

### Assignment 10: Experiments in Molecular Geometry Optimization: Biphenyl Minimization

See Insight II and Discover manuals for reference.

#### 1. Brief introduction to the Discover module of Insight II.

The Discover<sup>7</sup> software performs energy minimization and molecular dynamics simulations. This program constitutes a powerful modeling tool since it offers many features such as constrained and restrained minimization, calculation of vibrational frequencies, and analysis tools. Many variations of simulation conditions (e.g., constant temperature, constant pressure) are available.

We will access the Discover software from the Insight II environment. The **Discover** module of Insight II is a convenient interface to the Discover program. This module builds Discover input files from information provided through graphical interfaces, and it allows users to run Discover jobs interactively. Though more advanced users may prefer to use the independent version of Discover, the Insight II environment is more appropriate for a novice.

Before using Discover, make sure that Insight II contains all of the necessary information to define the topology, coordinates, and force field parameters. These include, for example, atom types and partial charges (see lecture notes for structure definitions).

If you succeed in displaying the molecule correctly on the screen, the topological and coordinate information is most likely in order. However, selecting the appropriate force field and assigning atom types and parameters is a separate task.

Such assignments are accomplished within the **Builder** or **Biopolymer** modules. To select the force field, use **Forcefield** **Select**. To assign atom types and charges, use **Forcefield** / **Potentials**. You can request that Insight II make these assignments by choosing **Fix**. Alternatively, first assign parameters with **Atom** / **Potential** and then notify Insight II whether to accept them using **Forcefield** / **Potentials** / **Accept**. Note that after each change in the force field you must assign atom types and charges anew.

For this assignment, choose **Accept** for **Potential Action** in **Forcefield** / **Potentials** and **Fix** for both **Partial Chg Action** and **Formal Chg Action**.

Once you specify the information about the structure and parameters, you are ready to move to the **Discover** module. (We will not use **Discover\_3** in this course).

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<sup>7</sup>Note that the name *Discover* has two separate meanings. The first, **Discover**, stands for the software package with minimization and molecular dynamics routines. The second, typed in bold (**Discover**), refers to the module available in Insight II.

The **Constraint** pulldown menu contains various atom-constraining and restraining procedures that you can select. In **Parameters**, you select the simulation type for Discover (**Minimize**, **Dynamics**, etc.), as well as the choice for cutoff parameters for nonbonded interactions, periodic boundary conditions (**Variables**), and dielectric constant (**Set**). Take time to familiarize yourself with the first three pulldown menus **Constraint**, **Parameters**, and **Run**, with `Insight_help` active, to learn about the various commands they contain.

To start a simulation, go to **Run/Run**, select desired options, choose the object for calculations, and execute.

Each Discover run is assigned a number in the order of the execution start time. The files created during the execution are identified by the calculation object (molecular system name) and the job integer (appended to the name). The file extension specifies the file type. Examples are listed below.

#### Discover Input Files:

- Commands ( `.inp`)
- Cartesian Coordinates ( `.car`)
- Molecular Data ( `.mdf`)
- Force field Parameters ( `.frc`)
- Restraints ( `.rstrnt`)

#### Discover Output Files:

- Standard Output ( `.out`)
- Cartesian Coordinates (final structure) ( `.cor`)
- Cartesian Coordinate Archive (multiple frames) ( `.arc`)
- Automatic Potential Parameter Assignment ( `.prm`)
- Discover Dynamics Restart Information ( `.rst`)

You can specify the files to save with **Run/Files**. By default, all are saved.

## 2. Setting up biphenyl minimization.

We will begin to learn about potential energy minimization for a simple yet interesting system, biphenyl (see Fig. D.2).

You will receive electronically two files containing the coordinates of biphenyl<sup>8</sup> The first, `biphenyl.car`, includes the structure with coplanar phenyl rings. This configuration was created with the **Builder** module by connecting two benzene rings.

The second file, `biphenyl_distorted.car`, contains the structure with each of the phenyl rings distorted from planarity.

Before displaying these structures, check that the AMBER force field is chosen. This will save work in assigning AMBER force field parameters. It

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<sup>8</sup>Files can be obtained through the link to the course web site or directly from the author.

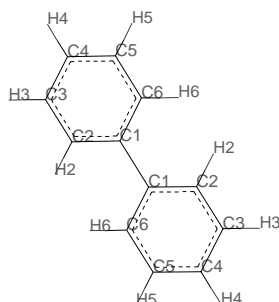


Figure D.2. Biphenyl

will also permit you to proceed to **Discover** directly. (For other force fields, you would have to assign parameters through **Forcefield** **Potentials** in the **Builder** or **Biopolymer** module). To open a coordinate file and display a structure, use **Molecule** **Get**, specify **Archive** as the **File Type**, and select the desired file.

### 3. Generation of energy profiles by restrained minimization.

A potential energy profile along some molecular coordinate,  $X$  (such as the rotamer dihedral angle  $\chi_1$ ), describes the dependence of the energy, minimized with respect to the remaining coordinates, on  $X$ . The simplest way to generate such a profile is to use minimization with *restraints*. Restraining a coordinate  $X$  to a specified value  $X^0$  can be accomplished by adding harmonic penalty term,

$$E_{rstr} = K (X - X^0)^2,$$

to the potential energy. After minimization,  $X$  should not deviate significantly from  $X^0$  when the force constant  $K$  is large.<sup>9</sup> For a complete profile, minimum energy values must be calculated for a series of values  $\{X_1^0, X_2^0, X_3^0, \dots\}$  in the range of  $X$ .

