the very beginning of the process of adding parameters. The program calls the USERDIR_CLICK() procedure, which allows choosing the files to be used in calculations (***Figure 13***). As a pattern **.hin* and **.dat* are used.

Figure 13. Choosing the files to be used for calculations.

When OK button (FORM5.COMMAND5) is pressed the caption of ***C*** button (calculations) is changed to ***Start*** and options of calculations are displayed (***Figure 14***). For the new calculations the ***Recalculate only*** CheckBox (CHECK7) is unchecked.

When ***Start*** button has been pressed the FOUR() procedure takes over the control.

Initial values needed for driving HyperChem are set (taken from *helper.ini* file), connections to MS Excel is established (if Excel is not running, HyperHelper will ask to open the necessary file and terminate). HyperChem is initialized by calling the INITIALIZEHYPERCHEM() procedure. The size of HyperChem window and white background are set. The calculation method and other conditions are defined in this state of program.

The program asks if *chem.log* file should be created. In case one chooses to record the log of the results of calculations to a file then the level of details is asked to be set (6 – is the default value which will store the default parameters values, assigned by HyperChem automatically, in the file). *Chem.log* will help analyzing the missing parameters.

The two new subdirectories are created: ***root_of_calculations**Results*** and temporary one called ***root_of_calculations* \Results*t***. Then the procedure checks if HIN files exist in starting directory. If not, program will notify the user and terminate.

When the HIN files are found they are loaded into an array (FP()). In case the CheckBoxes: ***Use list of angles*** and ***Use list of t-angles*** have been checked the program will look for LST and TOR files and check if the files are free of errors (Sub CHECKFILEPRESENCE()). If the number of lines differs from one defined in the first line of the LST, ANG and TOR the program will inform about the situation by displaying Form4 and quit (***Figure 15***).

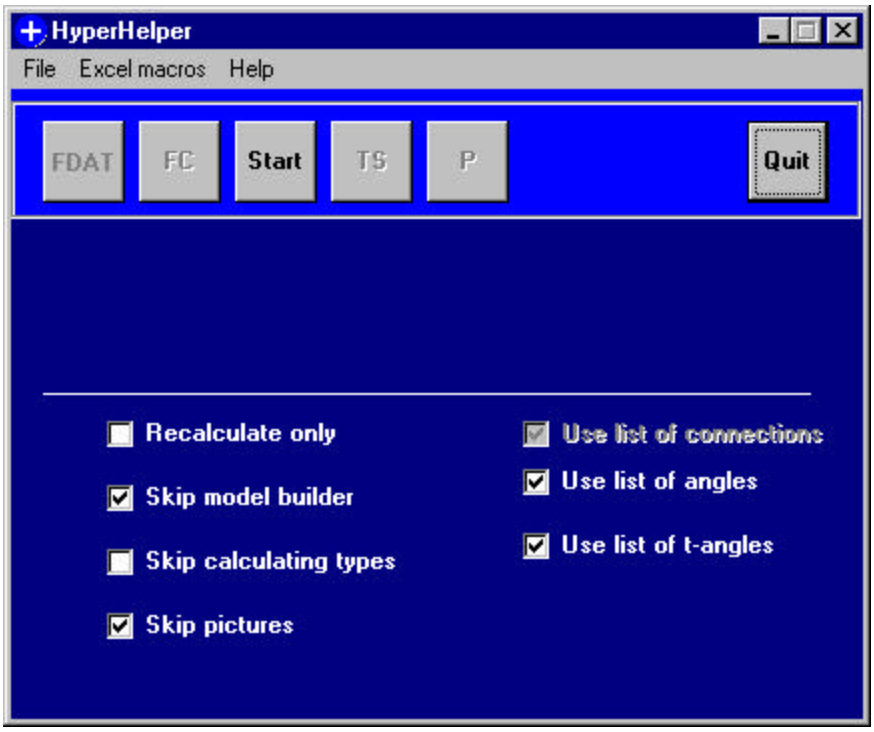


Figure 14. Options of calculations.

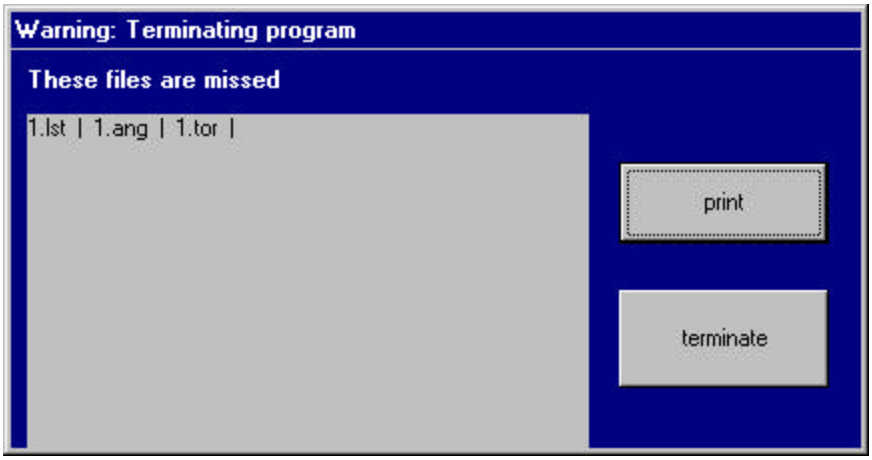


Figure 15. Missing files – program terminates.

For each of HIN files loaded into FP() array the following procedure takes place.

STOP (FORM2) window is called by the STOPWINDOW() procedure. It allows the user to stop proceeding. The window closes after the time defined in *helper.ini* in [Waiting for user break in sec. def. 5 (1...5)] section.

The HIN file is loaded into HyperChem. The number of atoms is calculated and display on the FORM1 (***Figure 16***) In case when ***Skip calculating types*** (CHECK4) is uncheck (default, ***Figure 14***), the types of atoms are assigned by HyperChem by calling the menu-build-calculate-types command. Otherwise the types written to HIN file are used. This can be useful if one wants to force HyperChem to doing calculations using atom types different to ones, which would be calculated automatically, according to rules included in *chem.rul* file but with ones previously saved with the HIN file.

ReadLstFile, ReadAngleFile (if ***Use list of angles*** is checked – default), ReadTorsionFile (if ***Use list of t-angles*** is checked) are called and the number of atoms taken from LST, ANG and TOR files, which form bonds, angles and torsion angles are stored in the array ConnectList() (full description of the array is presented in ***Table 5***). The initial values (crystallographic model) are sent to ConnectList(4,i).

The connection to MS EXCEL is checked and the worksheet, where the data will be put, is chosen. The name of the worksheet is constructed by adding the integers to the word “Sheet”. This gives the names “Sheet2”, “Sheet3”, etc. The sheets have to be prepared before the calculations by calling the macro A_ADDINGSHEETS() in MS EXCEL.

Single point calculations are taken, after which the energy components are sent to ConnectList().

If the CheckBox ***Skip pictures*** (Check8) is unchecked then the picture of the crystallographic model is taken and sent to “Sheet1”. The whole Workbook is then saved in case of any failures.

As the next step, HyperHelper uses “**mmplus”** (see ***Table 4***) parameter set (for MM+ calculations) and reopens HIN file in HyperChem. Atom types are recalculated (if this option has been chosen) and, if chosen in FORM1 (***Skip model builder*** – Check1-default checked) runs internal model builder. Then the distances, angles and torsional angles are measured and the results are sent to ConnectList(5,i) (Subs: BONDLENGTH(), ANGLEM(), TORSIONM()). In case of the default state of Check1

the above values will be the same as ones obtained after initial measurements. (ConnectList(4,i)). Geometry optimization is carried out.

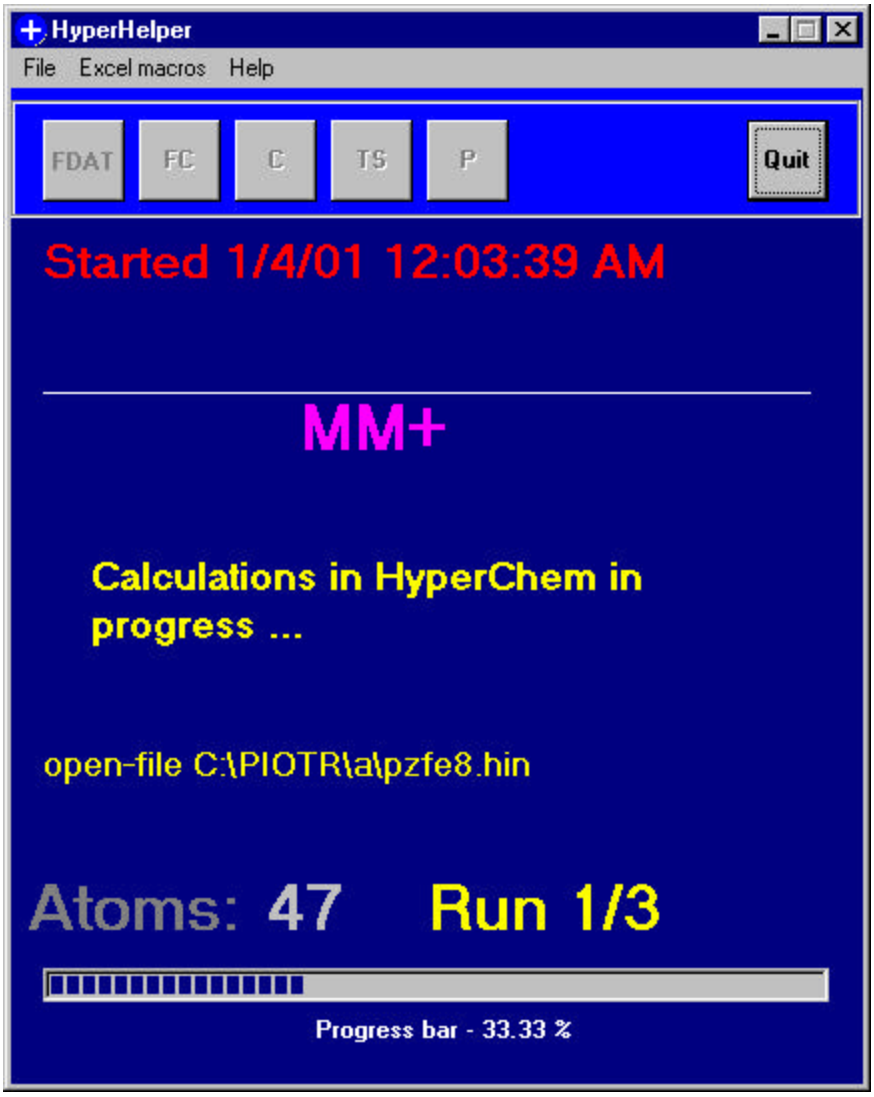


Figure 16. FORM1 during the calculations.

Table 5. ConnectList(15,i) array.

Array element number	Content
0,i	Number of atom 1
1,i	Number of atom 2
2,i	Type of atom 1
3,i	Type of atom 2
4,i	Value of bond distance or angle or torsional angle for crystallographic model
5,i	Value of bond distance or angle or torsional angle after building the model
6,i	Value of bond distance or angle or torsional angle after MM+ calculations
7,i	Value of bond distance or angle or torsional angle after MM* calculations
8,0	Total energy of initial model
8,1	Stretch energy of initial model
8,2	Bend energy of initial model
8,3	Rms gradient of initial model
8,4	Converged criterion (Yes/No)
8,5	Torsion energy of initial model
8,6	Nonbond energy of initial model
8,7	Estatic energy of initial model
8,8	Hbond energy of initial model
8,9	Dipole moment of initial model
9,0-9	Energy components, converged criterion and dipole moment after MM+ calculations
10,0-9	Energy components, converged criterion and dipole moment after MM* calculations
11,i	Number of atom 3
12,i	Number of atom 4
13,i	Type of atom 3
14,i	Type of atom 4

HyperHelper activity is frozen till the calculations in HyperChem are finished. This is done by using DoEvents command which forces VB to allow HyperChem and other programs to execute (On Error GoTo NoTimeErr).

When the calculations are finished, the energy components are sent to ConnectList() array. The measurements after this stage of calculations are stored in ConnectList(6,i). The measurements are performed by the following procedures:

BONDLENGTH(), ANGLEM(), TORSIONM(). The final structure is saved to the subdirectory ***\Results*** under the name **mm.hin* (where "*" is the root of the name of the structure).

Now HyperHelper changes the parameter set for PG ("use-parameter-set PG"), reopens the HIN file, assigns the atom types (if chosen) and starts the MM* calculation, which means the calculations using new set of parameters. It waits till the calculations are finished. The energy and structure results are sent to ConnectList(). The structure of the calculated structures saved under the name of "**pg.hin*". The root of the filename (*) is stored on "Sheet1", column "I".

If the CheckBox ***Skip pictures*** (Check8) is unchecked the picture of the MM+ and MM* models are taken and sent to "Sheet1".

When all calculations have been finished and all the measurements are loaded into ConnectList() the headings of columns are transmitted into Excel and all the data of the array ConnectList() is placed into proper cells of the *Structure Worksheet*. The first comparison calculations are performed. The example of exact content of such worksheet is presented in ***Table 6.***.

The program reads next HIN and the procedure is repeated. When all HIN files have been used for calculations the number of structures (plus one) is placed to "Sheet1", cell "A1".

At the end the program proposes executing the automatic macro (A_POST_ALL()), which will perform all necessary calculations in MS Excel workbook.

HyperHelper displays the date and time of finishing and informs of succeeding the calculations.

Table 6. The complete layout of the *Structure Worksheet*.

	A	B	C	D	E	F	G	H	I	J	K
1	At1	At2	Type1	Type2	Crystal	Builder	MM+	MM*	E-F	E-G	E-H
2	2	1	CL	CU4	2.207	2.207	2.165	2.264	0	0.04	-0.02
3	3	2	NA1	CU4	1.954	1.954	1.859	1.994	0	0.10	-0.04
4	3	11	NA1	CA1	1.341	1.341	1.316	1.330	0	0.03	0.01
5	3	14	CA1	NA1	1.297	1.297	1.314	1.342	0	-0.02	-0.04
6	4	12	NA1	CA1	1.324	1.324	1.358	1.345	0	-0.03	-0.02
7	4	13	NA1	CA1	1.343	1.343	1.358	1.348	0	-0.02	-0.01
8	5	1	NA	CU4	2.037	2.037	1.871	2.032	0	0.17	-0.01
9	5	15	NA	CA	1.377	1.377	1.270	1.359	0	0.11	-0.02
10	5	22	CA	NA	1.310	1.310	1.268	1.347	0	0.04	-0.04
…	…	…	…	…	…	…	…	…	…		
33	2	1	CL	CU4	166.49	166.49	124.24	164.00	0	42.25	2.49
…	…	…	…	…	…	…	…	…	…		
36	22	15	CA	CA	-54.36	-54.36	-70.17	-40.35	0	15.81	-14.0

	L	M	N	O	P	Q	R	S	T
1	|G|-|H|	OK?	B/A/T ?	addit	E1	E2	E3	At3	At4
2	-0.06		bond	open-filec:\	78.84	112.74	75.72		
3	-0.13		bond	pzcu_mo24	60.19	1.05	1.30		
4	-0.01		bond	35	6.56	87.40	48.63		
5	-0.03		bond		107.57	0.001	0.005		
6	-0.01		bond			TRUE	FALSE		
7	-0.01		bond						
8	-0.16		bond						
9	-0.09		bond						
10	-0.08		bond						
…	…	…	…	…	…	…	…	…	…
33	-39.76		angle					3	
…	…	...	…	…	…	…	…	...	...
36	29.82		t_ang					24	31

	U	V	W	X	Y	Z
1	Type3	Type4	Crystal	MM+	MM*	
2			78.84	112.74	75.72	total energy
3			60.19	1.05	1.30	stretching energy
4			6.56	87.40	48.63	bending energy
5			8.09	11.11	16.36	torsional energy
6			3.41	14.74	12.24	non-bonded energy
7			0.15	-1.68	-2.91	estatic energy
8			0.44	0.12	0.10	h-bond energy
9			3.85	3.12	2.89	dipole moment
10						
…	…	…	…	…	…	…
33	NA1					
…	…	…	…	…	…	…
36	CA	CA				

description of the elements of the table on next page

Column "A": the number of the first atom involved in the bond, the angle or the torsion angle,
Column "B": the number of the second atom,
Columns "S" and" T": the third and fourth atoms,
Columns "C", "D", "U" and "V": corresponding atom types.
*Columns "E","F","G" and "H": distance, angle or torsion angle, taken from the CSD structure, measured after applying HyperChem internal model builder (if the option is switched off in HyperHelper, then the values from column "E" are copied to column "F"), obtained after MM+ and MM * calculations, respectively.*
Columns "I"," J" and "K": the differences between the crystallographic and the calculated structures.
Column "L": the absolute difference between the results from Columns "J" and "K".
Column "M": an indicator of what has happened to the measurements after the parameters were changed (0,1,2 = worse, better, no change). This column is filled after the calculations using MS Excel macros.
Column "N": the type of parameter.
Column "O": additional information (location and the name of the structure, number of non-H atoms).
Columns "P","Q" and "R": the energy results of the calculations (Single point, MM+ and MM calculations, respectively). In row 2: total energy, in row 3: stretching energy, and in row 4: bending energy.*
Columns "W","X" and "Y": the full energy results (Single point, MM+ and MM calculations, respectively). In column "Z" explanation of the energies.*
Cells" Q5" and "R5": gradient at the end of calculations.
Cells "Q6" and "R6": indicate if the calculations converged.

- **Recalculating**

When ***Recalculating only*** CheckBox (Check7- ***Figure 14***) is checked and one clicks on ***Start*** button then the FOUR() procedure is called and HyperChem is initialized. After this step RESTARTCALC() procedure takes over the control and checks if on "Sheet1" of the workbook there is integer in "A1" cell stating number of sheets to proceed. In case when it cannot find the number it will terminate the program.

The names of *Structure Worksheets* are loaded from "Sheet1" column "I", into an array and CHECKFILEPRESENCE() sub is executed to check if all necessary files are located in the directory of calculations.

When all necessary files are present STOPWINDOW() is called, and in case when the program is not interrupted the first structure (taken from "I2" cell) is loaded into

HyperChem. Depending on the chosen options: ***Use list of angles***, ***Use list of t-angles*** (values of the Check5 and Check6 CheckBoxes) three procedures are called READLSTFILE(), READANGLEFILE() and READTORSIONFILE(). They load the number of atoms taken from LST, ANG and TOR files, which form bonds, angles and torsional angles into the array ConnectList().

HyperChem is forced to using PG parameter set (parameter containing new parameters) and to doing geometry optimization starting either form crystallographic structures or from the model obtained from internal model builder. The initial calculations (measurements of distances etc) are skipped. The calculations using original MM+ parameter set is omitted too, since the calculations were previously done before and the results already exist in the *Structure Worksheets*.

HyperHelper waits till the calculations are finished and then takes the energy values and measures selected distances, angles and torsion angles. The appropriate values are put into *Structure Worksheet*. The content of columns "C","D","U","V" (atom types), "H" (values of distances, angles and torsion angles) and "Y" (energies) are updated (***Table 6.***).

The **pg.hin* files is saved to Results subdirectory. Next file (cell "I3") is taken for calculations and the whole procedure is repeated till the program reaches the first empty cell in column "I".

At the end the program proposes executing the automatic macro (A_POST_ALL1()), which will perform all necessary calculations in MS Excel workbook.

3.7. TS – torsional search (FORM1.COMMAND6).

This sub will drive HyperChem to find the V_1, V_2 and V_3 barriers (needed for ***Equation 9*** of Functional form of MM+ force field chapter) by rotating atoms over selected bond with the step of 1, 5 or 10 deg. The methodology is explained in MS Excel macros section. The dihedral angles are defined in TOR files (if there are more than one torsion angles then the calculations are taken for all listings in TOR file). One can use the

structures defined in Sheet1 of Excel (form3.Option8=true) or from one file (form3.option6=true) or from all files found in UsedDir (form3.option7=true).
FORM3 is loaded and one can choose the option of the search (***Figure 17***).

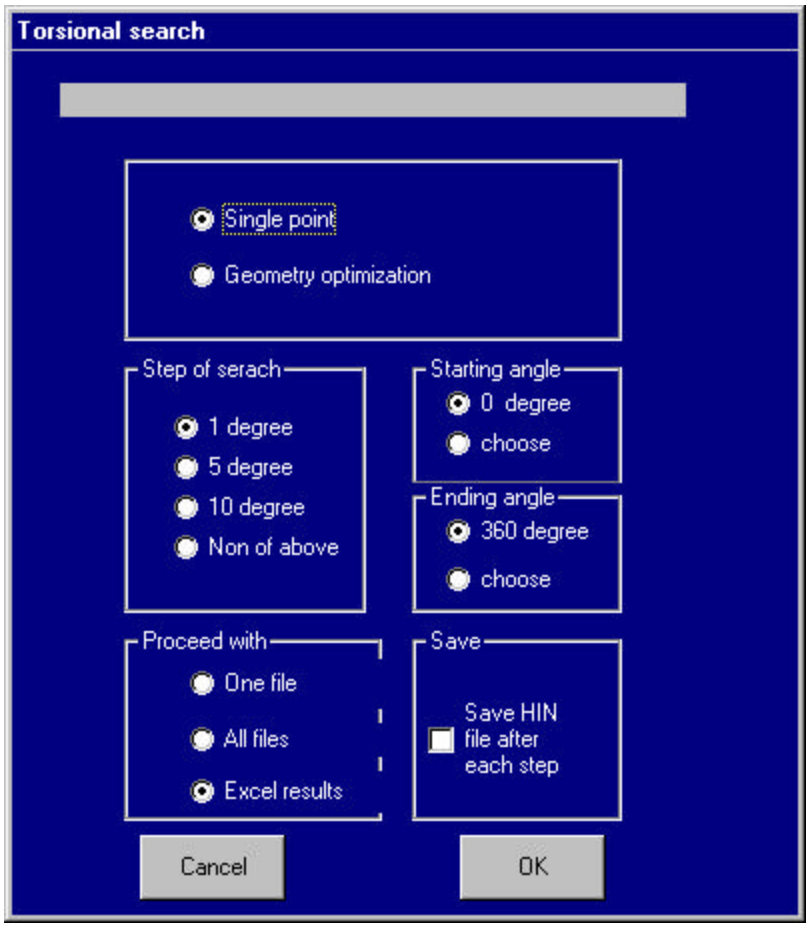


Figure 17. Torsional search form.

Single point will perform this type of calculations for each angle of rotation. ***Geometry optimization*** will optimize the structure after each step of rotation. ***Steps of search*** 1,5, 10 or user defined (possible values: 1.000 to 360.000) will determine the number of steps of calculations. The ***Starting angle*** and ***Ending angle*** may narrow the search.

Proceed with option allows to decide if one wants to perform calculations on one file, all HIN files located in calculation directory or all files taken from "Sheet1" column "I" (***Excel results***)

Save HIN file after each step option has been added for further treatment of structures obtained after having changed the torsion angle in each step of calculations. The name of the file is constructed of the root of the name of the structure followed by "_tr" and actual value of the angle. "*.hin*" file name extension is added *(test_tr_10.hin, test_tr_20.hin* etc).

When ***OK*** button is pressed then FORM7 is displayed and one can choose the directory where the files are located. After having chosen the files FORM1.TORS_SEARCH() is called by FORM7.COMMAND1()). HyperChem is initialized. HyperHelper loads the names of HIN files in FP() array and checks if all necessary files are present in calculations directory.

HyperHelper asks to choose the calculation method in HyperChem manually (since we may want to use MM or QM methods) and for each file and for each its torsion o performs the calculations by driving HyperChem to:

1. select the four atoms
2. name selection
3. check if the torsion angle of the starting structure is different to 180 deg. According to HyperChem support: "It appears that HyperChem has problems setting the torsion angle when 3 atoms are in a single line. Distorting the angle slightly does allow the setting of the torsion angle to work. This is due to the fact that the torsion angle is defined as the dihedral angle made by the plane containing the first 3 and the last 3 atoms. When 3 of the atoms are in line, one cannot define the second plane uniquely. **[38]**
4. set the selected torsion to certain value depending on the ***Step of search*** and ***Starting angle*** and ***Ending angle*** options
5. calculate single point or to do the geometry optimization
6. read the total and torsion energies
7. save the conformation file (if option selected)
8. change the value of the angle and return to point 4.

After finishing the values of energies and corresponding angles are passed to MS Excel "Sheet10006" for further treatment. The example of such worksheet is presented in ***Table 7.***

Table 7. Fragment of the data obtained after running the torsional search procedure.

	A	B	C	D
1	40	1		
2	pzfe8.hin / 1 28-20-11-1			
3	0	0.2539216	45.95808	0
4	10	0.2539217	45.95784	10
5	20	0.2539212	45.95708	20
6	30	0.2539213	45.95594	30
7	40	0.2539215	45.95437	40
8	50	0.2539217	45.95247	50
9	60	0.2539218	45.9504	60
10	70	0.2539211	45.94817	70
11	80	0.2539214	45.9459	80
12	90	0.2539199	45.94366	90
13	100	0.2539221	45.94152	100

Cell "A1" – number of rotations,
Cell "B1" – number of taken calculations
Cell "A2"- the name of the structure and the numbers of atoms involved in the torsion angle
Column "A" – angle reported by HyperChem
Column "B" – torsional energy
Column "C" – total energy
Column "D" – angle set by HyperHelper

3.8. P – placing the pictures of models into MS Excel worksheets (FORM1.THREE).

This procedure enables the user to put the pictures of the crystal model (**.hin*), models after MM+ (**mm.hin*) and MM* (**pg.hin*) calculations together to compare their geometries and to judge if the change of parameter sets had the positive influence on the models.

First, one has to choose the directory, where the **.hin*, files are located. The directory should contain the subdirectory ***\Results*** from which HyperHelper will take the **mm.hin* and **pg.hin* files. Then the THREE() procedure opens FORM5, where one can choose the options (***Figure 18***).

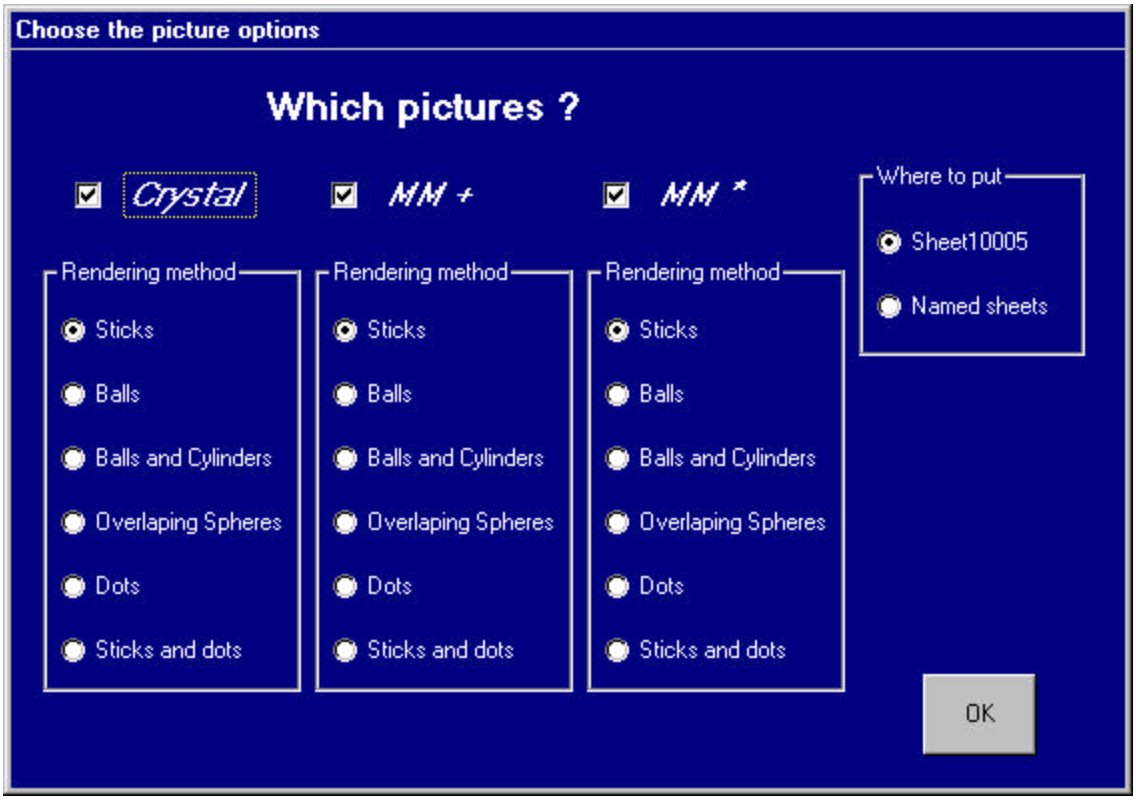


Figure 18. Form5 – Picture options.

It allows choosing which model will be taken (by default three are chosen: ***Crystal, MM+*** and ***MM****) and rendering method independently from the model.

One has to decide where the models are to be put. There are two possibilities: The pictures can be placed on "Sheet10005" (all pictures on one worksheet) or on the *Structure Worksheet*, whose name will correspond to the name of the HIN file.

After clicking on ***OK*** button (COMMAND1()) the procedure

FORM1.CHOOSEPICTURE() takes over. It reads all HIN files into HyperChem, sets the rendering method and copy-pastes the content of HyperChem window into Excel. After each step it clears the content of the clipboard to save memory.

