

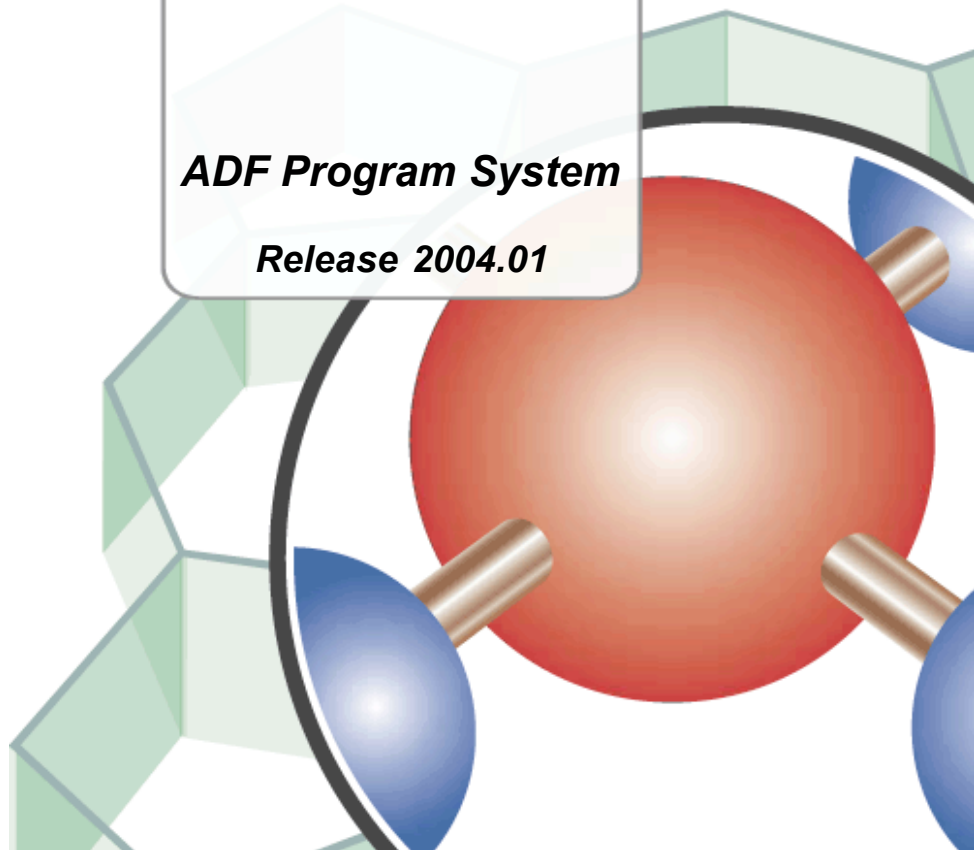


Scientific Computing & Modelling

# ***ADF QM/MM***

***ADF Program System***

***Release 2004.01***



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# 1 Introduction

## 1.1 General remarks

### About this Document

This document did not change since the adf2002.03 version.

This document describes the QM/MM option within ADF, how to use it, how to set up inputs, what features are available, what its limitations are, and so on. This manual assumes that the reader already has experience with ADF and has some basic knowledge of molecular mechanics (MM) and combined QM/MM theories. A brief overview of the combined QM/MM methods is included.

This document is organized in the following manner. First, concepts and naming conventions that are used throughout the document are introduced. In Chapter 2, setting up a QM/MM simulation with ADF is discussed with a detailed description of all the input options (sections 2.1 and 2.2) and the Force Field files (section 2.3). Section 2.4 contains a 'walk through' of how to set up QM/MM jobs.

The combined QM/MM code and the documentation are in continuous development. We appreciate any comments, bug reports and suggestions for its improvement.

### Summary of Functionality

Currently, the QM/MM implementation within ADF is based on a modified version [1] of the 'IMOMM' scheme of Maseras and Morokuma [2] (called the IMOMM/ADF scheme); alternatively, the recently developed AddRemove scheme [3] is available. The molecular mechanics code has been designed to be as flexible as possible, allowing for many levels of customization. As a result of this flexibility, operation of the program requires the user to have some experience with molecular mechanics methods. At the same time, ADF remains the main driver to control the simulation of the whole QM/MM system, since one of the objectives of the implementation has been to treat the MM subsystem as a perturbation to the QM system.

We summarize the current functionality and limitations of the implementation:

- Morokuma's IMOMM [2] QM/MM coupling scheme (IMOMM/ADF).
- AddRemove [3] coupling scheme.
- AMBER95 [4] and SYBYL (Tripos) [5] force fields provided.
- Free form and modifiable force field parameter file.
- Ability to mix and match force field functions.
- Geometry optimization, linear transit and transition state optimizations (In these optimizations, the MM region is fully optimized between each SCF cycle or in other words between each QM geometry step).
- All ADF input 'styles' available (Cartesian, Z-matrix, mixed...).
- Any number of covalent bonds can cross the QM-MM boundary.
- Global optimization of the MM subsystem available (simulated annealing and grid search algorithms).

Some notable limitations are:

- Symmetry constraints cannot be applied, unless the MM subsystem is frozen.
- Geometry constraints involving MM atoms are limited.
- Not more than one QM atom can be bonded to a single MM atom.
- Not compatible with some ADF extensions such as NMR, ESR, COSMO, IRC and excited states.
- The AddRemove model is available only when using Cartesian coordinates.
- The conjugate gradient optimizer is available only for Cartesian coordinates.

## Applicability

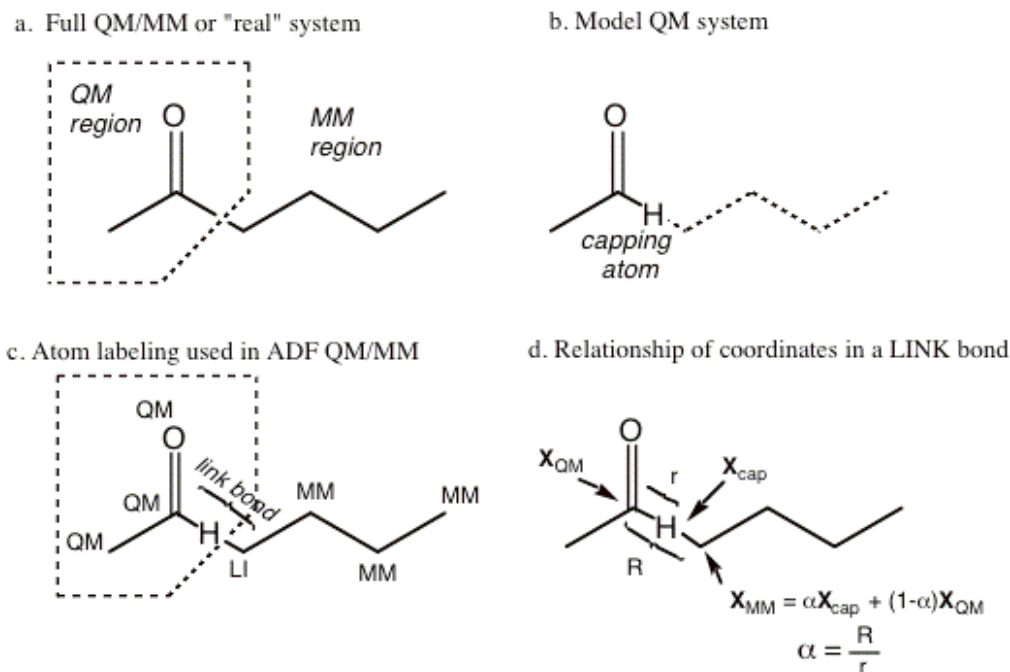
This QM/MM implementation evolved from research on organometallic complexes and catalytic systems. Since these systems are generally under 1000 atoms in size, the program had not been optimized to handle large macromolecular systems such as enzymes. In particular, the non-bonded code was not efficient for very large systems. It has been adjusted in the ADF2002.01 release, in order for the code to work efficiently on both small and large systems. Moreover, the calculation of the MM forces has been parallelized to further increase the efficiency and applicability. With the current release, systems with up to several thousand atoms have been tested without problems. Although the input is not designed to handle the topology of macromolecules such as amino acids and peptides, it can be constructed quite easily. For the large systems this amounts however to some 30000 lines; therefore, tools (pdb2adf) have been developed for creating input files automatically for a given PDB-file. This tool is available through a link on the 'Contributed Software' part of the SCM web site <http://www.scm.com>.

Currently, only the AMBER95 and SYBYL force fields are included. This might also limit the applicability. However, the force field parameters and potentials are fairly customizable and other force fields are easily added.

## 1.2 Concepts and Terminology

### LINK bonds

When performing a QM/MM simulation, one often wants to partition the system such that some covalent bonds cross the QM/MM boundary. These so-called 'link' bonds demand special attention in any QM/MM implementation. The link bonds are a critical aspect of the QM/MM method used here and a good understanding of the concepts is essential. In this section we describe how they are treated in ADF and we introduce the nomenclature that is used throughout the manual.



**Figure 1-1** Example of QM/MM partitioning and details of the naming conventions adopted in ADF.

Figure 1-1a depicts a simple molecular system that has been divided into QM and MM regions by the dotted polygon. In this example there is only one link bond, or one covalent bond that traverses the QM-MM boundary (that cross the dotted polygon). When a covalent bond traverses the QM-MM boundary, the electronic system of the QM region must in some way be truncated across this bond. Several methods of dealing with this problem have been proposed in the literature. By far the most commonly adopted method, which was originally introduced by Singh and Kollman [6], involves capping the QM system with a 'dummy atom' or what we call a 'capping atom' (We use capping atom to avoid confusion with the dummy atoms used in ADF). Since the pioneering work of Singh and Kollman [6] many variations of the basic capping atom approach have evolved. In ADF, one of the adopted approaches is the one developed by Maseras and Morokuma which has been given the name the 'Integrated Molecular Orbital and Molecular Mechanics' or the IMOMM method by the authors. The key feature of the capping atom approach is that the electronic structure calculation is performed on what is referred to as the 'QM model' system where the MM region is removed and replaced with capping dummy atoms (often hydrogen but not necessarily so). Figure 1-1b depicts the QM model system corresponding to the example system presented in Figure 1-1a. The capping atom satisfies the valence requirements of the QM region and allows for a standard electronic structure calculation to be performed on the QM fragment. It is important to realize that the capping atom is not part of the real system, but is simply an atom that is introduced to truncate the electronic system of the QM region. This is why it is often referred to as the dummy atom. For every 'link' bond there are three atoms of importance, the capping atom and the two atoms that are part of the 'real' link bond - one from the QM region and one from the MM region. Figure 1-1c illustrates the three atoms involved in the link bond. From this point on, we will refer to the MM atom that is part of the 'real' link bond as the link atom; it is labeled 'LI' in Figure 1-1c. Although both the QM and MM atoms that are part of the link bond could be considered 'link' atoms, we designate only the MM atom as the link atom, because it has a special place in the ADF QM/MM

input. It is this atom that is replaced by the capping atom in the electronic structure calculation of the QM model system.

Although the capping atom approach is convenient from the standpoint of the electronic structure calculation, the 'extra' capping atoms complicates the situation, as they do not exist in the real system, see Figure 1-1c. For each link bond, there are potentially three extra nuclear degrees of freedom (corresponding to the Cartesian coordinates of the capping atom) that are not present in the real system. In the IMOMM/ADF implementation [1] we alleviate the problem by removing the MM atom that is part of the 'real' link bond as a free variable. Instead we define its position in terms of the QM atom it is bonded to and the capping atom that replaces it in the QM model system. More specifically, the MM link atom is constrained to lie along the bond vector of the capping atom bond, via the simple relationship expressed in equation 1.1 and depicted in Figure 1-1d. Here,  $X_{MM}$ ,  $X_{cap}$  and  $X_{QM}$  refer to the Cartesian coordinates of the subscripted atoms and  $a$  is a constant defined as the ratio of the real link bond length to that of the length of the capping bond.

$$X_{LI} = a X_{cap} + (1 - a) X_{QM} \quad (1.1)$$

For each link bond, there is a unique  $a$  parameter that is held constant throughout the simulation. Since the capping atom is often at a shorter distance than the real MM atom,  $a$  is usually greater than unity. For example, when a Hydrogen capping atom is used to cap a C-C single bond,  $a$  is around 1.38. Note that the energy depends on the value chosen for this parameter  $a$ , and comparisons between two systems are meaningful only when the values for them are chosen equal.

Although the position of the MM atom is not an independent variable (or free degree of freedom), the bond length of the link bond can change during a geometry optimization. If the capping bond in the model QM system stretches or contracts, so does the link bond in the full system. Note that any forces exerted on the LI atom are projected onto the connected QM atom and onto the capping atom. For more details see references [1, 2].

In the AddRemove model [3] the position dependence is reversed. Instead of the *real* classical LI atom following the *artificial* capping atom, it is the position of the capping atom that is constrained:

$$X_{cap} = X_{QM} + R_{eq} U_{LI-QM} \quad (1.2)$$

Here  $R_{eq}$  is the equilibrium distance (from the force field !) for the QM-cap bond, while  $U_{LI-QM}$  is the unit vector pointing from QM to LI.

This means also that the artificial degrees of freedom of the *capping* atom are being removed ! Moreover, after every QM geometry optimization cycle, the interactions of the *artificial* capping atoms with the real QM atoms are corrected for by subtracting the corresponding MM interactions [3]. In this way, the capping atoms are Added and Removed. It has been shown [3] that this choice gives a much better description for the bonds involved in the QM/MM boundary region than the IMOMM/ADF scheme.

## The ADF QM/MM Hybrid Potential

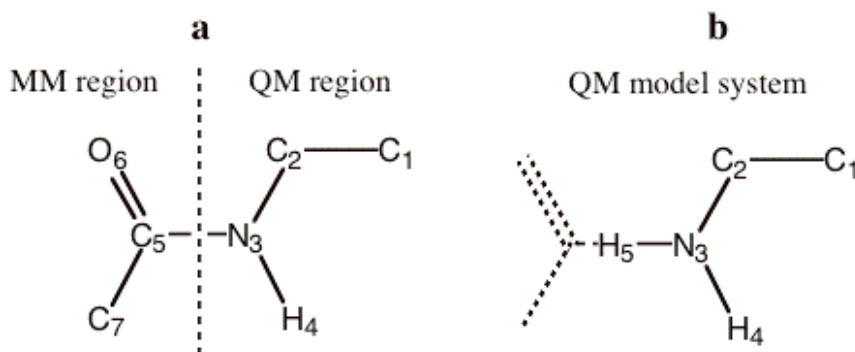
This section summarizes how the QM/MM hybrid potential is constructed in the IMOMM and AddRemove methods. A more detailed and formal discussion can be found in references [3] [2, 6]. The two basic components of the QM/MM potential are the potential arising from the electronic structure calculation of the QM model system and the potential arising from the molecular mechanics force field calculation.

In the IMOMM method the potential of the QM model system acts as a base where additional molecular mechanics potentials are added. When there are no covalent bonds that cross the QM/MM boundary the situation is straightforward. For example, consider a QM/MM simulation in which there are two molecules, one in the QM region and the other in the MM region such that no bonds cross the boundary. All MM potentials needed to define the MM molecule are included. Additionally, all non-bonded MM potentials between QM and MM atoms are included. All bonded MM potentials within the QM molecule are discarded because they are accounted for by the QM calculation.

When there are covalent bonds that cross the QM/MM boundary, the question of which MM potentials to accept and which to discard is not so easy to answer. Consider the system shown in Figure 1-2a, with one covalent bond that traverses the QM/MM boundary. Shown in Figure 1-2b is the equivalent QM model system with a capping hydrogen atom. In the IMOMM approach, MM potentials are only included if they depend on atoms that have no equivalent in the QM model system. Hence, any MM potential in which all atoms involved are QM atoms are NOT included in the total QM/MM potential, for instance the  $C_2-C_1$  bond stretching or

the  $C_2-N_3-H_4$  angle bending potentials. Furthermore, the  $C_5-N_3$  bond stretching potential is also not included, because an equivalent in the QM model system exists, namely the  $N_3-H_{cap}$  bond. The QM potential is assumed to adequately model the link bond. The same is true for the  $C_2-N_3-C_5$  bending potential. Again there is an equivalent in the QM model system that involves the capping hydrogen atom. The rule therefore also implies that any MM potentials in which only QM or LI atoms are involved, are NOT included in the hybrid QM/MM potential. On the other hand, all MM potentials that involve at least one or more MM atoms are included. For example,  $C_2-N_3-C_5-O_6$  torsion potential is included because there is no equivalent in the QM model system and the  $O_6$  atom is a pure MM atom.

There is only one exception. It involves the non-bonded interactions between QM atoms and LI atoms. From the rules above this MM potential should be discarded. However, in the IMOMM method this potential is included. The reasoning is that this interaction in the real system is not adequately modeled in the QM model system.



**Figure 1-2** a) QM/MM partitioning. b) The equivalent QM model system. The numeric subscripts simply refer to the atom numbering.

In the AddRemove model [3], things are less complicated. The classical LI atom is treated as a normal MM atom with corresponding MM potentials to both the MM and QM atoms. The same goes for the MM correction potentials of the capping atoms (only with the real QM atoms and other capping atoms). For the AddRemove model, it's best to view the setup as the setup of two systems, one with all *real* QM and MM atoms (case a) and one with the real QM atoms and the capping atoms (case b). For both you need to build up the force field; in the former case (a), all interactions involving only QM atoms are ignored (these are already present through the QM calculation), while in the latter case (b) all interactions without contributions from the capping atoms are ignored. The interactions of case (a) are the normal MM/MM and QM/MM interactions, while the interactions of case (b) are used for correcting the QM interactions of the capping atoms. This also means that an atomic force field type should be assigned to the capping atoms, which is being handled in the LINK\_BONDS block.