For biphenyl, we will analyze the dependence of energy on the torsion angle between the planes of phenyl rings. Four dihedral angles are defined about the C1–C1 bond connecting the two rings. They are specified by the following atom quadruplets  $\{1B:C2, 1B:C1, 1:C1, 1:C6\}$ ,  $\{1B:C6, 1B:C1, 1:C1, 1:C2\}$ ,  $\{1B:C2, 1B:C1, 1:C1, 1:C2\}$ , and  $\{1B:C6, 1B:C1, 1:C1, 1:C6\}$ . Restraining only one of them will result in a nonplanar geometry of phenyl rings (since the remaining dihedral angles will tend to assume values associated with a lower energy). To ensure that the phenyl-ring planes are not

<sup>9</sup>*Constrained*, as opposed to restrained, minimization entails a more complex procedure to guarantee that  $X = X^0$ .

distorted, it is necessary to restrain a *pair* of dihedral angles to the same value. You can choose the first two or the last two atom quadruplets from the list above.

The plot for the full range of the angle,  $[-180.0^\circ, 180.0^\circ]$ , can be created by first computing energy minima for a sequence of values in the range  $[0.0^\circ, 90.0^\circ]$  (e.g.,  $0.0^\circ, 10.0^\circ, 20.0^\circ, \dots, 90.0^\circ$ ), and then using symmetry operations.

Start with the coplanar structure (`biphenyl.car`). Make sure that potential parameters are properly assigned.

Then select `Constraint/TorsionForce`. You can now proceed in different ways to calculate the energy values for the profile. For instance, you can make 10 separate minimization runs, each time specifying both restraints (`Intervals` set to 1). Alternatively, you can execute one run specifying the range of values for both restraints (`Intervals` set to 9, `Starting_Angle` set to 0.0, and `Angle_Size` set to 90.0). In the latter case, you must extract the appropriate energy values from the output file. For two restraints, defined at ten points each, 100 energy values (corresponding to all restraints) will be listed as output. Extract only those values for which the restraint targets on both angles are identical.

Use `Force Constant` set to the range of 2000–5000.

Switch to `Parameters/Minimize` and select Conjugate gradient algorithm with `Gradient tolerance` set to 0.001.

Note that `Parameters/Set` and `Parameters/Variables` are left at their default values. Now proceed to `Run`.

Another possibility is to use `Run/Files` to limit the number of output files. Before executing the `Run/Run` command check the restraints and selected minimization options using the `List` option.

After minimization, the dihedral angle might deviate somewhat from the value specified in the restraint. If you run one long job, the minimized structures for each pair of restraints are saved in a file with the `.arch` suffix.

You can view these structures (frames) with `Trajectory/Get` and

`Trajectory/Conformation` from the **Analysis** module and determine the torsion angle value.

Plotting the profile should be done only after completing the next section of the assignment.

#### 4. Unrestrained minimization for biphenyl.

In addition to the restrained minimization calculations, perform unrestrained minimization to find the global energy minimum,  $E_{min}$ , for biphenyl.

Now express the profile energy  $E$  from the previous section relative to the  $E_{min}$  (i.e.,  $E - E_{min}$ ), and plot against the dihedral angle.

Note: You may choose Fix for Potential Action to let Insight II assign appropriate potential parameters.

**5. Comparison of different force fields.**

Repeat the energy profile calculations with the `cff91` force field. Plot the results obtained with the AMBER and `cff91` force fields on one plot and discuss your findings.

**6. Dependence on initial conditions — optimization of biphenyl starting with the coplanar-ring configuration.**

Perform unconstrained minimization of biphenyl starting with the structure specified in the `biphenyl.psv` file. Use the `cff91` or AMBER force field and any minimization algorithm you wish, but use the Derivative tolerance of 0.001.

Describe the minimization algorithm briefly and discuss your results.

**7. Assessment of the performance of various minimization algorithms in Insight II.**

For each minimization algorithm offered in Discover record the CPU time required for convergence of the energy gradient to the target values of 10.0, 0.1, 0.001, and 0.00001 kcal/Å. Use the AMBER force field.

For each algorithm, begin with the structure contained in the file `biphenyl_distorted.psv`. Select the desired Algorithm from **Parameters** / **Minimize**; set Iterations to 5000; specify the first target value of the derivative; execute; and proceed to execute the **Run/Run** command. After this job is completed, change the derivative tolerance to the next target value and repeat minimization. After reaching the gradient tolerance of 0.00001 kcal/Å, where possible, extract the timings from each output file. Do not increase the number of Iterations above 5000. If the specified convergence is not reached with this threshold, note that in your report.

Repeat this procedure for each of the remaining algorithms. (Remember to start with the structure from `biphenyl_distorted.psv` file.) Construct a table comparing the performance of minimization algorithms in the different regions of derivative tolerance (report the timings).

On the basis of these results, and the information you have learned in class, suggest a simulation schedule to achieve an optimal minimization of a large molecule. Note that for our small system the gradient norm associated with the initial configuration of biphenyl is not extremely large.

### Background Reading from Coursepack

- M. Karplus and G. A. Petsko, “Molecular Dynamics Simulations in Biology”, *Nature* **347**, 631–639 (1990).