The CLEARALLVARIABLES() executes to set all the public variables to null. Then the buttons: Command1,2,3,4 and 7 are enabled and visible. This procedure is called after FDAT, FC, TS and P calls.

3.9. Description of Microsoft Excel Set of macros.

The brief description of included macros is listed in ***Table 8.***. The detailed description of them is presented below.

3.9.1. A_ADDINGSHEETS() macro.

This macro prepares the whole workbook for calculations. It must be run before the first calculation and once only. It asks to input the number of *Structure Worksheets* to be added. The number of them equals the number of structures included in the subset of structures. Then the required number of sheets is added and columns "E"-"L" are formatted to show three decimal places (0.000). As the next step macro will create "Sheet10000"-"Sheet10006" and formats their columns.

On "Sheet1" it proposes the criteria of bond, angle and torsion angle comparison and the location of two parameter files *pgstr.txt* (new stretching parameters) and *pgben.txt* (new bending parameters). In case the default values are not correct they can be changed in the code of the macro in CRITERIA section (InputBox commands)

The macro terminates informing of having prepared the workbook for calculations.

3.9.2. A_DELETE_SHEET() macro.

The first action of this macro disables displaying alerts (*Are you sure ?*) and removes the current worksheet. After that it re-enables displaying alerts.

3.9.3. A_GOTOSHEET1() macro.

This macro is very useful to quickly move from one worksheet to another. Macro opens the worksheet whose name is input by the user. In case the worksheet is not found (its name is incorrect) the error message is displayed and the macro takes no action.

Table 8. The set of macros – second part of the HyperHelper application.

Name	Description	**Shortcut**
A_ADDINGSHEETS()	prepares workbook for calculations	<ctrl>+**q**
A_DELETE_SHEET()	removes active worksheet	<ctrl>+**d**
A_GOTOSHEET1()	asks for a worksheet name and opens it	<ctrl>+**g**
A_PRINT2()	prints just the active worksheet	<ctrl>+**y**
A_PRINTALL()	prints all sheets	none
A_POST_0()	renames the *Structure Worksheets*	<ctrl>+**k**
A_POST1()	compares the results in *Structure Worksheets*	<ctrl>+**e**
A_POST 2()	draws the charts on *Structure Worksheets*	<ctrl>+**r**
A_POST 3()	reads each of *Structure Worksheets* and calls A_POST1() and A_PARAMETERS() and A_POST4()	<ctrl>+**i**
A_POST4 ()	copies columns A-H from all *Structure Worksheets* and performs the RMS() calculation on all bonds, angles etc. The results go to *Statistical Worksheets:* bond results to "Sheet10000", angles to "Sheet10001" and torsion angles to "Sheet10002"	<ctrl>+**o**
RMS()	used only on "Sheet10000", "Sheet10001" and "Sheet10002" or on any of *Parameter Worksheets* Called from A_POST4()	<ctrl>+**j**
A_PARAMETERS()	reads each *Structure Worksheet*, creates new *Parameter Worksheets* containing one type of parameter and performs the calculations. The worksheets names are: Type1_Type2 for bonds, Type1_Type2_Type3 for angles, Type1_Type2_Type3_Type4 for torsion angles This macro also opens the *pgstr.txt, pgben.txt* file and checks if the parameter already exists if so – it gives the line number where the parameter can be found. It prepares the *Parameter Optimization Worksheets*	<ctrl>+**t**
RMS1()	proposes the equilibrium parameter value	none
UPDATE_ PARAMETERS()	opens "Sheet10003" reads the rows, opens "STR" worksheet, updates the lines there, makes back-up of *pgstr.txt* and creates *pgstr.txt* and finally compiles the "PG" parameter set	<ctrl>+**u**
A_THETA()	calculates V_1, V_2 and V_3 torsional barriers from the data of "Sheet10006"	<ctrl>+**m**
TEST()	tests the contents of "Sheet10003" for missing parameters in *pgstr.txt* file. Called from UPDATE_PARAMETERS()	none
COMPARE()	Compares the content of *mmpstr.txt* and *pgstr.txt* file. The output goes to "pg_vs_mm" worksheet	none
A_POST_ALL	called direct by HyperHelper after the first calculations	none
A_POST_ALL1	called direct by HyperHelper after the next calculations	none

3.9.4. A_PRINT2() macro.

This macro prints the active worksheet directly to the printer (the printer dialog box does not pop up).

3.9.5. A_PRINTALL() macro.

This macro asks if one wants to print the content of the workbook. In the case of a positive answer all worksheets are printed.

3.9.6. A_POST_0() macro.

The macro must be called only once, after the first calculations. After the first calculations the *Structure Worksheets* are named as "Sheet2", "Sheet3",…,"$Sheet_N$" ($_N$-integer). Macro changes their names to ones located on "Sheet1", column "I" (the names of the structures). Macro finishes its activity when the content of the next cell in column "I" is empty.

3.9.7. A_POST1() macro.

For each of *Structure Worksheets* one should run this macro. First it sets the colour of the character to black and the colour of the interior of the cells to transparent. Then for each row (n) it calculates the value of the cell of column "K" according to ***Equation 22:***

$$K_n = |E_n| - |H_n|$$

Equation 22. Value of the cell (n,K) – n – n^{th} row, K- column "K", E- column "E", H- column "H"

The column "L" is calculated as in ***Equation 23:***

$$L_n = |J_n| - |K_n|$$

Equation 23. Value of the cell (n,L) – n – n^{th} row, L- column "L", J column "J", H column "H"

In the next step it checks on the content of the atom type cells (n, C) and (n,D). If it finds double stars "**" (unknown atom type) it changes it to "UNN" (such an operation is necessary since Excel treats "*" as the multiply operator and not as string values, which is needed for further operations) and changes the interior colour of such a cell to blue.

The value in the cell of column "N" is read and depending on its contents (either it is "bond", "angle" or "t_ang") the comparison criteria are applied. The comparison criteria are read from Sheet1 cell "A3"-"A8". The value taken from the cell of column "L" (L_n) is compared with them. The result of such a comparison is displayed in two ways: as a number displayed in column "M", and by marking the row in colour. The manner in which it is done is listed in ***Table 9***.

Table 9. The comparison criteria.

Comparison criteria	for	Meaning	Column "M"	Row color
L_n < -(Sheet1.A3)	bond	Worse results	0	red
L_n < -(Sheet1.A5)	angle			
L_n < -(Sheet1.A7)	t_ang			
L_n >= (Sheet1.A3)	bond	Better results	1	green
L_n >= (Sheet1.A5)	angle			
L_n >= (Sheet1.A7)	t_ang			
L_n >= -(Sheet1.A3) L_n <= (Sheet1.A3)	bond	Neglected difference	2	transparent
L_n >= -(Sheet1.A5) L_n <= (Sheet1.A5)	angle			
L_n >= -(Sheet1.A7) L_n <= (Sheet1.A7)	t_ang			

In addition, in cases when the differences between results of subtraction in columns "J" or "K" is greater than the one defined in "Sheet1.A4" for bonds, "A6" for angles and "A8" for torsion angles, such a cell is marked in yellow. This information helps finding parameters needing basic refinement.

The colour markers are to help in a fast evaluation of the results. The exact estimation can be done using information from additional calculations done in the next step. In cells ("O6…17"-"R6…17") of each *Structure Worksheet* one can find the number of total, worse, better and none (neglected difference) results and their percentages (***Table 10.***).

Table 10. Percentage estimation of results.

	O	P	Q	R
6	Bonds	28		
7	better	16	57.14286	%
8	worse	3	10.71429	%
9	none	9	32.14286	%
10	Angles	12		
11	Better	3	25	%
12	Worse	0	0	%
13	Nothing	9	75	%
14	T-Ang	4		
15	Better	1	25	%
16	Worse	0	0	%
17	Nothing	3	75	%

In the final step, the macro centers the contents of the cells, draws the borders of the cells and defines the print area and removes the colours of columns ("O": "AA")

3.9.8. A_POST 2() macro.

Profiting from information located on *Structure Worksheet* in "O4" cell (number of rows occupied by measurements) this macro selects the rows which are marked in column "N" "bond" and prepares two XYScatter charts. The first one is done using the crystallographic distances and these after MM+ calculations. The second is based on crystallographic distances and theses obtained after MM* calculations. The graphs contain the determination coefficient (R^2) defined in Excel as ***Equation 24:***

$$R^2 = 1 - \left(\frac{\sum_{i=1}^{n} (Y_i - Yobs_i)^2}{(\sum_{i=1}^{n} Y_i^2) - \frac{(\sum_{i=1}^{n} Y_i)^2}{n}} \right)$$

Equation 24. Determination coefficient.

X (observed) and Y (calculated) axis are limited to 3 Å. Each chart is supplied with the name of the calculated structure and the type of calculations. An example of such chart is presented in ***Figure 19.***

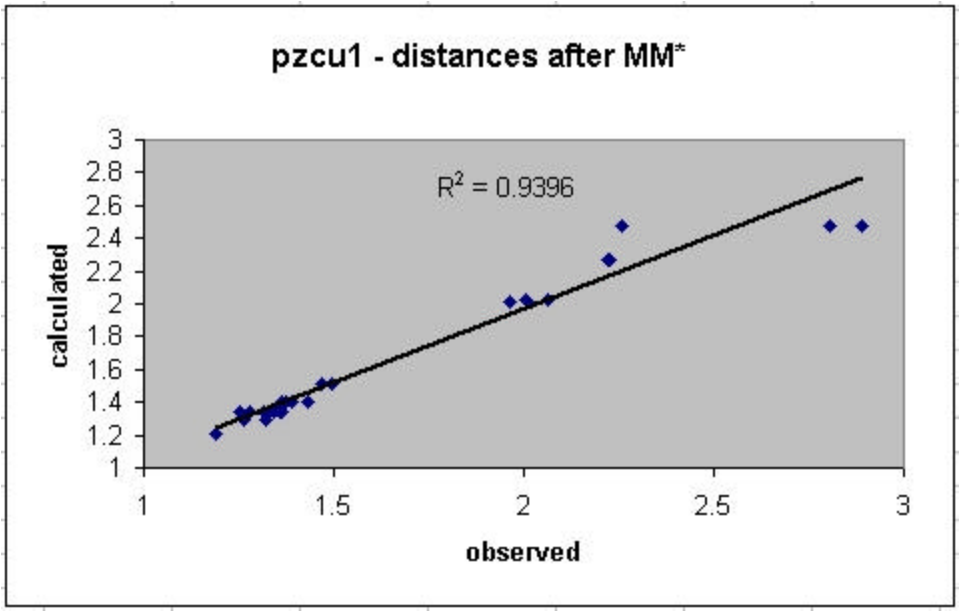


Figure 19. Example of the linear chart obtained in *Structure Worksheet* by calling A_POST2() macro.

3.9.9. A_POST 3() macro

This macro has been written to read each *Structure Worksheet* (the names are taken form "Sheet1" column "I") to compare the result by calling A_POST1().

3.9.10. A_POST 4() macro.

In the first step the macro reads the flag "Restarted1" located in "Sheet1.C1". In case the calculations have already been performed, "Sheet10000", "Sheet10001" and "Sheet10002" (*Statistical Worksheets*) are removed from the workbook. New ones are created.

"Sheet1" is selected and for each *Structure Worksheet* listed in column "I" the following procedure is followed.

First the *Structure Worksheet* is opened. The content of cell "N2" is read. Cells "A2","B2","C2","D2","E2","F2","G2" and "H2" are selected. The selection is copied to the first empty row of:

"Sheet10000" in case where "N2"="bond"
"Sheet10001" in case where "N2"="angle"
"Sheet10003" in case where "N2"="t_ang"

Next row of the *Structure Worksheet* is read and again the selection, depending on the cell $N_{(n)}$ ($_{(n)}$- integer), is copied to the appropriate worksheet.

When all the results have been copied from the first *Structure Worksheet* the next one is opened.

As the next step for "Sheet10000", "Sheet10001" and "Sheet10002" the RMS() macro is called and calculates RMS. For "Sheet10000" and "Sheet10001" macro A_POST 2() is called to draw the XYScatter and to calculate R^2 value.

3.9.11. RMS() macro.

The RMS gradient is calculated according to ***Equation 25:***

$$RMS = \sqrt{\frac{(X_{calc} - X_{obs})^2}{n}}$$

Equation 25. RMS value.

In the first step the macro sums up the expression: $(X_{calc} - X_{obs})^2$ where X_{calc} is the values of distance, angle or torsion angle for the model after MM+ or MM* calculations and X_{obs} are the values measured from the crystallographic model. The summation is done over all occupied rows in *Statistical Worksheet*. The results, divided by the number of steps are located in the first unoccupied row of columns "G" (for MM+) and "H" (for MM*). The square root is calculated for both of them and the RMS values are placed to column "L" below the data.

3.9.12. A_PARAMETERS() macro.

This macro reads the flag located in cell "B1" on "Sheet1" and in case it is greater than 1, which means that the *Parameter Worksheets* already exist, it removes the *Parameter Worksheets* defined in column "K" (bonds) "M" (angles) and "O" (torsion angles)

The first *Structure Worksheet* is opened. The second row is chosen. From cell "N2", the type of connection is obtained. Using the information from columns "C","D","U","V" and the type of connection two possible names of *Parameter Worksheets* (A or B) can be created (according to ***Table 11***).

Table 11. Constructing possible names of a *Parameter Worksheet*.

information from column:					Possible names	
N	C	D	U	V		
bond	Type1	Type2	-	-	A B	Type1_Type2 Type2_Type1
angle	Type1	Type2	Type3	-	A B	Type1_Type2_Type3 Type3_Type2_Type1
t_ang	Type1	Type2	Type3	Type4	A B	Type1_Type2_Type3_Type4 Type4_Type2_Type3_Type1

The macro checks if the worksheets A or B (according to ***Table 11***) exist. If none of them can be found new *Parameter Worksheet* is created and the name of type A is given. If the *Parameter Worksheet* exists (A or B) the values from cells (A-H,2) of

Structure Worksheet are copied to the first unoccupied row of it. The source (the name of the *Structure Worksheet*) is placed in column "I". The name of the *Parameter Worksheet* is stored in column "K" (for bonds) or "M" (for angles) or "O" (for torsion angles) of "Sheet1"

The next row is chosen and, again, from cell "N3" of the *Structure Worksheet* the type of connection is taken and two possible names are generated. When one of the names is found on "Sheet1" this *Parameter Worksheet* is opened and columns ("A3"-"H3") are copied to the next unoccupied row. If the name is not found the new *Parameter Worksheet* is created before copying the data.

The whole procedure is repeated for all rows of all of the *Structure Worksheets* of the workbook.

In the next step the macro changes the flag (Sheet1.B1) from "1" to"2" (meaning: worksheets generated).

The RMS gradient calculations start for bond *Parameter Worksheets* by opening each worksheet and calling RMS() macro. In the next step RMS1() macro is started to obtain the proposition of the equilibrium distance parameter.

For the angle *Parameter Worksheets* the average values of angles for columns "E", "G" and "H" are calculated. The same procedure has been written for torsion angles. It is possible to use it by removing " ' " in the code.

The example of the *Parameter Worksheet* is listed in ***Table 12.*.**

Taking the data from *Structure Worksheet* listed in ***Table 6*** macro a_Parameters() will create five bonds, one angle and one torsion *Parameter Worksheets* (***Table 13***)*:*

When all *Parameter Worksheets* are prepared, the RMS is calculated (average value in case of angles) and an equilibrium parameter is proposed then *Parameter Optimization Worksheets* ("Sheet10003" for stretching, "Sheet10004" for angle parameters) are created or updated. First, the macro takes the location of the *pgstr.txt* and *pgben.txt* files from "Sheet1", cells "A9" and "A10". It checks it the files exist and in case they cannot be found terminates warning of this situation.

Table 12. Example of *Parameter Worksheet.*

	A	B	C	D	E	F	G	H	I	K	L
1	2	1	CL	CU4	2.244	2.244	2.161	2.226	pzcu27		
2	23	30	CU4	CL	2.244	2.244	2.161	2.226	pzcu27		
3	2	5	CL	CU4	2.241	2.241	2.160	2.226	pzcu31		
4	2	36	CU4	CL	2.213	2.213	2.166	2.226	pzcu_mo12		
5	39	73	CU4	CL	2.213	2.213	2.166	2.226	pzcu_mo12		
6	2	1	CL	CU4	2.207	2.207	2.165	2.226	pzcu_mo24		
7							0.0045	0.0003	Results for MM+:RMS=		0.07
8							0.0003	0.0003			
9									Results for MM*: RMS=		0.02
10									Proposed parameter		2.22

Column A: the number of the first atom involved in the bond
Column B: the number of the second atom,
Columns C, D: corresponding atom types.
*Columns E, F, G and H: distance, angle or torsion angle, taken from the CSD structure, measured after applying HyperChem internal model builder, obtained after MM+ and MM * calculations, respectively.*
Column I: Source of the data.
Cells G7, G8, H7, H8 – intermediated calculations
Cells L7, L9 - RMS calculations taken from Columns G and H
Cell L10 – calculated in RMS1() equilibrium distance between two atoms.

Table 13. *Parameter Worksheet* obtained for the data from ***Table 6***.

row	*Parameter Worksheet* name	*Type*
2	CL_CU4	bond
3	NA1_CU4	bond
4,5,6,7	NA1_CA1	bond
8	NA_CU4	bond
9,10	NA_CA	bond
33	CL_CU4_NA1	angle
36	CA_CA_CA_CA	torsion angle

If the files exist, the macro checks whether the “STR” and “BEN” worksheets exist. These two worksheets contain the copy of the *pgstr.txt* and *pgben.txt* files. To have the most recent versions of these files the old “STR” and “BEN” worksheets are firstly deleted and then recreated. The content of parameter files (each column limited by the TAB character) is loaded to the worksheets.

The stretching and bending parameters are loaded into two arrays STR() and BEN() to speed up the search process.

In the next step the program updates (or creates) the content of columns "J" and "L" on "Sheet1" (the number of line in *pgstr.txt* or *pgben.txt* where the parameter exists). To do so the macro reads each of the occupied cells of columns "K" and "M", extracts the atom types from the name, creates two possible names according to ***Table 11*** and checks in STR() (for column "K") and BEN() (for column "M") if one of them can be found. If the name of the parameter is found updated information of its location is placed in "Sheet1" respectively in columns "J", "L" and "N".

In the next step the program handles the *Parameter Optimization Worksheets*: "Sheet10003" – for stretching parameters - and "Sheet10004" for bending parameters. First it checks if this is the first run of the procedure by reading the value of cell "B1" of "Sheet10003". If empty, it writes a "1" to the cell "D1" of "Sheet1" (still this is the first run of the procedure). Then for each parameter found in column "K" it places them in column "B" of "Sheet10003" and, using the data loaded into STR() array, it puts additional information to columns "A", "C"- "E" (***Table 14***). The Columns "F"-"H" are filled with the information copied from *Parameter Worksheets*.

The cells from column "M" of "Sheet1" (bending parameters) give another output to "Sheet10004" which is presented in ***Table 15***.

When this is not the first run of the procedure, the macro will update the columns "A" on both *Parameter Optimization Worksheets* using the data from the current *Parameter Worksheets* and then it tries to find if there are any parameters which are not used for calculations any more. This situation may happen in the case when the user has changed the atom types during the recalculation process. (N.B. in such cases the new workbook should be created and the entire calculations should be repeated.) If such parameter is found the row occupied by it is marked in red colour.

Table 14. The example of the *Parameter Optimization Worksheet* for stretching parameters (first run of the A_PARAMETERS macro).

	A	B	C	D	E	F	G	H
1	Line	Type	Ks	Lo	Dipole	RMS +	RMS *	P-Lo
2						Run-1		
3	258	CU5_CL2	3	2.47	0.000	0.265	0.239	2.473
4	257	CU5_CL	5	2.27	0.000	0.158	0.106	2.294
5	263	CU5_OC	5	2	0.000	0.209	0.070	2.012
6	255	CU5_NA1	5	2.02	0.000	0.191	0.086	2.034
7	323	OC_CO	11.09	1.285	0.000	0.064	0.032	1.267
8	17	O2_CO	5.05	1.338	-0.200	0.076	0.077	1.273
9		O5_CU2	0	0	0.000	0.157	0.173	1.974

Column A: Number of line in pgstr.txt where the parameter is found (in case of row 9th the parameter has not been found),
Column B: The parameter name,
Column C: Stretching force constant K_s,
Column D: Minimum energy bond length L_0,
Column E: Bond dipole,
Column F: RMS obtained (taken form Parameter Worksheet) after MM+ calculations,
Column G: RMS obtained (taken from Parameter Worksheet) after MM calculations,*
Column H: proposed minimum energy bond length taken form Parameter Worksheet.

Table 15. The example of *Parameter Optimization Worksheet* for bending parameters (first run of the a_Parameters macro).

	A	B	C	D	E	F	G
1	Line	Type	Ks	Phi	Av. cryst.	Av. MM+	Av. MM*
2						Run-1	
3	720	CU5_CL2_CU5	0.5	90	91.854	127.622	89.890
4		NA1_CU5_OC	0	0	83.789	86.130	82.543
5		CU5_OC_CO	0	0	116.383	116.099	117.123
6		OC_CO_CA1	0	0	115.835	114.993	115.164
7		CO_CA1_NA1	0	0	114.338	112.652	114.242

Column A: Number of line in pgben.txt where the parameter is found (only in case of the second row the parameter has been found),
Column B: The parameter name,
Column C: Bending force constant K_s,
Column D: Equilibrium angle,
Column E: Average value of the angles for crystallographic model,
Column F: Average value of the angles for model after MM+ calculations,
Column G: Average value of the angles for model after MM calculations,*

Next, since the columns "A"-"H" of "Sheet10003" ("A"-"G" of "Sheet10004") are prepared, the macro reads the new RMS after MM* calculations data from *Parameter Worksheets* and writes them to the column defined by ("Sheet1.D1")* 2 +6. In case of "Sheet10004" the macro reads the average value of angles calculated after MM* calculations from *Parameter Worksheets* and writes them to the column defined by (Sheet1.D1* 2 +6).

In the final step macro increases the value of the cell "D1" on "Sheet1" by adding one and finally informs of finishing.

3.9.13. RMS1()

This macro is called from A_PARAMETERS(). It is executed within each *Parameter Worksheet*. Its main function is to minimize the RMS defined as ***Equation 25***.

The summation $(X_{calc} - X_{obs})^2$ is done for all observed values from column "E" (X_{obs}) parallely for two values of X_{calc} One is calculated as the value taken from cell "H1" of the *Parameter Worksheet* (first results after MM* calculations) increased by 0.001. Second one is calculated as the value taken from the same cell but reduced of 0.001. The results of such summation divided by the number of steps (*n* in ***Equation 25***) are placed to the first empty cells of columns "G" and "H".

In the next step the macro calculates the RMS gradient taking as X_{calc} the previous values and adding and subtracting 0.001 again. Then the values of the calculations, divided by the number of steps, are placed in the next free cells of columns "G" and "H". The square root is calculated for all of them, placed in columns "N" and "O" and compared.

The comparison gives the direction of search of the minimum (one direction is eliminated since it gives a bigger RMS gradient for the next X_{calc} than for the former X_{calc})

The X_{calc} is increased (or reduced) again and the calculations and comparison is done until the minimum of RMS is found.

The final RMS value is proposed (column "K") as the equilibrium distance parameter.

3.9.14. UPDATE_PARAMETERS() macro.

In the first step the macro calls TEST() then it loads the atom types from columns "A" and "B" of "STR" worksheet into STR() array. Then starting from the third row of "Sheet10003" it reads the cell of column "B" and tries to find a match using information from the array by composing two possible names of the parameter. If the parameter is found in STR() array then the "STR" worksheet is updated with the equilibrium distance value taken from the relevant cell of "Sheet10003" column "I" ("K", "M" and so on). The column is calculated using information from "Sheet1" cell "D1" and depends on the number of runs of A_PARAMETERS() macro. The value of the relevant cell on "STR" worksheet is updated only if the related cell on *Parameter Optimization Worksheet* is not empty. The cells on *Parameter Optimization Worksheet* are updated manually by the user after each step of recalculations.

In case the parameter cannot be found in STR() array, the macro proposes adding a new row at the end of the "STR" worksheet. It asks (and proposes the default values) for atom types involved in a bond (as default values it proposes ones taken from STR() array), K_s (default: 5.000), L_0 (default taken from "Sheet10003"), L_1 (Alternative minimum energy bond lengths are used only if atoms involved in the bond have less than two hydrogens attached to each – default: 0.000), bond dipole (default: 0.000) and finally remark (default: the parameter name).

This procedure is repeated for all parameters defined in column "B" of *Parameter Optimization Worksheet* "Sheet10003".

The "STR" worksheet contains the updated minimum energy bond lengths. If any further changes are needed they can be updated or added manually later directly into the *pgstr.txt* file .

In the next step macro checks if *pgstr.txt* file exists (the path located on "Sheet1" in the cell "A9") and asks if one wants to create a backup of it. Answering "Yes" creates a copy of the parameter file: *PGSTR.TXTMMYYDDHHMISS* (MM=month, YY – year, DD – day, HH – hour, MI – minutes SS-seconds) and writes the name of the former stretching parameter file to column "A" of "Sheet1". DO UNTIL…LOOP procedure finds the first empty row of column "A".

The *pgstr.txt* file is opened for writing and the structure of the parameter file is restored using the data from "STR" worksheet by reading all occupied rows of it.

Finally the macro proposes compilation of the newly created parameter file in HyperChem. If this option is chosen, "menu-setup-compile-parameter-file" command is executed and HyperChem is closed (to be able to use the new parameters HyperChem needs to be restarted).

3.9.15. A_THETA() macro.

The mathematical model used is taken from the work of Hopfinger and Pearlstein **[39]**. They propose to compute the difference function:

$$P(\theta)=P_{QM}(\theta)- P_{MM}(\theta)$$

Equation 26. Difference function.

as a function of θ, where $P_{QM}(\theta)$ is the quantum mechanical energy and $P_{MM}(\theta)$ is the molecular mechanics energy. Both energies are determined as a function of θ at some incremental rotation (usually 30 deg). The V_1, V_2, V_3 parameters are calculated using the following equations:

$$V_j = \frac{\left[\sum_i (1+\cos\Theta_i)P(\Theta_i)\right]A_{j1} + \left[\sum_i (1-\cos 2\Theta_i)P(\Theta_i)\right]A_{j2} + \left[\sum_i (1-\cos 3\Theta_i)P(\Theta_i)\right]A_{j3}}{2D}$$

where

$$D = \frac{\sum_i (1+\cos\Theta i)^2 A_{1,1} + \sum_i (1+\cos\Theta_i)(1-\cos 2\Theta_i)A_{1,2} + \sum_i (1+\cos\Theta_i)(1+\cos 3\Theta_i)A_{1,3}}{4}$$

and

$$A_{1,1} = \sum_i (1-\cos 2\Theta_i)^2 \sum_i (1+\cos 3\Theta_i)^2 - \left[\sum_i (1-\cos 2\Theta_i)\ \ (1+\cos 3\Theta_i)\right]^2$$

$$A_{1,2} = -[\sum_i (1+\cos\Theta_i)(1-\cos 2\Theta_i)\sum_i (1+\cos 3\Theta_i)^2$$
$$\times \sum_i (1-\cos 2\Theta_i)(1+\cos 3\Theta_i)\sum_i (1+\cos\Theta_i)(1+\cos 3\Theta_i)]$$

$$A_{1,3} = -[\sum_i (1+\cos\Theta_i)(1-\cos 2\Theta_i)\sum_i (1-\cos 2\Theta_i)(1+\cos 3\Theta_i)$$
$$-\sum_i (1+\cos 2\Theta_i)^2 \sum_i (1+\cos\Theta_i)(1+\cos 3\Theta_i)$$

$$A_{2,2} = -[\sum_i (1+\cos\Theta_i)^2 \sum_i (1+\cos 3\Theta_i)^2$$
$$-\sum_i (1+\cos\Theta_i)(1+\cos 3\Theta_i)\sum_i (1+\cos\Theta_i)(1+\cos 3\Theta_i)$$

$$A_{2,3} = -[\sum_i (1+\cos\Theta_i)^2 \sum_i (1-\cos 2\Theta_i)$$
$$\times \sum_i (1+\cos 3\Theta_i) - \sum_i (1-\cos 2\Theta_i)^2 \sum_i (1+\cos\Theta_i)(1+\cos 3\Theta_i)]$$

The index i refers to the observations realized from the molecular structure calculations. In the macro the equations take form:

$$V_1 = \frac{A_7 * A(0,0) + A_8 * A(0,1) + A_4 * A(0,2)}{2 * D}$$

$$V_2 = \frac{A_7 * A(1,0) + A_8 * A(1,1) + A_4 * A(1,2)}{2 * D}$$

$$V_3 = \frac{A_7 * A(2,0) + A_8 * A(2,1) + A_4 * A(2,2)}{2 * D}$$

and

$$D = \frac{A_1 * A(0,0) + A_5 * A(0,1) + A_4 * A(0,2)}{4}$$

where

$$A_1 = A_1 + (1+\cos\Theta_i)^2$$

$$A_2 = A_2 + (1-\cos 2\Theta_i)^2$$

$$A_3 = A_3 + (1+\cos 3\Theta_i)^2$$

$$A_4 = A_4 + ((1+\cos\Theta_i) * (1+\cos 3\Theta_i))$$

$$A_5 = A_5 + ((1+\cos\Theta_i) * (1-\cos 2\Theta_i))$$

$$A_6 = A_6 + ((1 - \cos 2\Theta_i) * (1 + \cos 3\Theta_i))$$

$$A_7 = A_7 + ((1 + \cos \Theta_i) * P_i)$$

$$A_8 = A_8 + ((1 - \cos 2\Theta_i) * P_i)$$

$$A_9 = A_9 + ((1 + \cos 3\Theta_i) * P_i)$$

and

$$A(0, 0) = A_2 * A_3 - A_6 * A_6$$

$$A(0, 1) = -(A_5 * A_3 - A_4 * A_6)$$

$$A(0, 2) = A_5 * A_6 - A_2 * A_4$$

$$A(1, 0) = A(0, 1)$$

$$A(1, 1) = A_1 * A_3 - A_4 * A_4$$

$$A(1, 2) = -(A_1 * A_6 - A_4 * A_5)$$

$$A(2, 0) = A(0, 2)$$

$$A(2, 1) = A(1, 2)$$

$$A(2, 2) = A_1 * A_2 - A_5 * A_5$$

where

θ_i are taken from column "A" or "D" (user's choice) of "Sheet10006" (see ***Table 7***)

P_i are taken from column "B" or "C" of "Sheet10006" (see ***Table 7***). The values taken from column "B" or "C" should be taken from ***Equation 26***.