## Nomenclature and Terminology

This section summarizes the naming conventions that are used throughout this document. Some of the terminology has already been described in the previous section. Since the nomenclature describing the link bonds can be somewhat confusing we recommend that special attention be given to this section.

### Full QM/MM system vs. QM model system

When performing a combined QM/MM simulation, the molecular system is divided into QM and MM regions as shown in Figure 1-1a. We will refer to the total hybrid system as the 'full system' or sometimes we will refer to it as the 'real system'. The 'QM model system' is the capped system for which the electronic structure calculation is performed. Figure 1-1a shows the full system and Figure 1-1b depicts the corresponding QM model system.

### Link bonds and capping atoms

The 'link bonds' are those covalent bonds that cross the QM-MM boundary in the full QM/MM system. A link bond involves one

atom that belongs to the MM region and one from the QM region, see Figure 1-1a. The 'capping atoms' (sometimes termed dummy atoms) refer to the atoms that are used to cap the valence in the model QM system. Capping atoms are not part of the full system. The 'capping bond' is the covalent bond in the QM model system that corresponds to the link bond in the real system. The terms capping atom or capping bond only refer to the model QM system, whereas the term LINK only refers to bonds or atoms in the real system.

## QM, MM and LI atom types

In the ADF QM/MM input, each atom in the full system must be designated as a QM, MM or LI atom, where LI refers to link. Figure 1-1c shows these designations for the example system. Although two atoms are involved in a LINK bond, we only designate the atom in the MM region as the LI atom. We do so because this atom corresponds to a capping atom in the QM model system. In systems where there are no covalent bonds that cross the QM/MM boundary, there will be no LI atoms.

## Atom types

There are several different meanings of the term atom and atom type that have arisen because of the hybrid nature of the QMMM method, see the following items.

### QM/MM type or QM/MM atom type (MM, QM or LI)

Refers to the partitioning of the full system into QM and MM regions. As described above, there are only three QM/MM types allowed: QM, MM, and LI. Each atom in the full system is assigned a QM/MM atom type in the MM\_CONNECTION\_TABLE subkey block.

### Force Field atom type

The atom type used in the force field calculation. Each atom in the full system is assigned a force field atom type in the MM\_CONNECTION\_TABLE subkey block of the input. Force field atom types assigned to each atom must correspond to atom types defined in the Force field file. Force field atom types must be assigned to all atoms, even the QM atoms because the non-bonded interactions between QM and MM atoms are treated by a molecular mechanics potential.

### ADF atoms or ADF fragments

The atom types used for the electronic structure calculation of the model system. These are the atoms or fragments defined in the FRAGMENTS key block in a standard ADF calculation. The ADF fragment types used for the capping atoms are defined in the LINK\_BONDS subkey block. Note that capping atoms can only be single atom fragments, not compound fragments as allowed by ADF.

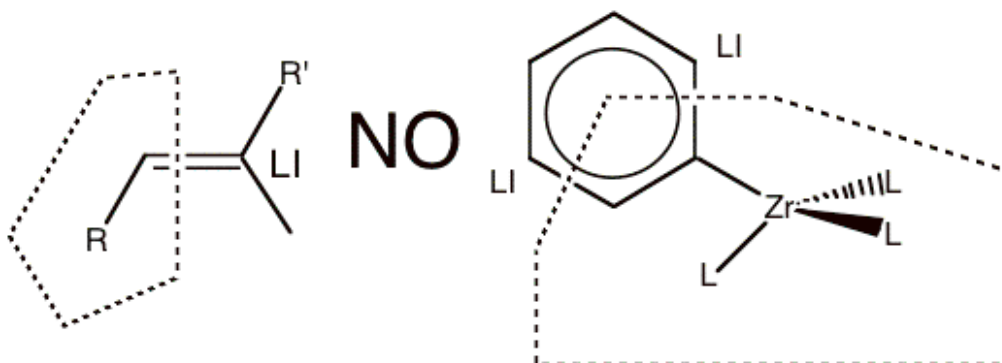
## Partitioning into QM and MM regions

In a QM/MM simulation the basic question is how to partition the system into QM and MM regions. When studying an active site of a catalyst, for example, one must decide where to put the QM/MM boundary. Putting the boundary too close to the reaction center will question the chemical realism of the model. On the other hand, if one makes the boundary too far away, the computational expense of the QM calculation may become problematic. Each system is different in this respect and the user must make the proper tests to validate the appropriateness of the QM/MM partitioning used. We strongly suggest that the reader examines the literature on QM/MM methods and understands the basic limitations of the approach.

Below we give examples of QM/MM partitioning that should not or can not be used. For comparison, we also give some

representative examples of QM/MM partitioning that the program does allow. In the examples, the region enclosed in the dotted polygon represents the QM region and the atoms labeled with 'LI' are the so-called Link atoms.

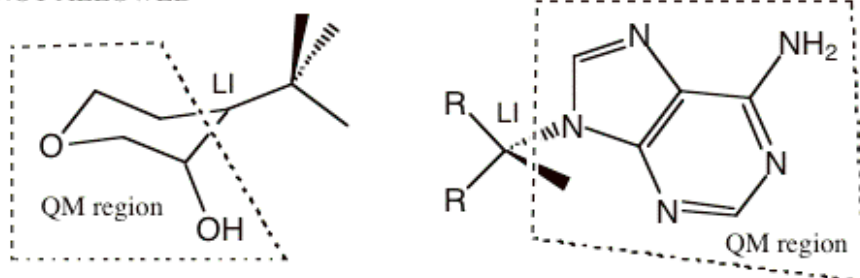
First, the QM/MM boundary should not cut across double, triple or aromatic bonds as shown in Figure 1-3. In these examples, a simple capping atom does not satisfy the valence of the QM fragment and the electronic structure of the QM model system would be drastically different from that of the 'real' system.



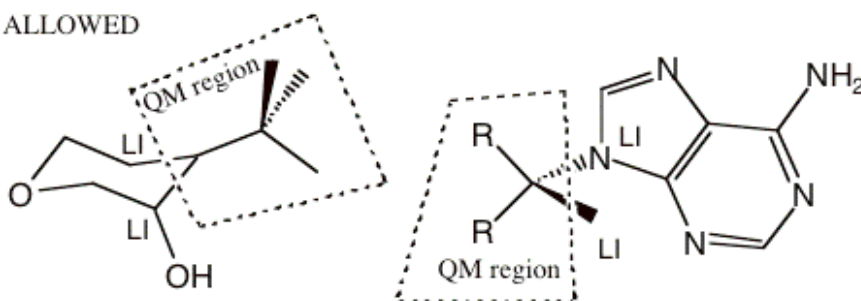
**Figure 1-3** Examples of partitioning that should not be used because the link bonds are double or aromatic bonds.

Next, figure 1-4a depicts examples of partitioning that are not allowed because the LI atom has a covalent bond to more than one QM atom. A LI atom can only be bonded to one QM atom. Figure 1-4b shows the opposite, which is allowed. In other words, one QM atom can be bonded to more than one LI atom. This is due to the partitioning scheme that was used and the geometric relationship expressed in Equation 1.1, which restricts the position of the link atom, based on the QM and dummy atom. Note that there is no limit to the number of LI atoms or link bonds, just that each LI atom can only be bonded to one QM atom.

**a NOT ALLOWED**



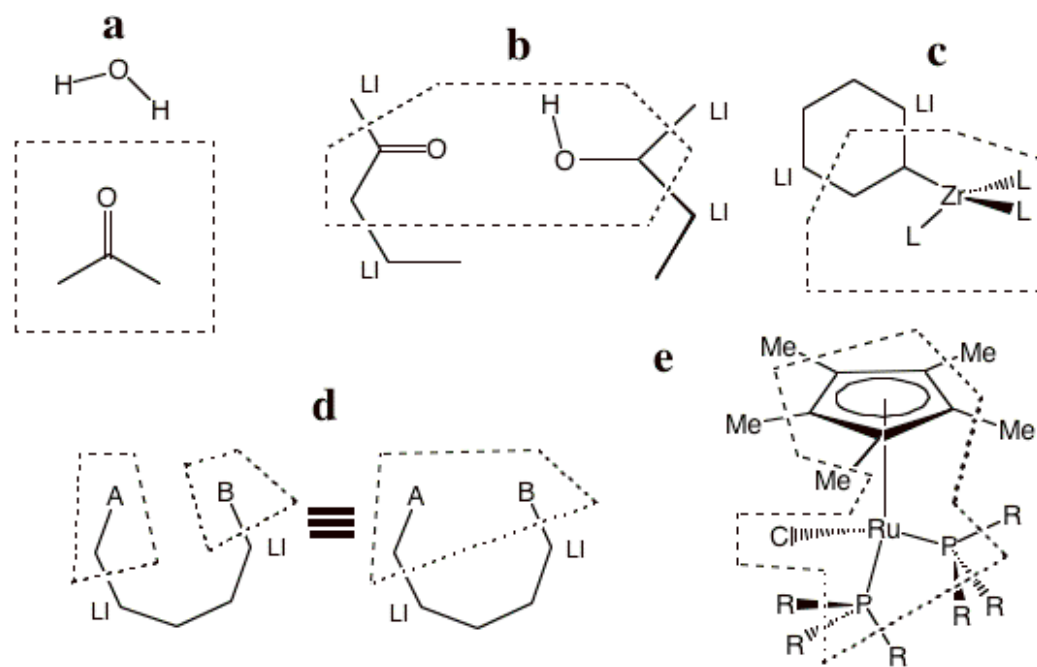
**b ALLOWED**



**Figure 1-4** a) Examples of partitioning that are not allowed because the LI atom has a covalent bond to more than one QM atom. b) The allowed reverse of the examples showed in (a). A LI atom **can** be bonded to more than one QM atom.

Then, figure 1-5 provides some representative examples of partitioning that the program does allow. Example **a** shows a typical solute-solvent QM/MM partitioning where there are no link bonds at all. Example **b** depicts two separate molecules each possessing a QM and a MM region. We emphasize that any number of molecules and link bonds can be used. Recall that in the IMOMM/ADF method all link bonds have a different parameter associated with them, each specified by the user, upon which the energy depends (and which are difficult to choose or generalize). In example **b** there would be four independent parameters. Example **c** seems very similar to the earlier example in Figure 1-3. The difference is that the ring in Figure 1-3c is not aromatic

and consequently the link bonds in example **d** cross *single* bonds. Example **d** shows a single molecule, with two QM regions separated a MM region. For this example, two equivalent pedagogic representations of the sample partitioning are displayed. Example **e** is a complex organometallic system that we have tested the QM/MM approach on.



**Figure 1-5** Representative examples of QM/MM partitioning that can be used in ADF QM/MM ADF.

## 1.3 Implementation

### ADF QM/MM

The basic philosophy of the ADF QM/MM implementation has been to treat the MM region as a perturbation to the QM model system. The atoms of the QM model system are controlled by ADF as they would in a regular pure QM run, whereas the MM atoms are treated 'separately'. For example, when geometry optimization is performed, the Hessian matrix is only generated / updated for the QM model system. This is possible because at each geometry step the MM subsystem is fully optimized (with the QM and LI atoms frozen). One should be aware however that there are not necessarily six zero eigenvalues of the Hessian, as the QM system is coupled to the MM system (and therefore not free to rotate/translate !). When internal coordinates are used to define the structure of the complex, the atoms of the QM model system are optimized using the internal coordinate system, whereas the MM subsystem is fully optimized at each step within the Cartesian coordinate system. Figure 1-6 shows the flow control of the ADF QM/MM implementation.

The geometry optimization of the MM subsystem is controlled separately from the QM system. For example, the default convergence criteria for the MM subsystem are far stricter than that of the QM system. Furthermore, there are options to use global optimization techniques on the MM subsystem, see the detailed description of input options later in this manual.

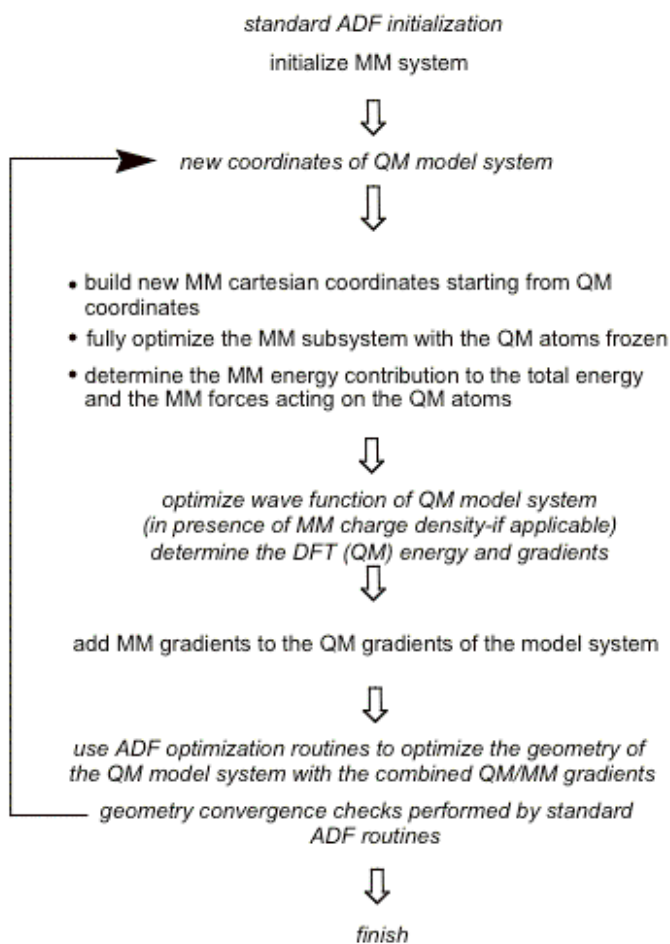


Figure 1-6. Schematic representation of the ADF QM/MM implementation

## Limitations, Bugs and Deficiencies

Listed here is a list of known bugs, deficiencies and limitations of the ADF QM/MM implementation. Please contact us if you find new entries to this list.

- The MOPAC input option introduced with ADF99 can not be used with the QM/MM option.  
The QM/MM feature of ADF requires the traditional ADF input styles.  
However, all options within the tradition ADF input format can be used, such as CART, ZMAT, and ZCART.
- Geometry constraints cannot be applied to MM atoms when using internal coordinates for optimization.  
Currently constraints can only applied to MM atoms when the optimization is performed in Cartesian coordinates.
- Linear transit coordinates cannot involve any MM atoms.
- See also the Limitations part at the beginning of this document.

## 2 ADF QM/MM

### 2.1 Input: The Essentials

#### Overview

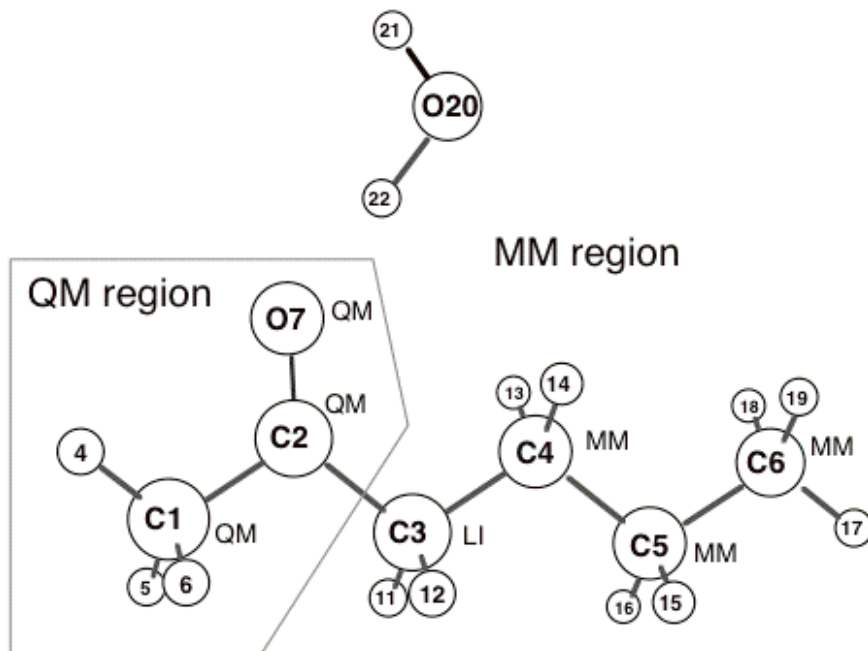
Compared to a standard ADF run, there are two additional input components required to run an ADF QM/MM simulation:

- The QMMM key block has to occur in the ADF input file
- A separate force field parameter file.

In this section we describe how to set up an ADF QM/MM simulation, assuming an appropriate force field file is already available. A full description of all of the options and of the FORCE FIELD file is provided in later sections.

#### Example Input

Let Figure 2-1 show the molecular system that we want to simulate and the intended partitioning. Note that this is the same system as shown in Figure 1-1 except that a non-bonded water molecule has been added to the MM region.



**Figure 2-1.** Sample structure. Atom numberings and the QM/MM atom types (QM, MM and LI) are shown.

Example 2.1 below shows the ADF input file for the simulation with the geometry defined in Cartesian coordinates. The initial atomic coordinates of the full QM/MM system are defined as they would be in a normal ADF run with the ATOMS and GEOVAR key blocks. Notice that the subkey blocks within the QMMM key block (e.g. MM\_CONNECTION\_TABLE) end with SUBEND. If they were closed by 'END' ADF would consider the QMMM key block complete at that point.