The results of calculation, i.e. V_1, V_2 and V_3 go to cells "I1", "I2", "I3". In the next step the macro prepares the scatter chart with data points connected by smoothed line without markers (***Figure 20***).

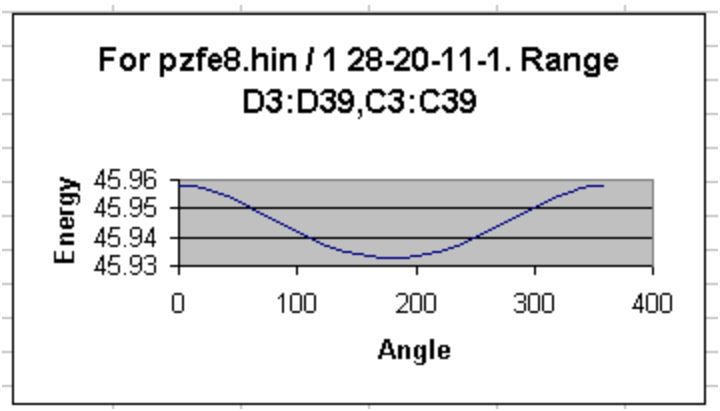


Figure 20. Energy vs. Angle chart obtained in "Sheet10006" after running A_THETA() macro.

As the final step, A_THETA() macro formats the cells in "Sheet10006" and terminates.

3.9.16. TEST() macro.

It can happen that when one wants to recalculate the subset of compounds the content of "STR" worksheet was used to recreate the stretching *pgstr.txt* parameter file during UPDATE_PARAMETERS() procedure. If the number of parameters in "STR" worksheet was less than the number in the most current version of *pgstr.txt* file then the files were overwritten by the incomplete number of parameters taken from "STR" worksheet. The macro checks on such situations by reading the current atom types from *pgstr.txt* to STR() array and reads each stretching parameter from "Sheet1" column "K" and checks if it exists in STR(). In case the parameter does not exist in STR() it proposes to add it. If the parameter has been found the macro checks and corrects (if necessary) the line number of its location in *pgstr.txt* file. The colour of column "A" of "Sheet10003" is changed either to light blue, meaning the parameter has been located in *pgstr.txt*, or to light yellow, after the parameter has been proposed and added to the parameter file. In case any parameter has been added to STR() array, the copy of *pgstr.txt* is made before a new one is created.

3.9.17. COMPARE() macro.

This macro checks if “pg_vs_mm” worksheet exists and prepares an empty worksheet. Then it reads the contents of columns A and B (atom types) of *mmstr.txt* (original stretching parameter file) and *pgstr.txt* into STRMM() and STR() arrays. For each parameter from STR() array it tries to find the match in STRMM(). In case a match cannot be found, which means the parameter does not exist in the original *mmpstr.txt* parameter file, such a parameter is reported to “pg_vs_mm_ worksheet by giving its location in *pgstr.txt* to column “A”, atom types involved in the bond to column “B” and “C”.

3.9.18. A_POST_ALL

This macro groups several single ones into one action. The macro can be called from the main program HyperHelper.Exe (Excel Macros menu second option) when first calculations are finished. The macro groups the following procedures:
A_POST_0(), A_POST3() and A_PARAMETERS()
Executing this macro automatizes the process of refinement of the parameters and is recommended for the novice users.

3.9.19. A_POST_ALL1

This macro has the same function as A_POST_ALL but should be run after each loop of calculations. It consists of :A_POST1() procedure for comparing the results on structure worksheets, A_POST4() macro to have the same parameters in the same worksheets (both of them are executed by calling A_POST3() macro) and a_parameters() macro. In HyperHelper.exe Excel macros menu there is an entry called "Automatic calculations in MS Excel - next runs" to execute this macro.

4. Methodology

For the calculations the existing force field parameters in MM+ were not changed but new force field atom types and their parameters were added. The manner in which this is done is shown in ***Figure 21***, and illustrates how the MM+ force field is upgraded.

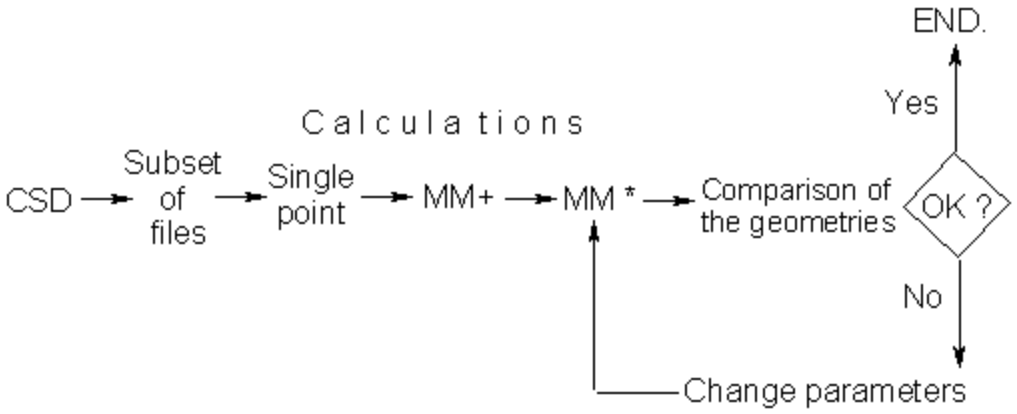


Figure 21. Updating the existing MM+ force field

MM+ - calculations where the original MM+ parameters are used.
MM - calculations with the new parameters.*

The methodology presented in this thesis is based upon restricted applications to problems of molecular geometry.

The first step is to search the Cambridge Crystallographic Structural Database (CSD) for a subset of substances in which one is interested. On the one hand one should find as many members of a subset as possible, but on the other hand the subset should contain a quite narrow range of types of compounds. In this way new atom types can be more easily defined.

Conditions of the search in CSD.

The 5.14 v. (April 1998) database was sought.

After having built the model, the **3D-CONSTRAIN…** option was chosen and then

ALL-BOND, **ALL-ANG** and/or **ALL-TORS** were activated for further treatment in VISTA.

The conditions of the search have been:

INSIST-NO-DISORDER
INSTIST-PERFECT-MATCH
INSTIST-RFACTOR<10%
INSITS-ERROR-FREE
SAVE-DATA-SUBSET
SAVE-FDAT
SAVE-REFCODE-LIST
SAVE-POSTSCRIPT-FILE

The multiple structure FDAT files obtained are transformed to PDB and HIN (HyperChem) format using the Babel program called by HyperHelper.

The input files for HyperChem are then prepared. This is the most important step in the process of adding the new parameters. HyperChem is equipped with a text file containing a set of rules for assigning atom types to each force field (*chem.rul*). When building a new model and executing the command "calculate-types" the automatic procedure looks for known atom types. If the type of the atom is unknown then, it is marked by a double asterisk "**". The aim of this part of the work is to define new types of atoms. It is extremely important to draw the bond order correctly or this may lead to defining the wrong atom types and, further more, incorrect parameters. Hence, the HIN files should be examined very carefully and all the types of bonds should be chosen with care.

In the case of polymeric structures we have extracted the monomers filling the coordination sphere of the metal with water molecules or other simple ligands. No solvent or counter-ions- have been allowed. In some cases we have used MSI Cerius^2 program **[35]** for extracting the molecules, mainly when SHELX **[40]** **.res* files only were available.

The next step is to carry out the calculations on the whole subset of compounds. Since we are interested in the geometrical arrangements of the metals involved in coordination compounds it is necessary to calculate and compare bond distances, bond angles and torsion angles. The results will help to answer the following questions, that is, does one need to

a. define a new atom type
b. define a new parameter
c. change the existing parameter.

The starting L_o and Θ_o parameters (equilibrium bond length and bond angle) can either be found by HyperHelper, or found in the literature **[6,41]** or taken from the CSD.

When all the new atom types and parameters have been added to the force field the calculations on the whole subset of compounds has to be repeated. This enables one to control if further changes are necessary. Each time any of the parameters are changed the calculations must be repeated to verify that the new models agree with the crystallographic structures.

In order to evaluate the results we have accepted the conditions proposed by Rapé et al. **[9]**. They proposed a working definition of acceptable errors: "**good agreement**" for bond distances errors of less than 0.02 Å (2º for the angles), "**fair agreement with experiment**" for bond distances errors of less than 0.08 Å (5º for angles) "**poor agreement with experiment**" for bond distances errors larger than 0.08 Å (5º for angles)***Table 16*** presents the definitions of the names of the geometrical arrangements according to **[17,42,43]**. This table and additionally ***Table 17*** are also useful for prediction of the coordination sphere for transition metals.

Refinement of the parameters is carried out while slight modifications of any of the individual parameters (bonds, angles, torsions) improves the RMS values. When this is not the case the refinement is stopped and the previous value of the parameter is accepted.

Such methodology, called trial-and-error techniques or empirical fitting, was proposed by Watson, Tschaufeser, Wall, Jackson and Parker in **[46]**, Hopfinger and Pearlstein in **[39]**, Comba and Hambley in **[5]** and others.

Table 16. Typical geometries of complexes for coordination numbers (CN) 2-6

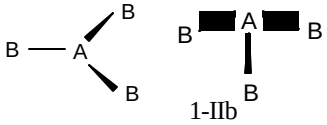
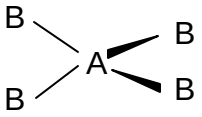
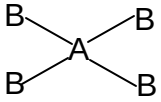
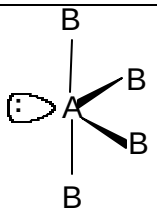
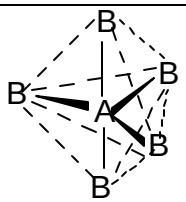
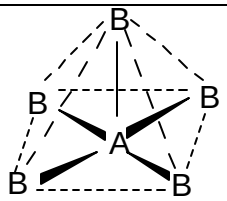
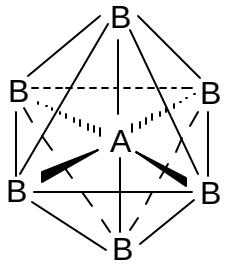
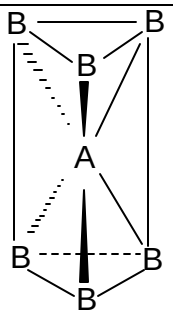
1	2	3	4	5	6
CN	Name	Picture	Frequency	Remarks	Point Group
2	Linear **(L-2)**	L-M-L	uncommon	Cu^{I},Ag^{I},Au^{I},Hg^{II}	D_{8h}
	Angular **(A-2)**	M / \ L L			C_{2v}
3	Trigonal: planar (TP-3), **pyramidal (TPY-3)**, T-shaped	 1-IIb	v.rare	Important for elements of Group 15	D_{3h}, C_{3v}, C_{2v}
4.	Tetrahedral **(T-4)**		Highly important	Usually formed by nontransition elements (oxo - thio-ligands, Be^{II}, B^{III},$Al^{III}$$Ga^{III}$ …	T_d
	Square planar **(SP-4)**			Transition metal complexes Rare outside the transition elements	
	Irregular				C_{2v}
5	Trigonal bipyramidal **(TBYP-5)**		Less common than 4 and 6	Elements of Group 15 in +V oxidation state	D_{3h}
	Square pyramidal **(SPY-5)**				C_{4v}

Table cont.

1	2	3	4	5	6
	Octahedral **(OC-6)**		Most common	Non-metalic and metalic centers of the Main Group elements and in many complexes of the Group 2,13 and 14 (with the exeption of C and Si)	O_h
	Trigonal Prismatic **(TP-6)**		Much rarer	MoS_2, WS_2, MM'_3S_6 (M=Mn,Fe,Co, Ni; M' = Nb, Ta) and complexes containing 1,2-dithiolene or 1,2-diselenolene type ligands	D_{3h}

Name – name and (polyhedral symbols) by IUPAC,
Picture – graphical representation of the arrangement
Frequency – frequency of the appearance
Remark - additional information
Point Group – for those who use group theoretical methods

Table 17. The most common coordination geometries for Cr, Mn, Fe, Co, Ni, Cu, Ru, Rh, Pd, Ag and Pt

	d^0	d^1	d^2	d^3	d^4	d^5	d^6	d^7	d^8	d^9	d^{10}
Element	PS **OST**	PS **OST**	PS **OST**	PS **OST**	PS **OST**	PS **OST**	PS **OST**	PS **OST**	PS **OST**	PS **OST**	PS **OST**
Cr	T-4 OC-6 **VI**	T-4 OC-6 **V**	T-4 OC-6 **IV**	OC-6 **III**	OC-6 **II**	OC-6 **I**	OC-6 **0**				
Mn	T-4 **VII**	T-4 **VI**	T-4 **V**	OC-6 **IV**	OC-6 **III**	OC-6 T-4 **II**	OC-6 **I**				
Fe			T-4 **VI**		OC-6 **IV**	OC-6 T-4 **III**	OC-6 T-4 **II**	OC-6 **I**			
Co						OC-6 **IV**	OC-6 **III**	T-4 OC-6 **II**	TBYP-5 **I**		
Ni								TBYP-5 OC-6 **III**	SP-4 OC-6 **II**	T-4 **I**	T-4 **0**
Cu									SP-4 OC-6 **III**	T-4 SP-4 TB-5 OC-6 **II**	T-4 **I**
Ru	T-4 **VIII**	T-4 **VII**	OC-6 **VI**		OC-6 **IV**	OC-6 **III**	OC-6 **II**				
Rh						OC-6 **IV**	OC-6 **III**		SP-4 **I**		
Pd							OC-6 **IV**		SP-4 **II**	SP-4 **I**	
Ag									SP-4 **III**	SP-4 **II**	L-2 T-4 **I**
Pt							OC-6 **IV**		SP-4 **II**		

PS – preferred structure
OST – oxidation state
The names of the coordination centers according to ***Table 16***

5. The sources of initial parameters.

Aléman et al. **[44]** proposed two ways of obtaining the missing parameters for the force field:

1. to use the same rigorous procedures employed to develop the original force field
2. to evaluate the lacking parameters approximately.

The first method gives the best results but the second one is the most currently used because of its simplicity.

Different authors (**[8, 39,45,46]**) proposed to obtain the b_o (equilibrium distance) and θ_o (equilibrium angles) from the literature (International Tables for Crystallography **[41]**) or from the databases (CSD **[4]**). They can also be calculated from ab initio molecular orbital theory or estimated by comparing the values of similar bonds (angles) **[46, 47]**.

Using the average values of bond lengths and angles taken from CSD **[4]** one has to examine the range of the distances very carefully. Using the VISTA program (included with CSD software) it is possible to analyze the histograms for selected distances or angles. One can expect several situations presented in ***Figure 22***. The first histogram presents the situation where the range of distances found for the subset of compounds is narrow and one can easily find the average value of the bond and then use it as a starting parameter. The second histogram is very broad which would suggest that the equilibrium value of such bond distance would be very difficult to model. In such a situation one should redefine the atom types (make more precise ones).

The torsional parameters can be calculated by curve fitting (scription) strategy described in detailed in Introduction to HyperHelper.

The parameters can be calculated using direct calculations (ab initio or DFT) **[5,7,44,45,47,48]**

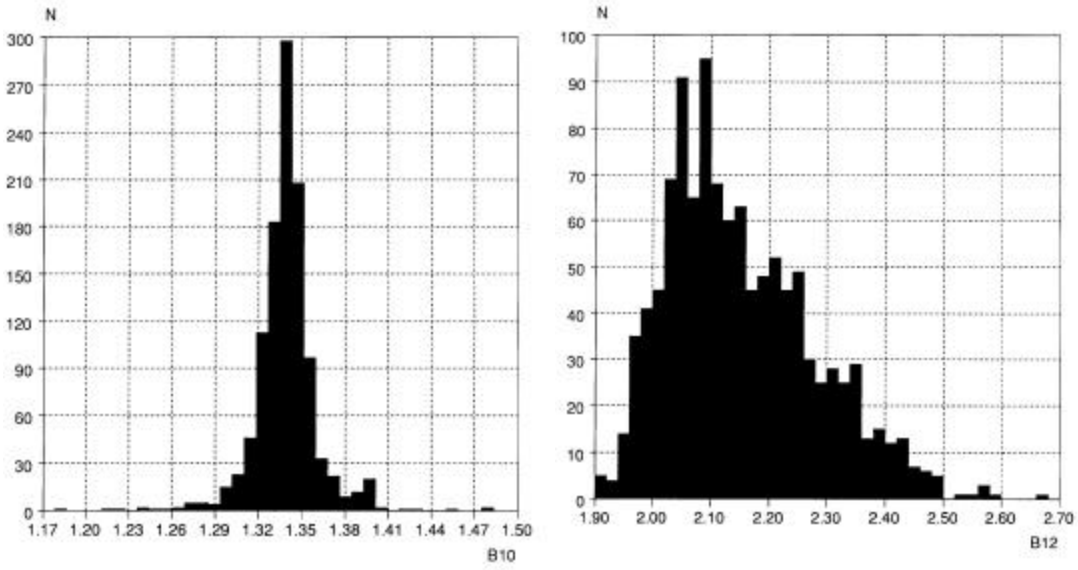


Figure22. Two examples of histograms obtained in VISTA (B10, B12 - distances in [Å]).

The "hardness" parameters can be taken from sources such as: vibrational spectra, microwave spectra (rotational barriers) **[49]** by solving the following equation:

$$n = (K_b / m)^{1/2} (2c)^{-1}$$

where

ν – wave number, K_b – "hardness" parameter, c – speed of light, μ – reduced mass of two atoms calculated as $\mu=(m_1 m_2)(m_1+m_2)^{-1}$

For van der Waals parameters, Comba in **[5]** states that the best approach is to use the van der Waals parameters developed for organic compounds. In the case of metal complexes it is difficult to obtain the van der Waals radius because the cation does not make close contacts with atoms which are free to move away from it. He proposes to use the van der Waals radius of more that 2.2 Å. HyperChem has a full list of the van der Waals parameter listed in Table 3 in Introduction to Molecular Mechanics computational methods**.** The value of 2.2 Å were introduced for the new metals.

The program for the Development of Empirical Force Field PEFF **[50]** might be another source of the parameters. The program calculates all necessary parameters and additionally proposes the optimum energy terms for the calculated compounds.

Table 18 present the parameters used in HyperChem in MM+ and MM* parameter sets, which should be either added or will be estimated by the program (for a detailed description how HyperChem calculates the missing parameter see chapter "MM+ parameter set"). The parameters calculated by HyperChem can be viewed in the log file at Mechanics Print Level=6 (started at the beginning of calculations from File menu /Start log…).

Table18. Structure of parameter files in HyperChem for MM+ (*mmp*.txt*) and MM* (*pg*.txt*) parameter sets **[51]**

Col.	Content	Type	Type of parameter	File
T1	Atom 1 (atom type) involved in bond	C	Bond Length	*Mmpstr.txt Pgstr.txt*
T2	Atom 2 (atom type) involved in bond	C		
KS	Stretching force constant in [millidynes/A]	N		
L0	Minimum energy (equilibrium) bond length in [A]	N		
L1	Alternative equilibrium bond length in [A], used only if atoms 1 and 2 have less than two hydrogens attached to each	N		
Dipole	Bond dipole moment in [Debyes]	N		
Remark		R		
T1	Atom type for end atom of bong angle	C	Bond Angle	*Mmpben.txt Pgben.txt (*ben3.txt *.ben4.txt)*
T2	Atom type for central atom of bond angle	C		
T3	Atom type for other end atom of bond angle	C		
KS	Bending force constant in [kcal/mol rad^2]	N		
TYPE1	Standard bond angle unless TYPE2 and TYPE3 are nonzero and their conditions are satisfied in [deg]	N		
TYPE2	Bond angle if one end atom is hydrogen in [deg]	N		
TYPE3	Bond angle if both end atoms are hydrogens in [deg]	N		
Remarks		R		
T1	Atom 1 (atom type) involved in torsion	C	Torsion Angle	*Mmptor.txt Pgtor.txt (*tor4.txt)*
T2	Atom 2 (atom type), a central atom, involved in torsion	C		
T3	Atom 3 (atom type), a central atom, involved in torsion	C		
T4	Atom 4 (atom type) involved in torsion	C		
V_1, V_2, V_3	Energy of torsional barrier, in [kcal/mol]	N		
Remark		R		
C	Atom type for central, sp^2 hybridized atom	C	Out-of-plane bending	*Mmpoop.txt Pgoop.txt*
A	Atom type for one of the atoms bonded to atom C	C		
COPB	Out-of-plane bending force constant, in [millidyne A/rad^2]	N		
Remark		R		
Atom	Atom type	C	Non-bonded	*Mmpnbd.txt Pgnbd.txt*
R_star	Half the minimum energy nuclear separation, in [A] (vdW radius, rj*). Uses an arithmetic mean for pair values	N		
EPS	Well depth in [kcal/mol] (minimum energy)	N		
Ref.		R		

Col. – the name of the column in the parameter file
Content – description of the content of the column
Type – type of a variable" C- character, N-number, R- remark
file – name of the file containing parameters
***in bold** – parameters to be developed*

6. *Calculations*

The calculations were carried out on a Pentium II 400 MHz/ 128 MB RAM computer with Windows NT 4.0 Sp6. Os. Excel 8 (Microsoft® Office97) and Excel 9 (Microsoft® Office2000), Babel v. 1.6 and HyperChem v. 5.11 were used. The applications were tested on a single/dual processor machines under the Windows NT operating system. C*hem51.reg* provided by HyperCube registry file was changed for the system as follows:

```
[HKEY_CURRENT_USER\Software\Hypercube\HyperChem Pro\5.1\mm+]
"CurrentFiles"="0"
"AtomTypeMass"="mmptyp.txt"
"FileFormat"="Text"
"CustomNames"="mmplus,PG"

[HKEY_CURRENT_USER\Software\Hypercube\HyperChem Pro\5.1\mm+\mmplus]
"FileFormat"="Text"
"MMPElectrostatics"="BondDipoles"
"MMPStretch"="mmpstr.txt"
"MMPBend"="mmpben.txt"
"MMPBend4"="mmpben4.txt"
"MMPBend3"="mmpben3.txt"
"MMPOOPBend"="mmpoop.txt"
"MMPStretchBend"="mmpoop.txt"
"MMPTorsion"="mmptor.txt"
"MMPTorsion4"="mmptor4.txt"
"MMPAtomVDW"="mmpnbd.txt"
"MMPPairVDW"="mmpnbd.txt"
"MMPCubicStretch"="-2"

[HKEY_CURRENT_USER\Software\Hypercube\HyperChem Pro\5.1\mm+\PG]
"FileFormat"="Text"
"MMPElectrostatics"="BondDipoles"
"MMPStretch"="pgstr.txt"
"MMPBend"="pgben.txt"
"MMPBend4"="pgben4.txt"
"MMPBend3"="pgben3.txt"
"MMPOOPBend"="pgoop.txt"
"MMPStretchBend"="pgoop.txt"
```

```
"MMPTorsion"="pgtor.txt"
"MMPTorsion4"="pgtor4.txt"
"MMPAtomVDW"="pgnbd.txt"
"MMPPairVDW"="pgnbd.tx"
"MMPCubicStretch"="-2"
```

The modified file was implemented in the Windows Registry.

The calculation conditions in HyperChem were:

MM+ (MMPLUS and PG parameter sets),
Electrostatic: Bond dipoles,
Cutoffs: None,
Optimization Algorithm: Polak-Ribiere,
Termination conditions: RMS gradient 0.001 (kcal / Å mol) or number of cycles less than 5000 (defined in *helper.in*i file).

It is important to note that the internal model builder in HyperChem was not used to rebuild the CSD models before minimization was carried out. For both MM+ and MM* calculations the crystallographic structures were used as input files.

All the input and output files have been published on the WEB at
http://www.unine.ch/chim/pg/r/results.html.

7.Results

The results of calculations are presented for each subset of compounds separately. The crystallographic, MM+ and final MM* structures are presented on the web site

http://www.unine.ch/chim/pg/r/results.html

as HIN (starting structure), HIN_MM+ (after calculations using old force field parameters) and HIN_MM* (obtained after calculations using modified parameters) files. The web page also offers access to DAT and postscript files containing the results of the search of CCSD, and to the Microsoft Excel Workbooks containing full results of calculations. The web page is divided into sections for each metal. Last section of the page contains the links to the newest atom type, type rule and parameter files to download.

When new stretching or bending parameters have been added or changed the tables contains the RMS comparison are presented. The description of the columns for the stretching results is as following:

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s

At1, At2 – atoms involved in the bond,
RMS MM+ - RMS gradient obtained after calculations using MM+ force field
RMS MM - RMS gradient obtained after calculations using new parameters*
*Agreement – according to Rapé et al.**[9]***
L_0 – equilibrium value of the bond distance [Å]
K_s – "strength" parameter [millidynes/ Å]

Columns of the bending tables are describes as:

At1	At2	At3	MM+ RMS	Agreement MM+	MM* RMS	Agreement MM*	Parameters: K_Θ Θ_o

At1, At2, At3 – atoms involved in the angle,
RMS MM+ - RMS gradient obtained after calculations using MM+ force field
RMS MM - RMS gradient obtained after calculations using new parameters*
*Agreement – according to Rapé et al.**[9]***
Θ_0 – equilibrium value of the angle [^{o}]
K_Θ – "strength" parameter [millidyne Å/rad^{-2}]

Units are:

bonds [Å],

angles [^{o}] ,

R^2 stands for the linear regression coefficient.

7.1. Calculations on Pyrazine-Cr structure

I. Structures used.

Only one structure was available for calculations and is given in ***Table 19***.

Table 19. Crystal structure of complex of chromium used for calculations.

Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzcr1	ACPCRB[1]	tetrakis(μ_2-Acetato-O,O') –(μ_2-N-pyrazine) – chromium	Cr CN=6	OC-6

The following rules are used for typing the Cr atoms :

```
Cr:
;connected to pyrazine
     connected to N@1~C~C~N~C~C~N@1?
     =CR2. ; numerical type 75
;connected to pyridine
     connected to N@1~C~C~C~C~C~N@1?
     =CR1.; numerical type 74
```

II. Results of calculations.

The final adjustment of the parameters gave the RMS gradient calculated over all bonds of 0.018. MM+ calculations gave the value of 0.147. ***Table 20*** lists the stretching parameters obtained during the process of optimisation of the bond lengths. ***Figure 23*** shows the comparison chart of the bond distances after MM+ and MM* calculations.

Table 20. Final parameters for Cr complex – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
CR2	O2	0.194	Poor	0.002	Good	2.005	11.000
CR2	NA1	0.423	Poor	0.001	Good	2.314	11.090
CR2	CR2	0.098	Poor	0.034	Fair	2.329	11.090
CR	O2	0.095	Poor	0.003	Good	1.252	5.000

The default bending parameters were used for calculations.

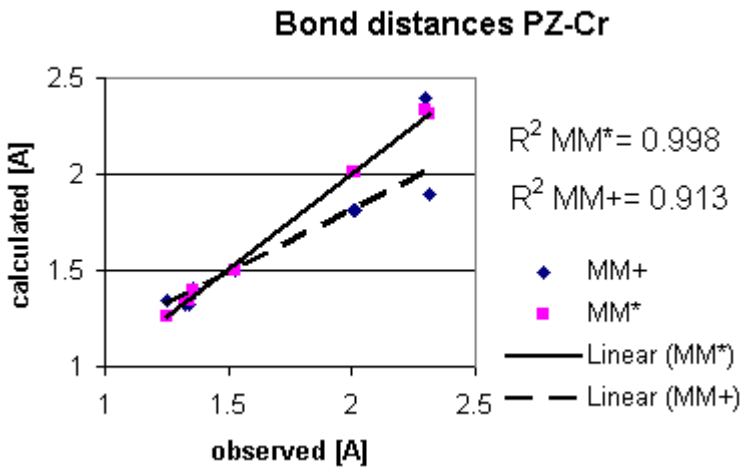


Figure 23. Comparison of the bond distances after MM+ and MM* calculations.

All the results are included in the *PZCR.xls* file of the web page http://www.unine.ch/chim/pg/r/results.html in chromium section.

III. Conclusions.

It was possible to decrease the RMS calculated over all bonds of the pzcr1 model. The arrangement of the atoms surrounding the chromium center was preserved during MM+ and MM* calculations.

7.2. Calculations on Pyrazine-Mn subset

I. Structures used.

Nine structures were used for calculations and are listed in ***Table 21.***

Table 21. Crystal structures of complexes of manganese used for calculations.

Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzmn1	HACWIR[2]	catena-(bis(Pyrazine-2,3-dicarboxylato) – manganese (II) bis(oxonium))	Mn(II) CN=6	OC-6
2	Pzmn2	JIHLIV[3]	cis-Diaqua-(N,N'-bis(2-methylpyrazyl) ethane-1,2-diamine-N,N')-manganese (II) diperchlorate monohydrate	Mn(II) CN=6	OC-6
3	Pzmn3	SEVNAI[4]	Diaqua-bis(pyrazinecarboxylato-N,O)-manganese(II)	Mn(II) CN=6	OC-6
4	Pzmn4	SEVNAI01[5]	Diaqua-bis(pyrazinecarboxylato)-manganese(II)	Mn(II) CN=6	OC-6
5	Pzmn5	SULSUN[6]	(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-bis(aqua-bis(nitrato-O,O')-manganese(II))	Mn(II) CN=7	HEPTA
6	Pzmn6	TEPRUB[7]	bis((2,6-Dimethoxybenzoato-O)-aqua-(3-methylpyrazine))-manganese(II)	Mn(II) CN=6	OC-6
7	A_1	-[8]	(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-bis(tiocyanato)-manganese(II)	Mn(II) CN=6	OC-6
8	A_2	-[9]	(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-trichloro-aqua-manganese(II)	Mn(II) CN=6	OC-6
9	A_3	-[10]	(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-bis(tiocyanato-)-aqua-manganese(II)	Mn(II) CN=6	OC-6

We have defined new atom types in the *chem.rul* file :

```
Mn:
; connected to pyrazine CN=7
     connected to (-*)(-*)(-*)(-*)(-*)(-*)(-*)?
     connected to N@1~C~C~N~C~C~N@1?
     =MN3. ; numerical type 117
; connected to pyrazine CN=6
     connected to (-*)(-*)(-*)(-*)(-*)(-*)?
     connected to N@1~C~C~N~C~C~N@1?
     =MN2. ; numerical type 77
; connected to pyrazine for pzmn1 termination groups
     connected to (-*)(-*)(-*)?
     connected to N@1~C~C~N~C~C~N@1?
     =MN2. ; numerical type 77
;connected to pyridine
     connected to N@1~C~C~C~C~C~N@1?
     =MN1. ; numerical type 76
```

II. Results of calculations.

Six runs of refinement of the parameters were necessary to achieve the lowest RMS gradients. After the sixth run of the program we have obtained the RMS values calculated over bonds and some bond angles and the final parameters are presented in ***Table 22*** and ***23.***

Table 22. Final parameters for manganese complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
MN2	CL	0.299	Poor	0.060	Fair	2.490	5.000
MN2	N1	0.417	Poor	0.003	Good	2.256	5.000
MN2	N2	0.248	Poor	0.014	Good	2.119	5.000
MN2	N3	0.360	Poor	0.008	Good	2.262	5.000
MN2	NA	0.385	Poor	0.011	Good	2.275	5.000
MN2	NA1	0.429	Poor	0.019	Good	2.305	5.000
MN2	O2	0.345	Poor	0.031	Fair	2.193	5.000
MN2	OC	0.315	Poor	0.016	Good	2.139	5.000
MN3	NA	0.359	Poor	0.004	Good	2.243	5.000
MN3	NA1	0.387	Poor	0.000	Good	2.274	5.000
MN3	O2	0.422	Poor	0.093	Poor	2.325	5.000

Table 23. Final parameters for iron(II) complexes – bending parameters.

At1	At2	At3	MM+ RMS	Agreement MM+	MM* RMS	Agreement MM*	Parameters : K_Θ Θ_o
MN2	N2	C2	44.12	Poor	8.03	Poor	0.500 165.00
N2	MN2	N2	5.75	Poor	1.96	Good	0.500 100.00
N3	MN2	N3	10.04	Poor	1.1	Good	0.500 80.00
O2	MN2	OC	7.63	Poor	5.91	Poor	0.500 90.00
S2	C2	N2	1.37	Good	1.23	Good	0.500 178.00

III. Conclusions.

All the results are included in the *PZMN.xls* file. The structures can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Mn*** section of the page.

The new parameters gave better reproduction of the bond distances with an RMS 0.036 versus 0.176 for calculations with MM+ parameters. The RMS calculated over selected angles gave the values of 11.00 for MM* and 14.40 for MM+ calculations. The comparison of the results is shown in ***Figure 24*** and ***25.***

The bending parameters added to the original MM+ force field parameter set allowed improve the angles of the subset. The angles of MN2-N2-C2 angle of A_3 and A_1 structure were corrected to the value of an average value of 161.771 deg for MM* structures in comparioson of 165.320 deg for cryatsllografic and 122.043 deg for MM+ structures.

In general the OC-6 coordination was obtained for all models.

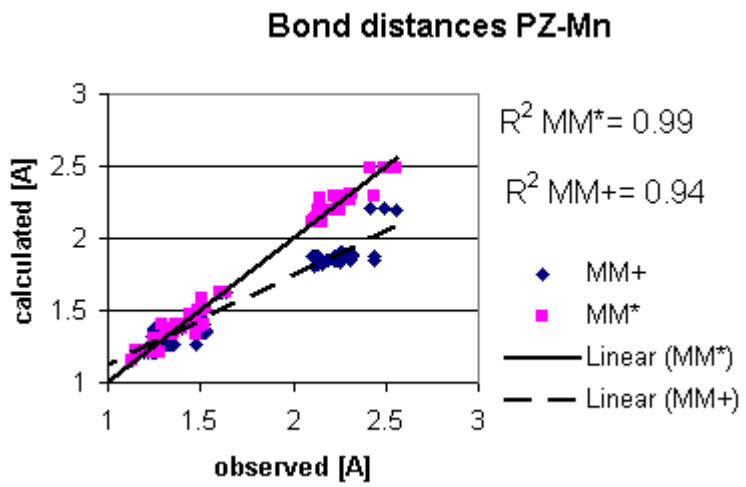


Figure 24. Comparison of the bond distances after MM+ and MM* calculations.

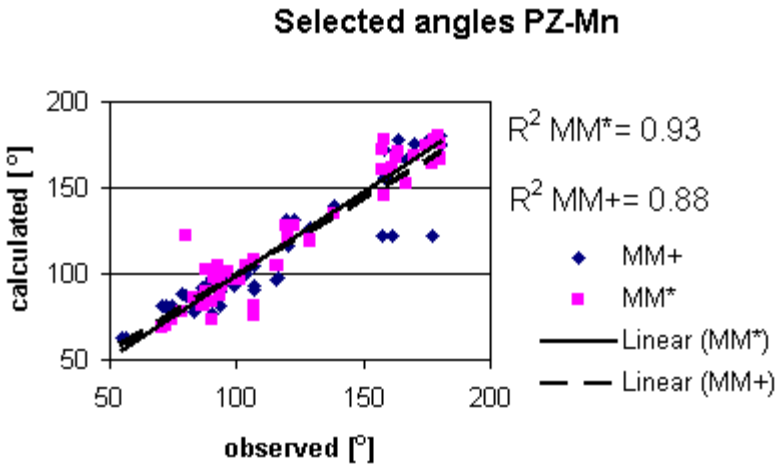


Figure 25. Comparison of the angles after MM+ and MM* calculations.

7.3. Calculations on Pyrazine-Fe(II) subset of structures

I. Used structures.

Eleven structures were used for calculations and are listed in ***Table 24.***

Table 24. Crystal structures of complexes of Iron used for calculations.

Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzfe1	BOFFIL[11]	Diaqua-bis(pyrazinecarboxylato)-iron(II)	Fe(II) CN=6	OC-6
2	Pzfe2	FITFOD[12]	Bis(Pyrazine-N)-(5,10,15,20 – tetraphenylporphinato-N,N',N'',N''')-iron(II)	Fe(II) CN=6	OC-6
3	Pzfe3	NIKFAO[13]	Bis((2-dimethylamino-4(3H)-pteridonato)-methanol)-iron(II) methanol solvate	Fe(II) CN=6	OC-6
4	Pzfe4	POHLON[14]	Bis(1,4,5,8-Tetra-azaphenathrene)-di-isothiocyanato-iron(II) acetonotrile solvate	Fe(II) CN=6	OC-6
5	Pzfe5	POHLON01	Bis(1,4,5,8-Tetra-azaphenathrene)-di-isothiocyanato-iron(II) acetonotrile solvate	Fe(II) CN=6	OC-6
6	Pzfe6	PYZTCI[15]	Pyrazine-tetracarbonyl iron	Fe(II) CN=5	TBY-5
7	Pzfe7	RIZSOI[16]	Bis(2-(Pyrazin-2-ylamino)-4-4(pyridin-2-yl)thiazole)-iron(II)	Fe(II) CN=6	OC-6
8	Pzfe8	SODHUO[17]	Catena-(bis(μ_2-Pyrazine-N,N')-di-isothiocyanato-iron(II)	Fe(II) CN=6	OC-6
9	Pzfe9	WEYWEC	Bis(2-(pyrazin-2-ylamino)-4-(pyridin-2-yl)thiazolato-N,N',N'')-iron(II) benzene solvate	Fe(II) CN=6	OC-6
10	Pzfe10	ZIFRUB[19]	Catena(Dicholor-bis(μ_2-pyarzine)-iron(II)	Fe(II) CN=4	T-4
11	L3-FE	-[20]	Tetraqua-(5,6-bis(2-pyridyl)-pyrazine-2,3-dicarboxilic)-iron(II)	Fe(II) CN=6	OC-6

At the beginning we have defined new atom types: FE5 (coordination number CN=6), FE6 (coordination number CN=4) and FE7 (coordination number CN=5) according to the following entrance in the *chem.rul* file

```
Fe:
; connected to pyrazine
; CN=6
     connected to (-*)(-*)(-*)(-*)(-*)(-*)?
     connected to N@1~C~C~N~C~C~N@1?
     =FE5. ; numerical type 79
; CN=5
     connected to (-*)(-*)(-*)(-*)(-*)?
     connected to N@1~C~C~N~C~C~N@1?
     =FE7. ; L=5 numerical type 79
; CN=4
     connected to (-*)(-*)(-*)(-*)?
     connected to N@1~C~C~N~C~C~N@1?
     =FE6. ; L=4
;connected to pyridine
     connected to N@1~C~C~C~C~C~N@1?
     =FE4. ;numerical type 78
; Iron (II) by HyperChem
;     =FE2.; numerical type 61
; Iron (III) by HyperChem
;    =FE3. ; numerical type 62

O:
      connected to (-Fe)(-C-C~N-Fe)?
     =O3.
     connected to (-Fe)(-C~C~N-Fe)?
     =O3.
```

II. Results of calculations.

Four runs of refinement of the parameters were necessary to achieve the lowest RMS gradients. After the fourth run of the program the RMS values obtained, calculated over bonds and some angles and the final parameters are presented in ***Table 25*** and ***25.***

Table 25. Final parameters for iron(II) complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
Fe5	O2	0.270	Poor	0.040	Fair	2.140	5.000
Fe5	O3	0.281	Poor	0.028	Fair	2.086	10.000
Fe5	OC	0.292	Poor	0.006	Good	2.104	5.000
Fe5	NA1	0.249	Poor	0.099	Poor	2.121	5.000
Fe5	N2	0.138	Poor	0.057	Fair	1.991	5.000
Fe5	NP	0.088	Poor	0.008	Good	1.949	5.000
Fe5	NA	0.245	Poor	0.097	Poor	2.065	5.000
Fe6	CL	0.243	Poor	0.003	Good	2.400	5.000
Fe6	NA1	0.377	Poor	0.001	Good	2.230	11.000
Fe7	CO	0.120	Poor	0.015	Good	1.780	5.000
Fe7	NA1	0.164	Poor	0.000	Good	2.023	11.000
NA1	CA1	0.074	Fair	0.023	Fair	1.340	11.090
CA1	CA1	0.029	Fair	0.028	Fair	1.396	11.090
CA1	CO	0.167	Poor	0.008	Good	1.511	4.500
C3	CA	0.134	Poor	0.019	Good	1.480	9.600
CA	CA	0.025	Fair	0.015	Good	1.373	9.600
CA1	O3	0.059	Fair	0.001	Good	1.286	5.500
NA	CA	0.078	Fair	0.013	Good	1.346	11.090
NA	CA1	0.016	Good	0.012	Good	1.329	5.500
N2	CA	0.017	Good	0.001	Good	1.329	10.000
N2	CA1	0.024	Fair	0.019	Good	1.365	10.000

Table 26. Final parameters for iron(II) complexes – bending parameters.

1	2	3	4	5	6	7	8
At1	At2	At3	MM+ RMS	Agreement MM+	MM* RMS	Agreement MM*	Parameter K_Θ Θ_o
NA	FE5	O3	12.93	Poor	1.98	Good	a
NA1	FE5	NA	5.83	Poor	3.53	Fair	a
N2	FE5	CA1	4.35	Fair	1.14	Good	a
N2	FE5	NA	3.23	Fair	3.17	Fair	a
FE7	CO	O1	59.68	Poor	2.04	Fair	0.500 89.00
CO	FE7	CO	26.05	Poor	9.06	Poor	a
NA1	FE7	CO	36.33	Poor	3.4	Fair	a
FE5	N2	C2	40.31	Poor	8.15	Poor	0.500 170.00
N2	C2	S2	2.11	Good	0.8	Good	0.500 178.00

Table cont.							
1	2	3	4	5	6	7	8
NA1	FE5	O2	6.87	Poor	8.51	Poor	a
N2	FE5	NP	1.24	Good	1.93	Good	a
N2	FE5	NA1	6.79	Poor	4.68	Fair	a
N2	FE5	N2	4.54	Fair	2.9	Fair	a
CL	FE6	CL	70.98	Poor	3.46	Fair	5.500 180.0
NA1	FE6	CL	18.28	Poor	0.91	Good	a
NA1	FE6	NA1	19.45	Poor	0.14	Good	0.500 89.00
O2	FE5	O2	0.4	Good	3.62	Fair	a
FE5	O3	CO	3.01	Fair	0.43	Good	a
O3	FE5	O2	1.28	Good	2.48	Fair	a
O3	FE5	O3	0	Good	0	Good	a
NA1	FE5	O3	3.48	Fair	2.83	Fair	a
NA1	FE5	NA1	6.51	Poor	4.5	Fair	a

a – parameter assigned by HyperChem automatically

III. Conclusions.

.

All the results are included in the *PZFE.xls* file. The structures can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Fe*** section of the page.

The new parameters reproduced the bond distances with an RMS of 0.039 versus 0.103 for calculations with MM+ parameters. The comparison of the results is shown in ***Figure 26***.

In general it was not necessary to improve the bending parameters (coordination number CN=6) for coordination centers. In one case (Pzfe6) it was not possible to define the bending parameter due to the *unique labeling problem* (*ULP*) **[49]**. In this case HyperChem was unable to reproduce the geometrical arrangement correctly. The results of the calculations and the final parameters for angles are presented in ***Table 26***. ***Figure 27*** shows the comparison charts.

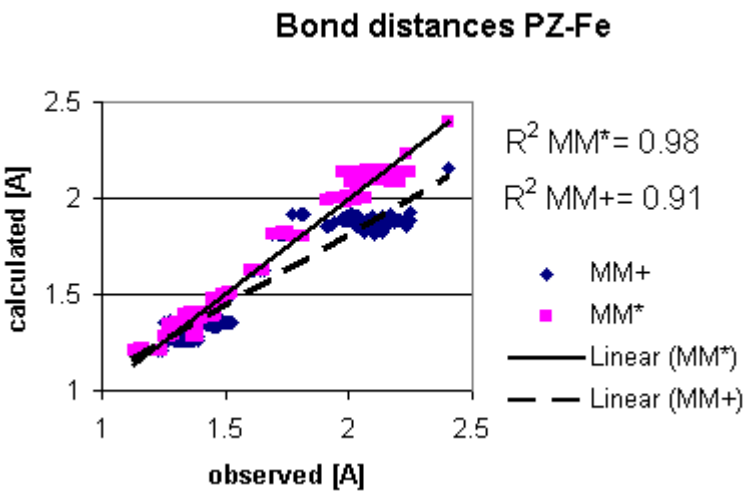


Figure 26. Comparison of the bond distances after MM+ and MM* calculations.

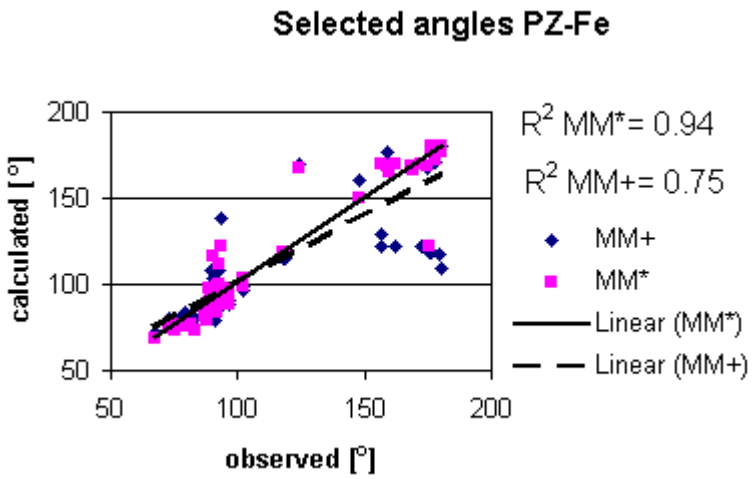


Figure 27. Comparison of the angles after MM+ and MM* calculations.

Comparing the arrangements around the iron atom three different cases of results were obtained.

Case I. Arrangement around Fe^{2+} is the same for crystallographic, MM+ and MM* calculations (example shown in ***Figure 28***). The bond lengths for MM* are in better agreement than those obtained after MM+ calculation. Such a situation occurred for 9 structures.

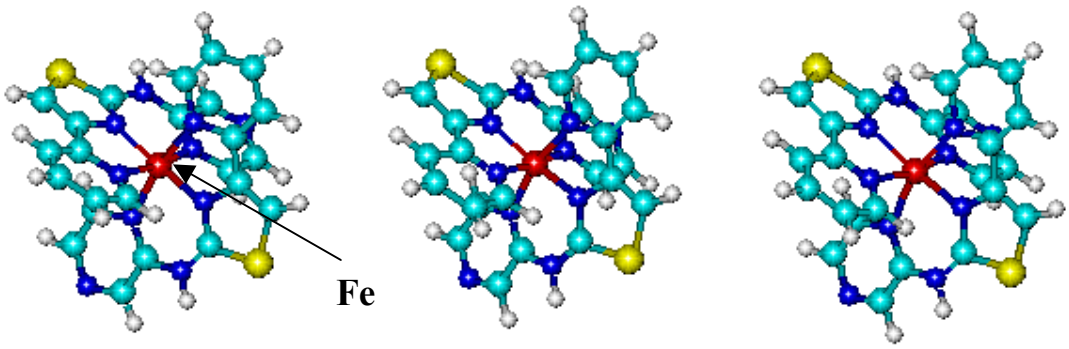


Figure 28. PZFE7 as an example of correct geometry reproduced after MM+ and MM* calculations.

From left to right: crystallographic, MM+ and MM models*

Case II. Arrangement around Fe^{2+} is better reproduced by MM* calculation.

In one case (PZFE10 – ***Figure 29***) it was possible to define the parameters forming the Cl-Fe6-Cl angle. Such defined parameter corrected the arrangement of the atoms around iron.

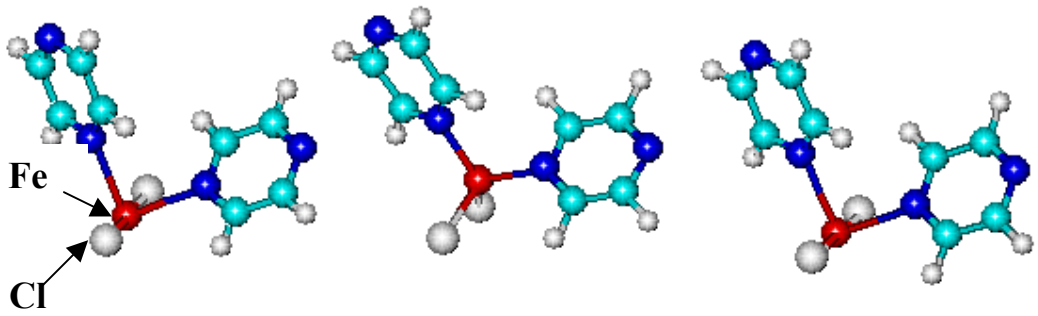


Figure 29. Coordination sphere around iron in the case of PZFE10.

Form left to right: crystallographic, MM+ and MM models*

Case III. Arrangement around Fe^{2+} cannot be reproduced correctly due to the Unique Label Problem.

In one case (PZFE6 – ***Figure 30***) we were not able to correct the geometry around the iron due to the Unique Label Problem. It was possible to correct the Fe-C=O angle by defining the proper angle parameters listed in ***Table 26***.

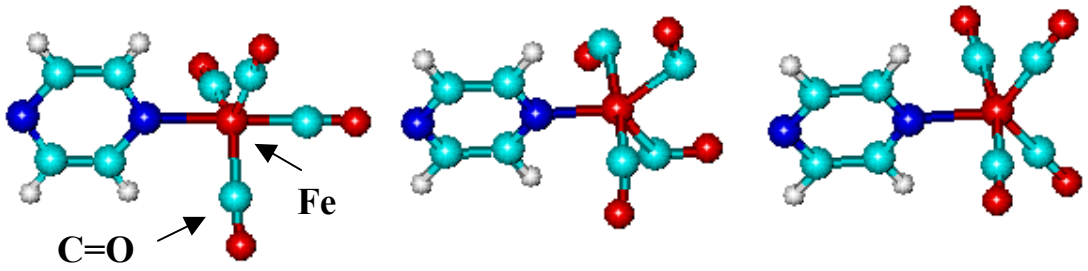


Figure 30. A case of PZFE6.

From left to right: crystallographic, MM+ and MM models*

7.4. Calculations on Pyrazine-Co subset of structures

I. Used structures

Twenty four structures were used for calculations and are listed in ***Table 27***.

Table 27. Crystal structures of complexes of cobalt used for calculations.

1	2	3	4	5	6
Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzco1	DIMMOB10[21]	trans-Chloro-bis (dimethylglyoximato-N,N') -(2,6-dimethylpyrazine-N^4)-cobalt(III)	Co(III) CN=6	OC-6
2	Pzco2	DIMMUH10[22]	trans-Bromo-bis (dimethylglyoximato-N,N') -(2,6-dimethylpyrazine-N^4) -cobalt(III)	Co(III) CN=6	OC-6
3	Pzco3	FATPIZ[23]	Chloro-(2,6-dimethylpyrazine-N^4)-bis(glyoximato-N,N')-cobalt(III) dichloromethane solvate	Co(III) CN=6	OC-6
4	Pzco4	GIPMIB[24]	Diaqua-bis(2-ethylthio-4-hydroxypteridinate-N,O)-cobalt(II) dimethylformamide solvate	Co(II) CN=6	OC-6
5	Pzco5	HAFYOC[25]	bis(3,5-Di-t-butyl-1,2-semiquinonato)- (2,2' -bipyrazine)-cobalt(II)	Co(II) CN=6	OC-6
7	Pzco7	JUHVIR[26]	(2,3-bis(2-Pyridyl) benzoquinoxalinato)-bis (hexafluoroacetylacetonato) -cobalt(II)	Co(II) CN=6	OC-6
8	Pzco8	JUHVOX[27]	(6,7-Dimethyl-2,3-bis(2-pyridyl)quinoxalinato)-bis (hexafluoroacetylacetonato)-cobalt(II)	Co(II) CN=6	OC-6

Table cont.

1	2	3	4	5	6
9	Pzco9	NIKFES[28]	bis((2-Dimethylamino-4(3H)-pteridonato)-methanol)-cobalt(II) methanol solvate	Co(II) CN=6	OC-6
10	Pzco10	NOWTEY[29]	bis((μ_2-2,3-bis(2,2'-Bipyrid-6-yl)pyrazine)-acetonitrile-cobalt(II)) tetraperchlorate trihydrate	Co(II) CN=6	OC-6
11	Pzco11	PRZCOA[30]	Diaqua-bis(3-carboxy-pyrazine-2-carboxylato-N,O)-cobalt(II)	Co(II) CN=6	OC-6
12	Pzco12	PRZCOB[31]	Diaqua-bis(pyrazine-2-carboxylato)-cobalt(II) dihydrate	Co(II) CN=6	OC-6
13	Pzco13	PRZCOB[32]	Diaqua-bis(pyrazine-2-carboxylato-N,O)-cobalt(II) dihydrate	Co(II) CN=6	OC-6
14	Pzco14	PRZCOC[33]	Diaqua-bis(pyrazine-2-carboxylato)-cobalt(II)	Co(II) CN=6	OC-6
15	Pzco 15	PRZCOC01[34]	Diaqua-bis(pyrazine-2-carboxylato-N,O)-cobalt(II)	Co(II) CN=6	OC-6
16	Pzco16	PRZCOC02[35]	Diaqua-bis(2-pyrazinecarboxylato)-cobalt(II)	Co(II) CN=6	OC-6
17	Pzco17	PYDXCO[36]	catena-(Diaqua-(μ_2-2,3-pyrazinedicarboxylato) -cobalt(II))	Co(II) CN=6	OC-6
18	Pzag4	TAMKOH[37]	1,1,1,1,1,2,2,2,2,2-Deca-ammine-3,3-diaqua-1,3;2,3 - bis(μ_2-pyrazinato-N,N')-di-cobalt(III)-silver(I) heptanitrate tetrahydrate	Co(III) CN=6	OC-6
19	Pzcu45	TAMKUN[38]	1,1,1,1,1-Penta-ammine-2-(diethylenetriamine-N,N',N'')-1,2-(μ_2-pyrazinato-N,N')-cobalt(III)-copper(II)	Co(III) CN=6	OC-6
20	Pzco20	YEKSEM[39]	(μ_2-Pyrazine)-bis(penta-aqua-cobalt) disulfate dihydrate	Co(II) CN=6	OC-6

Table cont.					
1	2	3	4	5	6
21	Pzco21	ZECKIB[40]	bis(Acetylpyrazine-3-azabicyclo(3.2.2)nonylthio semicarbazone)-cobalt(III) tetrafluoroborate	Co(III) CN=6	OC-6
22	co-7	-[41]	bis(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-carboxylato-cobalt(III)	Co(III) CN=6	OC-6
23	co-8	-[42]	(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-carboxylato-triaqua-cobalt(III)	Co(III) CN=6	OC-6
24	co-9	-[43]	(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-carboxylato-bis(iaqua-chloro-cobalt(III))	Co(III) CN=6	OC-6

We have added the following entry for Cobalt atom types in *chem.rul* file:
For cobalt:

```
Co:
; connected to pyrazine
connected to N@1~C~C~N~C~C~N@1?
   =CO5.; numerical type 81
;connected to pyridine
 connected to N@1~C~C~C~C~C~N@1?
   =CO4.; numerical type 80
; Cobalt (II)
   =CO2.; numerical type 65
; Cobalt (III)
   =CO3.; numerical type 66
```

For nitrogen:

```
N:
connected to (-Co)(=C-C~N-Co)?
   =N4.
```

For oxygen:

```
O:
connected to (-Co)(-C-C~N-Co)?
   =O3.
connected to (-Co)(-N~C~N-Co)?
   =O3.
connected to (-Co)(-C~C~N-Co)?
   =O3.
connected to (-Co)(-C-C-N-Co)?
connected to -N-Co?
   =O2.; numerical type 6
```

II. Results of calculations.

The RMS gradient calculated over all bonds and final stretching parameters are presented in ***Table 28.***

Table 28. Final parameters for Cobalt complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
CO5	NA1	0.226	Poor	0.070	Fair	2.090	5.000
CO5	NA	0.247	Poor	0.039	Fair	2.110	5.000
CO5	O3	0.272	Poor	0.026	Fair	2.072	5.000
CO	O3	0.085	Poor	0.018	Good	1.255	5.500
CO5	O2	0.251	Poor	0.036	Fair	2.080	5.000
CO5	CL	0.144	Poor	0.085	Poor	2.280	5.000
CR	O3	0.134	Poor	0.020	Good	1.238	5.000
CO5	NC	0.025	Fair	0.009	Good	1.872	5.000
CO5	N1	0.296	Poor	0.003	Good	2.127	5.000
CO5	BR	0.002	Good	0.001	Good	2.328	11.090
CO5	S2	0.057	Fair	0.004	Good	2.210	8.000
CO5	N4	0.027	Fair	0.006	Good	1.815	5.000
CR	CR	0.022	Fair	0.005	Good	1.485	4.400
CR	CR	0.093	Poor	0.004	Good	1.559	4.400
NA1	O3	0.084	Poor	0.003	Good	1.250	5.000
CO5	O1	0.274	Poor	0.012	Good	2.080	5.000
C4	P1	0.550	Poor	0.100	Poor	1.290	8.000

III. Conclusions.

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All the results are included in the *PZCO.xls* file. The structures can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Co*** section of the page.