#### Example 2.1:

```
| Title example QM/MM input
| Fragments
```

```
C C.t21
H H.t21
O O.t21
End
```

```
Symmetry NOSYM
Charge 0 0
```

## ATOMS

```
1 C 0.00000 0.00000 0.00000
2 O 1.48700 0.00000 0.00000
3 C -0.76430 1.32381 0.00000
4 C -0.76428 -1.32378 -0.00002
5 H -0.50028 -1.89680 -0.89230
6 H -0.50028 -1.89683 0.89224
7 H -1.83868 -1.12409 -0.00002
8 H -1.40364 1.39261 -0.88358
9 H -1.40364 1.39261 0.88358
10 C 0.22461 2.48208 0.00000
11 H 0.85235 2.42365 -0.89260
12 H 0.85235 2.42365 0.89260
13 C -0.53689 3.80103 0.00000
14 H -1.16478 3.85787 -0.89260
15 H -1.16478 3.85787 0.89260
16 C 0.45222 4.95913 -0.00000
17 H 1.08538 4.90988 -0.88932
18 H 1.08538 4.90988 0.88932
19 H -0.08590 5.91026 0.00000
20 H 2.43700 1.64545 0.00000
21 O 3.03926 2.50556 -0.00000
22 H 3.96191 2.28678 -0.45094
```

END

## QMMM

```
FORCE_FIELD_FILE sybyl.ff
RESTART_FILE mm.restart
OUTPUT_LEVEL=1
WARNING_LEVEL=1
ELSTAT_COUPLING_MODEL=0
LINK_BONDS
1-3 1.38000 H
SUBEND
```

## MM\_CONNECTION\_TABLE

```
1 C_2 QM 2 3 4
2 O_2 QM 1
3 C_3 LI 1 8 9 10
4 C_3 QM 1 5 6 7
5 H QM 4
6 H QM 4
7 H QM 4
8 H MM 3
9 H MM 3
10 C_3 MM 3 11 12 13
11 H MM 10
```

```

12 H MM 10
13 C_3 MM 10 14 15 16
14 H MM 13
15 H MM 13
16 C_3 MM 13 17 18 19
17 H MM 16
18 H MM 16
19 H MM 16
20 H MM 21
21 O_3 MM 20 22
22 H MM 21
SUBEND
END

GEOMETRY
  ITERATIONS 20
  CONVERGE E=1.0E-3 GRAD=0.0005
  STEP RAD=0.3 ANGLE=5.0
  DIIS N=5 OK=0.1 CYC=3
END

XC
  LDA VWN
  GGA POSTSCF Becke Perdew
End

Integration 3.0

SCF
  Iterations 60
  Converge 1.0E-06 1.0E-6
  Mixing 0.20
End
End Input

```

## Defining the Coordinates

The initial coordinates of the full QM/MM system are defined with the ATOMS and GEOVAR key blocks as in a normal ADF run. All input methods allowed by ADF can be used with the exception of the new MOPAC option introduced in ADF1999. For example the coordinates can be defined in Cartesian coordinates as in the example above, by a Z-matrix or by the mixed Z-CART method. It is important to realize that only the initial coordinates of the full or real system are required as input. There is no need to define the coordinates of the QM model system or of the dummy capping atoms. The partitioning of the system into QM and MM regions, and the parameters required to define the capping atoms are given in another part of the input. The program will automatically generate the QM model system and the position of the capping atoms.

**IMPORTANT:** There is a strict rule concerning the order of the atoms in the ADF input during a QM/MM simulation. Namely, **the QM atoms and the LI atoms must precede any MM atoms in the input.** The QM and LI atoms can come in any order as long as they come before any MM atoms. The program will check this and abort if this is violated.

### ADF atoms and fragments

The typical ATOMS key block in ADF has the following format:

```

| ATOMS
| {n} atom coordinates {f=fragment}

```

```

| ...
| END

```

For the QM atoms, the atom labels and fragments should be defined as in a normal ADF run. The atom labels for the MM atoms are not read by the program. Instead, the MM force field atom types for all atoms are defined in the MM\_CONNECTION\_TABLE subkey block. Similarly if fragments are defined for the MM atoms, the program also ignores these. This is also true of the LI atoms, since in the calculation of the QM model system, capping atoms replace link atoms. The replacement atom type used for the electronic structure calculation is defined in the LINK\_BONDS subkey block.

## QMMM key block

The QMMM key block, which is in bold face in example 2.1, is a mandatory key block. This key block is necessary to invoke a combined QM/MM simulation. It contains the connection table and the force field atom types needed to define the molecular mechanics potential. If link bonds are present then it defines the necessary parameters for each link bond.

This section also explains how to specify the Force Field file to use and various other options.

### FORCE\_FIELD\_FILE

Keyword (required, default = amber95.ff)

This keyword simply defines the full path of the force field file to be used for the molecular mechanics potential. The location of the force field file is given after the keyword. The full path can be given, or just the file name. In the latter case, the program looks in the current directory that ADF is executing in.

Examples:

```

| FORCE_FIELD_FILE /home/username/sybyl.ff
|
| FORCE_FIELD_FILE sybyl.ff

```

### MM\_CONNECTION\_TABLE

Subkey block (required)

This key block defines the connection table, the force field atom types and the partitioning of the full system into QM and MM regions. It is critical that the atoms specified in this key block are in the same order as in the ATOMS key block. This is important, because the program may not detect this type of input error and you would get ridiculous results.

```

| MM_CONNECTION_TABLE
|   n FF_LABEL MM_TYPE connection numbers
|   ...
| END

```

The labels are defined in the following table.

<i>input column</i>		
1	N	atom number
2	FF_LABEL	Force field atom type. These labels correspond to the atom types defined in the force field file. They can be up to four characters long. Xx defines dummy atoms.
3	MM_TYPE	QM, MM or LI
4-	connection numbers	These define to which atoms the current atom has a covalent bond. These connections are used to generate the molecular mechanics potential. Currently, a maximum of 6 connections is allowed per atom.

The connection table should be a fully redundant one. In other words, if atom #1 is bonded to atom #5, they each should have the other atom listed in their connections.

Example:

```

1 C_2 QM 2 3 4 5
2 O_2 QM 1
3 H QM 1
4 C_3 QM 1 5 6 7
5 Cu QM 4 1
6 H QM 4

```

A fully non-redundant connection table is also supported. In such a connection table, once a bond is mentioned, it is not mentioned again. In other words, the connection list for any atom cannot contain an atom, which precedes it in the atom numbering.

Example:

```

1 C_2 QM 2 3 4 5
2 O_2 QM
3 H QM
4 C_3 QM 5 6 7
5 Cu QM
6 H QM

```

These two connection tables are equivalent. Connection tables that are semi-redundant might cause problems. We recommend the fully redundant connection table.

#### LINK\_BONDS

Required for systems with LINK bonds

This key block required for systems with covalent bonds that cross the QMMM boundary. These bonds are referred to in this document as the link-bonds. Each link bond has a constant parameter '*alpha*' associated with it, which is defined as the ratio of the bond length in the real system and of the capping bond in the model QM system. See Section 1 or reference [1] more details. To determine the *alpha* parameters for each link bond, one can take the capping atom bond distance in a 'pure QM' calculation of the QM model system and ratio it to the corresponding bond distance in the real system. These ratios are typically around 1.30 to 1.50 when hydrogen as a capping atom. The LINK\_BONDS subkey block has the following format:

```

LINK_BONDS
  atom_a - atom_b alpha replacement_fragment [addremove_force_field_type]
  ....
SUBEND

```

Example:

```

LINK_BONDS
  15 - 3 1.42 H H1
  8 - 1 1.40 Cl.dzp Cl
SUBEND

```

The integers *atom\_a* and *atom\_b* refer to the numbering of the two atoms involved in the link bond. One of the atoms will be a LI type atom whereas the other will be a QM type atom. *atom\_a* and *atom\_b* must be separated by " - " with at least one space between the integer and the hyphen. In other words '3 - 4' is OK, but not '3-4' '3 -4'. Atoms need not be in any particular order, and the order of the link bonds is also not important. Following this is the *alpha* parameter for that specific bond. The *replacement\_fragment* is the ADF atom used for the capping atom in the electronic structure calculation of the QM model system. Often the capping atom is a hydrogen atom, however, it need not be. The *replacement\_fragment* must be present in the FRAGMENT key block in the ADF input file. The *addremove\_force\_field\_type* need only be present for the AddRemove model [3], and indicates the force field type of the capping atom (similar to FF\_LABEL in the MM\_CONNECTION\_TABLE block).

Important note: It is very important to realize that the Hamiltonian depends on the a parameters used. Thus, when comparing relative energies for example, one has to take care that the a's corresponding to the same bonds are identical.

## Restarts

For the most part, restarts with ADF QM/MM are the same as in a standard ADF run. In other words to specify a restart, one

needs to use the RESTART keyword. This signals the QM/MM extension to read the data from the QM/MM restart file as opposed to the input. It is important to emphasize that the **QM/MM extension has its own restart file**. Thus, the user will have to keep track to two restart files, the standard ADF restart file (TAPE21) and the QM/MM restart file. By default the QM/MM restart file is 'mm.restart', but you can change this by using the RESTART\_FILE keyword **within the QMMM key block**. A truncated example of an ADF QM/MM restart input is given below:

```

RESTART ADF_restart.file & {same as in a standard ADF run}
  NOHES
END

QMMM
  RESTART_FILE mm_restart.file {optional, with default filename of 'mm.restart'}
  FORCE_FIELD_FILE sybyl.ff
  OUTPUT_LEVEL=1
  WARNING_LEVEL=1
  ...
  ...
  ...
END

```

At the moment, when the RESTART keyword is used, the QM/MM extension will always look for the QM/MM restart file. There is no way to bypass this. However, the QM/MM restart file is simply a text file whose contents resemble those of the QMMM key block in the ADF QM/MM input and you can easily modify it.

It is also important to note that the RESTART\_FILE both specifies the file to be read at the beginning of a restarted run, and the file that will be written to. In an ADF QM/MM run that was restarted, the initial QM/MM restart file is overwritten.

## Geometry Constraints and Fixing Coordinates of MM atoms

Constraints can be applied to coordinates in the same way they are done with a standard ADF run (i.e. most commonly through the GEOVAR key block). There are no limitations to applying geometry constraints to QM or LI atoms, however, there exist some limitations to applying geometry constraints to MM atoms, particularly when using a Z-matrix.

When a geometry optimization is performed in Cartesian coordinates there is almost no limitation to applying constraints to MM atoms. One important exception is that linear transit constraints can not involve MM atoms. At the moment constraints cannot be applied to the coordinates that define the position of the MM atoms when internal (ZMAT) coordinates are used. Note that constraints still can be applied to the coordinates of the QM atoms, but just not to the MM atoms.

**Symmetry constraints** can not be applied with a QM/MM run, unless all of the MM atoms are frozen. Furthermore, the program will not check that the atoms of the MM region satisfy the imposed symmetry.

## Miscellaneous Notes

### Using ADF Dummy Atoms

It is often necessary to use dummy atoms when defining a Z-matrix for a geometry optimization. (Here we are **not** referring to the capping dummy atoms) Dummy atoms are allowed in a QM/MM simulation and they can be used just as they would in a normal ADF run. There are a few things to remember when using dummy atoms in a QM/MM run.

If a dummy atom is to be used to define the coordinates of QM atoms in a Z-matrix for geometry optimization, the dummy atom must precede any MM atoms in the atom list. In this case one should consider the dummy atom as part of the model QM system.

Atom should be given the Xx force field atom type in the MM\_CONNECTION\_TABLE key block. (In this way the atom is excluded from the non-bonded pair list)

Do not make any bonds to the dummy atom in the connection table; otherwise the program may require the user to define

molecular mechanics potentials involving the dummy atom.

Dummy atoms are allowed in the MM region, however, they will only be used to define the initial coordinates. This is because the MM subsystem is always optimized in Cartesian space where dummy atoms are not necessary.

One can consider dummy atoms as part of the model QM system. For example, the following is not allowed because the dummy atom, which is assigned to the QM region, comes after atoms 5 and 6, which are MM, atoms.

```
MM_CONNECTION_TABLE
1 C_2 QM 2 3 4
2 O_2 QM 1
3 C_3 LI 1 8 9 10
4 C_3 QM 1 5 6 12
5 C_3 MM 4
6 C_3 MM 4>
7 Xx QM
8 H MM 3
...
SUBEND
```

The example below is almost identical to the above example except that the dummy atom is assigned as a MM atom. Although this is allowed, this dummy atom will be optimized as a MM atom.

```
MM_CONNECTION_TABLE
1 C_2 QM 2 3 4
2 O_2 QM 1
3 C_3 LI 1 8 9 10
4 C_3 QM 1 5 6 12
5 C_3 MM 4
6 C_3 MM 4
7 Xx MM
8 H MM 3
...
SUBEND
```

The final example below, is probably what is wanted. Here the dummy atom is a QM atom and comes before any MM atoms. In this way, the dummy atom can be used to define the Z-matrix with the QM model system.

```
MM_CONNECTION_TABLE
1 C_2 QM 2 3 4
2 O_2 QM 1
3 C_3 LI 1 8 9 10
4 C_3 QM 1 5 6 12
5 Xx QM
6 C_3 MM 4
7 C_3 MM 4
8 H MM 3
...
SUBEND
```

### Linear Transit Runs.

The QM/MM option can be used with the LINEAR TRANSIT option in ADF. However, the linear transit parameter or coordinate cannot involve any MM atoms. In other words, the linear transit parameter can only be defined in terms of QM atoms only.

### Frequency Runs with QM/MM

At the moment, a FREQUENCY run can not be performed when using a QM/MM potential in ADF. This option has been implemented but has been disabled in this release for further testing.

## 2.2 QMMM keyblock options

### Introduction

Chapter 2 explains setting up an ADF QM/MM simulation. This section describes the available options that you can define in the QMMM key block. This section is essentially a reference source. The main components of the QMMM key block, the MM\_CONNECTION\_TABLE, the FORCE\_FIELD\_FILE, and the LINK\_BONDS key blocks that are described in detail in the previous chapter are repeated here (with some additional notes). Please note that the global optimization options are not well tested and are prone to crashing the run. If one is interested in using these options, please be aware of this fact. We appreciate reports of any failures.

### Example Input

In this section we simply provide a few examples of the QM/MM key block. In some examples, the MM\_CONNECTION\_TABLE and LINK\_BONDS subkey blocks are not filled.

**Example 3.1** This example depicts a global optimization of the MM region with the simulated annealing-like optimizer available in the QM/MM program. The global search involves 100 ps of MD at 1000 K with 100 structures sampled in regular intervals during the simulation. Each of the 100 structures is then partially optimized, and then the 10 best are fully optimized. At the end of this, the lowest energy structure is used for the QM/MM run. Note that in this MD search, the QM atoms, including the link atoms are frozen.

```

QMMM
  FORCE_FIELD_FILE sybyl.ff
  OUTPUT_LEVEL 1
  WARNING_LEVEL 1
  ELSTAT_COUPLING_MODEL 1
  OPTIMIZE
    GLOBAL
      METHOD MD_SEARCH
      FREQUENCY ONCE
    SUBEND
  SUBEND
  MD_SEARCH
    TIME{PS} 100.0
    N_STRUCTURES 100
    TEMPERATURE 1000.0
  SUBEND
  MM_CONNECTION_TABLE
    ...
  SUBEND

  LINK_BONDS
    ...
  SUBEND
END

```

**Example 3.2** In this example, custom charges are assigned to some of the atoms. Charges for atoms that were not given specific charges in the QMMM key block are assigned on a per atom-type basis from the force field file. Also note that this example has no LINK\_BONDS subkey block. This is only allowed if there are not link bonds, as in the example in Figure 1-2a.

```

| QMMM

```

```

FORCE_FIELD_FILE sybyl.ff
OUTPUT_LEVEL 1
WARNING_LEVEL 1
ELSTAT_COUPLING_MODEL 1
MM_CONNECTION_TABLE
...
SUBEND

CHARGES
  0.4
  0.3
  3 -0.1
SUBEND
END

```

## Description of Options

### FORCE\_FIELD\_FILE

Keyword (required, default = amber95.ff)

This keyword simply defines the full path of the force field file to be used for the molecular mechanics potential. The location of the force field file is given after the keyword. The full path can be give, or just the file name. In the latter case, the program checks the current directory that ADF is executing in.

Examples:

```

| FORCE_FIELD_FILE /home/username/sybyl.ff
|
| FORCE_FIELD_FILE sybyl.ff

```

### OUTPUT\_LEVEL

Keyword (Default = 1)

The integer following this keyword specifies the amount of output to be printed to the ADF output file.

0: minimal output

1: normal output

2: trouble shooting output

OUTPUT\_LEVEL 2 is recommending for initially setting up a job. However, once the job is set up properly this output level is probably too verbose.

### WARNING\_LEVEL

Keyword (Default = 1)

The performs some checking of the input, ranging from examining all interatomic distances to examining the input order of the QM, LI and MM atoms. The integer following this keyword specifies how many warnings to report and when to stop the run due to the warning.

-1: Report only the most severe warnings, and never stop the run. Useful when user is knowingly violating the 'rules'.

0: Report severe warnings and only stop at 'fatal' errors.

1: Report all warnings, stop at severe and fatal errors. This is the default.

2: Report all warnings and stop at any of them. Useful when initially setting up a job.

### MDC\_LEVEL

Keyword (Default = 3)

The integer following this keyword specifies the level of the Multipole Derived Charge analysis [7] used in conjunction with ELSTAT\_COUPLING\_MODEL=4.

1: MDC-m charges are used to update charges of QM system.

2: MDC-d charges used.

3: MDC-q charges used.

#### MM\_CONNECTION\_TABLE

Subkey block (required)

This key block defines the connection table, the force field atom types and the partitioning of the full system into QM and MM regions. It is critical that the atoms specified in this key block are in the same order as in the ATOMS key block. This is important because it is difficult for the program to detect this type of input error.

```
MM_CONNECTION_TABLE
  n FF_LABEL MM_TYPE connection numbers
  ...
SUBEND
```

The labels are defined in the following table.

input column		
1	n	atom number
2	FF_LABEL	Force field atom type. These labels correspond to the atom types defined in the force field file. They can be up to four characters long. Xx defines dummy atoms.
3	MM_TYPE	QM, MM or LI
4-	connection numbers	These define the atoms to which the current atom has a covalent bond. These connections are used to generate the molecular mechanics potential. Currently, a maximum of 6 connections is allowed per atom.

The connection table should be a fully redundant one. In other words, if atom #1 is bonded to atom #5, they each should have the other atom listed in their connections.

Example:

```
1 C_2 QM 2 3 4 5
2 O_2 QM 1
3 H QM 1
4 C_3 QM 1 5 6 7
5 Cu QM 4 1
6 H QM 4
```

A fully non-redundant connection table is also supported. In such a connection table, once a bond is mentioned, it is not mentioned again. In other words, the connection list for any atom cannot contain an atom that precedes it in the atom numbering.

Example:

```
1 C_2 QM 2 3 4 5
2 O_2 QM
3 H QM
4 C_3 QM 5 6 7
5 Cu QM
6 H QM
```

These two connection tables are equivalent. Connection tables that are semi-redundant might cause problems. We suggest using the fully redundant connection table.

#### LINK\_BONDS

Required for systems with LINK bonds

This key block required for systems with covalent bonds that cross the QM/MM boundary. These bonds are referred to in this document as the link-bonds. Each link bond has a constant parameter '*alpha*' associated with it, which is defined as the ratio of the bond length in the real system and of the capping bond in the model QM system. See Section 1 and the Appendix for more details.

To determine the *alpha* parameters for each link bond, one can take the capping atom bond distance in a 'pure QM' calculation of the QM model system and ratio it to the corresponding bond distance in the real system. These ratios are typically around 1.30 to 1.50 when hydrogen as a capping atom. The LINK\_BONDS subkey block has the following format:

```
LINK_BONDS
  atom_a - atom_b alpha replacement_fragment addremove_force_field_type
  ....
SUBEND
```

Example:

```
LINK_BONDS
  15 - 3 1.42 H H1
  8 - 1 1.40 Cl.dzp Cl
SUBEND
```

The integers *atom\_a* and *atom\_b* refer to the numbering of the two atoms involved in the link bond. One of the atoms will be a LI type atom whereas the other will be a QM type atom. *Atom\_a* and *atom\_b* must be separated by " - " with at least one space between the integer and the hyphen. In other words '3 - 4' is correct, but not '3- 4' '3 -4'. Atoms need not be in any particular order, and the order of the link bonds is also not important. Following this is the *alpha* parameter for that specific bond. The *replacement\_fragment* is the ADF atom used for the capping atom. Often the capping atom is a hydrogen atom, however, it need not be. The *replacement\_fragment* must be present in the FRAGMENT key block in the ADF input file. The *addremove\_force\_field\_type* need only be present for the AddRemove model [3], and indicates the force field type of the capping atom (similar to FF\_LABEL in the MM\_CONNECTION\_TABLE block).

Important note: It is very important to realize that the Hamiltonian depends on the a parameters used. When comparing relative energies for example, one needs to take care that the a's corresponding to the same bonds are identical.

## CHARGES

Key block (optional)

This key block defines the initial charges on each atom based on their atom **number**. Atom numbers must be carefully specified because the program does not assume any order. Charges can also be assigned based on their atom **type** from the force field file in the CHARGE PARAMETERS key block. If this key block does not specify charges, the program looks for charge assignments from the force field file. If charges are not assigned in either this key block or the force field file, then a charge of 0.0 is assigned. When polarizable electrostatic coupling is invoked, the charges for QM and LI atoms are not read, because the MM point charges interact with the QM charge distribution. With ELSTAT\_COUPLING\_MODEL=4, these charges (for the QM system) are used only in the first cycle of the geometry optimization: after each cycle, the QM charges are replaced with the Multipole Derived Charges.

Example:

```
CHARGES
  3 -0.10000
  1 0.05000
  2 0.05000
SUBEND
```

## ELSTAT\_COUPLING\_MODEL

Keyword (optional, default=1)

This keyword controls the type of electrostatic model that is used, including whether true electrostatic coupling between the QM and MM regions is evoked.

Coupling Model	Description
0	Electrostatics OFF
1	Simple electrostatic coupling, where there is no polarization of the QM wave function, i.e. pure MM coupling.

2	Electrodynamic coupling, where the point charges in the MM region can polarize the wave function. <b>This option is not currently functional.</b>
4	Simple electrostatic coupling, like option 1. But the point charges of the QM region are updated throughout the geometry optimization using the Multipole Derived Charge analysis [7] (MDC-x level depending on MDC_LEVEL).

## OPTIMIZE

Key block (optional)

This key block allows the user to modify the geometry optimization settings. An example of a key block with many available options is shown below:

```

OPTIMIZE
  MAX_STEPS 1000
  MAX_GRAD 0.001
  PRINT_CYCLES 20
  METHOD BFGS

  GLOBAL
  METHOD GRID
  FREQUENCY ONCE
  SUBEND

  GRID
  INCREMENT 20.0
  BOND 2 - 4
  BOND 2 - 3
  SUBEND
SUBEND

```

Sub-options to this key are described next.

OPTIMIZE: MAX\_STEPS

Keyword (optional, default = 1000)

This keyword defines the maximum number of optimization steps allowed before the optimization is discontinued.

OPTIMIZE: MAX\_GRADIENT

Keyword (optional, default = 0.01 kcal/mol·Å)

This keyword allows the user to change the convergence criteria. For now, the optimization is considered converged when the maximum gradient on any MM atom is less than MAX\_GRADIENT. The default value will provide gradients that are very small, especially when compared to the convergence criteria specified most electronic structure codes. NOTE: The gradients on the QM atoms due to the MM potentials are not accounted for in the convergence criteria. Large MM forces can exist on the QM atoms after the optimization.

OPTIMIZE: METHOD

Keyword (optional, default = BFGS, available: BFGS, STEEPEST\_DESCENT, CONJGRAD)

For the most part, the default quasi-Newton optimizer with BFGS Hessian update scheme is very stable, and converges well. Other optimizers available are the steepest descent method (STEEPEST\_DESCENT) and conjugate gradient (CONJGRAD). STEEPEST\_DESCENT and CONJGRAD are almost always less efficient than the BFGS optimizer (particularly close to the minimum). It is notable that the Hessian based BFGS method requires more memory than the STEEPEST\_DESCENT method and so for very large systems may be problematic to use. In that case, it is best to use the CONJGRAD method.

OPTIMIZE: MM\_NOTCONVERGED

Keyword (optional, default = 1)

This keyword defines what should happen if the MM geometry is not fully optimized after MAX\_STEPS steps; set this to zero for large (biochemical) systems where it may be problematic to get the optimization to converge fully in a limited number of steps (1000): the QMMM run will continue as if the MM-optimization had converged.

OPTIMIZE: FIX\_MM\_GEOMETRY

Keyword (optional, default = .false.)

If this keyword is specified in the OPTIMIZE subblock, the MM system will be frozen, i.e. no geometry optimization will be done on any of its atoms.

OPTIMIZE: PRINT\_CYCLES

Keyword (optional, default = 100)

PRINT\_CYCLES represents the number of optimization cycles between which the optimization status is printed and the MM restart file is written.

OPTIMIZE: GLOBAL

Sub key block (optional) - CURRENTLY IN A BETA STATE

This subkey block controls the global optimization options in the program. Currently the global optimization option has not been thoroughly tested and should be considered to be in beta form. The normal optimizers are designed only to locate the "nearest" local minimum and therefore you are not guaranteed to find the best overall structure, which is termed the global minimum structure. Currently, only two global optimization algorithms have been implemented:

- Molecular dynamics based optimizer related to a simulated annealing algorithm
- A grid search, which generates conformations by rotations about bonds specified by the user.

Both optimizers generate a number of structures (100s to 1000s), which are all partially optimized. The partially optimized structures are then sorted based on their energies. The best 10 of these structures are then fully optimized. The best of these fully optimized structures is kept and assumed to be the global minimum. The global optimization is only applied to the MM region with the QM atoms frozen. Therefore, the structure can only be considered the global minimum structure on the constrained surface where the QM atoms and QM charge density are frozen.

```

OPTIMIZE
  GLOBAL
    METHOD MD_SEARCH
    FREQUENCY ONCE
  SUBEND
  MD_SEARCH
    TIME{PS} 100.0
    N_STRUCTURES 100
    TEMPERATURE 1000.0
  SUBEND
SUBEND

```

Global optimization is not the default. Therefore, to invoke a global optimization, the GLOBAL subkey block must exist. It is important to note that the subkey blocks that control the global optimization schemes are subkey blocks of the OPTIMIZE key block and not sub-sub key blocks within the GLOBAL subkey block. The above example demonstrates this.

OPTIMIZE: GLOBAL: METHOD

Keyword (optional, default = MD\_SEARCH)

This key block specifies the global optimization method to be used. To date there are only two methods, MD\_SEARCH which is the default and GRID. More detail on how these methods work is given in the description of the MD\_SEARCH and GRID subkey blocks.

OPTIMIZE: GLOBAL: FREQUENCY

Keyword (optional, default = ONCE)

This key block specifies how often the global optimization algorithm, if it is specified, is called. Since the global optimization is

very time consuming it is not recommended that it be used every QM iteration. The default is that it is done only on the first iteration. The options available are tabulated below.

ONCE	Only at the first iteration
EVERY_TIME	At every iteration
N_CYCLES X	At each X-th iteration including the first. Here X is the integer following the "N_CYLES" keyword. e.g. N_CYCLES 4

OPTIMIZE: MD\_SEARCH

Subkey block (optional, default settings specified below)

The MD\_SEARCH method involves performing molecular dynamics on the MM subsystem at a high temperature. The high temperature dynamics allows the MM subsystem to "get out of" the local minimum of the initial structure and explore other regions phase space, potentially leading to lower energy structures. During the molecular dynamics, structures are sampled at specified intervals and stored. When the dynamics is complete, the stored structures are optimized and sorted in terms of their energy. This procedure is similar to simulated annealing, except that the temperature of the dynamics is not ramped up and down in a cyclic fashion. At the beginning, the dynamics is immediately pulsed up to the specified temperature with a random excitation on each of the free MM degrees of freedom. An example of the key block, with good settings is given below.

```
MD_SEARCH
  TIME{PS} 100.0
  N_STRUCTURES 100
  TEMPERATURE 700.0
SUBEND
```

In the above example, the MM subsystems are heated up to a temperature of 700 Kelvin. Dynamics is run for a total of 100 picoseconds, with a total of 101 structures sampled (100 plus the initial structure). Each structure is sampled every 1.0 picoseconds. The default timestep is 0.5 femtoseconds, and therefore in the above example 200,000 timesteps will be performed. This global search technique is the most general and robust of the two methods implemented. It is therefore the default global optimization method. This subkey block is optional, since the default settings should work reasonably with most systems.

OPTIMIZE: GRID

Subkey block (optional, required if method selected)

The GRID method provides a systematic search for global minimum by rotating about specified covalent bonds in the MM subsystem. This method is only efficient for small systems or systems where the conformational variability is confined to torsions involving a few bonds. The user must specify the bonds that are to be rotated in the search, up to a maximum of 10, and the increment (in degrees) by which the bonds are to be rotated between subsequent structures. The program does not allow bonds that are

- completely within the QM subsystem (link bonds are allowed, however, or
- part of a ring system.

Finally, since QM atoms cannot be rotated, at least one of the two fragments resulting from splitting the specified bond must contain no QM atoms. An example of the key block is shown below where three bonds are rotated, in 60° increments. 216 structures (6x6x6) will be generated corresponding to a full 360° rotation about the three bonds in 60° increments and all combinations thereof.

```
GRID
  INCREMENT 60.0
  BOND 7 - 6
  BOND 8 - 7
  BOND 9 - 8
SUBEND
```

NOTE: It is important to realize that the program uses the connection table specified in the input to determine which atoms to rotate.

MASSSES

**Key block (optional)**

This is used to assign custom masses to individual atoms. If no custom masses are specified, then the default masses defined in the force field file are used. Below is example input.

```
MASSES
 15 32.066
  8  2.0
SUBEND
```

The first column is an integer specifying the atom number and the second column is a real specifying the custom mass of that atom in atomic mass units. The atoms need not be in any particular order and it is not necessary to specify custom masses for all atoms. It should be noted that only masses of the MM atoms and the link atoms could be customized. Masses of the QM atoms and the capping atoms are taken from the QM code.

## 2.3 The Force Field File

This required file must contain the force field parameters and the MM potential for each kind of MM interaction. Although predefined force field files (AMBER and SYBYL) are provided with ADF, these force field files can be customized. For example, one may want to change a particular force constant, or one may need to introduce a new atom type, for instance a transition metal. This section provides a detailed description of the force field file.

### General Notes

#### Format

The force field file is keyword driven with each key block defining parameters for each molecular mechanics interaction type such as bond types, angle types, torsion types, ...etc. The key block begins with the keyword, such as "BONDS".

The lines that actually contain the parameters are sandwiched between two lines that contain "=====". The lines between the keyword and the first line containing "=====" are not read by the program. These lines are intended for the user to define the columns as shown below. There can be as many lines between the keyword and the first '=====' as needed.

Example:

```

BONDS
Atoms  pot  K                ro  Notes
i - j   type (kcal/molA^2)  (Ang)
=====
...
CA CA  1    938.0            1.400  amber95
CT CT  1    620.0            1.526  amber95
...
=====

```

### Force Field Atom types

The force field atom types are the labels given to each atom in the real system that is used to generate the molecular mechanics portion of the QM/MM potential. These are separate from the atomic fragment types used by ADF for the electronic structure calculation. It is important to realize that QM atoms will have both an atomic fragment type and a force field atom type.

There are some limitations to the force field label types that the user can specify:

- Labels can be a maximum of four characters long, with no spaces.
- The atom types are case sensitive.
- They can contain letters, numbers and other characters except ',', '!' or '=' and tabs.

Example of atom types that are not compatible with the program: C.3, C 3, C=3, C\_sp3, \*

Examples of atom types that are correct: C\_3, C3, Csp3, and C\*

### Wild Cards

Wild cards can be specified with the asterisk, '\*'. Wild cards can be specified for angles, torsions and out-of-plane bends. Please refer to the specific sections for the limitations.

**CAUTION:** When using wild cards, place the wild cards at the beginning of the data section, beginning with the parameters with the most wild cards and ending with those that possess the least wild cards.

Example:

```
*      C_3      *      100.310    111.000    two wild cards
*      C_3      C_3    100.310    111.000    one wild card
C_2    C_3      C_3    100.310    111.000    no wild cards
```

If this ordering is not followed, then the wild card parameters will over-ride the specific parameters.

## Dummy Atoms

If the QM program uses dummy atoms, they are specified 'Xx' or 'XX'. The program will automatically remove dummy atoms from the non-bonded pair list. Please note that if the user specifies bonds to the dummy atom in the connection table, the program will look for the appropriate parameters in the force field file. The program does not filter out this possibility because sometimes it is useful to specify MM bonds to dummy atoms).

## Miscellaneous Notes

- Do not remove the '=====' separator lines.
- Units are in kcal/mol, Angstroms, degrees, amu unless otherwise specified
- Sections can be in any order; i.e. BENDS can come before BONDS.
- All keywords are case sensitive and most are in ALL-CAPS
- Input is all free format
- Blank lines will be ignored
- Comment lines can be added to parameter data sections by beginning the line with the '#' symbol.

Example:

```
H H 1.0080
HC H 1.0080
# example of comment line denoted with # mark.
H1 H 1.0080
H2 H 1.0080
```

### 4.3 A (partial) Example File

In this section we provide an example force field file to illustrate the format of the file. Only a limited number of parameters are included. A detailed description of each section of the force field file is provided in the next section.

```
FORCE_FIELD_SETTINGS
=====
ELSTAT_1-4_SCALE          1.0000
VDW_1-4_SCALE             1.0000
VDW_DEFAULT_POTENTIAL    1      (1:6-12 2:exp-6 3:exp purely repulsive)
DIELECTRIC_CONSTANT      1.000
=====

MASSES & ATOM LABELS
-----
force_field  atomic
atom_type   symbol  mass    NOTES
=====
C_3         C      12.0110  sp3 hybridized carbon
```

C_2	C	12.0110	sp2 hybridized carbon
C_1	C	12.0110	sp1 hybridized carbon
C_ar	C	12.0110	aromatic
N_3	N	14.0070	
N_2	N	14.0070	
O_3	O	15.9990	

=====

BONDS Ebond = 0.5\*K(r-ro)\*\*2

Atoms		pot		K	R	NOTES
i - j	type					
C_2	C_2	1		1340.00	1.335	WHITE_77
C_2	C_3	1		639.00	1.501	WHITE_75
C_3	C_3	1		633.60	1.540	*
C_3	N_2	1		760.20	1.440	*

=====

BENDS Ebend = 0.5\*k(a-ao)^2

Atoms		pot		K	theta	NOTES
i - j - k	type					
*	C_2	*	1	78.79	120.00	WHITE_77
*	C_3	*	1	65.66	109.50	WHITE_77
*	C_ar	*	1	78.79	120.00	*
C_ar	C_2	N_2	1	131.31	120.00	*
C_3	C_3	C_ar	1	78.79	109.50	*

=====

TORSIONS

Atoms		pot		k	per	NOTES		
i - j - k - l	type							
*	C_2	C_2	*	2	12.5000	-2.0		
*	C_1	C_3	*	2	0.0000	1.0		
C_2	C_2	C_3	*	2	0.1260	-3.0		
C_3	C_2	C_3	*	2	0.1260	3.0		
H	C_2	C_3	*	2	0.2740	3.0		
*	C_ar	C_ar	C_ar	2	2.3500	-2.0		
*	C_2	C_3	C_2	2	0.1260	3.0		
*	C_2	C_3	C_3	2	0.1260	3.0		
C_3	C_3	C_3	C_3	0	0.5000	3.0	no torsion potential	
C_2	C_2	C_3	C_2	2	0.1260	-3.0		
C_3	C_3	N_2	C_2	1	0.5000	4	180.0	This and the next 3 lines
&					0.1500	3	180.0	are part of a multi-component
&					0.5300	1	0.0	Fourier potential
C_3	C_3	C_2	N_2	1	0.1000	4	0.0	
&					0.0700	2	0.0	'&' is a continuation marker

=====

OUT-OF-PLANE

Atoms	pot
-------	-----

i - j - k - l	type	K	NOTES
* * C_2 *	2	480	TRIPOS_85
* * N_2 *	2	120	TRIPOS_85
H H N_2 C_3	2	120	TRIPOS_85
C_3 H N_2 *	2	120	TRIPOS_85

## VAN DER WAALS

atom(s)	Emin	Rmin	gamma	NOTES
C_3	0.1070	3.4000	12.00	
C_2	0.1070	3.4000	12.00	
C_ca	0.1070	3.4000	12.00	
C_ar	0.1070	3.4000	12.00	
C_1	0.1070	3.4000	12.00	
N_3	0.0950	3.1000	12.00	
N_2	0.0950	3.1000	12.00	
N_2 - N_2 2	0.0950	3.1000	12.00	purely repulsive potential for this pair

type	charge(e)	NOTES
OW	-0.82	TIP3P water model
HW	0.41	TIP3P water model

## Section by Section Description

### FORCE\_FIELD\_SETTINGS

Key block (required)

This key block specifies various global options for the force field file, mostly concerned with the treatment of the non-bonded potentials.