With the new parameters the bond distances were reproduced with an RMS of 0.043 versus 0.143 for calculations with MM+ parameters. The comparison of the results is shown in ***Figure 31.***

It was not necessary to define new parameters for Cobalt complexes since for all cases an OC-6 coordination geometry was observed. We used the values of missing bending parameters calculated by HyperChem. The RMS gradients calculated over

selected angles are 4.43 for MM* (fair results) and 5.68 for MM+ (poor results). ***Figure 32*** illustrates the comparison of angles obtained during the calculations.

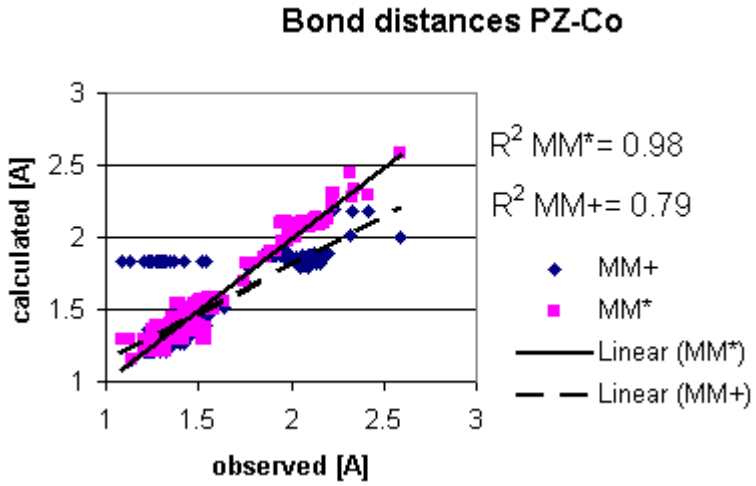

Figure 31. Comparison of the bond distances after MM+ and MM* calculations

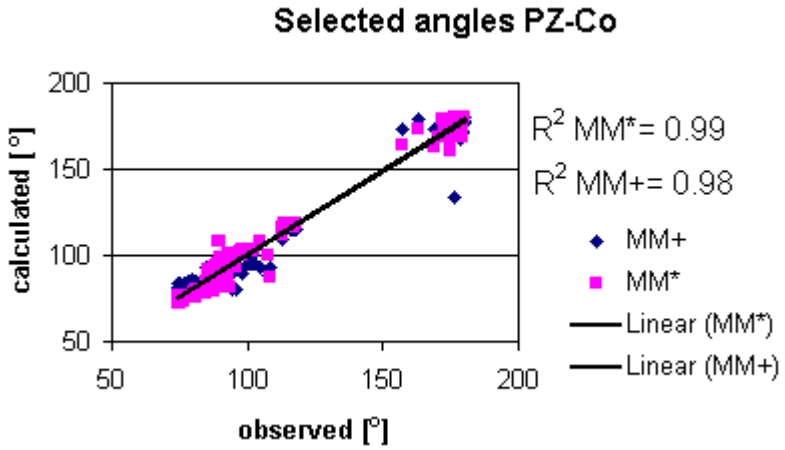

Figure 32. Comparison of the angles after MM+ and MM* calculations

7.5. Calculation on Pyrazine-Ni subset

I. Used structures.

Eleven structures were used for calculations and are listed in ***Table 29***.

Table 29. Crystal structures of complexes of Nickel used for calculations.

1	2	3	4	5	6
Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzni1	BRMPYN[44]	catena (Dibromo-2,5-dimethylpyrazine nickel(II))	Ni(II) CN=4	SP-4
2	Pzni2	HEDJIJ[45]	bis (Acetylpyrazine N-μ_2 dimethylthiosemicarbazonato)-nickel(II) dichloromethane solvate	Ni(II) CN=6	OC-6
3	Pzni3	NEVGOK[46]	(μ_2-2,5-bis (2-Pyridyl) pyrazinato) -bis(tetra-aqua-nickel(II)) disulfonate dihydrate	Ni(II) CN=6	OC-6
4	Pzni4	NEVGUO[47]	Catena- (bis (μ_2-Chloro) -(μ_2-2,5-bis(2-pyridyl) pyrazinato)-diaqua – dimethanol -di -nickel(II) dichloride)	Ni(II) CN=6	OC-6
5	Pzni5	RERPOT[48]	(μ_2-2,3,5,6-tetrakis (2-Pyridyl) pyrazinato)-bis (triaqua-nickel(II)) tetranitrate hydrate	Ni(II) CN=6	OC-6
6	Pzni6	TEBYOO[49]	Diaqua-bis (pyrazine-3-carboxy-2-carboxylato) – nickel(II)	Ni(II) CN=6	OC-6
7	Pzni7	TEBZEF[50]	catena-(μ_2-Pyrazine -2,3-dicarboxylato) -diaqua-nickel(II) dihydrate)	Ni(II) CN=6	OC-6
8	Pzni8	TEWMUD[51]	Diaqua-bis (2-pyrazinecarboxylato) -nickel(II)	Ni(II) CN=6	OC-6
9	Pzni9	TEXGIM[52]	catena-((μ_2-1,4-Pyrazine)-bis(isopropylxanthato)-nickel(II))	Ni(II) CN=6	OC-6
10	Pzni10	WEJLUS[53]	(2-Pyrazinylacetyl N^4-methyl-thiosemicarbazone-S,N,N') -chloro-nickel(II)	Ni(II) CN=4	SP-4

Table cont.					
1	2	3	4	5	6
11	Pzni11	WEJMAZ[54]	(2-Pyrazinylacetyl N^4,N^4-dimethyl-thiosemicarbazone-S,N,N') -chloro -nickel(II)	Ni(II) CN=4	SP-4

We have defined new atom types: NI5 (coordination number CN=6), NI6 (coordination number CN=4) and NI4 (for connection with pyridine) according to the following entrance in *chem.rul* file

```
Ni:
; connected to pyrazine CN=6
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)(-*)(-*)?
     =NI5. ; numerical type 83
; connected to pyrazine CN=4
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)?
     =NI6. ; numerical type 83
;connected to pyridine
     connected to N@1~C~C~C~C~C~N@1?
     =NI4. ; numerical type 82

Cl:
; Chlorine
; Chloride-bridges
     connected to (-Ni)(-Ni) ?
     =CL2. ; numerical type 102
```

II. Results of calculations.

Six runs of refinement of the parameters were necessary to achieve the lowest RMS gradients. After the sixth run of the program the RMS values obtained, calculated over bonds and some angles, and final parameters are presented in ***Table 30*** and ***31.***

III. Conclusions.

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All the results are included in the *PZNI.xls* file. The structures can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Ni*** section of the page.

Table 30. Final parameters for Nickel complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
NI5	CL2	0.040	Fair	0.013	Good	2.450	5.000
NI5	N2	0.135	Poor	0.005	Good	2.015	10.000
NI5	NA	0.225	Poor	0.027	Fair	2.065	11.090
NI5	NA1	0.217	Poor	0.040	Fair	2.003	11.090
NI5	O2	0.250	Poor	0.036	Fair	2.065	5.000
NI5	OC	0.243	Poor	0.017	Good	2.031	5.000
NI5	S2	0.117	Poor	0.009	Good	2.241	7.000
NI6	BR	0.010	Fair	0.000	Good	2.309	5.000
NI6	CL	0.026	Fair	0.003	Good	2.171	5.000
NI6	N2	0.010	Fair	0.021	Fair	1.830	5.000
NI6	NA1	0.052	Fair	0.041	Fair	1.895	5.000
NI6	S2	0.082	Poor	0.014	Good	2.150	5.000

Table 31. Final parameters for Nickel complexes – bending parameters.

At1	At2	At3	MM+ RMS	Agreement MM+	MM* RMS	Agreement MM*	Parameters: K_Θ Θ_o
BR	NI6	BR	43.34	Poor	0.00	Good	1.500 180.00
N2	NI6	CL	51.36	Poor	1.52	Good	1.500 180.00
NA1	NI6	NA1	30.61	Poor	0.02	Good	1.500 180.00
NA1	NI6	S2	30.76	Poor	3.99	Fair	1.500 180.00

The new parameters reproduced the bond distances with an RMS of 0.035 versus 0.104 for calculations with MM+ parameters. The comparison of the results is shown in ***Figure 34***.

Adding four bending parameters improved the reproduction of the angles. The SP-4 conformations of three starting structures (pzni1, pzni10 and pzni11) remained preserved during MM* calculations as it is shown in ***Figure 33***.

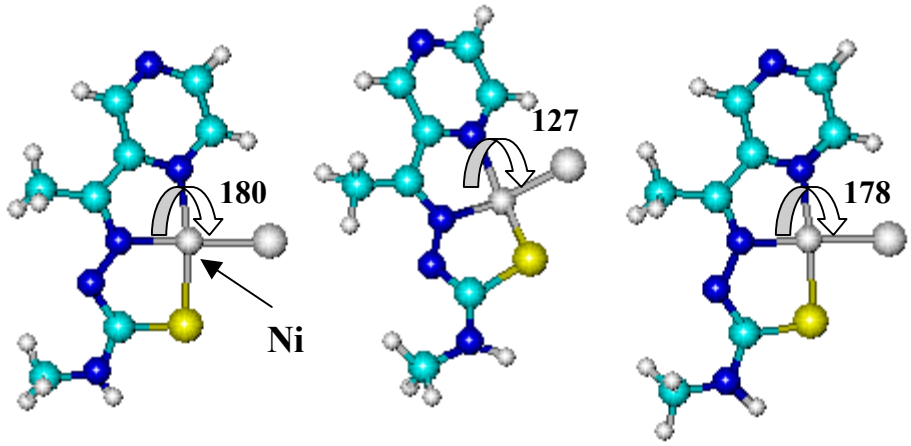


Figure 33. Comparison of the structures of pzni10.

From left to right: crystallographic, MM+ and MM structures*

The RMS calculated over selected angles was 4.87 for MM* (fair agreement) and 20.09 for MM+ calculations (poor agreement). The comparison chart is presented in ***Figure 35.***

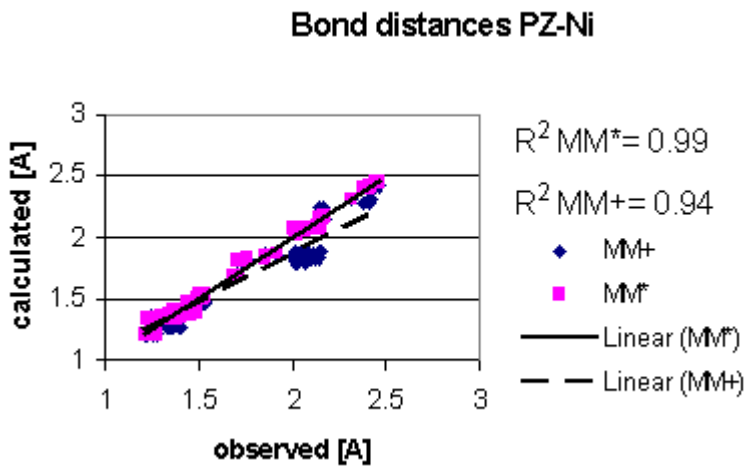


Figure 34. Comparison of the bond distances after MM+ and MM* calculations.

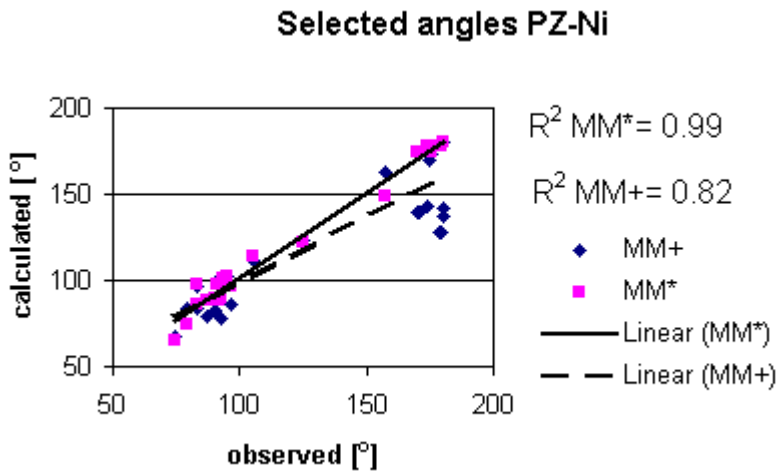
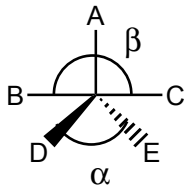


Figure 35. Comparison of the angles after MM+ and MM* calculations.

7.6. Calculations on Pyrazine-Cu subset of structures

I. Used structures.

Forty eight structures were used for calculations and are listed in ***Table 32***. The subset of structures is very rich in different coordination numbers and geometrical arrangements. For the pentacoordinated complexes the trigonality index (τ) was calculated according to Addison et al. [55] (***Figure 36***)



$$\tau = \frac{(\beta - \alpha)}{60}$$

Figure 36. Definition of the index of trigonality.

For a perfect square-pyramidal geometry (SPY-5) τ=0. For a perfect trigonal bipiramid geometry (TBYP-5) τ=1.

Table 32. Crystal structures of complexes of copper used for calculations.

1	2	3	4	5	6
Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzcu1	BAGSOR[56]	Bis(μ_2-chloro)-bis(chloro-(pyrazine-2-carboxylato)-copper(II)	Cu(II) CN=5	SPY-5 τ=0.12
2	Pzcu2	BEHBIZ[57]	2,3-pyrazinecarboxylato-copper(II) hydrochloride	Cu(II) CN=5	SPY-5 τ=0.37
3	Pzcu3	BEYPUQ[58]	bis(pyrazine-2-carboxylato-N^1,O)-copper(II)	Cu(II) CN=4	SP-4
4	Pzcu4	BEYRAY[59]	Diaqua-bis(pyrazine-2-carboxylato-N^1,O)-copper(II)	Cu(II) CN=6	OC-6
5	Pzcu5	BEYRAY01[60]	Diaqua-bis(2-pyrazinecarboxylato)-copper(II)	Cu(II) CN=6	OC-6
6	Pzcu6	BUNWEM[61]	Dihydroxy-bis(2,3-pyrazinecarboxamide- N^1, N^9)-copper(II) dihydrate	Cu(II) CN=6	OC-6

Table cont.

1	2	3	4	5	6
7	Pzcu7	BUNWIQ[62]	bis((μ_2-chloro)-chloro-(2,3-pyrazinecarboxamide- N^2, O^8)-copper (II))	Cu(II) CN=5	SPY-5 τ=0.02
8	Pzcu9	FEWKIB[63]	(μ_2-pyrazine)-bis(Diaqua-(iminodiacetato-N,O,O')-copper(II))dihydrate	Cu(II) CN=6	OC-6
9	Pzcu10	HEDRIR[64]	bis((μ_2-chloro)-chloro(2-(2'-pyridil)quinoxalinato-N,N')-copper(II)	Cu(II) CN=5	SPY-5 τ=0.43
10	Pzcu11	HEDRIR10[65]	bis(μ_2-chloro)-dichloro-bis(2-(2'-pyridyl)-quinoxaline)-di-copper(II)	Cu(II) CN=5	SPY-5 τ=0.43
11	Pzcu12	HEVDUH[66]	(2,3-bis(2-pyridil)pyrazine)-bis(triphenylphosphine)-copper(I) nitrate ethanol solvate	Cu(I) CN=4	T-4
12	Pzcu13	JETHOF[67]	(μ_2-2,5-bis(Dimethylamino)methyl) pyrazine)-bis((diethylenetriamine)-copper(II))tetraperchlorate	Cu(II) CN=5	TBYP-5 τ=0.64
13	Pzcu14	JEVHAT[68]	(2,5-bis(N,N-bis(2'-Pyridylethyl)aminomethyl)pyrazine)-di-copper(I) diperchlorate	Cu(I) CN=4	T-4
14	Pzcu15	JIMKUL[69]	bis(2-(Ethylthio)-4-oxopteridine-N,O)-(1,10-phenanthroline)-copper dimethylformamide solvate	Cu() CN=6	OC-6
15	Pzcu17	JUVKIU[70]	triaqua-bis(quinoxalinato)-copper(II) diperchlorate	Cu(II) CN=5	SPY-5 τ=0.27
16	Pzcu18	JUXVUT[71]	(μ_2-phenazine) bis (methanol-phenazine-copper (I))bis(hexafluorophosphate) phenazine solvate	Cu(I) CN=3	TP-3
17	Pzcu19	JUXWAA[72]	Aqua-diphenazine-copper(I) perchlorate	Cu(I) CN=3	TP-3
18	Pzcu20	JUXWEE[73]	Diphenazine- (nitrato-O-O')-copper(I)	Cu(I) CN=4	T-4
19	Pzcu21	KIFYON[74]	(μ_2-Piperazine-N,N')-bis((diethyltriamine-N,N',N'')-(diperchlorato-O)-copper(II)	Cu(II) CN=6	OC-6

Table cont.

1	2	3	4	5	6
20	Pzcu23	LETWAI[75]	catena-(bis(μ_4-4,4'-Bipyridyl)-copper hexafluorosilicate)	Cu() CN=3	TP-3
21	Pzcu24	NIDRUN[76]	Diaqua-bis(5-methoxycarbonyl-3,6-dimethylpyrazine-2-carboxylato)-copper(II)	Cu(II) CN=6	OC-6
22	Pzcu25	NIKFIW[77]	bis((2-Dimethylamino-4(3H)-pteridonato)-methanol-copper(II)	Cu(II) CN=6	OC-6
23	Pzcu26	PEJJIX[78]	tetrakis(2-Methylpyrazine)-bis(perchlorato-O)-copper(II)	Cu(II) CN=6	OC-6
24	Pzcu27a	PITXIZ[79]	Dichloro-(μ_2-tetrakis(aminomethyl)pyrazine)-di-copper dichloride hydrate	Cu(II) CN=4	SP-4
25	Pzcu28	PIVNEN[80]	(μ_2-pyrazine)-bis((2,6-xyxylaminodiacetato)-aqua-copper(II))	Cu(II) CN=5	SPY-5 τ=0.10
26	Pzcu29	PYCXCV[81]	Diperchlorato-bis(pyrazine-2,3-dicarboxamide)-copper(II)	Cu(II) CN=6	OC-6
27	Pzcu30	PICXCV01[82]	bis(Perchlorato)-bis(pyrazine-2,3-dicarboxamide)-copper(II)	Cu(II) CN=6	OC-6
28	Pzcu31	PYEZCU[83]	trichloro-μ-(N,N'-bis(2-(2-pyridyl)ethyl)-2,3-pyrazinedicarboxamidato)-dicopper(II)	Cu(II) CN=5 CN=4	SPY-5 τ=0.47 T-4
29	Pzcu32	PYZCCU[84]	bis(pyrazine-2-carboxamide) copper(II) perchlorate	Cu(II) CN=4	SP-4
30	Pzcu33	PZFACU[85]	μ-pyrazine-bis(di(hexafluoroacetylacetonato)copper(II))	Cu(II) CN=5	SPY-5 τ=0.07
31	Pzcu34	PZFACU01[86]	(μ_2-pyrazine)-bis(bis(hexafluoroacetylacetonato)-copper(II))	Cu(II) CN=5	SPY-5 τ=0.07
32	Pzcu35	RABXIX[87]	(μ_2-2,3-bis(2-Pyridyl)quinoxaline)-bis((bis(triphenylphosphine)-copper(I))diperchlorate	Cu(I) CN=4	T-4

Table cont.					
1	2	3	4	5	6
33	Pzcu36	RATNAB[88]	bis(tetrakis(2-pyridyl)pyrazine)-copper(II) diperchlorate acetonitrile solvate	Cu(II) CN=6	OC-6
34	Pzcu37	REBGUA[89]	Pyrazinyl-hydrogen-tris(3,5-dipheniylpyrazolyl)borate-copper(I)	Cu(I) CN=4	TPY-4
35	Pzcu38	RERPIN[90]	(μ_2-2,3,5,6-tetrakis(2-Pyridyl)pyrazinato)-bis(dichloro-copper(II)) pentahydrate	Cu(II) CN=5	SPY-5 τ=0.09
36	Pzcu39	RIGPUS[91]	Diaqua-bis(1,3-dimethylpteridine-2,4(1H,3H)-dionato)-copper(II) dinitrate dihydrate	Cu(II) CN=6	OC-6
37	Pzcu40	RIVYEA[92]	(pyrazine-N)-(N-salicylidene-alpha-amino-2-methylpropanoato-O,N,O')-copper(II)	Cu(II) CN=4	SP-4
38	Pzcu41	RUVMEA[93]	Dichloro-tetrakis((2-pyridyl)pyrazine)-copper(II)	Cu(II) CN=5	SPY-5 τ=0.12
39	Pzcu42a	SENDEU[94]	Bromo-bis(2,3-di(2-pyridyl)quinoxaline)-copper(II) 2,3-di(2-pyridyl) quinoxaline hydrogen sulfate	Cu(II) CN=5	SPY-5 τ=0.3
40	Pzcu44	SULTAU[95]	(μ_2-2,5-bis(2'-Pyridyl(pyrazine-N,N',N'',N''')-bis(diaqua-(nitrato-O)-copper(II)) dinitrate	Cu(II) CN=5	SPY-5 τ=0.07
41	Pzcu45	TAMKUN[96]	1,1,1,1,1-Penta-amine-2-(diethylenetriamine-N,N',N'')-1,2-(μ^2-pyrazinato-N,N')-cobalt(III)-copper(II) pentaperchlorate	Cu(II) CN=4	SP-4
42	Pzcu46	TELHUX[97]	(μ_2-N,N'-bis(2-Aminoethyl)oxamido)-bis(aqua-(quinoxaline)-copper(II)) diperchlorate	Cu(II) CN=5	SPY-5 τ=0.01

Table cont.					
1	2	3	4	5	6
43	Pzcu48	WAGPEZ[98]	bis(Diaqua-(μ_2-2,3,5,6-tetrakis (2-pyridyl)pyrazine-N,N',N'',N''',N'''',N''''')-copper(II)) tetraperchloratedihydrate	Cu(II) CN=5	SPY-5 τ=0.27
44	pzcu50	WEGZOX[99]	trans-diaqua-bis(3-methylpyrazine)-(bisperchlorato-O)-copper(II)	Cu(II) CN=6	OC-6
45	pzcu51	WEGZUD[100]	aqua-tetrakis(3-methylpyrazine)-(perchlorato-O)-copper(II)	Cu(II) CN=6	OC-6
46	pzcu_mo11	-[101]	(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-trichloro-aqua-bis(bis (cloro)-copper(II))	Cu(II) CN=5	SPY-5 τ=0.24
47	pzcu_mo12	-[102]	(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')-carboxylato-aqua-copper(II)	Cu(II) CN=5	SPY-5 τ=0.07
48	pzcu_mo24	-[103]	chloro-(μ_2-2,5-bis(2'-Pyridyl) pyrazine-N,N',N'',N''')- copper(II)	Cu(II) CN=4	SP-4

The following rules are used for the determination of the atom types:

```
Cu:
; connected to pyrazine CN=6, 5, 4, 3
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)(-*)(-*)?
     =CU2. ; numerical type 85
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)(-*)?
     =CU5. ; numerical type 110
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)?
     =CU4. ; numerical type 109
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)?
     =CU3. ; numerical type 108
;connected to pyridine
     connected to N@1~C~C~C~C~C~N@1?
     =CU1. ; numerical type 84

N:
     connected to (-Cu)(-C-C~N-Cu)?
     =N4.
O:
     connected to (-Cu)(-H)(-C-C~N-Cu)?
```

```
      =OC.  ; numerical type 47
      connected to (-C-H)(-Cu)-H ?
      =O3. ; numerical type 6 pzcu39
      connected to  @1-Cu-N-C-C-O@1 ?
      =O5.  ; numerical type 106 pzcu28
      connected to (-Cu-O-Cl=O)(-H)(-H) ?
      =O6. ; numerical type 6 pzcu51 and pzcu51
      connected to (-Cu)(=C-O-H)?
      =OC.  ; numerical type 47
      connected to (-Cu)(=C-N-H)?
      =OC.  ; numerical type 47
; perchloride
      connected to (-Cu)(-Cl=O)?
      =O7.
; 5 or 6 ring in complex

      connected to (-Cu)(=C-C=C-O-Cu)?
      =O4. ; Next has to be changed too
      connected to (-Cu)(-C=C-C=O-Cu)?
      =O4. ;The one up has to be changed to
      connected to (-Cu)(~C~C~C~O-Cu)?
      =O4. ; Next has to be changed too
      connected to (-Cu-O-Cl=O)(-H)-H ?
      =O2.  ; numerical type 6 pzcu50
      connected to (-H)(-Cu-O=C)-H ?
      =O2. ; numerical type 6 pzcu39
      connected to (-Cu)(-H)-H ?
      =O3.
Cl:
; Chlorine
; Chloride-bridges
      connected to (-Cu-O-*)(-Cu) ?
      =CL.
      connected to (-Cu)(-Cu) ?
      =CL2. ; numerical type 102
```

II. Results of calculations.

Fourteen cycles of refinement of the parameters were necessary to achieve the lowest RMS values. The RMS values calculated over bonds and selected angles and their final parameters are presented in ***Table 33*** and ***34.***

III. Conclusions.

.

All the results are included in the *PZCU.xls* file. The structures can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Cu*** section of the page.

Table 33. Final parameters for copper complexes – Stretching parameters.

1	2	3	4	5	6	7	8
At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
B4	N2	0.052	Fair	0.014	Good	1.550	5.000
C4	NH	0.047	Fair	0.047	Fair	1.500	5.100
C4	O3	0.053	Fair	0.007	Good	1.371	5.000
CA	C3	0.094	Poor	0.040	Fair	1.480	9.600
CA	N2	0.009	Good	0.021	Fair	1.329	10.000
CA	O2	0.056	Fair	0.087	Poor	1.390	6.000
CL	O1	0.365	Poor	0.029	Fair	1.185	10.000
CL	O7	0.555	Poor	0.018	Good	1.196	10.000
CU2	CL	0.431	Poor	0.307	Poor	2.500	5.000
CU2	CL2	0.682	Poor	0.003	Good	2.870	5.000
CU2	N3	0.077	Fair	0.008	Good	1.977	5.000
CU2	NA	0.232	Poor	0.073	Fair	2.100	5.000
CU2	NA1	0.126	Poor	0.035	Fair	2.005	5.000
CU2	NH	0.118	Poor	0.039	Fair	1.980	5.000
CU2	O1	0.376	Poor	0.298	Poor	1.900	5.000
CU2	O2	0.341	Poor	0.204	Poor	2.000	5.000
CU2	O3	0.579	Poor	0.081	Poor	2.425	5.000
CU2	O5	0.157	Poor	0.012	Good	1.970	5.000
CU2	O6	0.271	Poor	0.185	Poor	1.970	5.000
CU2	O7	0.669	Poor	0.084	Poor	2.530	5.000
CU2	OC	0.114	Poor	0.055	Fair	1.937	5.000
CU3	NA1	0.076	Fair	0.047	Fair	1.970	5.000
CU3	O2	0.247	Poor	0.002	Good	2.096	10.000
CU3	O3	0.350	Poor	0.002	Good	2.238	10.000
CU4	CL	0.065	Fair	0.018	Good	2.226	10.000
CU4	N2	0.190	Poor	0.040	Fair	2.030	5.000
CU4	N3	0.099	Poor	0.004	Good	2.000	10.000
CU4	N4	0.308	Poor	0.001	Good	2.200	5.000
CU4	NA	0.208	Poor	0.046	Fair	2.035	5.000
CU4	NA1	0.176	Poor	0.065	Fair	2.005	5.000
CU4	NH	0.109	Poor	0.019	Good	2.010	10.000
CU4	O1	0.570	Poor	0.080	Fair	2.385	5.000
CU4	O2	0.104	Poor	0.015	Good	1.870	5.000
CU4	O5	0.139	Poor	0.007	Good	1.920	5.000
CU4	OC	0.143	Poor	0.043	Fair	1.980	5.000
CU4	P	0.044	Fair	0.012	Good	2.275	5.000
CU5	BR	0.118	Poor	0.002	Good	2.446	5.000
CU5	CL	0.205	Poor	0.162	Poor	2.270	5.000
CU5	CL2	0.232	Poor	0.233	Poor	2.470	3.000
CU5	N2	0.071	Fair	0.114	Poor	1.800	5.000
CU5	N3	0.131	Poor	0.020	Good	2.017	5.000

Table cont.							
1	2	3	4	5	6	7	8
CU5	N4	0.345	Poor	0.000	Good	2.242	10.000
CU5	NA	0.160	Poor	0.041	Fair	2.010	5.000
CU5	NA1	0.191	Poor	0.086	Poor	2.020	5.000
CU5	NH	0.188	Poor	0.038	Fair	2.075	5.000
CU5	O2	0.231	Poor	0.051	Fair	2.040	5.000
CU5	O3	0.318	Poor	0.148	Poor	2.100	5.000
CU5	O4	0.148	Poor	0.011	Good	1.947	10.000
CU5	O5	0.107	Poor	0.008	Good	1.910	5.000
CU5	OC	0.208	Poor	0.070	Fair	2.000	5.000
O2	NO	0.076	Fair	0.040	Fair	1.200	5.000
O5	CO	0.078	Fair	0.018	Good	1.272	5.000

Table 34. Final parameters for copper complexes – bending parameters.