#### FORCE\_FIELD\_SETTINGS

ELSTAT_1-4_SCALE	0.5	
VDW_1-4_SCALE	0.5	
VDW_DEFAULT_POTENTIAL	1	(1:6-12 2:exp-6 3:exp purely repulsive)
DIELECTRIC_CONSTANT	1.000	

#### ELSTAT\_1-4\_SCALE & VDW\_1-4\_SCALE

Most force fields scale the non-bonded interactions by a factor of 0.5 if the atoms are the terminal atoms of a defined torsion. This scaling factor, which is termed the 1-4 scaling factor, can also be different for the electrostatic potential and for the Van der Waals potentials and thus they are separately defined in the input.

#### VDW\_DEFAULT\_POTENTIAL

This keyword defines what kind of potential is used for the non-bonded van der Waals interactions. The potential types have been assigned integer values as defined in the following table.

VDW potential type	constants required (in
--------------------	------------------------

		order)
0	no potential	none
1	Lennard-Jones 12-6 $E_{vdw}(R) = D_o \left[ \left( \frac{R_o}{R} \right)^{12} - 2 \left( \frac{R_o}{R} \right)^6 \right]$	$D_o, R_o$
2	Exponential-6 or Buckingham $E_{vdw}(R) = D_o \left\{ \left[ \left( \frac{6}{\xi-6} \right) e^{\xi \left( 1 - \frac{R}{R_o} \right)} \right] - \left[ \left( \frac{\xi}{\xi-6} \right) \left( \frac{R_o}{R} \right)^6 \right] \right\}$	$D_o, R_o, \xi$ x=12.0 is standard
3	Purely Repulsive $E_{vdw}(R) = D_o \left( \frac{6}{\xi-6} \right) e^{\xi \left( 1 - \frac{R}{R_o} \right)}$	$D_o, R_o, \xi$
4	Purely Attractive (dispersion term) $E_{vdw}(R) = -2 D_o \left( \frac{R_o}{R} \right)^6$	$D_o, R_o$

## DIELECTRIC\_CONSTANT

Default = 1.00

This defines the dielectric constant used for the calculation of the electrostatic interactions. For example, 1.00 = vacuum and 80 is that of bulk liquid water. Currently, only a constant dielectric has been implemented.

## BONDS

Key block (required)

This key block specifies the potential type and parameters for each kind of MM bond stretching interaction. An example is given below.

## BONDS

Atoms i - j	pot type	K (kcal/molA <sup>2</sup> )	ro (Ang)	NOTES
CA CA	1	938.0	1.400	amber95
CT CT	1	620.0	1.526	amber95
HC Zr	0	0.0		no potential found

The first two columns are the atom types (up to four characters long) and the third column is an integer specifying the potential type.

BOND potential type	constants required (in order)
0 no potential	none
1 simple harmonic: $E_b^{ij} = \frac{1}{2} K (R_{ij} - R_o)$ AMBER95, Sybyl	$K, R_o$

## BENDS

Key block (required)

This key block specifies the potential type and parameters for each kind of MM bond angle interaction. An example is given below.

## BENDS

Atoms i - j - k	pot type	k (kcal/mol)	ao deg	NOTES
* CA *	1	70.00	120.00	example of wild card
* CA CA	1	126.00	120.00	

```

CA  CA  N2  1  140.00  120.10  amber95 N2-CA-CM
CA  CA  CT  1  140.00  120.00  amber95
=====

```

The first three columns specify the atom types and the fourth column is an integer specifying the potential type. The angle bend potential types are described in the table below with the additional constants required.

BEND potential type		constants required (in order)
0	no potential	none
1	theta harmonic: $E_{\theta}^{ijk} = \frac{1}{2} K_{\theta} (\theta_{ijk} - \theta_o)$ AMBER95, SYBYL	K, q <sub>o</sub> (q in degrees)

Notice that wild cards can be specified for both terminal positions of the bend or just one as in the example above. It is important that the parameters be ordered from the least specific (those containing the most wild cards) to the most specific parameters.

#### TORSIONS

Key block (required)

This key block specifies the potential type and parameters for each kind of MM bond torsion interaction. For the bond stretching and bending potentials, only one potential has to date been implemented since both AMBER and SYBYL both use simple harmonic potentials. However, AMBER and SYBYL use different functional forms to represent the torsion potentials, each with their own set of parameters. The AMBER and SYBYL torsional potentials used in this program are defined in the table below.

TORSION potential type		constants required (in order)
0	no potential	none
1	AMBER: $E_{tors} = \frac{K_{tors}}{N_{tors}} [1 + \cos(n\phi - \phi_o)]$	K <sub>i</sub> , n <sub>i</sub> (periodicity-integer), f <sub>o,i</sub> (phase shift)
2	SYBYL: $E_{tors} = \frac{1}{2} K_{tors} [1 + \cos(n\phi_o) \cos(n\phi)]$	K, s

Notice that the two potentials have a different number of parameters. For example, when the program reads 'potential type' number 1, it will expect three parameters K<sub>i</sub>, n<sub>i</sub>, f<sub>o,i</sub>. Further notice that the AMBER torsional potential is a sum of Fourier components (this is what the index i refers to).

Below is an example of the TORSIONS key block, made up of AMBER force field types.

#### TORSIONS

Atoms i - j - k - l	pot type	k	per. n	shift to	NOTES
* CV NB *	1	2.4000	2	180.0	JCC,7,(1986),230
* CW NA *	1	1.5000	2	180.0	JCC,7,(1986),230
&		0.1000	3	0.0	
C N CT C	1	0.2000	2	180.0	
N CT C N	1	0.4000	4	180.0	
&		1.3500	2	180.0	
&		0.7500	1	180.0	
CT CT N C	1	0.5000	4	180.0	

Most AMBER torsion potentials are not specific to all four atoms i-j-k-l, but only on the central two, j-k. Wild cards are specified with the '\*' symbol as illustrated above. Again, the ordering is important. The parameters should be ordered from least specific (those containing the most wild cards) to most specific. The AMBER torsion potential can be composed of more than one Fourier component for a single torsion potential. Additional Fourier components are specified with the '&' continuation symbol as in the example above. At the moment, up to 6 Fourier components are allowed. Notice that the individual components need not be specified in any particular order. In the above example key block, there are only 5 torsional potentials defined, not 8. Two of the potentials are composed of more than one Fourier component as indicated by the '&' continuation line.

Below is an example of the TORSIONS key block for the SYBYL force field. Notice that the potential types are all '2'. There are fewer parameters and no multi component potentials. Also, some potentials are defined with two or only one wild card.

## TORSIONS

```

-----
Atoms          pot
i - j - k - l  type    k      per    NOTES
=====
*      C_ar  S_3  *      2      1.0000  3.0    *
*      S_3   S_3  *      2      0.0000  2.0    EXP
C_2    C_2   C_3  *      2      0.1260 -3.0    WHITE_77
C_3    C_2   C_3  *      2      0.1260  3.0    WHITE_77
H      C_2   C_3  *      2      0.2740  3.0    *
*      C_ar  C_ar  C_ar  2      2.3500 -2.0    *
*      C_2   C_3   C_2  2      0.1260  3.0    WHITE_77
*      C_2   C_3   C_3  2      0.1260  3.0    WHITE_77
*      C_2   C_3   H    2      0.2740  3.0    WHITE_77
*      C_3   C_3   H    2      0.3200  3.0    MC_88
O_2    C_2   C_3   C_3  2      0.7000 -3.0    JL_ES_
O_∞    C_2   C_3   C_3  2      0.7000 -3.0    MAC_1
C_2    C_3   C_3   C_2  2      0.0400  3.0    WHITE_77
C_2    C_3   C_3   C_3  2      0.1260  3.0    WHITE_77
=====

```

One can also mix different potential types within the same force field file, as illustrated below. In this example, there are three potentials. The first two are SYBYL type potentials whereas the last one is a multi component AMBER potential.

```

H      C_2   C_3  *      2      0.2740  3.0
*      C_ar  C_ar  C_ar  2      2.3500 -2.0
N      CT   C    N    1      0.4000  4      180.0
&
&      1.3500  2      180.0
&      0.7500  1      180.0

```

## OUT-OF\_PLANE

## Key block (required)

This key block specifies the potential type and parameters for each kind of MM out of plane bend. This potential is sometimes referred to as the inversion potential or improper torsions (depending on the force field). The potential types currently supported are provided in the table below.

out-of-plane potential type	description	constants required (in order)
0	no potential	none
1	AMBER: $E_{inv} = K[1 + \cos(n\phi - \phi_o)]$	K, n, $f_o$ ( $n=2, f_o = 180^\circ$ for planar, $n=3, f_o = 120^\circ$ for tetrahedral)
2	SYBYL: $E_{oopl} = K * d^2$ d is the distance of the plane in Ang.	K

An example of the key block for the AMBER type potentials is given below. It is important to realize that the atom k is the **atom k is the central atom**. (We have adopted the somewhat odd standard of AMBER in this respect).

## OUT-OF-PLANE

```

=====
Atoms          pot
i - j - k - l  type   K      to      NOTES
=====
*      *      CA   H4    1      1.10   180.0   bsd.on C6H6 nmodes
*      *      CA   H5    1      1.10   180.0   bsd.on C6H6 nmodes
*      O2     C    O2    1      10.50  180.0   JCC,7,(1986),230
*      N2     CA   N2    1      10.50  180.0   JCC,7,(1986),230
*      CT     N    CT    1      1.00   180.0   JCC,7,(1986),230
CK     CB     N*   CT    1      1.00   180.0
=====

```

## VAN DER WAALS

Key block (required)

This key block specifies the potential type and parameters for each kind of MM van der Waals interaction between two atoms. A sample key block is shown below:

```

=====
atom(s)  type  emin  rmin  alpha  NOTES
=====
CA              -0860  3.81600  12.00  amber95
HA              -0150  2.91800  12.00  amber95
Ni - HA        2    -0480  2.7     12.00  NOTE potential type
Ni - CA        D    -0480  2.7     12.00  default potential
=====

```

The van der Waals key block is somewhat different than the previous key blocks, because generally not every atom pair is defined with its own parameters. Rather, the parameters are assigned on a per atom basis and then special combination rules are used to construct the parameters for each atom pair combination. For this reason, a default potential type is defined in the FORCE\_FIELD\_SETTINGS key block.

VDW potential type		constants required (in order)
0	no potential	none
1	Lennard-Jones 12-6 $E_{vdw}(R) = D_o \left[ \left( \frac{R_o}{R} \right)^{12} - 2 \left( \frac{R_o}{R} \right)^6 \right]$	$D_o, R_o$
2	Exponential-6 or Buckingham $E_{vdw}(R) = D_o \left[ \left( \frac{6}{\zeta - 6} \right)^{\zeta} \exp\left(-\frac{\zeta R}{R_o}\right) - \left[ \left( \frac{\zeta}{\zeta - 6} \right) \left( \frac{R_o}{R} \right)^6 \right] \right]$	$D_o, R_o, \zeta$ x=12.0 is standard
3	Purely Repulsive $E_{vdw}(R) = D_o \left( \frac{6}{\zeta - 6} \right)^{\zeta} \exp\left(-\frac{\zeta R}{R_o}\right)$	$D_o, R_o, \zeta$

For each type of van der Waals interaction, the program first scans the key block for pair specific parameters. For pair specific potentials, the default potential type can be replaced by any of the available potentials. The three sample lines below specify pair-specific potentials. The two atom types must be separated by a hyphen with spaces between the hyphen and the atom type. Following the specification of the atom pair, the potential type is defined. If D or d is specified here, then this means to use the default potential type. Following the potential type are the parameters needed for that potential type (see above table).

CA - CA	1	0.0860	3.81600	12.00	amber95
Ni - HA	0				
Ni - CA	D	0.0480	2.7	12.00	default potential type

If a pair specific parameter can't be found, then the program looks for individual atom parameters corresponding to each of the atom types in the pair. The pair specific parameters are then constructed from combination of the two individual atom parameters using the following combination rules:

VDW potential type		
1	Lennard-Jones 12-6	$D_{ij} = (D_i * D_j)^{1/2}$ , $R_{ij} = (R_i + R_j)/2$
2	Exponential-6 or Buckingham	$D_{ij} = (D_i * D_j)^{1/2}$ , $R_{ij} = (R_i + R_j)/2$ $z_{ij} = (z_i * z_j)^{1/2}$
3	Purely Repulsive	$D_{ij} = (D_i * D_j)^{1/2}$ , $R_{ij} = (R_i + R_j)/2$ $z_{ij} = (z_i * z_j)^{1/2}$

When individual atom parameters are not used, no potential type is specified since the default potential type is always used. An example is given below.

CA	0.0860	3.81600	12.00	amber95
HA	0.0150	2.91800	12.00	amber95

The ability to define pair specific parameters is especially useful for those force fields that have different combination rules than used in the program. For example, Jorgensen's TIP3P water force field uses geometric averages for both  $D_{ij}$  and  $R_{ij}$ .

#### MASSES & ATOM LABELS

Key block (required)

This key block specifies the default masses for each MM atom type and the element label for each MM atom type. In an ADF QM/MM run, the element label defined for each atom type is the label used for printing out to the LOGFILE. This allows one to easily cut and paste the generated coordinates to a molecule viewing program without having to go in and changing all of the "CT"s to "C"s.

A sample key block is shown below:

#### MASSES & ATOM LABELS

```

=====
Ni          Ni          58.70
CM          C           12.011
CA          C           12.011
CT          C           12.011
HC          H           1.0079
HA          H           1.0079
=====

```

The first column is the MM atom type, the second is the label used for printing and the third column is the mass of the atom type. The atoms do not have to be specified in any particular order.

#### CHARGES

Key block (optional)

This key block specifies the parameters for the charges on the atoms by atom type. To date only the initial charge is available, however if some sort of charge equilibration scheme was introduced the parameters would go here. NOTE: initial charges can also be specified on a per atom basis in the MM INPUT file.

#### CHARGES

```

atoms      initial
label      charge
=====

```

OW	-0.8
HW	0.4

=====

## 2.4 Setting up a QM/MM Simulation: a 'Walk Thru'

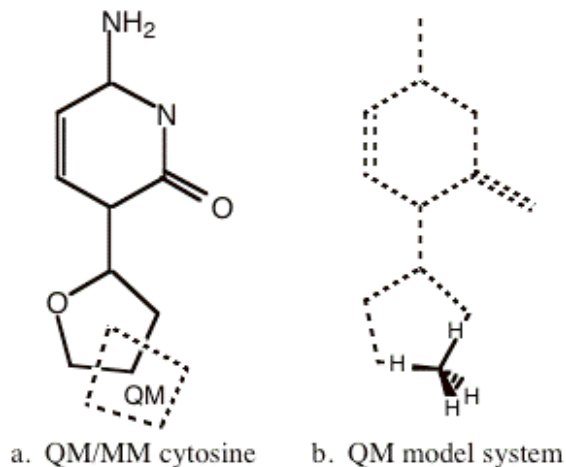
In this section we provide a detailed 'walk thru' of the process of setting up an ADF QM/MM simulation. There will be two examples, the first being a fairly straightforward example and the second one being fairly complex.

### Example A: Cytosine

This is a straightforward example, where the input necessary to perform a QM/MM simulation of cytosine (Figure 5-1) will be constructed.

#### Step 1. Partitioning the System and the Model QM system

First one must decide where to partition the system into QM and MM regions. This is actually a very important step since the partitioning can be considered the 'original sin'. Much thought and testing should be put into deciding where to place the QM/MM boundary. In this example, we have chosen the partitioning depicted in Figure 5-1a in order to keep the example simple. In this figure the QM region enclosed in the dotted polygon, with two covalent bonds crossing the QM/MM boundary. One must also choose an appropriate QM model system for which the electronic structure calculation will be performed. To preserve the  $sp^3$  hybridization of the carbon center in the QM region, we must keep the carbon tetravalent. Thus, we will cap the two dangling bonds with dummy or capping hydrogen atoms. One can use any monovalent atom such as H or F, but H is probably best. The reason that monovalent atoms should be used for capping atoms is that one does not want capping atom to have any 'dangling' bonds. Capping or dummy groups can not be used. Figure 5-1b, depicts the QM model system with two capping hydrogen atoms. Thus, the electronic structure calculation will be performed on methane such that the capping hydrogen atoms lie along the bond vector of the link bond in the real system as shown in Figure 5-1b.

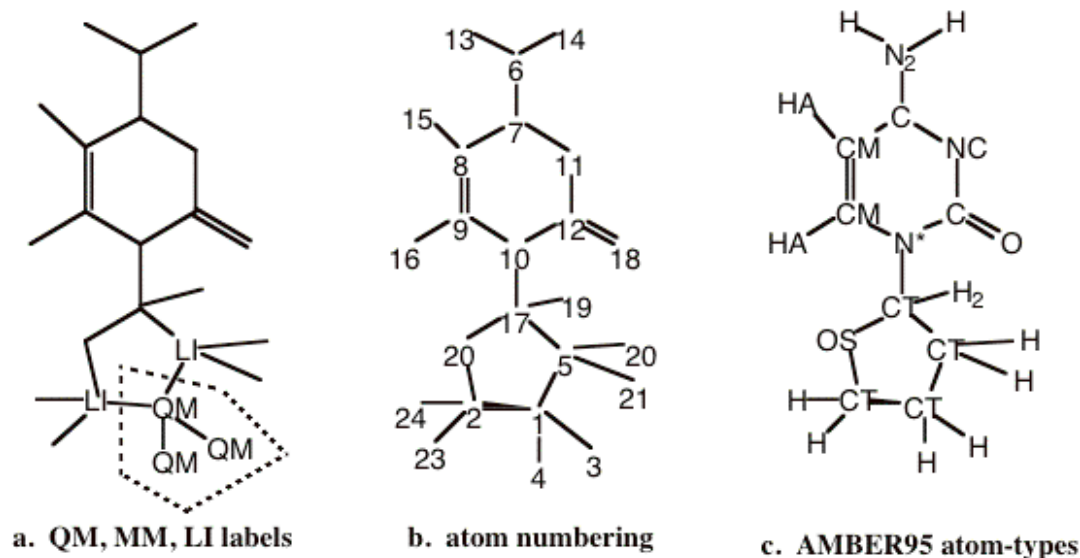


**Figure 5-1** Cytosine QM/MM example model. a) Shows the whole system with the atoms enclosed in the dotted polygon making up the QM system. b) Shows the equivalent QM model system. The remainder of the cytosine molecule is shown ghosted to demonstrate the relationship between the model system and the full system. The QM model system consists of a closed shell methane molecule.

#### Step 2. Labeling of Atoms (QM, MM or LI)

Once a partitioning of the system has been established, one needs to designate each of the atoms in the full system as QM, LI or MM atom type. For the example system, these designations are shown in Figure 5-2a, where the atoms that are not labeled are

MM atoms.



**Figure 5-2** Labeling of the example model. a) QM, MM and LI designations. Atoms not labeled are 'MM' atoms. The dotted polygon encloses the QM region of the model. b) Atom numbering of the entire system. Note that the QM and LI atoms precede any MM atoms. c) The AMBER95 force field atom type designations.

All atoms within the dotted polygon are 'QM' type atoms. The atoms outside of the QM region will either be MM or LI atoms depending on whether they are part of a link bond or not. The covalent bonds that cross the QM/MM boundary are termed the link bonds. In the example system, there are two such covalent bonds. The atoms that lie on the MM side of the link bonds are labeled the LI atoms. Thus, these are all of the atoms that lie outside the dotted polygon that have a covalent bond to QM atoms. If there are no covalent bonds that traverse the QM/MM boundary, then there will be no LI atoms.

### Step 3. Renumbering of Atoms

There is a strict rule concerning the ordering of the atoms, based on the QM, MM, or LI atom type designation. All QM and LI atoms must come before any MM atoms. A valid atom numbering for the example system is shown in figure 5-2b. Here the atoms labeled 'QM' or 'LI' in Figure 5-2a are the first five atoms of the molecular system.

### Step 4. ADF QM/MM input: Atomic coordinates

Now we can begin to construct the input. We will begin with the atomic coordinates. For this example, we will optimize the geometry of the complex in Cartesian coordinates. Coordinates of the whole QM/MM complex or the 'real' complex should be defined here. DO NOT define the coordinates of the capping atoms. The program will calculate their positions, and add them automatically. The definition of the coordinates is done exactly as they are in a standard ADF run. Below is the ATOMS key block for our example system.

```

ATOMS Cartesian
  1 C  1.94807  3.58290 -0.58162
  2 C  1.94191  3.61595  1.09448
  3 H  1.69949  4.49893 -1.05273
  4 H  2.99455  3.17964 -0.86304
  5 C  0.94659  2.40054 -0.92364
  6 N -1.74397 -3.46417  0.31178
  7 C -1.00720 -2.20758  0.33536
  8 C -1.66928 -1.00652  0.31001

```

```

 9 C -0.92847  0.25653  0.34895
10 N  0.43971  0.26735  0.38232
11 N  0.36409 -2.20477  0.28992
12 C  1.09714 -0.95413  0.22469
13 H -2.89781 -3.50815  0.31746
14 H -1.21484 -4.49217  0.31721
15 H -2.80940 -0.93497  0.30550
16 H -1.55324  1.21497  0.33885
17 C  1.23309  1.44017  0.30994
18 O  2.58277 -1.01636  0.23914
19 H  2.37276  1.25557  0.29984
20 O  1.02358  2.43085  1.50880
21 H  1.17136  1.95097 -1.87367
22 H -0.10600  2.77333 -0.80348
23 H  1.62170  4.54039  1.51392
24 H  2.99608  3.28749  1.41345
END

```

## Step 5. Connection Table and MM force field types

In order to construct a molecular mechanics potential, the program needs to know the connectivity of the molecular system and the molecular mechanics force field atom-type designations. In this example we are using the AMBER95 force field of Kollman and coworkers [4]. The appropriate AMBER95 atom-types for this molecule are shown in Figure 5-2c. No new atom types need to be introduced to the standard AMBER95 force field to treat this system. However, if this were needed, then the force field file would have to be modified.

Next a connection table needs to be constructed. For this program this needs to be done on an atom by atom basis. Either a fully redundant connection table or a fully non-redundant connection table is acceptable. A redundant connection table refers to one in which the covalent bonds are defined for all atoms. For example, if X is bonded to Y, in the connections for atom X, a bond is defined to atom Y. For the connections to atom Y, a bond is also defined to atom X even though the bond has already been defined. In a non-redundant connection table, when a bond is defined in the connections for atom X, it is not again defined in the connections for atom Y.

We now can begin to construct part of the input, namely the MM\_CONNECTION\_TABLE subkey block of the QMMM key block. For this example, the MM\_CONNECTION\_TABLE key block is given below.

```

MM_CONNECTION_TABLE
 1 CT QM 2 3 4 5
 2 CT LI 1 20 23 24
 3 HC QM 1
 4 HC QM 1
 5 CT LI 1 17 21 22
 6 N2 MM 7 13 14
 7 CA MM 6 8 11
 8 CM MM 7 9 15
 9 CM MM 8 10 16
10 N* MM 9 12 17
11 NC MM 7 12
12 C MM 10 11 18
13 H MM 6
14 H MM 6
15 HA MM 8
16 H4 MM 9
17 CT MM 5 10 19 20
18 O MM 12
19 H2 MM 17

```

```

20 OS MM 2 17
21 HC MM 5
22 HC MM 5
23 H1 MM 2
24 H1 MM 2
SUBEND

```

The first column is simply the atom number. The atoms defined here MUST be in the same order as defined in the ATOMS key block provided in the previous section. Again, we do not include the capping atoms. The second column shows the AMBER95 atom-types for our system, displayed in Figure 5-2c. The third column is the MM, QM or LI designation. Notice that the QM and LI atoms appear before any MM atoms. The remaining columns are reserved for the connection table. In the above example, a fully redundant connection table is provided.

## Step 6. LINK\_BONDS

When there are covalent bonds that cross the QM/MM boundary, the LINK\_BONDS subkey block is required. Since one only defines the 'real system' in both the ATOMS key block and the MM\_CONNECTION\_TABLE subkey block, this key block defines both the initial position of the capping atom and what kind of ADF fragment atom will be used as a capping atom. In this example we have two link bonds, both of which will be 'capped' with capping hydrogen atoms as shown in Figure 5-1b. Below is the LINK\_BONDS subkey block for our example.

```

LINK_BONDS
  1 - 5 1.380 H
  1 - 2 1.375 H
SUBEND

```

The first part of the input specifies the atoms involved in link bonds. Here QM atom 1 forms link bonds with atoms 5 and 2. The column in the input is the link bond a parameter, which is defined as the ratio between the capping bond length in the QM model system and the bond length of the corresponding link bond in the real system. This ratio can be determined by taking the necessary bond lengths from a pure QM calculation of the model QM system, and the bond length from the whole complex. If those are not available, they can be taken from tabulated bond lengths or bond lengths of similar bonds in other complexes. There is an independent parameter for each link bond. It is VERY IMPORTANT to emphasize that the total energy of the QM/MM system is dependent upon the a parameters. Thus, if one is comparing the energetics of two conformational isomers calculated with the QM/MM method, this comparison is only valid if the a parameters used are the same. In our example, ratios of 1.38 and 1.375 were used. This is somewhat typical ratio of C-H to C-C bond lengths, in aliphatic hydrocarbons. The last column in the LINK\_BONDS input refers to the ADF fragment for which will be used for the capping atom in the electronic structure calculation. Please, note this fragment must be present in the FRAGMENTS key block of the ADF input.

## Step 7. Assignment of Atomic Charges

Perhaps the most dubious aspect of the QM/MM approach involves the non-bonded electrostatic interaction between the QM and MM regions. The ADF QM/MM extension currently only supports placement of static point charges on MM atoms. At the moment, you have two options. First, you can choose to have the MM point charges to interact with the electron density of the QM model system, thereby allowing the wave function of the QM system to be polarized. Alternatively, you can assign static point charges to the QM atoms which interact with MM point charges as would happen if the whole system were treated with a molecular mechanics force field. In this example, we will choose the latter, using the standard AMBER95 charges cytosine. To specify how the electrostatic interactions between the two regions are treated, one uses the ELSTAT\_COUPLING\_MODEL keyword in the QMMM key block and sets it equal to 1.

In ADF QM/MM the atomic point charges can be assigned on an atom-type basis, where the point charges are taken from the force field file. It can also be defined on a per atom basis, where a unique charge is assigned to each atom in the molecular system in the CHARGES subkey block. Since the charges in AMBER95 are assigned according to the nucleic or amino acid, we must assign the charges on a per-atom basis. Given below is the CHARGES subkey block with the appropriate AMBER95 point charges assigned to the system. The first column in this subkey block is the atom numbering. It is important to use the right atom

number instead because the program actually determines the charges on each atom individually by searching for the atom number within this key block. Charges don't have to be in order.

```

ELSTAT_COUPLING_MODEL=1
CHARGES
 1 0.0000
 2 0.0000
 3 0.0000
 4 0.0000
 5 0.0000
 6 -0.9530
 7 0.8185
 8 -0.5215
 9 0.0053
10 -0.0484
11 -0.7584
12 0.7538
13 0.4234
14 0.4234
15 0.1928
16 0.1958
17 0.0066
18 -0.6252
19 0.2902
20 -0.2033
21 0.0000
22 0.0000
23 0.0000
24 0.0000
SUBEND

```

## Step 8. Remainder of the QMMM key block

The ADF QM/MM input is almost complete. Now only a few settings need to be defined in the QMMM key block. The remainder of the QMMM key block is given below.

```

FORCEFIELD_FILE /usr/bob/QMMM_data/amber95.ff
RESTART_FILE mm.restart
OUTPUT_LEVEL=1
WARNING_LEVEL=2

```

The FORCEFIELD\_FILE defines the filename of the force field file to be used. If the force field file is not in the running directory of the ADF job, then the full path needs to be specified. The RESTART\_FILE specifies the name of the QM/MM restart to be written. If the job is a restart itself, this keyword also specifies the QM/MM restart file to read.

The OUTPUT\_LEVEL specifies how much output to print during the course of the ADF QM/MM run. OUTPUT\_LEVEL=1 is good for most purposes. Using an OUTPUT\_LEVEL=2 is good when trouble shooting, but probably provides too much output when the job is running normally. The WARNING\_LEVEL keyword specifies when to stop the job. When it is set to 2, the run stops at any spot where a potential QM/MM problem is detected. This is good when first setting up a job because the program attempts to point out potential problems.

## Step 9. Putting it all together: The whole ADF QM/MM input

The whole ADF QM/MM input for the sample system is given below. The following will be a QM/MM geometry optimization

performed in Cartesian coordinates with no constraints. Some comments are provided in bold.

Title CYT amber95 test - CARTESIAN GEOMETRY OPTIMIZATION NO CONSTRAINTS

Fragments

C T21.C.III.1s **Notice that only fragments for the calculation of**

H T21.H.III **model system are needed.**

End

Symmetry NOSYM

Charge 0 0 **This refers to the charge of the QM model system, not the 'real' system**

ATOMS Cartesian

```
1 C 1.94807 3.58290 -0.58162
2 C 1.94191 3.61595 1.09448
3 H 1.69949 4.49893 -1.05273
4 H 2.99455 3.17964 -0.86304
5 C 0.94659 2.40054 -0.92364
6 N -1.74397 -3.46417 0.31178
7 C -1.00720 -2.20758 0.33536
8 C -1.66928 -1.00652 0.31001
9 C -0.92847 0.25653 0.34895
10 N 0.43971 0.26735 0.38232
11 N 0.36409 -2.20477 0.28992
12 C 1.09714 -0.95413 0.22469
13 H -2.89781 -3.50815 0.31746
14 H -1.21484 -4.49217 0.31721
15 H -2.80940 -0.93497 0.30550
16 H -1.55324 1.21497 0.33885
17 C 1.23309 1.44017 0.30994
18 O 2.58277 -1.01636 0.23914
19 H 2.37276 1.25557 0.29984
20 O 1.02358 2.43085 1.50880
21 H 1.17136 1.95097 -1.87367
22 H -0.10600 2.77333 -0.80348
23 H 1.62170 4.54039 1.51392
24 H 2.99608 3.28749 1.41345
```

END

QMMM

FORCEFIELD\_FILE amber95.ff

RESTART\_FILE mm.restart

OUTPUT\_LEVEL=1

WARNING\_LEVEL=2

ELSTAT\_COUPLING\_MODEL=1

LINK\_BONDS

1 - 5 1.38000 H

1 - 2 1.38030 H

SUBEND

MM\_CONNECTION\_TABLE

1 CT QM 2 3 4 5

2 CT LI 1 20 23 24

3 HC QM 1

4 HC QM 1

5 CT LI 1 17 21 22

6 N2 MM 7 13 14

7 CA MM 6 8 11  
8 CM MM 7 9 15  
9 CM MM 8 10 16  
10 N\* MM 9 12 17  
11 NC MM 7 12  
12 C MM 10 11 18  
13 H MM 6  
14 H MM 6  
15 HA MM 8  
16 H4 MM 9  
17 CT MM 5 10 19 20  
18 O MM 12  
19 H2 MM 17  
20 OS MM 2 17  
21 HC MM 5  
22 HC MM 5  
23 H1 MM 2  
24 H1 MM 2

SUBEND

CHARGES

1 0.0 CT  
2 0.0 CT  
3 0.0 HC  
4 0.0 HC  
5 0.0 CT  
6 -0.9530 N2  
7 0.8185 CA  
8 -0.5215 CM  
9 0.0053 CM  
10 -0.0484 N\*  
11 -0.7584 NC  
12 0.7538 C  
13 0.4234 H  
14 0.4234 H  
15 0.1928 HA  
16 0.1958 H4  
17 0.0066 CT  
18 -0.6252 O  
19 0.2902 H2  
20 -0.2033 OS  
21 0.0000 HC  
22 0.0000 HC  
23 0.0000 H1  
24 0.0000 H1

SUBEND

END

GEOMETRY

ITERATIONS 20  
CONVERGE E=1.0E-3 GRAD=0.0005  
STEP RAD=0.3 ANGLE=5.0  
DIIS N=5 OK=0.1 CYC=3

END

XC

LDA VWN

```

GGA POSTSCF Becke Perdew
End

Integration 3.0

SCF
  Iterations 60
  Converge 1.0E-06 1.0E-6
  Mixing 0.20
  DIIS N=10 OK=0.500 CX=5.00 CXX=25.00 BFAC=0.00
End

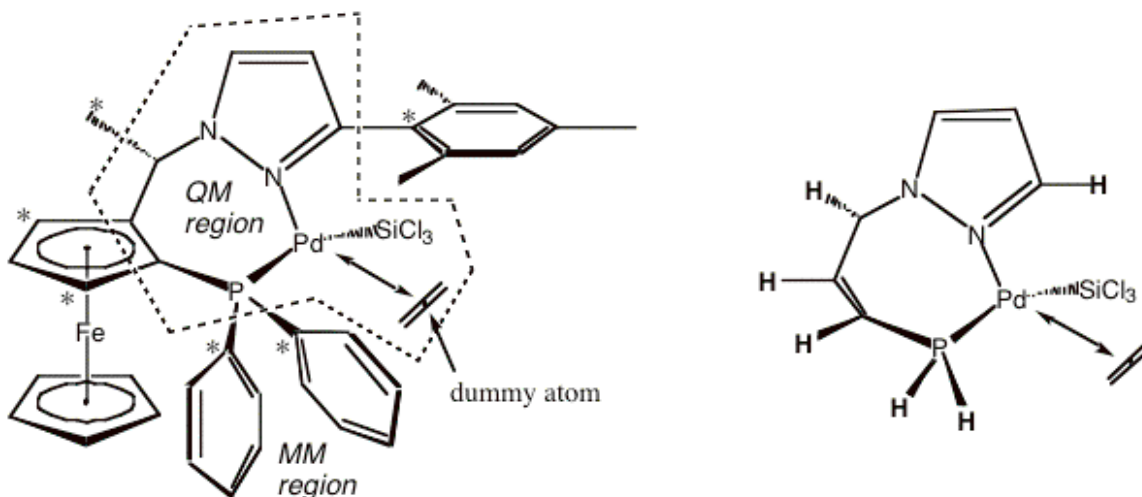
End Input

```

In the above example, the geometry was defined with Cartesian coordinates and the geometry optimization was also done in Cartesians. The same input could also have easily been defined with a Z-matrix in the ATOMS key block.