1	2	3	4	5	6	7	8
At1	At2	At3	MM+ RMS	Agreement MM+	MM* RMS	Agreement MM*	K_Θ Θ_o
CL	CU5	CL	38.76	Poor	32.180	Poor	0.500 104.00
CU5	CL2	CU5	34.77	Poor	3.54	Fair	0.500 90.00
CL2	CU5	CL2	35.70	Poor	3.12	Fair	1.500 90.00
NA	CU5	CL2	13.74	Poor	9.11	Poor	a
NA1	CU5	CL2	20.21	Poor	9.11	Poor	a
NA	CU5	CL	4.91	Fair	6.44	Poor	a
CL	CU5	CL2	16.72	Poor	12.00	Poor	a
NA	CU5	NA1	2.85	Fair	5.98	Poor	a
CU5	CL2	CL	16.72	Poor	9.370	Poor	a
CU5	CL2	NA	18.13	Poor	10.89	Poor	0.500 100.00
CU5	CL2	NA1	27.46	Poor	1.15	Good	a
CU5	CL	NA1	5.24	Poor	2.06	Fair	a
NA	CU4	P	6.23	Poor	2.47	Fair	a
NA1	CU4	P	5.81	Poor	5.34	Poor	a
NA1	CU5	N3	10.37	Poor	5.08	Poor	0.500 90.00
NA1	CU5	N4	7.30	Poor	2.73	Fair	0.500 90.00
NA1	CU5	NH	7.86	Poor	5.590	Poor	a
CA1	C4	N4	2.21	Fair	0.74	Good	a
NA1	CU5	NA1	22.62	Poor	11.22	Poor	1.500 170.00

Table cont.

1	2	3	4	5	6	7	8
O3	CU5	O3	25.86	Poor	10.09	Poor	0.500 90.00
*NA1	CU3	O2	19.83	Poor	4.97	Fair	0.500 100.00
*NA1	CU3	O3	21.660	Poor	4.370	Fair	0.500 100.00
NA1	CU4	NA1	37.940	Poor	7.590	Poor	0.500 180.00
N3	CU2	NA1	1.410	Good	3.120	Fair	a
O7	CU2	O7	3.880	Fair	1.310	Good	0.500 180.00
CU2	O7	CL	26.110	Poor	12.980	Poor	0.500 140.00
CU2	O1	CO	7.380	Poor	66.390	Poor	0.500 109.00
OC	CU4	OC	50.000	Poor	0.000	Good	0.500 180.00
NA1	CU4	OC	10.950	Poor	3.640	Fair	0.500 90.00
NA1	CU4	CL	33.100	Poor	23.610	Poor	0.500 150.00
NA1	CU4	N2	29.350	Poor	21.580	Poor	0.500 180.00
N2	CU4	O2	8.060	Poor	0.190	Good	a
O3	CU5	O2	24.590	Poor	23.870	Poor	0.500 90.00
NA1	CU4	N3	42.980	Poor	3.490	Fair	0.500 180.00

*a – parameters assigned by HyperChem * - parameter removed – see text*

The bonds:

With the new parameters we have obtained better reproduction of bond distances. RMS bond distances gradient is 0.056 (versus 0.138 for calculations with old parameters). The comparison of results is shown in ***Figure 38***. We found that the *unique labeling problem* can also be very important for modeling the bonds. In the case of PZCU7 (***Figure 37***) the CU5 copper atom (23) is connected to three chlorines 2, 22 and 24. The bond distances are: 23-2 = 2.236 Å, 23-2 = 2.920 Å 23-24 = 2.2282 Å. Although we have defined a new atom type for the Cl bridge (CL2) it was not possible to

distinguish between longer and shorter distance. That is the main reason why the RMS gradient calculated over all CU5-CL2 bonds is high (0.23 for MM* and MM+ calculations).

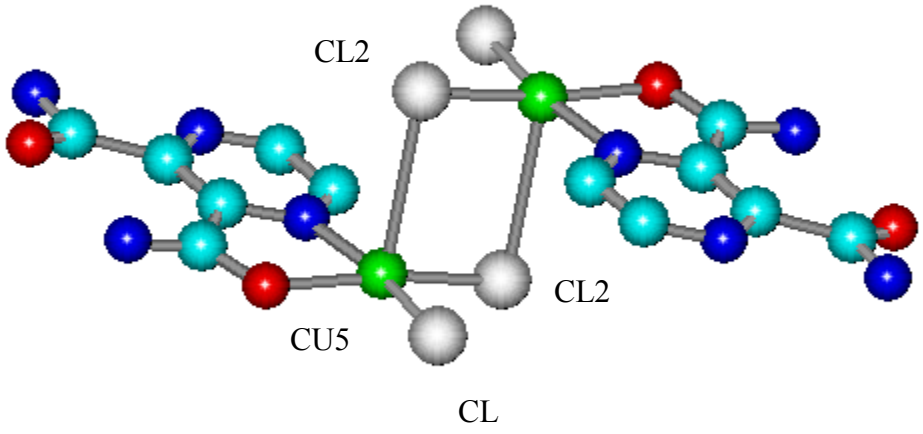


Figure 37. PZCU7 - Cu-Cl bond distortion.

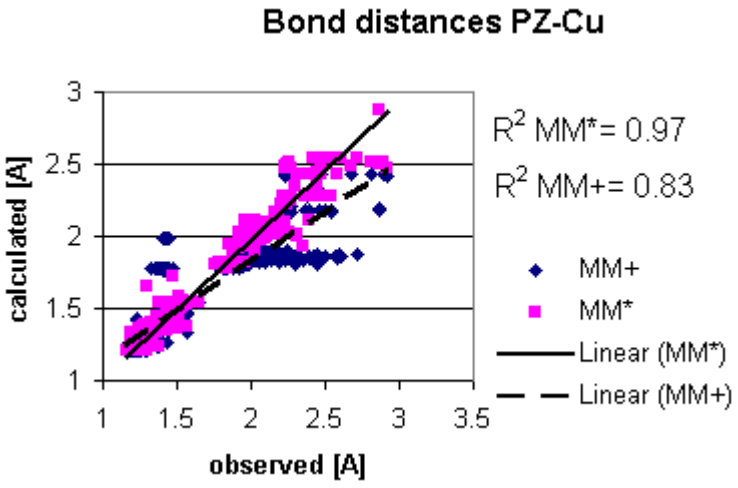


Figure 38. Comparison of the bond distances after MM+ and MM* calculations.

The angles:

The RMS gradient calculated over selected angles is 11.32 for MM* and 16.72 for MM+ calculations. The comparison of results for both parameter sets is presented in ***Figure 39.*** The coefficient of determination is poor for this subset of molecules.

Using the results listed in ***Table 34*** we prepared another chart (***Figure 40***), which shows how adding the bending parameters has great influence for RMS gradient calculated for each of the them. The MM* series are much lower than the MM+ ones which proves that having added the parameters to the *pgben.txt* file corrects the reproduction of the angles.

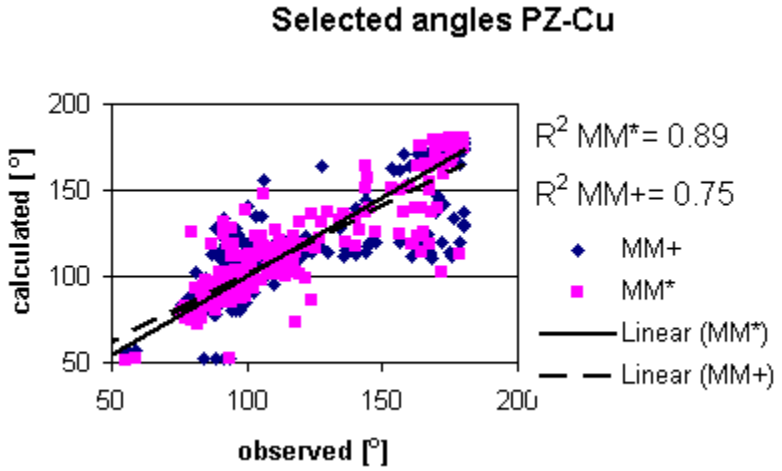


Figure 39. Comparison of the angles after MM+ and MM* calculations.

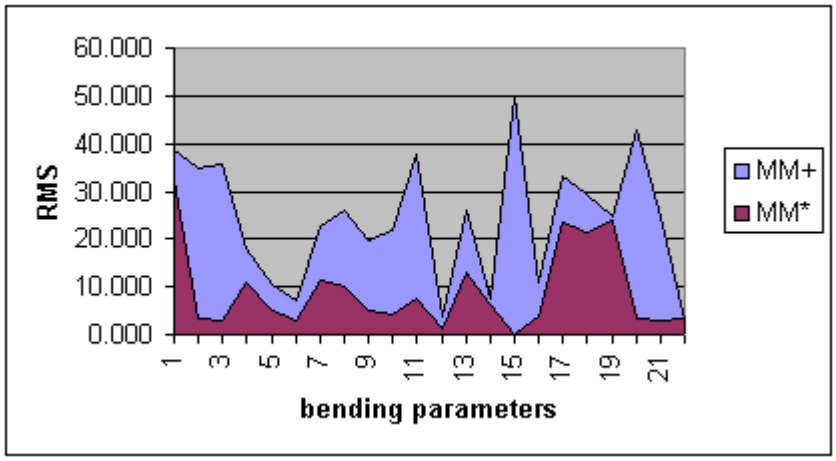


Figure 40. Influence of adding the bending parameter.

RMS – RMS gradient calculated over selected angles
n – n^{th} angle type
MM* in front of MM+

For valence angles the modified force field was generally capable of generating a better fit than the MM+ parameter set. In some cases (pzcu18, pazcu19) defining the bending parameters caused problems with the geometrical arrangements. In case of atoms 3-1-2 of pzcu19 (NA1-CU3-O3) and atoms 5-1-2 of pzcu18 (NA1-CU3-O2) adding the following lines:

```
na1     cu3     o3     0.500   100.000     0.000   0.000   " "
na1     cu3     o2     0.500   100.000     0.000   0.000   " "
```

to the *pgben.txt* file caused that the program changed the geometrical arrangement of the Cu sphere from disordered TP-3 to TPY-3. Removing such defined parameters forced HyperChem to apply the default parameters, which reproduced ideal TP-3 geometry correctly.

The geometrical arrangements:

As it is shown in ***Table 35*** HyperChem can model octahedral coordination geometry reasonably. Difficulties were encountered with square planar geometry (SP-4), where the coordination centers were transformed to tetrahedral geometries. Similar situations occurred for square pyramidal conformations (SPY-5, **τ** between 0 and 0.5), which flipped to trigonal bipyramidal (TBYP-5, **τ** between 0.51 and 1).

Trigonal planar complexes are modelled in a such way that the geometry is preserved but the angle between the three bonds differs on the crystal structure.

Table 35. Comparison of the coordination centers.

1	2	3	4			5	6
	File	Angle definition	Models			MM+	MM*
	name		DAT	MM+	MM*	agreement	
1	Pzcu1	**α** = 9-2-5(OC-CU5-CL) **β** = 13-2-6(NA1-CU5-CL2)	**τ**=0.12 SPY-5	**τ**=0.54 TBYP-5	**τ**=0.62 TBYP-5	P	P
2	Pzcu2	**α** = 3-1-2(OC-CU5-CL) **β** = 8-1-7(NA1-CU5-CL2)	**τ**=0.37 SPY-5	**τ**=0.78 TBYP-5	**τ**=0.60 TBYP-5	P	P
3	Pzcu3	15-1-4 (NA1-CU4-NA1) 14-1-2 (OC-CU4-OC)	180.00 180.00 SP=4	137.54 129.97 T-4	179.99 180.00 SP-4	P P	G G

Table cont.

1	2	3	4	5	6	7	8
4	Pzcu4	19-1-5 (NA1-CU4-NA1) 19-1-18 (NA1-CU4-O3)	180.00 85.08 OC-6	180.00 90.19 OC-6	180.00 87.54 OC-6	G P	G F
5	Pzcu5	5-1-21(NA1-CU4-NA1) 5-1-2(NA1-CU4-O3)	180.00 95.23 OC-6	180.00 90.35 OC-6	180.00 89.88 OC-6	G F	G P
6	Pzcu6	7-3-25(NA1-CU4-NA1) 7-3-6(NA1-CU4-O3)	180.00 85.90 OC-6	178.10 88.82 OC-6	174.025 88.07 OC-6	G F	F F
7	Pzcu7	**α** = 26-23-24(NA1-CU5-CL) **β** = 25-23-22(OC-CU5-CL2)	**τ**=0.02 SPY-5	**τ**=0.59 TBYP-5	**τ**=0.43 SPY-5	P	P
8	Pzcu9	2-1-4(O5-CU2-O5) 9-1-8 (NA1-CU2-N3)	166.83 174.09 OC-6	170.47 176.04 OC-6	164.95 175.27 OC-6	F G	G G
9	Pzcu10	**α** = 3-1-2(CL2-CU5-CL) **β** = 4-1-29(NA1-CU5-CL2)	**τ**=0.43 SPY-5	τ_i=0.20	**τ**=0.12 SPY-5	P	G
10	Pzcu11	**α** = 2-1-3(CL-CU5-CL2) **β** = 4-1-29(NA1-CU5-CL2)	**τ**=0.43 SPY-5	τ_i=0.20	**τ**=0.12 SPY-5	P	P
11	Pzcu12	2-1-3(P-CU4-P) 5-1-4(NA1-CU4-NA1	118.52 79.19 T-4	121.35 88.30 T-4	119.16 80.95 T-4	F P	G G
12	Pzcu13	**α** = 4-1-2(NH-CU5-NH) **β** = 5-1-3(NA1-CU5-N3)	**τ**=0.64 TBYP-5	**τ**=0.43 SPY-5	**τ**=0.74 TBYP-5	P	G
13	Pzcu14	1-3-5(NA1-CU4-NA1) 2-1-4(N4-CU4-NA1)	140.43 99.44 T-4	112.31 109.43 T-4	117.93 104.05 T-4	P P	P F
14	Pzcu15	36-1-41(NA1-CU2-NA1) 32-1-40(NA1-CU2-NA1) 32-1-41(NA1-CU2-NA1)	174.56 168.50 92.12 OC-6	168.78 168.78 98.34 OC-6	156.58 156.01 100.22 OC-6	P G P	P P P
15	Pzcu17	**α** = 3-1-2(O3-CU5-O3) **β** = 7-1-5(NA1-CU5-NA1)	**τ**=0.26 SPY-5	τ_i=0.49	τ_i=0.48	P	P
16	Pzcu18	5-1-3(NA1-CU3-NA1) 5-1-2(NA1-CU3-O2)	156.34 97.83 TP-3	120.12 119.91 TP-3	120.78 119.98 TP-3	P P	P P
17	Pzcu19	5-1-3(NA1-CU3-NA1) 5-1-2(NA1-CU3-O2)	163.21 95.25 TP-3	120.50 119.57 TP-3	121.33 119.09 TP-3	P P	P P
18	Pzcu20	5-1-7(NA1-CU4-NA1)	144.29 T-4	117.84 T-4	157.44 T-4	P	P
19	Pzcu21	13-1-15(N3-CU2-NA1) 15-1-12(NA1-CU2-NH) 1-10-3(CU2-O7-CL)	176.35 96.86 129.50 OC-6	176.17 96.60 114.23 OC-6	172.18 97.26 137.15 OC-6	G G P	F G P
20	Pzcu23	3-1-8(NA1-CU3-NA1)	147.38 TP-3	120.03 TP-3	125.07 TP-3	P	P
21	Pzcu24	5-1-32(NA1-CU2-NA1)	180.00 OC-6	180.00 OC-6	180.00 OC-6	G	G
22	Pzcu25	39-1-6(NA1-CU2-NA1)	180.00 OC-6	180.00 OC-6	180.00 OC-6	G	G

23	Pzcu26	1-6-2(CU2-O7-CL) 18-1-14(NA1-CU2-NA1)	162.20 177.44 OC-6	121.825 179.33 OC-6	139.33 179.73 OC-6	P F	P F
Table cont.							
1	2	3	4	5	6	7	8
24	Pzcu27	3-1-1(CL-CU4-NA1) 4-1-9(NH-CU-NH)	180.00 163.231 SP-4	132.439 134.48 T-4	166.32 123.36 T-4	P P	P P
25	Pzcu28	**α** = 2-15-5(05-CU5-O5) **β** =1-15-12(N3-CU5-NA1)	**τ**=0.1 SPY-5	τ_i=0.05	**τ**=0.14 SPY-5	P	G
26	Pzcu29	10-1-21(NA1-CU2-NA1)	180.00 OC-6	176.93 OC-6	177.36 OC-6	F	F
27	Pzcu30	25-1-3(NA1-CU2-NA1)	180.00 OC-6	180.00 OC-6	180.00 OC-6	G	G
28	Pzcu31	**α** = 45-4-1(N2-CU5-CL) **β** = 44-4-46(NA1-CU5-NA1) 47-5-49(NA1-CU4-NA1) 48-5-2(N2-CU4-CL)	**τ**=0.47 SPY-5 172.24 145.269 T-4	**τ**>1 TBYP-5 119.26 113.74 T-4	**τ**=0.86 TBYP-5 101.897 93.00 T-4	P P P	P P P
29	Pzcu32	11-1-7(NA1-CU4-NA1) 12-1-10(OC-CU4-OC)	180.00 180.00 SP-4	137.40 129.60 T-4	179.74 180.00 SP-4	P P	G G
30	Pzcu33	**α** = 34-1-31(O4-CU5-O4) **β** = 32-1-33(O4-CU5-O4)	**τ**=0.07 SPY-5	τ_i=1 TBYP-5	τ_i=0.65 TBYP-5	P	P
31	Pzcu34	**α** = 16-1-14(O4-CU5-O4) **β** = 15-1-17(O4-CU5-O4)	**τ**=0.07 SPY-5	τ_i=1 TBYP-5	τ_i=0.65 TBYP-5	P	P
32	Pzcu35	8-1-7(NA1-CU4-NA1) 5-1-6(P-CU4-P)	82.44 121.93 T-4	87.78 116.64 T-4	81.79 117.98 T-4	P P	G F
33	Pzcu36	2-1-48(NA1-CU2-NA1) 38-1-8(NA1-CU2-NA1)	177.38 154.05 OC-6	180.00 161.27 OC-6	180.00 150.20 OC-6	F P	F F
34	Pzcu37	30-1-2(N2-CU4-N2) 58-1-86(NA1-CU4-NA1)	93.62 119.63 T-4	97.86 119.02 T-4	94.98 122.25 T-4	F G	G F
35	Pzcu38	**α** = 12-1-9(NA1-CU5-NA1) **β** = 7-1-3(NA1-CU5-CL)	**τ**=0.09 SPY-5	τ_i=0.83 TBYP-5	τ_i=0.53 TBYP-5	P	P
36	Pzcu39	38-1-12(NA1-CU2-NA1)	180.00 OC-6	179.98 OC-6	179.37 OC-6	G	G
37	Pzcu40	5-1-3(NA1-CU4-N2) 6-1-2(O5-CU4-O2)	175.54 178.83 SP-4	111.12 119.40 T-4	163.94 112.50 T-4	P P	P P
38	Pzcu41	**α** = 7-1-6(NA1-CU5-NA1) **β** = 2-1-4(CL-CU5-NA1)	**τ**=0.12 SPY-5	τ_i=0.85 TBYP-5	τ_i=0.55 TBYP-5	P	P
39	Pzcu42a	**α** = 6-2-8(NA1-CU5-NA1) **β** = 3-2-7(NA1-CU5-NA1)	**τ**=0.3 SPY-5	**τ**=0.25 SPY-5	**τ**=0.40 SPY-5	G	G
40	Pzcu44	**α** = 4-2-15(NA1-CU5-O2) **β** = 3-2-5(NA1-CU5-O3)	**τ**=0.07 SPY-5	**τ**=0.80 TBYP-5	**τ**=0.84 TBYP-5	P	P
41	Pzcu45	9-2-12(NA1-CU2-N3) 10-2-11(NH-CU4-NH)	176.24 169.37 SP-4	133.26 137.58 T-4	179.71 172.10 SP-4	P P	F F
42	Pzcu46	**α** = 7-1-3(N2-CU5-NA1) **β** = 9-1-4(O2-CU5-NH)	**τ**=0.01 SPY-5	**τ**=0.83 TBYP-5	**τ**=0.86 TBYP-5	P	P
43	Pzcu48	**α** = 4-1-3(NA1-CU5-NA1) **β** = 2-1-5(03-CU5-NA1)	**τ**=0.27 SPY-5	τ_i=0.78 TBYP-5	**τ**=0.58 TBYP-5	P	P

Table cont.							
1	2	3	4	5	6	7	8
44	Pzcu50	5-1-4(NA1-CU2-NA1) 20-1-24(O7-CU2-O7) 1-20-2(CU2-O7-CL)	178.12 175.45 143.77 OC-6	180.00 180.00 113.43 O6-6	178.54 176.79 135.90 OC-6	G F P	G G P
45	Pzcu51	10-2-6(NA1-CU3-NA1)	177.91 OC-6	166.68 OC-6	177.73 OC-6	P	G
46	Pzcu_mo11	**α** = 7-1-4(OC-CU5-NA1) **β** = 46-1-2(OC-CU5-NA1)	**τ**=0.24 SPY-5	τ_i=0.78 TBYP-5	τ_i=0.72 TBYP-5	P	P
47	Pzcu_mo12	**α** = 31-1-10(OC-CU5NA1) **β** = 35-1-4(CL-CU5-NA1)	**τ**=0.1 SPY-5	τ_i=0.73 TBYP-5	**τ**=0.19 SPY-5	P	G
48	Pzcu_mo24	2-1-3(CL-CU4-NA1) 5-1-7(NA1-CU4-OC)	166.49 160.736 SP-4	124.24 142.81 T-4	164.00 127.17 T-4	P P	G P

DAT – results for the crystal structure
MM+ - results after MM+ calculations
MM - results after MM* calculations*
τ_1 – calculated of absolute values of ***(β- α)***
P – poor, F- fair, G- good agreement with the experiment defined in ***[9]***

In the case of pzcu23 we were not able to model the orientation of the monosubstituted pyrazine groups in respect to the bisubstituted one. The difference of the orientation between observed and calculated model was 90 degrees according to ***Figure 41.***

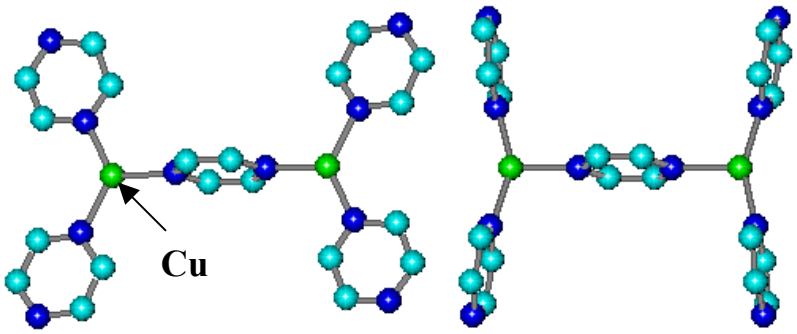


Figure 41. Case of Pzcu23 Left – model after calculations, Right – crystal structure.

7.7. Calculations on Pyrazine-Zn subset

I. Structures used

Eight structures were userd for calculations and are listed in ***Table 36***.

Table 36. Crystal structures of complexes of Zinc used for calculations.

Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzzn1	AZNPYD[104]	catena (Diaqua-(μ_3-2,3-pyrazinedcarboxylate) – zinc monohydrate)	Zn(II) CN=6	OC-6
2	Pzzn2	HALTOD[105]	Tetraphenylporhyrin-pyrazine-zinc(II) hemipyrazine clathrate	Zn(II) CN=5	SPY-5 τ=0.01
3	Pzzn3	HAMJUA[106]	bis (3-methoxypyrazine)-tetraphenylporphyrin-zinc(II)	Zn(II) CN=6	OC-6
4	Pzzn4	PITXOF[107]	tetrachloro- (μ_2-tetrakis (aminomethyl) pyrazine)-di-zinc	Zn(II) CN=5	SPY-5 τ=0.47
5	Pzzn5	TEWNEO[108]	Diaqua-bis(2-pyrazinedcarboxylato) – zinc(II)	Zn(II) CN=6	OC-6
6	Pzzn6	TISTAO[109]	catena (bis (μ_2- -Chloro) – (μ_2-pyrazine) –zinc(II)	Zn(II) CN=6	OC-6
7	Pzzn7	WAGPOJ[110]	Dichloro- (2,3,5,6-tetrakis(2-pyridyl) pyrazine-N,N',N'')-zinc(II)	Zn(II) CN=5	SPY-5 τ=0.08
8	Pzzn8	WIBVOS[111]	octakis(μ_2-Chloro) – bis(μ_2-2,3,5,6-terakis(2-pyridyl)pyrazine) – dodecachloro-tetra-aqua-deca-zinc	Zn(II) CN=4 CN=5	T-4 SPY-5 τ=0.15

We have defined new atom types:

- ZN2 (coordination number CN=6),
- ZN3 (coordination number CN=5),
- ZN4 (coordination number CN=4) and
- ZN1 (for connection with pyridine) according to the following entrance in *chem.rul* file :

```
Zn:
; connected to pyrazine CN=6
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)(-*)(-*)?
     =ZN2. ; numerical type 87
; connected to pyrazine CN=5
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)(-*)?
     =ZN3. ; numerical type 118
; connected to pyrazine CN=4
     connected to (-*)(-*)(-*)(-*)?
     =ZN4. ; numerical type 119
;connected to pyridine
     connected to N@1~C~C~C~C~C~N@1?
     =ZN1. ; numerical type 86
```

For chlorine definitions :

```
Cl:
     connected to (-Zn)(-Zn) ?
     =CL2.
     connected to (-Zn) ?
     =CL.
```

II. Results of calculations.

Six cycles of refinement of the parameters were necessary to achieve the lowest RMS gradients. After the sixth run of the program we have obtained the RMS values calculated over bonds and some angles and final parameters presented in ***Table 37*** and ***38.***

III. Conclusions

All the results are included in the *PZZN.xls* file. The structures can be found at http://www.unine.ch/chim/pg/r/results.html in the *Zn* section of the page.

The new parameters obtained better reproduced the bond distances with an RMS of 0.044 versus 0.095 for calculations with MM+ parameters. The comparison of the results is shown in ***Figure 42.***

New bending parameters decreased the RMS calculated over selected angles from 24.52 for MM+ to 14.12 for MM* calculations. The comparison chart is shown in ***Figure 43***.

Table 37. Final parameters for Zinc complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
1	2	3	4	5	6	7	8
CA1	CR	0.059	Fair	0.003	Good	1.520	5.000
ZN2	CL2	0.022	Fair	0.041	Fair	2.210	5.000
ZN2	N2	0.094	Poor	0.013	Good	2.062	5.000
ZN2	NA1	0.290	Poor	0.137	Poor	2.200	5.000
ZN2	O2	0.210	Poor	0.039	Fair	2.100	5.000
ZN2	OC	0.211	Poor	0.044	Fair	2.070	5.000
ZN3	CL	0.041	Fair	0.020	Good	2.279	5.000
ZN3	CL2	0.098	Poor	0.098	Poor	2.249	5.000
ZN3	N2	0.112	Poor	0.006	Good	2.065	5.000
ZN3	NA	0.178	Poor	0.076	Fair	2.200	5.000
ZN3	NA1	0.204	Poor	0.038	Fair	2.110	5.000
ZN3	NH	0.216	Poor	0.003	Good	2.186	5.000
ZN3	NP	0.099	Poor	0.004	Good	2.050	5.000
ZN3	O2	0.175	Poor	0.005	Good	2.091	5.000
ZN4	CL	0.035	Fair	0.020	Good	2.199	5.000
ZN4	CL2	0.144	Poor	0.078	Fair	2.380	5.000
ZN4	NA1	0.252	Poor	0.004	Good	2.177	5.000
ZN4	O2	0.094	Poor	0.005	Good	2.000	5.000
ZN3	O2	0.175	Poor	0.005	Good	2.091	5.000

Table 38. Final parameters for Nickel complexes – bending parameters.

At1	At2	At3	MM+ RMS	Agreement MM+	MM* RMS	Agreement MM*	Parameters: K_Θ Θ_o
CL	ZN4	CL	6.27	Poor	0.570	Good	0.500 118.00
ZN4	CL2	ZN4	71.06	Poor	0.910	Good	1.500 109.00
ZN3	CL2	ZN4	56.99	Poor	0.450	Good	0.500 120.00

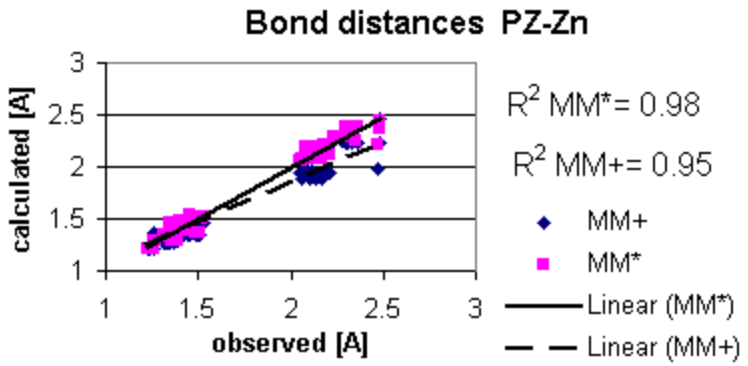


Figure 42. Comparison of the bond distances after MM+ and MM* calculations

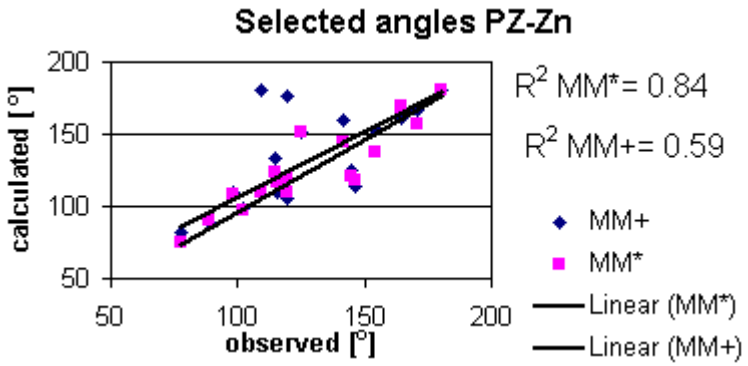


Figure 43. Comparison of the angles after MM+ and MM* calculations.

7.8. Calculations on Pyrazine-Ru subset

I. Structures used.

Eleven structures were used for calculations and are listed in ***Table 39***.

Table 39. Crystal structures of complexes of Ruthenium used for calculations.

1	2	3	4	5	6
Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzru1	CABYIN[112]	Chloro-(1-6-η-p-cymene) – bis(pyrazine)-ruthenium(II) hexafluorophosphate	Ru(II) CN=4	T-4
2	Pzru2	DUMWOX[113]	Penta-ammine-(N-methylpyrazinium) – ruthenium(II) tri-iodide	Ru(II) CN=6	OC-6
3	Pzru3	PAJWAZ[114]	(μ_2-Pyrazine-N,N') – bis(tetrakis(μ_2-6chloro-2-hydroxypyridinato-N,O) – di-ruthenium) bis(tetrafluoroborate) dichloromethane solvate	Ru(II) CN=6	OC-6
4	Pzru4	POGCOD[115]	(μ_2-2,3-bis(2-Pyridyl)pyrazine-N,N',N'',N''') –bis(2,2'-μ_2 bipyridyl) –dichloro-platinium(II)-ruthenium(II) bis(hexafluorophosphate)	Ru(II) CN=6	OC-6
5	Pzru5	POGCUJ[116]	(μ_2-2,3-bis(2-Pyridyl)pyrazine) -dichloro-palladium(II)-bis(2,2'-bipyridyl) -ruthenium(II) bis(hexafluorophosphate)	Ru(II) CN=6	OC-6
6	Pzru6	POGCUJ01[117]	(μ_2-2,3-bis(2-Pyridyl)pyrazine) -dichloro-palladium(II)-bis(2,2'-bipyridyl) -ruthenium(II) bis(hexafluorophosphate)	Ru(II) CN=6	OC-6
7	Pzru7	PYZRUA [118]	Penta-ammine-pyrazine – ruthenium(II) bis(tetrafluoroborate)	Ru(II) CN=6	OC-6

Table cont.					
1	2	3	4	5	6
8	Pzru8	RIMKED[119]	trans-(μ_2-Pyrazine) –bis (bis (1,2-bis (dimethylarsino) benzene) –chloro - ruthenium) bis (hexafluorophosphate) acetonitrile diethyl ether solvate	Ru(II) CN=6	OC-6
9	Pzru9	TAZDUT[120]	(4,4'-Diemethyl-2,2'-bipyridine) -chloro-(2, 3, 5, 6-tetrakis(2-pyridyl)pyrazine) - ruthenium(II) hexafluorophosphate	Ru(II) CN=6	OC-6
10	Pzru11	VEZTAV[121]	tris(2,2'-Bipyrazine)- - ruthenium(II) bis (hexafluorophosphate) dimethylformamide solvate monohydrate	Ru(II) CN=6	OC-6
11	Pzru12	VOSPIC[122]	(μ_2-Pyrazine-N,N') – bis(dichloro)-(η_3, η_3-1,2-bis(2-methylallyl)ethane)-ruthenium) chloroform solvate	Ru(II) CN=6	OC-6

We have defined new atom types: RU2 (coordination number CN=6), RU3 (coordination number CN=4, case of pzru1), RU1 (coordination number CN=5, connected to pyridine) and AS for Arsenic connected to four atoms according to the following entrance in *chem.rul* file

```
Ru:
; connected to pyrazine
; to 9 atoms pzru1.hin
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)(-*)(-*)(-*)(-*)(-*)?
     =RU3. ; numerical type 126
; CN=6
     connected to N@1~C~C~N~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)(-*)(-*)?
     =RU2. ; numerical type 89

;connected to pyridine CN=5
     connected to N@1~C~C~C~C~C~N@1?
     connected to (-*)(-*)(-*)(-*)(-*)?
```

```
     =RU1. ; numerical type 88
As:
; connected to 4 atoms
     connected to (-*)(-*)(-*)(-*)?
     =AS. ; numerical type 127
```

II. Results of calculations.

Eleven runs of refinement of the parameters were necessary to achieve the lowest RMS gradients. After the eleventh run of the program we have obtained the RMS values calculated over bonds and final parameters presented in ***Table 40.***

Table 40. Final parameters for Ruthenium complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
AS	C4	0.039	Fair	0.019	Good	1.940	5.000
AS	CA	0.022	Fair	0.019	Good	1.945	5.000
RU1	NA	0.128	Poor	0.004	Good	2.081	11.090
RU1	RU2	0.234	Poor	0.002	Good	2.251	5.000
RU2	AS	0.055	Fair	0.006	Good	2.414	5.000
RU2	CL	0.146	Poor	0.024	Fair	2.400	5.000
RU2	NA	0.093	Poor	0.023	Fair	2.040	11.000
RU2	NA1	0.140	Poor	0.088	Poor	2.070	11.090
RU2	NH	0.186	Poor	0.018	Good	2.150	5.000
RU2	O2	0.107	Poor	0.005	Good	1.977	5.000
RU3	C4	0.053	Fair	0.033	Fair	2.190	5.000
RU3	CA	0.024	Fair	0.018	Good	2.050	5.000
RU3	CL	0.135	Poor	0.028	Fair	2.420	5.000
RU3	NA1	0.155	Poor	0.016	Good	2.145	5.000

All the results are included in several Microsoft Excel files. The files illustrate the whole process of determination of the new stretching parameters.

pzru_0.xls was been saved when the first calculations had been finished. No Excel macros were executed yet.

pzru_1.xls was saved after A_POST_0 macro had been executed. This caused the *structure worksheets* to have their proper names (pzru1, pzru2 etc. instead of "Sheet2", "Sheet3" etc).

pzru_2.xls shows the results after having executed A_POST3 macro. The results were compared in *structure worksheets*, the *parameter worksheets* were created

(NA1_CA1 etc.) and finally the *parameter worksheets* ("Sheet10003" and "Sheet10004") were filled. On the "Sheet10003" in column "H" the program proposes the starting stretching L_o parameters. It is quite easy to determine if the parameter has to be added by examining the columns "C" and "D" (null values of L_o and K_s). The first statistical results can be found on statistical worksheets ("Sheet10000" and "Sheet10001"). RMS after MM+ = 0.068, RMS after MM* calculations 0.056.

pzru_3.xls. It was decided create new parameters (column "I" of "Sheet10003"). These parameters were used for the second run of the calculations.

pzru_4.xls. The A_POST_3 macro was executed. The values of column "H" of each of the *structure worksheets* were updated and the comparison calculations were done. All the *parameter worksheets* and finally the *parameter optimization worksheet,* "Sheet10003", were updated. The RMS values after the second run of calculations were written to column "J" of "Sheet10003". Column "K" contains the new parameters, which were taken for the third run of the calculations. New statistical calculations were written to "Sheet10000" and "Sheet10001". RMS after MM* calculation = 0.066.

pzru_5.xls. A_POST_3 macro executed. RMS MM* 0.080 shows that further revision of stretching parameters is necessary.

pzru_6.xls contains the parameters for the fourth run of calculations. It also contains the results of this loop of calculation and the proposition of the parameters for the fifth run. RMS after MM* calculations 0.040.

pzru_7xls. The fifth run of calculations was finished. The parameters for the sixth run were prepared ("Sheet10003", column "Q"). The RMS after MM* calculations = 0.041.

pzru_8.xls shows the results after the sixth run of calculations. New parameters were proposed on "Sheet10003" column "S". The optimized parameters are marked in green. NA1_RU2 parameter was not optimized any more since the RMS value of 0.088 is the lowest one. The pictures of the molecules were placed in "Sheet10005" to decide if it was necessary to add the bending parameters to the *pgben.txt* file. The RMS calculated over selected angles, located in "Sheet10001" is also useful in the process of determination of the bending parameters. Since the angular RMS is low (around 3 degs.) the default parameters given by HyperChem will be used for the calculations for the

whole subset of Ruthenium compounds. The stretching RMS after MM* calculations = 0.039.

pzru_9.xls till *pzru13.xls* workbooks contain the results after each step of the calculations.

The structures of the subset of Ruthenium complexes and all Excel files can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Ru*** section of the page.

III. Conclusions.

The new parameters reproduce of the bond distances with an RMS of 0.037 versus 0.068 for calculations with MM+ parameters. The comparison of the results is shown in ***Figure 44.*** The comparison of selected angles is presented in ***Figure 45.*** The RMS calculated over selected angles takes the value of 3.87 for MM+ and 2.46 for MM* calculations. Both MM+ and MM* reproduced the atom arrangements around ruthenium correctly.

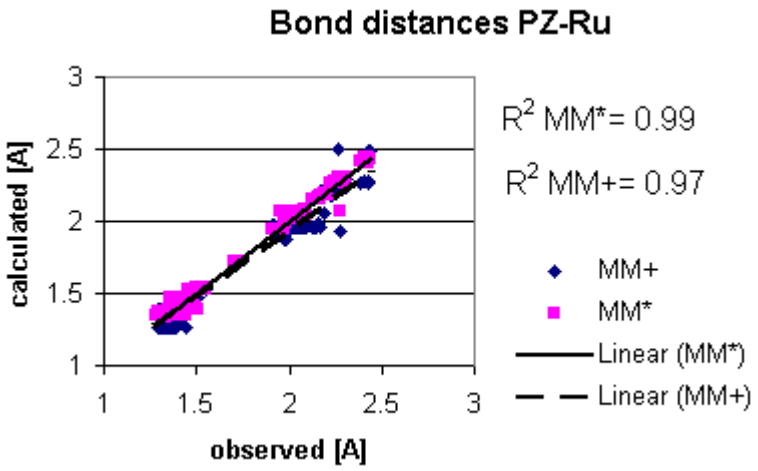


Figure 44. Comparison of the bond distances after MM+ and MM* calculations.

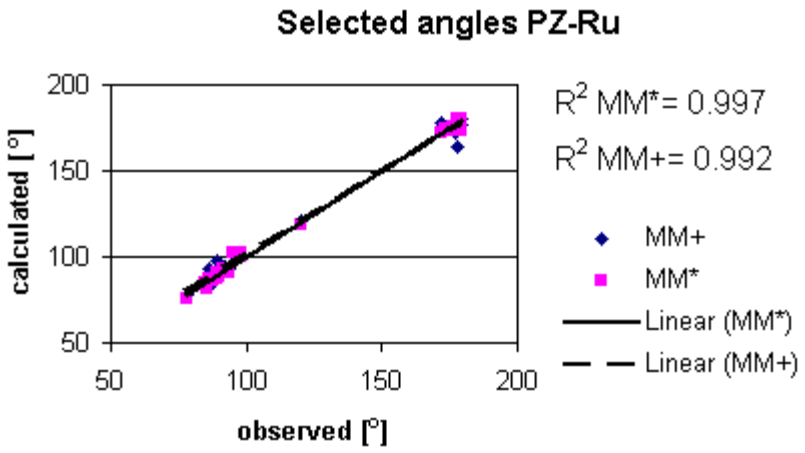


Figure 45. Comparison of the angles after MM+ and MM* calculations.

7.9. Calculation on Pyrazine-Rh subset

I. Used structures.

Four structures were used for calculations and are listed in ***Table 41***.

Table 41. Crystal structures of complexes of Rhodium used for calculations.

Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzrh1	BUZZAX[123]	(μ_2-Pyrazine)-bis(chloro - η^4-cyclo-octadiene) -rhodium)	Rh(II) CN=4	SP-4
2	Pzrh2	JEWLEC[124]	Dibromo-bis(2,3-bis (2-pyridyl)quinoxaline) -rhodium(III) hexafluorophosphate acetonitrile solvate	Rh(III) CN=6	OC-6
3	Pzrh3	WAZSAR[125]	bis(bis(μ_2-Acetato-O,O') -(2-(pyrrol-1-yl)pyrazine-N^4)-rhodium(II))	Rh(II) CN=6	OC-6
4	Pzrh4	YESGEI[126]	Chloro-(η^5-pentamethyl -cyclopentadienyl)- (1,3-dimethyllumazine -N,O)- rhodium(III) hexafluorophosphate	Rh(III CN=6	OC-6

We have defined new atom types: RH2 (coordination number CN=6) and RH1 (connected to pyridine) according to the following entrance in *chem.rul* file

```
Rh:
; connected to pyrazine
      connected to N@1~C~C~N~C~C~N@1?
      connected to (-*)(-*)(-*)(-*)(-*)(-*)?
      =RH2. ; numerical type 91 L=6
;connected to pyridine
      connected to N@1~C~C~C~C~C~N@1?
      =RH1. ; numerical type 90
```

II. Results of calculations.

Eight cycles of refinement of the parameters were necessary to achieve the lowest RMS gradients. After the eighth run of the program we have obtained the RMS values calculated over bonds and final parameters presented in ***Table 42*.**

***Table 42*.** Final parameters for Rhodium complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM *	Agreement MM*	L_0	K_s
CR	N2	0.057	Fair	0.003	Good	1.352	5.000
CR	O2	0.093	Poor	0.008	Good	1.252	5.000
RH2	BR	0.029	Fair	0.006	Good	2.440	5.000
RH2	C3	0.055	Fair	0.056	Fair	2.020	5.000
RH2	CA	0.028	Fair	0.014	Good	1.996	5.000
RH2	CL	0.111	Poor	0.006	Good	2.360	10.000
RH2	NA	0.062	Fair	0.003	Good	2.010	5.000
RH2	NA1	0.192	Poor	0.063	Fair	2.120	11.090
RH2	RH2	0.125	Poor	0.002	Good	2.387	10.000

All the results are included in the *PZRH.xls* file. The structures of the subset of Rhodium complexes can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Rh*** section of the page.

III. Conclusions.

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The new parameters reproduced of the bond distances with an RMS of 0.042 versus 0.073 for calculations with MM+ parameters. The comparison of the results is shown in ***Figure 46*.** The comparison of selected angles is presented in ***Figure 47*.** Both MM+ and MM* reproduced the atom arrangements around Rhodium correctly except for the case of compound pzrh1, where SP-4 geometry was switched to T-4. Only default bending parameters were used for the calculations.

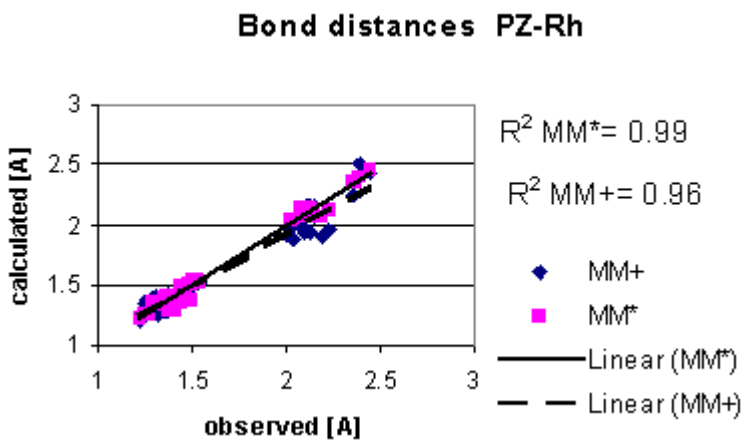

Figure 46. Comparison of the bond distances after MM+ and MM* calculations.

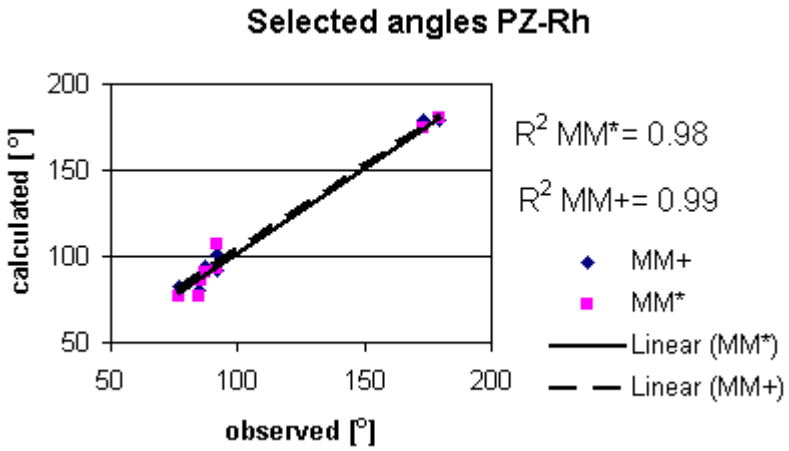

Figure 47. Comparison of the angles after MM+ and MM* calculations.

7.10. Calculations on Pyrazine-Pd subset

I. Used structures.

Eleven structures were used for calculations and are listed in ***Table 43***.

Table43. Crystal structures of complexes of Palladium used for calculations.

1	2	3	4	5	6
Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzpd1	BENDAZ[127]	(μ_2-Pyrazine)-bis(2,6-bis(2,2'-bis(carbethoxy)-ethyl)-pyridine-palladium(II))	Pd(II) CN=4	SP-4
2	Pzpd2	LIHPUN[128]	(2,3,8,9,14,15-Hexamethyl-5,6,11,12,17,18-hexa-azatrinaphthalene-N,N')-dichloro-palladium(II) chlorobenzene methanol solvate	Pd(II) CN=4	SP-4
3	Pzpd3	LIHREZ[129]	(μ_2-2,3,8,9,14,15-Hexamethyl-5,6,11,12,17,18-hexa-azatrinaphthalene-N,N',N'',N''')-trichloro-tricarbonyl-palladium(II)-rhenium(II) 1,2-dichlorobenzene solvate	Pd(II) CN=4	SP-4
4	Pzpd4	NICXOM[130]	(2,2'-Bipyrazine)-(ethylenediamine)-palladium(II) diperchlorate	Pd(II) CN=4	SP-4
5	Pzpd5	NIHSUS[131]	Diammine-(pyrazine-2,3-dicarboxylato)-palladium(II)	Pd(II) CN=4	SP-4
6	Pzpd6	NOHPOP[132]	Dichloro-(2-(2-pyridyl) quinoxalinato)-palladium(II)	Pd(II) CN=4	SP-4
7	Pzpd7	POGCUJ[133]	(μ_2-2,3-bis(2-Pyridyl) pyrazine)-dichloro-palladium(II)-bis(2, 2'-bipyridyl)-ruthenium(II) bis(hexafluorophosphate)	Pd(II) CN=4	SP-4

Table cont.					
1	2	3	4	5	6
8	Pzpd8	POGCUJ01[134]	(μ_2-2,3-bis(2-Pyridyl) pyrazine)-dichloro-palladium(II)-bis(2,2'-bipyridyl)-ruthenium(II) bis(hexafluorophosphate)	Pd(II) CN=4	SP-4
9	Pzpd9	SUJLIS[135]	(μ_2-Pyrazine-N,N')-bis(trans-bis((μ_2-1-methylcytosine-N3,N4)-bis(methylamine-N)-platinum(II)-palladium(II)) tetranitrate tetrahydrate	Pd(II) CN=4	SP-4
10	Pzpd10	VIBXAF[136]	bis(Acetylacetonato-O,O')-(μ_2-2,3-diphenylpyrazine-C,C',N,N')-di-palladium(II))	Pd(II) CN=4	SP-4
11	Pzpd10	ZAGCUF[137]	(1,3-bis (Diphenylphosphino) propane-P,P')-bis(pyrazin-1-yl)-palladium bis (trifluoromethanesulfonate) dichloromethane solvate	Pd(II) CN=4	SP-4

We have defined new atom types: PD1 (for complexes with pyridine) and PD2 (complexes with pyrazine) according to the following entrance in *chem.rul* file

```
Pd:
; connected to pyrazine
     connected to N@1~C~C~N~C~C~N@1?
     =PD2. ; numerical type 93
;connected to pyridine
     connected to N@1~C~C~C~C~C~N@1?
     =PD1. ; numerical type 92
Re:
; connected to pyrazine
     connected to N@1~C~C~N~C~C~N@1?
     =RE2. ; numerical type 101
```

II. Results of calculations.

Five cycles of refinement of the parameters were necessary to achieve the lowest RMS gradients. After the fifth run of the program we have obtained the RMS values calculated over bonds and final parameters presented in ***Table 44.***

Table 44. Final parameters for Palladium complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
PD2	C4	0.115	Poor	0.020	Good	2.150	10.000
PD2	CA	0.054	Fair	0.004	Good	1.957	5.000
PD2	CL	0.006	Good	0.004	Good	2.276	10.000
PD2	N2	0.037	Fair	0.002	Good	1.995	10.000
PD2	NA	0.045	Fair	0.038	Fair	2.036	10.090
PD2	NA1	0.076	Fair	0.018	Good	2.036	10.090
PD2	NH	0.039	Fair	0.003	Good	2.020	10.000
PD2	O2	0.149	Poor	0.044	Fair	2.020	10.000
PD2	OC	0.115	Poor	0.003	Good	2.020	10.000
PD2	PT2	0.093	Poor	0.005	Good	2.492	10.000
PT2	N2	0.081	Poor	0.017	Good	2.045	5.000
PT2	N3	0.036	Fair	0.034	Fair	1.990	5.000
RE2	CL	0.162	Poor	0.003	Good	2.450	10.000
RE2	CO	0.115	Poor	0.018	Good	1.920	10.000
RE2	NA1	0.210	Poor	0.019	Good	2.200	10.000

III. Conclusions.

.

All the results are included in the *PZPD.xls* file. The structures can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Pd*** section of the page.

The new parameters reproduce the bond distances with an RMS of 0.037 versus 0.054 for calculations with MM+ parameters. The comparison of the results is shown in ***Figure 48.*** Default bending parameters were used for calculations. The comparison chart is shown in ***Figure 49***. HyperChem was not able to reproduce the geometry of the metal centers correctly. It was not possible to correct this problem due to unique labeling problem. Instead of SP-4 the program modeled tetrahedral geometries of palladium complexes.

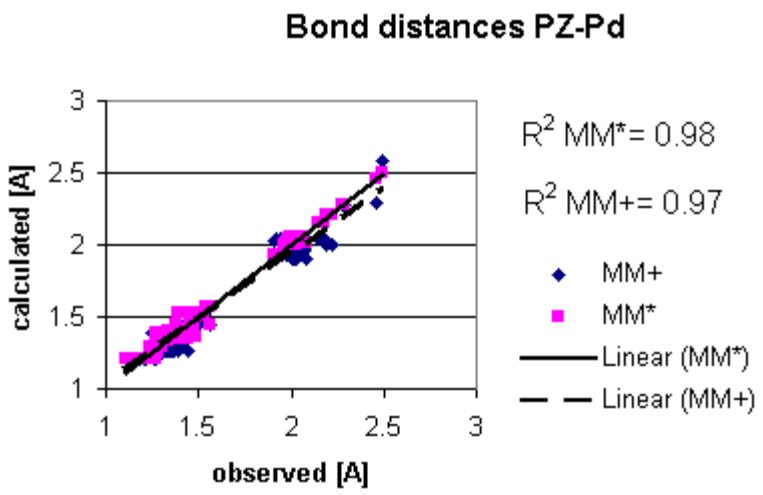

Figure 48. Comparison of the bond distances after MM+ and MM* calculations.

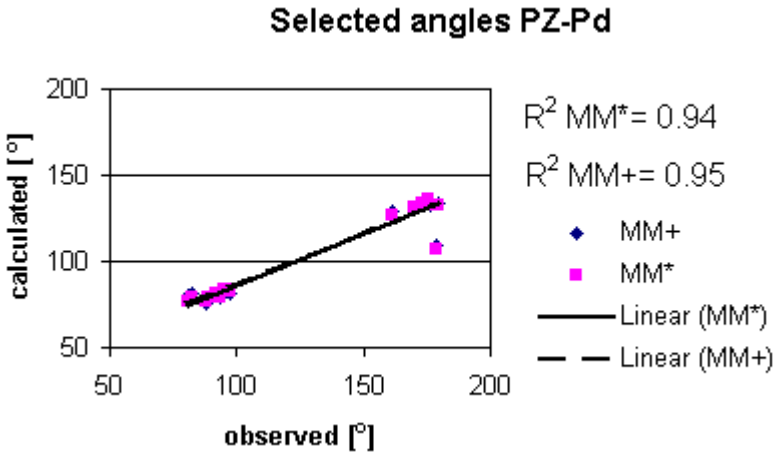

Figure 49. Comparison of the angles after MM+ and MM* calculations.

7.11. Calculations on Pyrazine-Ag subset

I. Used structures.

Six structures were used for calculations and are listed in ***Table 45***.

Table 45. Crystal structures of complexes of Silver used for calculations.

Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzag1	JAHRAL[138]	bis (1,4,5,8-Tetra-azaphenanthrene-N,N') – silver(I) nitrate	Ag(I) CN=4	T-4 irregular
2	Pzag2	JAHRAL01[139]	bis (1,4,5,8-Tetra-azaphenanthrene-N,N') – silver(I) nitrate	Ag(I) CN=4	T-4 irregular
3	Pzag3	JUXWOO[140]	catena ((μ_2-Diphenazine) – bis((μ_2-nitrato-O,O') silver(I)))	Ag(I) CN=3	TPY-3
4	Pzag4	RABWEW[141]	Catena-(ammonium(μ_3-pyrazine-2,3-dicarboxylato)-silver(I)	Ag(I) CN=3	TP-3
5	Pzco18	TAMKOH[142]	1,1,1,1,1,2,2,2,2,2-Deca-ammine-3,3-diaqua-1,3;2,3 - bis(μ_2-pyrazinato-N,N')-di-cobalt(III)-silver(I) heptanitrate tetrahydrate	Ag(I) CN=4	T-4
6	Pzag6	TOZGOE[143]	catena (tris (μ_2-1,4-Pyrazino) – bis(trifluoromethanesulfonato) –di -silver(I))	Ag(I) CN=4	T-4 irregular

A new silver atom type has been added to the *mmptyp.txt* file and the rules to determine it added to *chem.rul* file :

```
Ag :
; connected to pyrazine
     connected to N@1~C~C~N~C~C~N@1?
     =AG2. ; numerical type 95
```

II. Results of calculations.

Five cycles of refinement of the parameters were necessary to achieve the lowest RMS gradient values. After the fifth run of the program we have obtained the RMS values calculated over bonds and final parameters presented in ***Table 46.***

Table 46. Final parameters for silver complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
NA1	CA1	0.028	Fair	0.038	Fair	1.340	11.090
CA1	CA1	0.035	Fair	0.060	Fair	1.396	11.090
AG2	NA1	0.411	Poor	0.145	Poor	2.360	11.090
CA	CA1	0.043	Fair	0.024	Fair	1.380	8.065
CA	CA	0.012	Good	0.033	Fair	1.373	8.065
AG2	O2	0.561	Poor	0.073	Fair	2.540	11.090
O2	NO	0.079	Fair	0.026	Fair	1.210	5.000
O2	N1	0.086	Poor	0.017	Good	1.250	5.000
O1	N1	0.168	Poor	0.127	Poor	1.235	5.000
AG2	OC	0.393	Poor	0.022	Fair	2.350	5.000
CA1	CO	0.055	Fair	0.007	Good	1.511	4.500
OC	CO	0.092	Poor	0.027	Fair	1.285	11.090
S4	O2	0.242	Poor	0.006	Good	1.432	5.000

III. Conclusions.

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All the results are included in the *PZAG.xls* file. The structures can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Ag*** section of the page.