## Example B: Pd<sup>+</sup>-Ethene pi-complexation Linear Transit

This example is more complex to demonstrate some problems that one might encounter in a more advanced problem. For instance, the simulation will involve the customization of the standard Tripos force field, the use of dummy atoms in the MM region and the use of constraints. Figure 5-3a depicts the system that we intend to simulate. More specifically we wish to determine the reaction profile of removing the olefinic substrate from the metal center of Pd<sup>+</sup>-phosphino-ferrocenyl-pyrazole complex. For this purpose we wish to perform a linear transit run with ADF, whereby the distance between the metal center and the midpoint of the olefinic carbons is used as a reaction coordinate. The linear transit geometry optimization will be done in internal coordinates. This reaction coordinate is shown as the arrow line in Figure 5-3. This example originates from our research on similar neutral bis-trichlorosilyl compounds. The system has been changed slightly to introduce additional technical considerations when using dummy atoms and linear transit calculations. The QM/MM calculations of these related compounds reveal that the approximations introduced in this system are quite reasonable. Also, in terms of predicting the geometry of this class of complexes, the QM/MM method performs exceptionally well.



a b

**Figure 5-3** Example system – Pd<sup>+</sup>-ethene pi-complex. a) Full system, with linear transit coordinate indicated by the arrow line. The QM/MM boundary is shown as the dotted polygon with the QM region residing inside. The 'L' atoms are denoted with the asterisks. b) The QM model system with the capping hydrogen atoms depicted in bold.

## Step 1. Partitioning the System and the Model QM system.

First one must decide where to partition the system into QM and MM regions. For this example, we have decided to partition the system as illustrated in Figure 53b, whereby the QM region is contained in the dotted polygon. The corresponding QM model system, for which the electronic structure calculation will be performed, is depicted in Figure 5-3b. In the model QM system the link atoms have been replaced by capping hydrogen atoms. Notice that the QM/MM boundary cuts through the cyclopentadienyl ring of the ferrocenyl ligand. Based on experimental studies of this complex, it is assumed that the ferrocenyl ligand acts only as a spectator ligand and can be modeled effectively on a steric basis only. Using an olefinic group will approximate the sp<sup>2</sup> hybridization of the Cp rings. Here, special care must be taken to preserve the structural features of the Cp ring. For example the C-C bond distance in the ferrocenyl ligand is approximately 1.45 Ang whereas it is about 1.34 Ang in an olefin. This will be elaborated on later. The replacement of the phenyl phosphine in the real system by hydrogen phosphine will have some consequences due to the different electronic properties of the substituents. It is known that the phenyl substitution on the phosphine is more electron withdrawing than the hydrogen substituent. The replacement of the phenyl phosphine with hydrogen phosphine will result in a contraction of the Pd-P bond in the QM model system and hence the Pd-P bond will be too short in our QM/MM model.

## Step 2. Labeling of Atoms

Once a partitioning of the system has been established, one needs to label each of the atoms in the full system as QM, LI or MM atom type. For the example system, all atoms contained within the dotted polygon in Figure 5-3a are 'QM' atoms. All atoms that are marked with asterisks in Figure 5-3a are 'LI' atoms and finally the remaining atoms outside the dotted polygon are 'MM' atoms. The dummy atom that we need in order to define our reaction coordinate is designated a QM atom. This dummy atom will be made to lie midway between the two olefinic carbon atoms of the ethene moiety. It is important to realize that the linear transit constraint cannot involve any MM atoms. Two dummy atoms representing the center of the Cp rings of the ferrocenyl ligand will also be introduced. They will be part of the MM subsystem.

## Step 3. Renumbering of Atoms

It will be re-emphasized that there is a strict rule concerning the ordering of the atoms, based on their QM, MM, or LI atom type designation. All QM and LI atoms must come before any MM atoms. This rule also applies to the dummy atoms. All atoms in the QM model system shown in Figure 5-3b and their equivalent LI atoms in the real system must come first. Given below are the Cartesian coordinates of the initial geometry with the atoms renumbered. Although the optimization will be performed in internal coordinates, this is a complex example, and it might help the reader to examine the 3D structure of the complex with their favorite molecule viewer.

```

Pd 0.00000 0.00000 0.00000
N 2.18381 0.00000 0.00000
P -0.19353 2.33087 0.00000
Si -2.09382 -0.72920 0.40993
Cl -3.11786 -1.66043 -1.19030
Cl -3.49847 0.77293 1.00006
Cl -2.26795 -2.09058 2.02296
C 1.00751 3.35326 -0.90266
C 2.19320 2.92863 -1.63738
C 2.55933 1.49397 -1.90948
N 3.04680 0.78384 -0.70880
C 4.30216 0.71267 -0.18548
C 4.25805 -0.16196 0.88628
C 2.91893 -0.57760 0.96569
Xx 0.74788 -1.69468 -1.67891
C 1.00986 -2.06361 -1.18981
C 0.48590 -1.32574 -2.16801
H 0.42486 -2.82737 -0.67948

```

H 2.04440 -1.93825 -0.86750  
H 1.06712 -0.55943 -2.68284  
H -0.54392 -1.46716 -2.49409  
C -0.02313 3.09172 1.69751  
C -1.80681 3.04317 -0.56800  
C 1.06326 4.78500 -0.83878  
C 2.90531 4.10963 -2.00851  
H 1.82015 0.84892 -1.41063  
C 2.56571 1.10455 -3.38246  
H 5.13150 1.27389 -0.59600  
H 5.08293 -0.44584 1.52605  
C 2.28008 -1.58274 1.88382  
Fe 1.04114 4.20972 -2.75447  
H 3.29128 1.69565 -3.95722  
H 2.82573 0.03883 -3.48724  
H 1.57260 1.26129 -3.82619  
C 2.23262 5.27491 -1.51096  
H 3.82950 4.13635 -2.57654  
H 2.53722 6.31008 -1.62736  
H 0.35288 5.41923 -0.32204  
C -0.36634 3.33949 -3.93243  
C -0.80398 4.62382 -3.46691  
C 0.14944 5.60144 -3.90508  
C 1.17457 4.92275 -4.64218  
C 0.85084 3.52607 -4.66695  
H 1.38331 2.75840 -5.21594  
H -0.88905 2.39926 -3.80335  
H -1.70862 4.82843 -2.90699  
H 0.10418 6.66814 -3.70967  
H 2.03573 5.38561 -5.11158  
C -2.52881 2.31699 -1.52071  
C -3.74190 2.80302 -2.01422  
C -4.24163 4.02394 -1.55340  
C -3.52216 4.75609 -0.60549  
C -2.30668 4.26891 -0.11529  
H -2.14465 1.36750 -1.87729  
H -4.29443 2.23258 -2.75379  
H -5.18572 4.40286 -1.93263  
H -3.90891 5.70542 -0.24710  
H -1.76468 4.85404 0.61704  
C -1.11030 3.12908 2.57588  
C -0.97634 3.68572 3.85061  
C 0.25426 4.20707 4.25852  
C 1.35020 4.15676 3.39277  
C 1.21425 3.58782 2.12359  
H -2.06730 2.72549 2.27375  
H -1.82678 3.71355 4.52356  
H 0.35921 4.64813 5.24539  
H 2.30826 4.55806 3.70733  
H 2.08227 3.52803 1.47710  
C 2.71278 -2.91472 1.84328  
C 2.09262 -3.86832 2.66014  
C 1.02394 -3.51226 3.48850  
C 0.62539 -2.17333 3.54762  
C 1.26348 -1.20208 2.77018  
C 3.85077 -3.34061 0.90256

```

H 2.44054 -4.89548 2.65117
C 0.28665 -4.56067 4.32981
H -0.18696 -1.88618 4.20708
C 0.83254 0.25922 2.93922
H 4.81150 -3.02160 1.33267
H 3.72469 -2.87842 -0.08835
H 3.87528 -4.43158 0.76399
H 1.55468 0.95128 2.48757
H 0.75353 0.50536 4.00860
H -0.15276 0.39937 2.47265
H -0.79950 -4.40165 4.25848
H 0.51050 -5.58360 3.99174
H 0.59686 -4.45719 5.38063
Xx 1.88038 4.09028 -1.37966
Xx 0.20091 4.40271 -4.12271

```

## Step 4. Z-matrix and constraints

This simulation will be a linear transit simulation where the reaction coordinate will be the distance from the Pd center to the midpoint of the complexed ethene molecule. In order to use midpoint of the ethene molecule as the reaction coordinate we must use a dummy atom to define the midpoint and a few constraints to maintain the dummy atom at the midpoint. The dummy atom is atom number 15 and the two carbon atoms of the ethene moiety are atoms 16 and 17. Each of the two carbons of the ethene will be 'bonded' to the midpoint using the same (free) bond distance variable 'B15'. This will ensure that the midpoint dummy atom is always equidistant to each ethene carbon. To ensure that the midpoint dummy atom always lies along the C-C bond vector the dihedral variable 'D14' will be constrained to 180 degrees. Finally, to prevent C-C bond distance of olefinic group used to model the ferrocenyl ligand to revert to its natural bond length of approximately 1.34 Ang, the C-C distance (B8) will be constrained to 1.45 Ang. This is the distance found in the C-C bond distance in the ferrocenyl ligand. One might be concerned about the internal coordinate definition of the cyclopentadienyl rings of the ferrocenyl ligand. Since the ferrocenyl ligand is part of the MM region, the Z-matrix will be used only to construct the initial geometry. From there the molecular mechanics code takes over and where the optimization is done in Cartesian coordinates. For MM atoms it is important that care be taken when defining the connection table.

```

ATOMS internal
Pd 0 0 0 0 0 0
N 1 0 0 B1 0 0
P 1 2 0 B2 A1 0
Si 1 2 3 B3 A2 D1
Cl 4 1 2 B4 A3 D2
Cl 4 1 5 B5 A4 D3
Cl 4 1 5 B6 A5 D4
C 3 1 2 B7 A6 D5
C 8 3 1 B8 A7 D6
C 9 8 3 B9 A8 D7
N 10 9 8 B10 A9 D8
C 11 2 1 B11 A10 D9
C 12 11 2 B12 A11 D10
C 2 1 11 B13 A12 D11
XX 1 2 3 B14 A13 D12
C 15 1 2 B15 A14 D13
C 15 1 16 B15 A15 D14
H 16 15 1 B17 A16 D15
H 16 17 18 B18 A17 D16
H 17 16 18 B19 A18 D17
H 17 16 18 B20 A19 D18
C 3 1 8 B21 A20 D19
C 3 1 8 B22 A21 D20

```

C 8 3 9 B23 A22 D21  
C 9 8 10 B24 A23 D22  
H 10 9 8 B25 A24 D23  
C 10 9 26 B26 A25 D24  
H 12 11 13 B27 A26 D25  
H 13 12 11 B28 A27 D26  
C 14 2 1 B29 A28 D27  
Fe 24 8 3 B30 A29 D28  
H 27 10 9 B31 A30 D29  
H 27 10 32 B32 A31 D30  
H 27 10 32 B33 A32 D31  
C 25 9 8 B34 A33 D32  
H 25 9 35 B35 A34 D33  
H 35 25 9 B36 A35 D34  
H 24 8 31 B37 A36 D35  
C 31 24 8 B38 A37 D36  
C 39 31 24 B39 A38 D37  
C 40 39 31 B40 A39 D38  
C 41 40 39 B41 A40 D39  
C 39 31 40 B42 A41 D40  
H 43 39 31 B43 A42 D41  
H 39 31 40 B44 A43 D42  
H 40 39 41 B45 A44 D43  
H 41 40 42 B46 A45 D44  
H 42 41 40 B47 A46 D45  
C 23 3 1 B48 A47 D46  
C 49 23 3 B49 A48 D47  
C 50 49 23 B50 A49 D48  
C 51 50 49 B51 A50 D49  
C 52 51 50 B52 A51 D50  
H 49 23 50 B53 A52 D51  
H 50 49 51 B54 A53 D52  
H 51 50 52 B55 A54 D53  
H 52 51 53 B56 A55 D54  
H 53 52 51 B57 A56 D55  
C 22 3 1 B58 A57 D56  
C 59 22 3 B59 A58 D57  
C 60 59 22 B60 A59 D58  
C 61 60 59 B61 A60 D59  
C 62 61 60 B62 A61 D60  
H 59 22 60 B63 A62 D61  
H 60 59 61 B64 A63 D62  
H 61 60 62 B65 A64 D63  
H 62 61 63 B66 A65 D64  
H 63 62 61 B67 A66 D65  
C 30 14 2 B68 A67 D66  
C 69 30 14 B69 A68 D67  
C 70 69 30 B70 A69 D68  
C 71 70 69 B71 A70 D69  
C 72 71 70 B72 A71 D70  
C 69 30 70 B73 A72 D71  
H 70 69 71 B74 A73 D72  
C 71 70 72 B75 A74 D73  
H 72 71 73 B76 A75 D74  
C 73 72 71 B77 A76 D75  
H 74 69 30 B78 A77 D76

H 74 69 79 B79 A78 D77  
H 74 69 79 B80 A79 D78  
H 78 73 72 B81 A80 D79  
H 78 73 82 B82 A81 D80  
H 78 73 82 B83 A82 D81  
H 76 71 70 B84 A83 D82  
H 76 71 85 B85 A84 D83  
H 76 71 85 B86 A85 D84  
XX 24 8 31 B87 A86 D85  
XX 41 40 42 B88 A87 D86

END

GEOVAR

B1=2.18381  
B2=2.33889  
B3=2.25474  
B4=2.11579  
B5=2.13955  
B6=2.11791  
B7=1.81730  
B8=1.45807 F  
B9=1.50544  
B10=1.47768  
B11=1.36193  
B12=1.38405  
B13=1.34409  
B14=2.50000 5.000  
B15=0.66631  
B17=1.08903  
B18=1.09082  
B19=1.09092  
B20=1.08943  
B21=1.86801  
B22=1.85275  
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B25=1.10060  
B26=1.52360  
B27=1.08226  
B28=1.08182  
B29=1.50380  
B30=2.00032  
B31=1.09827  
B32=1.10198  
B33=1.09896  
B34=1.43456  
B35=1.08513  
B36=1.08532  
B37=1.08347  
B38=2.03122  
B39=1.43448  
B40=1.43413  
B41=1.43347  
B42=1.43383  
B43=1.08361  
B44=1.08347

B45=1.08341  
B46=1.08540  
B47=1.08451  
B48=1.39867  
B49=1.39691  
B50=1.39740  
B51=1.39722  
B52=1.39822  
B53=1.08455  
B54=1.08520  
B55=1.08569  
B56=1.08594  
B57=1.08280  
B58=1.39816  
B59=1.39740  
B60=1.39734  
B61=1.39754  
B62=1.39750  
B63=1.08166  
B64=1.08484  
B65=1.08604  
B66=1.08530  
B67=1.08396  
B68=1.40109  
B69=1.40042  
B70=1.39823  
B71=1.39824  
B72=1.39818  
B73=1.53667  
B74=1.08452  
B75=1.53315  
B76=1.08501  
B77=1.53287  
B78=1.09990  
B79=1.10064  
B80=1.10001  
B81=1.09746  
B82=1.10018  
B83=1.09915  
B84=1.10005  
B85=1.10036  
B86=1.10053  
B87=1.20119  
B88=1.21941  
A1=94.7463  
A2=158.2223  
A3=117.0192  
A4=115.6423  
A5=115.0054  
A6=120.3960  
A7=128.6001  
A8=124.4982  
A9=113.0381  
A10=110.6944  
A11=107.5291  
A12=123.1566

A13=72.5934  
A14=90.0001  
A15=90.0001  
A16=121.4060  
A17=121.7463  
A18=121.7273  
A19=121.2990  
A20=113.4758  
A21=117.0770  
A22=124.4140  
A23=107.1936  
A24=108.2564  
A25=114.7923  
A26=122.2418  
A27=126.8321  
A28=119.5733  
A29=70.7204  
A30=111.7865  
A31=109.8825  
A32=110.4946  
A33=110.3514  
A34=125.5260  
A35=127.2980  
A36=125.4579  
A37=133.3349  
A38=68.8766  
A39=107.9605  
A40=108.0463  
A41=69.7028  
A42=125.7664  
A43=129.5676  
A44=126.2672  
A45=125.9595  
A46=126.0404  
A47=117.3031  
A48=120.5489  
A49=119.8703  
A50=119.8287  
A51=120.1922  
A52=119.7123  
A53=120.0017  
A54=120.0478  
A55=119.9075  
A56=118.9447  
A57=120.7197  
A58=120.6090  
A59=119.9563  
A60=119.7586  
A61=120.0640  
A62=120.1660  
A63=120.0615  
A64=120.1253  
A65=119.9602  
A66=119.0914  
A67=119.1156  
A68=119.5849

A69=120.7057  
A70=119.1275  
A71=120.7701  
A72=120.6568  
A73=119.8697  
A74=121.2330  
A75=119.5074  
A76=118.2033  
A77=109.0914  
A78=110.4834  
A79=111.6228  
A80=111.7639  
A81=109.9169  
A82=109.0716  
A83=109.9009  
A84=111.6715  
A85=108.9122  
A86=55.1829  
A87=54.0180  
D1=-150.6568  
D2=-100.8347  
D3=-119.5809  
D4=123.4778  
D5=35.1598  
D6=-2.9958  
D7=7.2171  
D8=-72.9107  
D9=164.5027  
D10=0.9220  
D11=163.0063  
D12=135.2677  
D13=65.6662  
D14=180.0000 F  
D15=90.0000  
D16=179.5031  
D17=-179.9904  
D18=-0.4168  
D19=-117.3520  
D20=124.7005  
D21=-169.6021  
D22=-179.2713  
D23=-3.3919  
D24=119.3500  
D25=179.9891  
D26=-179.9514  
D27=17.4102  
D28=-129.2972  
D29=60.6432  
D30=120.3390  
D31=-120.3043  
D32=1.2969  
D33=179.4155  
D34=179.5397  
D35=123.6746  
D36=68.3005  
D37=62.0893

```
D38=58.4426
D39=0.0736
D40=119.7199
D41=127.1496
D42=-120.1862
D43=178.4186
D44=-179.8093
D45=179.5019
D46=-30.2454
D47=-178.8402
D48=-0.0598
D49=0.3012
D50=-0.1575
D51=-179.8476
D52=-179.9824
D53=179.8951
D54=-179.8926
D55=179.8489
D56=-81.7949
D57=179.3002
D58=-0.2287
D59=-0.6445
D60=0.0510
D61=-179.9960
D62=179.9913
D63=-179.8879
D64=-179.8700
D65=-178.0390
D66=114.6178
D67=-177.7647
D68=1.7082
D69=-3.4460
D70=1.3564
D71=179.4189
D72=179.8505
D73=-179.9397
D74=-179.8352
D75=-176.6101
D76=76.9134
D77=-120.1615
D78=119.9038
D79=165.3767
D80=-119.6911
D81=121.2928
D82=-135.8162
D83=120.3122
D84=-119.4211
D85=-58.7928
D86=0.0762
END
```

## Step 5. Connection Table, MM force field atom-types and Force Field Modification

In order to construct a molecular mechanics potential, the program needs to know the connectivity of the molecular system and the

molecular mechanics force field atom-type designations. In this example we are using the Tripos or Sybyl force field. The Tripos force field does not support either Pd or ferrocenyl ligands, so we need to modify the standard force field file to handle these groups. Modification of a molecular mechanics force field without re-parameterization of the force field may not always be appropriate. However, in this case sort of 'ad hoc' additions to the Tripos force field can be justified. For Pd, all of the principle interactions will be contained within the QM region and only weak non-bonded interactions involving Pd will be approximated by the molecular mechanics potential. The ferrocenyl ligand is assumed to act as a spectator ligand and therefore it is adequate to simply attain the approximate structure of the complex with the molecular mechanics potential.