The new parameters reproduce the bond distances with an RMS bond distances gradient of 0.063 versus 0.176 for calculations with MM+ parameters. We were not able to obtain better results for the AG2_NA1 parameter (RMS gradient 0.145) due to a wide range of the distanced observed in the subset of silver structures. The bonds vary from 2.246 to 2.570 Å. The original force field parameters were not able to reproduce this distance either. The RMS gradient obtained after MM+ calculations is 0.411. The comparison of results is shown in ***Figure 50.***

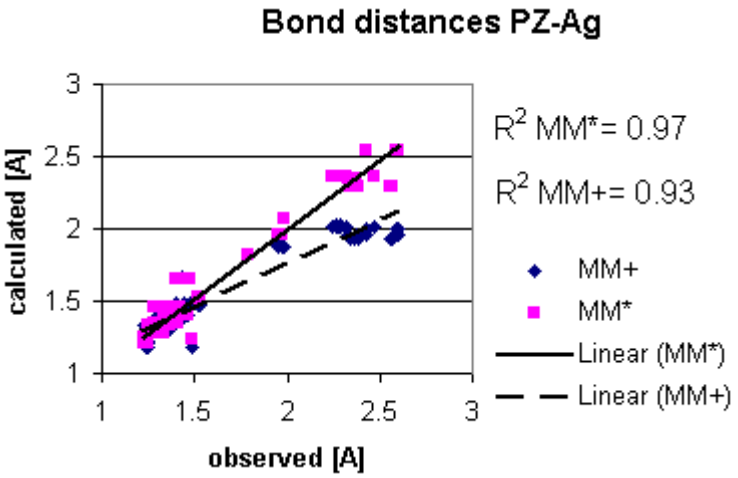

Figure 50. Comparison of the bond distances after MM+ and MM* calculations.

In general it was not possible to improve the bending parameters for the coordination centers due to the *unique labeling problem* **[48]**. The RMS values were 36.66 for MM+ and 32.93 for MM* calculations. Only two bending parameters have been added to the parameter file: NA1_AG2_NA1 and O2_AG2_O2. For both of them K_s=20.000, Θ= 180.00.

In one case (Pzco18 - ***Figure 51***) it was possible to define the bending parameter to model the tetrahedral arrangement of the nitrogen and oxygen atoms.

HyperChem is unable to model the irregular structures for coordination numbers 3 and 4 correctly. The comparison chart is presented in ***Figure 52.***

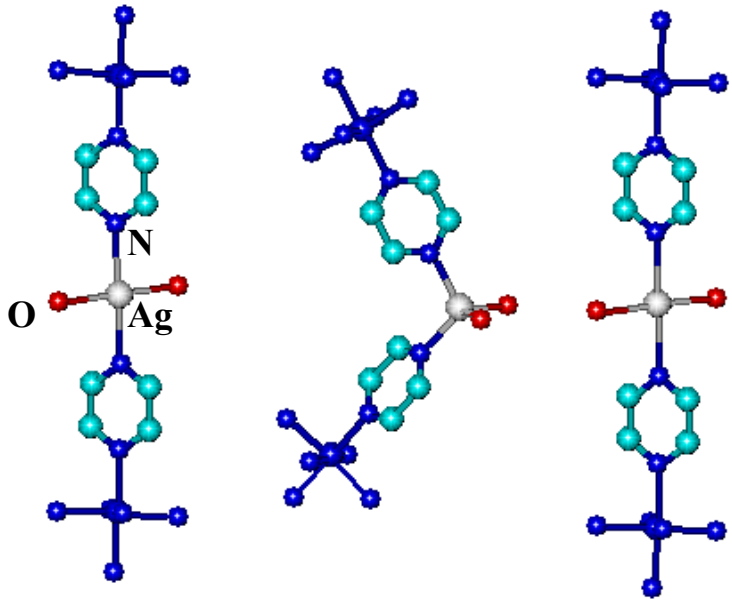

Figure 51. PZCO18 - arrangement around silver
from left to right: starting structure, after MM+ and MM calculations.*

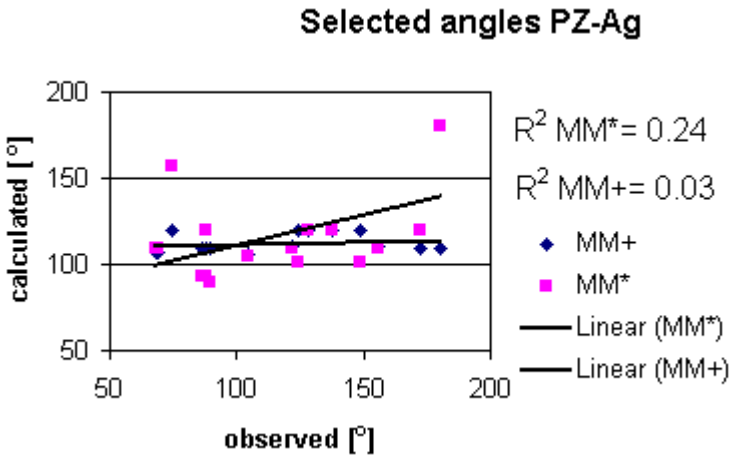

Figure 52. Comparison of the angles after MM+ and MM* calculations.

7.12. Calculations on Pyrazine-Pt subset

I. Structures used.

Five structures were used for calculations and are listed in ***Table 47***.

Table 47. Crystal structures of complexes of Platinum used for calculations.

Number	File name	CSD REFC	Formula	Metal	Geometry
1	Pzpt1	NICXUS[144]	Cyclo-tris((μ_2-bipyrazine)-ethylenediamine-platinum(ii)) hexanitrate trihydrate clathrate monohydrate	Pt(II) CN=4	SP-4
2	Pzpt2	POGCOD[145]	(μ_2-2,3-bis(2-Pyridyl) pyrazine-N,N',N'',N''') -bis(2,2'-bipyridyl) - dichloro-platinum(II) -ruthenium(ii) bis(hexafluorophosphate)	Pt(II) CN=4	SP-4
3	Pzpt3	TOXYAG[146]	Dichloro-(2,3-bis(2 -pyridyl)pyrazine) -platinum(II) acetonitrile solvate	Pt(II) CN=4	SP-4
4	Pzpt4	TOXYEK[147]	Diphenyl-(2,3-bis(2 -pyridyl)pyrazine) -platinum(ii)	Pt(II) CN=4	SP-4
5	Pzpt5	TOXYIO[148]	bis(2-Phenylethynyl)-(2,3 -bis(2-pyridyl)pyrazine) -platinum(ii)	Pt(II) CN=4	SP-4

We have defined new atom types: PT2 (coordination number CN=4) and PT1 (connected to pyridine) according to the following entrance in *chem.rul* file

```
Pt:
; connected to pyrazine
     connected to N@1~C~C~N~C~C~N@1?
     =PT2. ; numerical type 97
;connected to pyridine
     connected to N@1~C~C~C~C~C~N@1?
     =PT1. ; numerical type 96
```

II. Results of calculations.

Eleven runs of refinement of the parameters were necessary to achieve the lowest RMS gradients. After the eleventh run of the program we have obtained the RMS values calculated over bonds and the final parameters are presented in ***Table 48.*** No bending parameters were defined for the subset, instead the default parameters were accepted.

Table 48. Final parameters for Platinum complexes – Stretching parameters.

At1	At2	RMS MM+	Agreement MM+	RMS MM*	Agreement MM*	L_0	K_s
PT2	C2	0.042	Fair	0.010	Good	1.950	11.000
PT2	CA	0.053	Fair	0.028	Fair	1.970	11.000
PT2	CL	0.010	Good	0.009	Good	2.295	11.000
PT2	NA	0.091	Poor	0.072	Fair	2.005	10.000
PT2	NA1	0.059	Fair	0.045	Fair	2.000	11.090
PT2	NH	0.032	Fair	0.036	Fair	1.980	10.000

All the results are included in the *PZPT.xls* file. The structures of the subset of Platinum complexes can be found at http://www.unine.ch/chim/pg/r/results.html in the ***Pt*** section of the page.

III. Conclusions.

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The new parameters reproduce the bond distances with an RMS 0.032 versus 0.055 for calculations with MM+ parameters. The comparison of the results is shown in ***Figure 53.*** The comparison of selected angles is presented in ***Figure 54.*** The RMS calculated over selected angles takes the value of 20.00 for MM+ and 19.98 for MM* calculations. The main reason why the difference is huge can be explain by the fact that both, MM+ and MM*, do not reproduce the atom arrangements around Platinum correctly. HyperChem finishes its calculations giving T-4 coordination instead of SP-4 which is typical for Pt complexes.

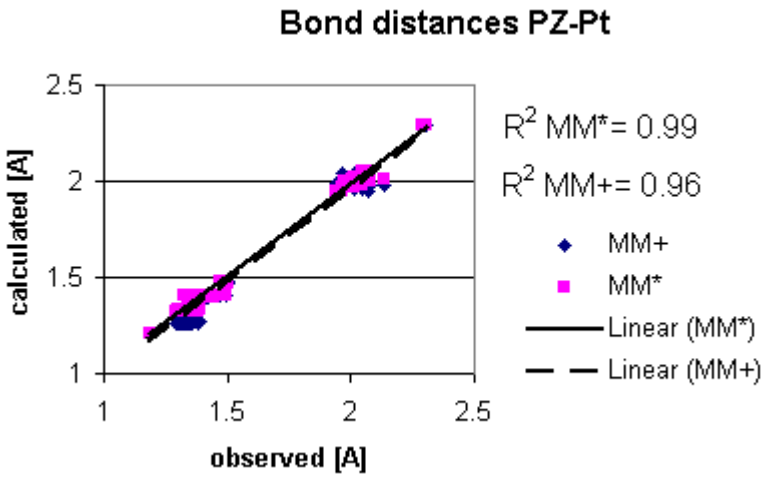

Figure 53. Comparison of the bond distances after MM+ and MM* calculations

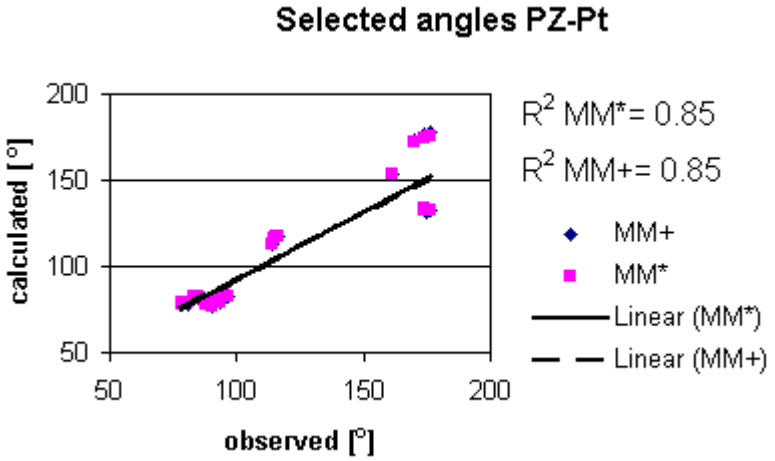

Figure 54. Comparison of the angles after MM+ and MM* calculations.

8.Discussion-Conclusion

The comparison of the results has been prepared in such way that all the results taken from the separate workbooks of all subset of results have been compiled into one workbook called *pz_all.xls*. The Excel file is available at

http://www.unine.ch/chim/pg/r/results.html

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6'186 bond connections were used to calculate the RMS after MM+ and MM* calculations. When the new parameter set was used the value of RMS was 0.047 Å (fair agreement). For the original parameter set, using only default values calculated by HyperChem in the case of missing parameters, the RMS value was 0.126 Å (poor agreement).

In general the modified MM* force field is better at reproducing the bond lengths. These facts are demonstrated by the decrease of the RMS gradients calculated over all bonds as well in the improvements of the coefficients of determination of linear regression (R^2MM*=0.98, R^2MM+=0.88) presented in ***Figure 55***.

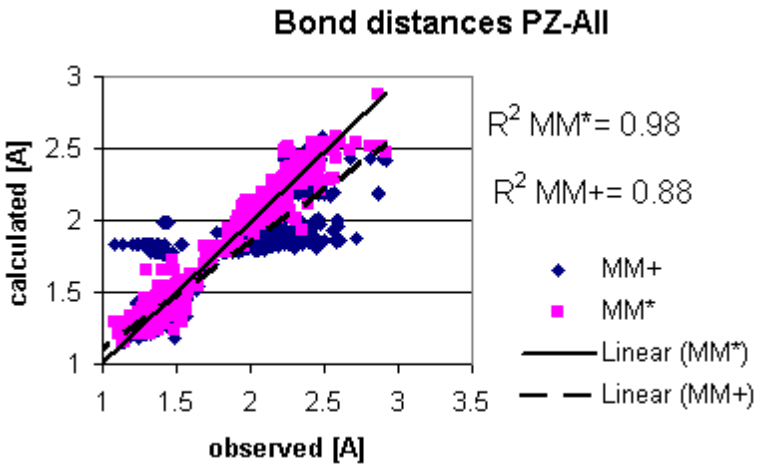

Figure 55. Comparison of all bonds in the subset of calculated complexes

Analysis of 1040 selected angles shows that the MM* calculations are slightly better at reproducing the valence angles. The comparison chart is show in ***Figure 56***.

The way HyperChem models the valence angles depends on the geometrical arrangement of the coordination center.

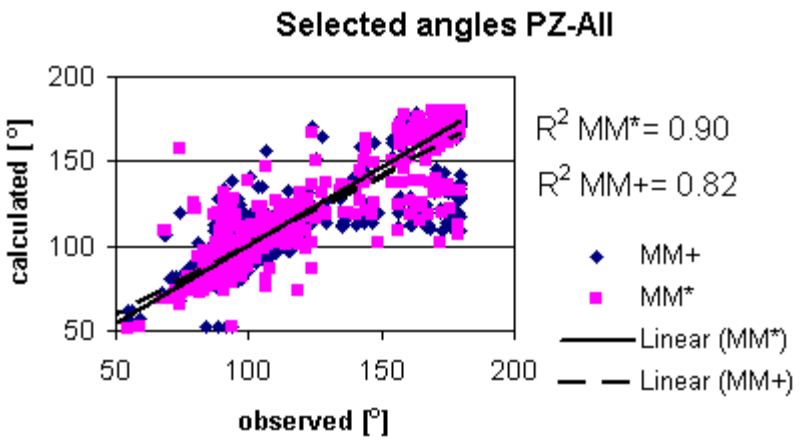

Figure 56. Comparison of selected angles in the subset of calculated complexes

In ***Table 49*** we summarize the ability of HyperChem to model them in an automatic way.

Table 49. The ability of reproducing the geometry around metals

Coordination	MM+ ability	MM* ability	Remarks
T-4	Yes	Yes	Perfect T-4
SP-4	No	No	goes to T-4
TBYP-5	Yes	Yes	Perfect TBYP-5
SPY-5	No	No	goes to TBYP-5
OC-6	Yes	Yes	Perfect OC-6

As it shown in the above table HyperChem prefers certain geometries: T-4, TBYP-5 and OC-6. In the automatic ("black box") mode it cannot model SP-4, SPY-5 and TP-4 correctly. Instead, other "perfect" geometries are obtained.

When the automatic procedures fail, mainly due to the *ULP* problem, it was possible to solve the geometry problem by using special technique (*restraints* - available only for MM and semi-empirical calculations) described below.

When the valence bending parameters are applied by HyperChem automatically one can restore forces applied to certain atoms (by adding harmonic restoring forces) and therefore keep the structure of the compound close to specific values.

The larger the force constant for the restraint, the stronger the restoring force. Restraints can be applied to atomic positions (tethering, single atoms), distances (two atoms), angles (three atoms), and torsion angles (four atoms).

Comparing the results obtained after calculations for the *pzpt5.hin* structure (***Figure 57***-left), it was observed that SP-4 geometry was not preserved for *pzpt5mm.hin* and *pzpt5pg.hin* (***Figure 57***-right structure) structures (after MM+ and MM* calculations). The valence angles between atoms 2-PT2-6 for the crystallographic structure was 174.8^{o} and 132.0 for MM*. For the angles between Na-PT2-C2 atoms the values are 173.9^{o} for crystal structure and 131.9^{o} for MM* calculations.

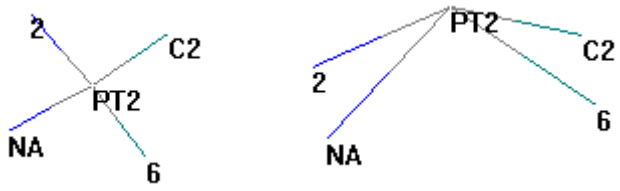

Figure 57. Coordination geometry around Platinum in crystallographic – left – and MM* - right - structures (PZPT5).

To restore the forces applied to the angles two selections were made and named: NA-PT2-C2 – ***ang1*** 2-pt2-6 – ***ang2*** (***Figure 58***).

Figure 58. Naming the selection

In the next step the restraint forces were defined for each angle separately, according to ***Figure 59***. The default values of angles and force constants are proposed for

molecular dynamics calculations. For geometry optimization purposes the force constants must be much larger (for example,10^5) but calculations take more time **[51]**.

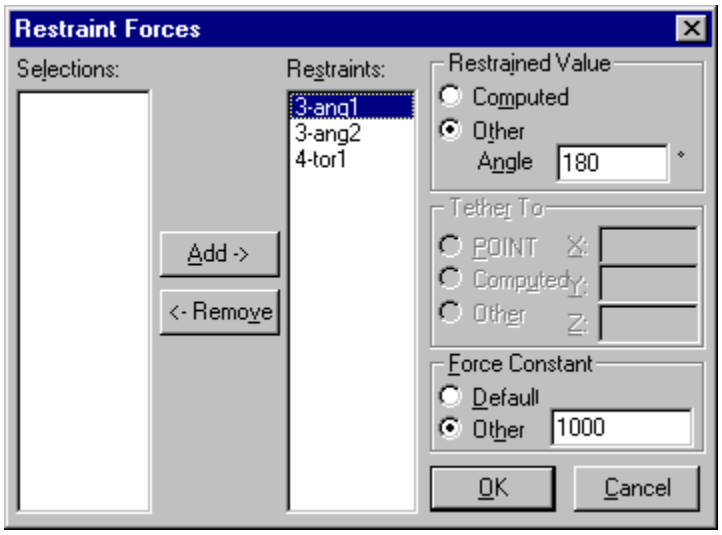

Figure 59. Defining the restraints forces for the angles.

To keep the geometry stable the value of 180.00 [deg] and 500 [kcal*mol^{-1}*deg^{-2}] were chosen. One restoring force was also added for the improper torsion angle defining the plane of the benzene rings (for atoms number 8,11,16 and 19) – (-180) [^{o}]. The resulting structure is shown in ***Figure 60***:

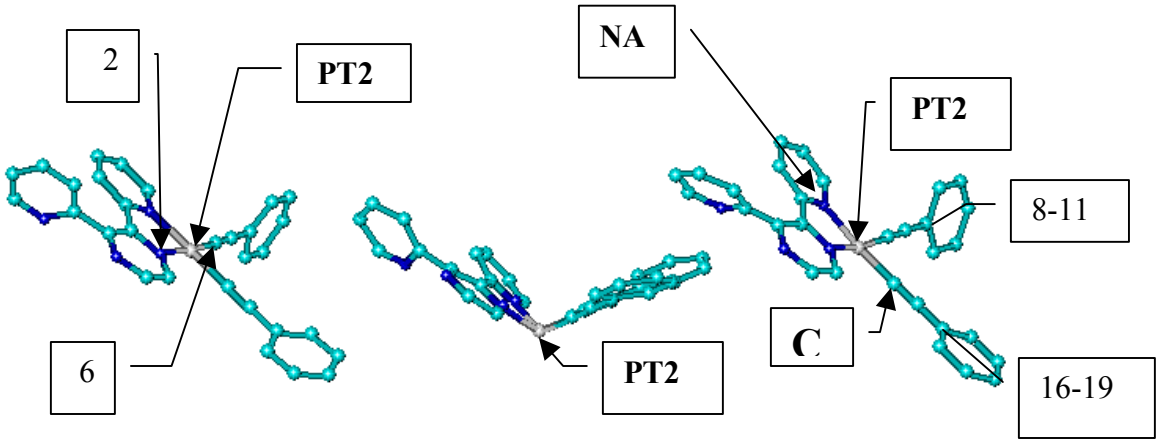

Figure 60. PZTP5 - results of calculations - restratins applied

From left to right: crystallographic, MM+ and MM structures*
PT2, NA,C2 – atom types

The values of the most important bond angles obtained after calculations are listed in ***Table 50***:

Table 50. Resulting angles of PZPT5 structure.

Definition of Angle	Crystallographic structure	Model after MM+ calculations	Model after MM* calculations
2-PT2-6	174.80	132.27	174.82
NA-PT2-C2 (3-1-14)	174.0	131.95	173.89
8-11-16-19	170.0	179.9	180.0

Comparing the results one can observe that it is possible to obtain the square planar geometry using the restraints method.

There is another approach to solve the geometry problem. One can use the dummy (pseudo) atom method. Attaching uncharged unbonded atoms, for which the van der Waals ε parameter is zero, it is possible to control the orientation of the neighbouring atoms.

Calculations on PZCU1 showed that HyperChem couldn't reproduce the SPY-5 conformation correctly. When one adds the "lone pair" to the system it has no influence on the atom types of copper but keeps the SPY-5 geometry at the Cu atom. The results of such a calculation are shown in ***Figure 61***. Structure obtained using original MM+ force field parameters, shown in ***Figure 61 b***, is destroyed. Instead of SPY-5 (τ=0.12) HyperChem modeled a TBY-5 (τ=0.62) conformation. Calculations using the new MM* force field parameters gave a value of the index of trigonality = 0.11, which is close to the starting crystallographic structure.

HyperChem seems to be a good tool to reproduce the geometrical arrangements around metal atoms in molecular complexes. If it is not possible to define all the necessary parameters needed for the calculations, HyperChem calculates them automatically. In case they are not good enough it is still possible to take over and change the parameters using the restraint technique. If the parameters can be defined one can use HyperHelper application to prepare them (stretching, bending and torsional parameters). The parameters are obtained by a trial-and-error method. Starting parameters can be taken form the literature or estimated using the HyperHelper program.

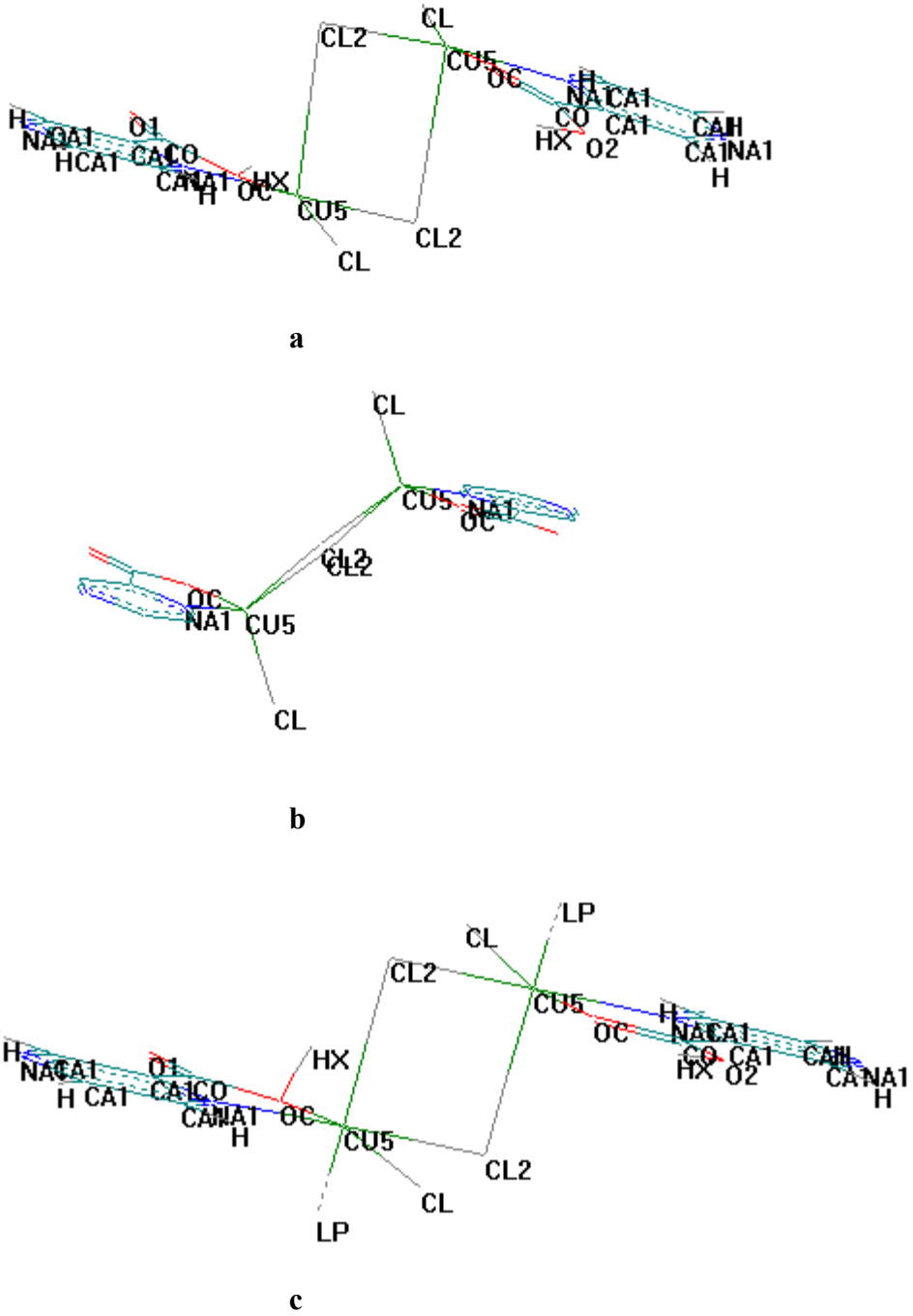

Figure 61. PZCU1 - "dummy" atom approach.

a- CCSD structure, b- MM+ calculations, c- MM "dummy" atom approach*
LP – "lone pair"

Suggestions for further investigations

The research described here has revealed several possibilities for further work:

1. In last quarter of 2000, Hypercube released a new version of HyperChem – v.6, it would be interesting to change the code of HyperHelper to be able to use the AMBER and OPLS force fields which have now been equipped with the Default Parameter Scheme. It would then be possible to use three Force Fields instead of one, MM+. This would enlarge the number of force fields for which the new parameters could be obtained and the old ones could then be modified using the HyperHelper software.
2. The procedure for the determination of the new force field parameters could be further automated by running the refinement process of the parameters without user intervention.
3. When it is difficult or impossible to solve the crystal structure from powder diffraction data (data collection, powder pattern, Rietveld refinement of the powder data) one can build and optimize a possible structure of an unknown compound (starting point), build the crystal cell containing the starting point structure, generate the powder pattern and compare it with the one given by the X-ray experiment. Such a method is illustrated in ***Figure 62***. Such computational minimization of models was used successfully for solving the structures of zeolite Nu87 **[52]** and aluminophosphates: MAPO36 and DAF1 **[53,54]**. An interface to the powder diffraction analysis program could be written and added to HyperHelper according to ***Figure 62.*** The mathematical model, which can be used to perform the calculations and further references, can be found in **[45]** and in **[35]**.
4. Further Applications – modeling more complex systems not just pyrazine and pyridine transition metal complexes.

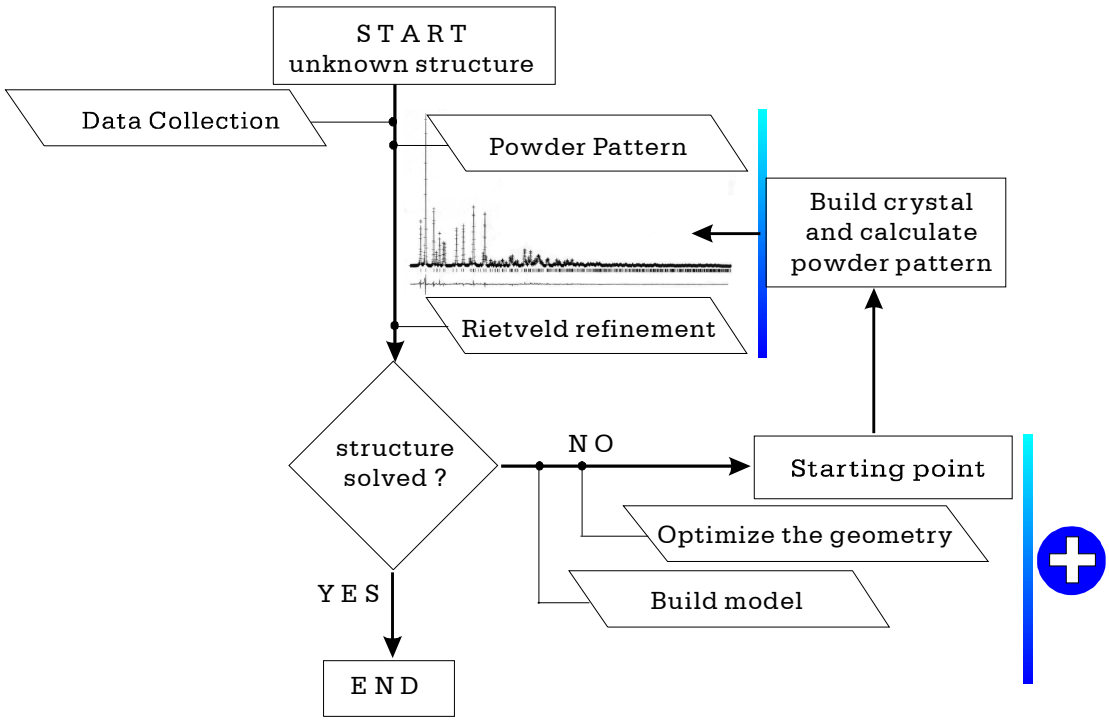

Figure 62. Combining standard and energy minimization methods to solve the powder crystal structure.

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