In the Tripos force field, the nitrogen atoms of the pyrazole ring should be assigned the 'N\_2' atom-type; the P atom of the phosphine should be assigned the 'P\_3' atom-type. The Cl, H and Si atoms are given the 'Cl', 'H', and 'Si' atom types respectively. The carbon atoms of the phenyl substituents are given the 'C\_ar' atom-type, while the sp<sup>3</sup> hybridized carbon atoms are given the 'C\_3' atom-type.

Connections involving the dummy atom defining the midpoint of the ethene molecule are really not needed since this atom is contained within the QM region.

For the ferrocenyl ligand the ferrocene force field of Bosnich and coworkers will be used. Four new MM atom types will be introduced, C\_cp, H\_cp and CEN, representing the carbon, hydrogen and centroid of the cyclopentadienyl rings, respectively and Fe. In the connection table, the C\_cp atoms will be bonded to the centroid and not the Fe center. The only two bonds made to the Fe center will be to the (two) central dummy atoms of the Cp rings. In making a connection between the C\_cp atom and the centroid, a direct bond will be made to a QM atom and a MM atom. A warning will be issued during the run but as long as the 'WARNING\_LEVEL' flag is set to 1 the job will continue. In this case the link bond between the C\_cp atom and the centroid does not need to be mediated by a capping atom. This bond is used only for the construction of the MM potential for the ferrocenyl ligand. Special bond stretching, bending, torsion and out-of-plane potentials need to be added to the force field file. For the most part these parameters are taken from the Bosnich Ferrocene force field. For example for the bond stretches, the following potentials need to be added to the force field.

```
# Parameters added for Pd - ethene complex
C_cp  C_cp  1      1400.00      1.434      From the Bosnich ferrocene force field.
C_cp  H_cp  1      692.00      1.085      Bosnich
CEN   Fe   1      600.00      1.617      Bosnich
CEN   C_cp 1      600.00      1.220      Bosnich
```

The force field file is simply a text file and so the above section needs to be added to the 'BONDS' key block between the two '=====' separator lines. Bond potentials need to be defined between the centroid of the Cp rings with the Fe center and the carbon atoms.

For the angle and torsion terms, the additions are somewhat more complex. The following angle potential terms need to be introduced.

```
# Parameters added for Pd - ethene complex
C_cp  C_cp  C_cp  1      78.80      126.0      Bosnich
C_cp  C_cp  H_cp  1      78.80      126.0      Bosnich
CEN   C_cp  C_cp  1      0.00      0.0        no potential
CEN   C_cp  H_cp  1      0.00      0.0        no potential
C_cp  CEN   C_cp  1      0.00      0.0        no potential
C_cp  CEN   Fe   1      100.00     90.0       Bosnich
CEN   Fe   CEN  1      100.00     180.0      Bosnich
CEN   C_cp  P_3  1      0.00      0.0        no potential
CEN   C_cp  C_3  1      0.00      0.0        no potential
```

Any angle potentials involving the Cp centroid and any atoms outside of the ferrocenyl ligand have been set to zero since the centroid was only a construct for the optimization of the ferrocenyl ligand. For the torsions, the following potentials have been added to the standard Tripos force field.

```
# Parameters added for Pd - ethene complex
P_3   C_cp  C_cp  C_cp  2      2.0000     -2.0       Sybyl *-C_ar-C_ar-* aromatic bond
P_3   C_cp  C_cp  H_cp  2      2.0000     -2.0       Sybyl *-C_ar-C_ar-* aromatic bond
```

C_3	C_cp	C_cp	H_cp	2	2.0000	-2.0	Sybyl *-C_ar-C_ar* aromatic bond
H_cp	C_cp	C_cp	H_cp	2	2.0000	-2.0	Sybyl *-C_ar-C_ar* aromatic bond
*	C_cp	C_cp	C_cp	2	2.3500	-2.0	same as SYBYL * C_ar C_ar C_ar
*	Fe	CEN	*	0	0.0000	-2.0	no potential involving centroid
*	C_cp	CEN	*	0	0.0000	0.0	no potential involving centroid
*	C_cp	C_cp	CEN	0	0.0000	0.0	no potential involving centroid
Pd	P_3	C_cp	CEN	0	0.0000	0.0	no potential involving centroid
CEN	C_cp	P_3	C_ar	0	0.0000	0.0	no potential involving centroid
N_2	C_3	C_cp	CEN	0	0.0000	0.0	no potential involving centroid
CEN	C_cp	C_3	H	0	0.0000	0.0	no potential involving centroid
CEN	C_cp	C_3	C_3	0	0.0000	0.0	no potential involving centroid

Here any torsional potentials involving the Centroid atom of the ferrocenyl ligand were set to zero. Torsional potentials involving atoms outside of the ferrocenyl ligand and having the C\_cp-C\_cp atoms central atom pair, these potentials were equated with those of the Tripos '\*-C\_ar - C\_ar - \*' torsional potentials. Again, these somewhat arbitrary choices for the MM potentials involving the ferrocenyl ligand are justified by the fact that the ferrocenyl ligand acts only as a spectator group.

The van der Waals parameters used for the five new atoms types, Pd, Fe, CEN, C\_cp and H\_cp were taken from either existing Tripos van der Waals parameters of similar atom-types or they were taken from Rappe's UFF (Universal Force Field). They are given below with their origins provided in the 'NOTES' column.

#### # Parameters added for Pd - ethene complex

C_cp	0.1070	3.4000	12.00	same as Tripos C_ar
Fe	0.0130	2.9120	12.00	UFF92 Fe6+2
Pd	0.0480	2.8990	12.00	UFF92 Pd4+2
CEN	0.0000	1.0000	12.00	zero
H_cp	0.0420	3.0000	12.00	same as Tripos H

Now that the addition of the new MM potentials and atom-types has been discussed, the 'MM\_CONNECTION\_TABLE' subkey block is given below. In practice, one typically constructs the input first, and then runs the program to see what force field potentials/parameters are missing. If any force field parameters are missing in the force field file, the ADF QM/MM program will print all missing potentials that need to be defined in the force field and then stop.

```
MM_CONNECTION_TABLE
 1 Pd QM 2 3 4 0 0 0
 2 N_2 QM 1 11 14 0 0 0
 3 P_3 QM 1 8 22 23 0 0
 4 Si QM 1 5 6 7 0 0
 5 Cl QM 4 0 0 0 0 0
 6 Cl QM 4 0 0 0 0 0
 7 Cl QM 4 0 0 0 0 0
 8 C_cp QM 3 9 24 88 0 0
 9 C_cp QM 8 10 25 88 0 0
10 C_3 QM 9 11 26 27 0 0
11 N_2 QM 2 10 12 0 0 0
12 C_ar QM 11 13 28 0 0 0
13 C_ar QM 12 14 29 0 0 0
14 C_ar QM 2 13 30 0 0 0
15 XX QM 16 17 1 0 0 0
16 C_2 QM 15 17 18 19 0 0
17 C_2 QM 15 16 20 21 0 0
18 H QM 16 0 0 0 0 0
19 H QM 16 0 0 0 0 0
20 H QM 17 0 0 0 0 0
21 H QM 17 0 0 0 0 0
22 C_ar LI 3 59 63 0 0 0
23 C_ar LI 3 49 53 0 0 0
```

24	C_cp	LI	8	35	38	88	0	0
25	C_cp	LI	9	35	36	88	0	0
26	H_QM		10	0	0	0	0	0
27	C_3	LI	10	32	33	34	0	0
28	H_QM		12	0	0	0	0	0
29	H_QM		13	0	0	0	0	0
30	C_ar	LI	14	69	73	0	0	0
31	Fe	MM	88	89	0	0	0	0
32	H	MM	27	0	0	0	0	0
33	H	MM	27	0	0	0	0	0
34	H	MM	27	0	0	0	0	0
35	C_cp	MM	24	25	37	88	0	0
36	H_cp	MM	25	0	0	0	0	0
37	H_cp	MM	35	0	0	0	0	0
38	H_cp	MM	24	0	0	0	0	0
39	C_cp	MM	40	43	45	89	0	0
40	C_cp	MM	39	41	46	89	0	0
41	C_cp	MM	40	42	47	89	0	0
42	C_cp	MM	41	43	48	89	0	0
43	C_cp	MM	39	42	44	89	0	0
44	H_cp	MM	43	0	0	0	0	0
45	H_cp	MM	39	0	0	0	0	0
46	H_cp	MM	40	0	0	0	0	0
47	H_cp	MM	41	0	0	0	0	0
48	H_cp	MM	42	0	0	0	0	0
49	C_ar	MM	23	50	54	0	0	0
50	C_ar	MM	49	51	55	0	0	0
51	C_ar	MM	50	52	56	0	0	0
52	C_ar	MM	51	53	57	0	0	0
53	C_ar	MM	23	52	58	0	0	0
54	H	MM	49	0	0	0	0	0
55	H	MM	50	0	0	0	0	0
56	H	MM	51	0	0	0	0	0
57	H	MM	52	0	0	0	0	0
58	H	MM	53	0	0	0	0	0
59	C_ar	MM	22	60	64	0	0	0
60	C_ar	MM	59	61	65	0	0	0
61	C_ar	MM	60	62	66	0	0	0
62	C_ar	MM	61	63	67	0	0	0
63	C_ar	MM	22	62	68	0	0	0
64	H	MM	59	0	0	0	0	0
65	H	MM	60	0	0	0	0	0
66	H	MM	61	0	0	0	0	0
67	H	MM	62	0	0	0	0	0
68	H	MM	63	0	0	0	0	0
69	C_ar	MM	30	70	74	0	0	0
70	C_ar	MM	69	71	75	0	0	0
71	C_ar	MM	70	72	76	0	0	0
72	C_ar	MM	71	73	77	0	0	0
73	C_ar	MM	30	72	78	0	0	0
74	C_3	MM	69	79	80	81	0	0
75	H	MM	70	0	0	0	0	0
76	C_3	MM	71	85	86	87	0	0
77	H	MM	72	0	0	0	0	0
78	C_3	MM	73	82	83	84	0	0
79	H	MM	74	0	0	0	0	0

```

80 H MM 74 0 0 0 0 0
81 H MM 74 0 0 0 0 0
82 H MM 78 0 0 0 0 0
83 H MM 78 0 0 0 0 0
84 H MM 78 0 0 0 0 0
85 H MM 76 0 0 0 0 0
86 H MM 76 0 0 0 0 0
87 H MM 76 0 0 0 0 0
88 CEN MM 8 9 24 25 35 31
89 CEN MM 39 40 41 42 43 31
SUBEND

```

## Step 6. LINK\_BONDS

In this example there are 6 link bonds as depicted in Figure 5-3a. The link bond parameters  $a$  for each of these bonds will be determined by comparing bond lengths in the X-ray structure of a similar bis-trichlorosilyl Pd complex with that of the calculated pure QM gas-phase structure of the QM model system. As shown in Figure 5-3b all link bonds will be capped with Hydrogen atoms. Although the MM connection table defines direct bonds between atoms 8 and 9 (C Cp atoms) with the centroid of the Cp rings, they are not mediated by capping atoms. In other words the Cp centroid is defined as a MM atom-type not a LI atom type. Therefore, no link parameters are necessary for those two bonds.

```

LINK_BONDS
:: -----
:: atoms alpha dummy
:: -----
22 - 3 1.2990 H
23 - 3 1.2990 H
24 - 8 1.3200 H
25 - 9 1.3200 H
27 - 10 1.3710 H
30 - 14 1.3800 H
:: -----
SUBEND

```

## Step 7. CHARGES

In this example, the Pd center has a formal positive charge. In order to obtain the proper electronic structure in the calculation of the QM model system, we must define in the ADF input a formal positive charge with the CHARGE keyword.

```

| CHARGE 1 {note this is in the main ADF input}

```

The original Tripos force field was parameterized without explicit electrostatic terms. Thus, we will use this convention and turn off the electrostatic coupling between the QM and MM regions using the ELSTAT\_COUPLING\_MODEL keyword in the QMMM key block.

```

| ELSTAT_COUPLING_MODEL=0

```

Although this may seem like a dubious choice, experience with organometallic complexes has shown that this is a good approximation. For other types of molecular systems, namely amino and nucleic acids it is not a good choice to turn off the electrostatic coupling between the QM and MM regions. Furthermore, force fields designed for this biochemical species almost always have charges included in the parameterization process.

## Step 9. Putting it all together: The whole ADF QM/MM input.

The whole ADF QMMM input for the sample system is given below. Some comments are provided in bold. Additionally, some lengthy sections have been omitted that have already been given in full above.

```
TITLE Complex force field Example of Pd+-Ethene complex.
MAXMEMORYUSAGE 60
NOPRINT SFO
Fragments
Pd T21.Pd.3d.rel
C T21.C.1s.rel
Si T21.Si.2p.rel
Cl T21.Cl.2p.rel
H T21.H.rel
N T21.N.1s.rel
P T21.P.2p.rel
End

RELATIVISTIC SCALAR
COREPOTENTIALS ADF.t12 &
Pd 1
P 2
Si 3
Cl 4
N 5
C 6
H 7
END

SYMMETRY NOSYM

CHARGE 1 CHARGE is defined from the QM model system

GEOMETRY
LINEAR TRANSIT 4
ITERATIONS 2
HESSUPD BFGS
CONVERGE E=2.0E-3 GRAD=0.002
DIIS N=5 OK=0.005 CYC=2
END

XC
LDA VWN
GGA Becke Perdew
End

Integration 3.0 3.0

SCF
Iterations 60
Converge 1.0E-06 1.0E-06
Mixing 0.20
DIIS N=10 OK=0.500 CX=5.00 CXX=25.00 BFAC=0.00
LShift 0.00
End

QMMM
FORCE_FIELD_FILE sybyl.ff
OUTPUT_LEVEL=1
```

```
WARNING_LEVEL=-1

ELSTAT_COUPLING_MODEL=0

MM_CONNECTION_TABLE
  SAME AS IN ABOVE
SUBEND
LINK_BONDS
:: -----
:: atoms alpha dummy
:: -----
  22 - 3 1.2990 H
  23 - 3 1.2990 H
  24 - 8 1.3200 H
  25 - 9 1.3200 H
  27 - 10 1.3710 H
  30 - 14 1.3800 H
:: -----
SUBEND
END

ATOMS internal
  SAME AS IN ABOVE
END

GEOVAR
  SAME AS IN ABOVE
END

END INPUT
```

## References

1. Woo, T.K.; Cavallo, L.; Ziegler, T. *Theor Chem Acc* 1998, 100, 307.
2. Maseras, F.; Morokuma, K. *J Comput Chem* 1995, 16, 1170.
3. Swart, M. *Int J Quantum Chem* 2003, 91, 177.
4. Cornell, W.D., *et al.* *J Am Chem Soc* 1995, 117, 5179.
5. Clark, M.; Cramer III, R.D.; Van Opdenbosch, N. *J Comput Chem* 1989, 10, 982.
6. Singh, U.C.; Kollman, P.A. *J Comput Chem* 1986, 7, 718.
7. Swart, M.; van Duijnen, P.T.; Snijders, J.G. *J Comput Chem* 2001, 22, 79.

## Appendix A. List of Publications Using ADF QM/MM

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