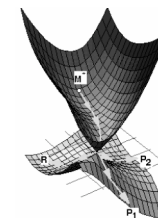




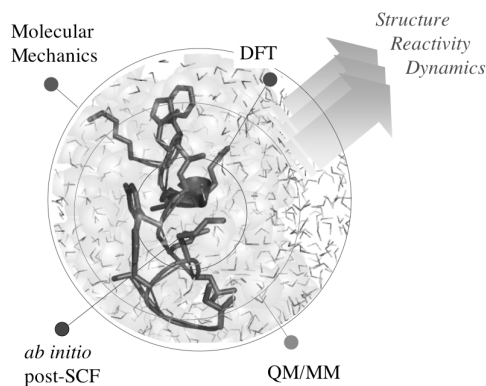
Gruppo di Chimica e Fotochimica Computazionale
Dipartimento di Chimica - Università di Siena

<http://ccmaol1.chim.unisi.it/>



Chapter 1

"Reactivity and Organocatalysis"



Part 4. Exercise

Contents:

a) Case study:

"Origin of the stereoselectivity of the Direct Aldol Reaction between Acetone and Isobutyraldehyde"

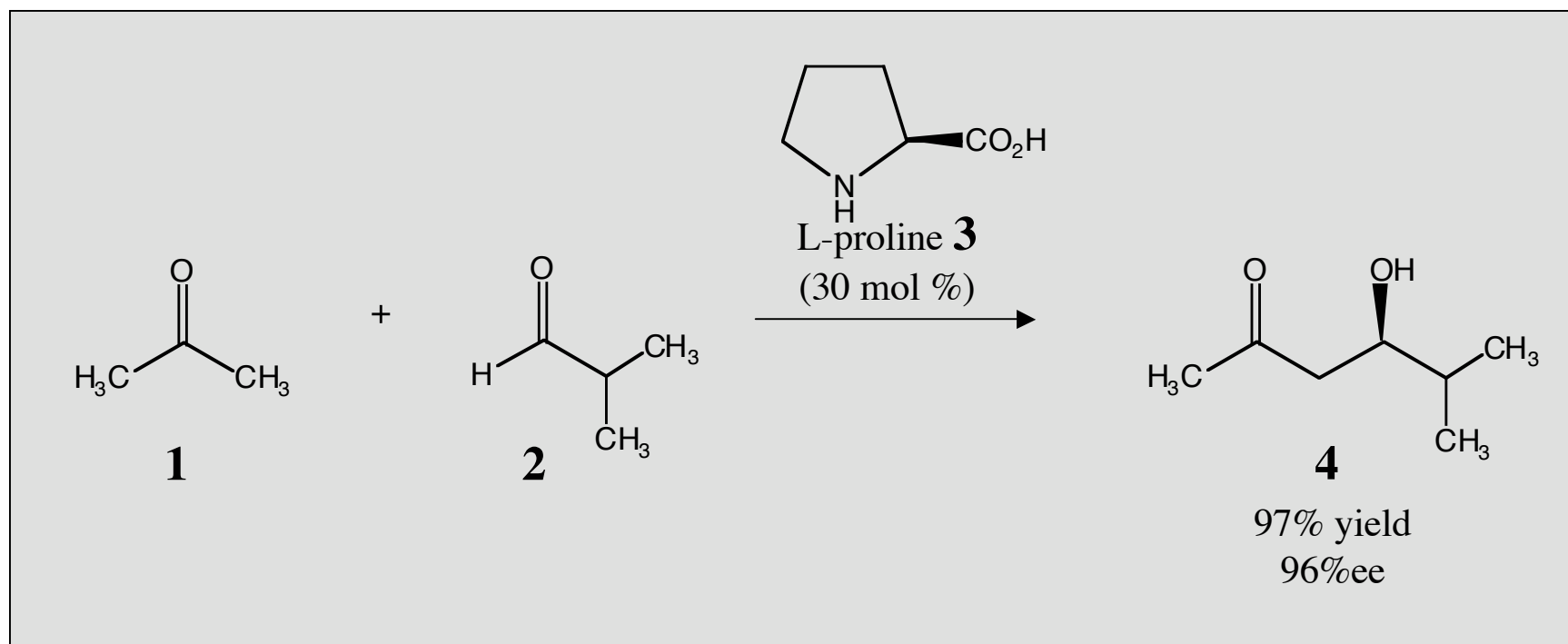
b) Steps of the exercise:

- 1. Create an initial geometry for transition states**
- 2. Prepare the approximate Hessian**
- 3. Search for transition states**
- 4. Calculating frequencies at transition states**
- 5. Comparing results for TSs to confirm the expected stereoselectivity**

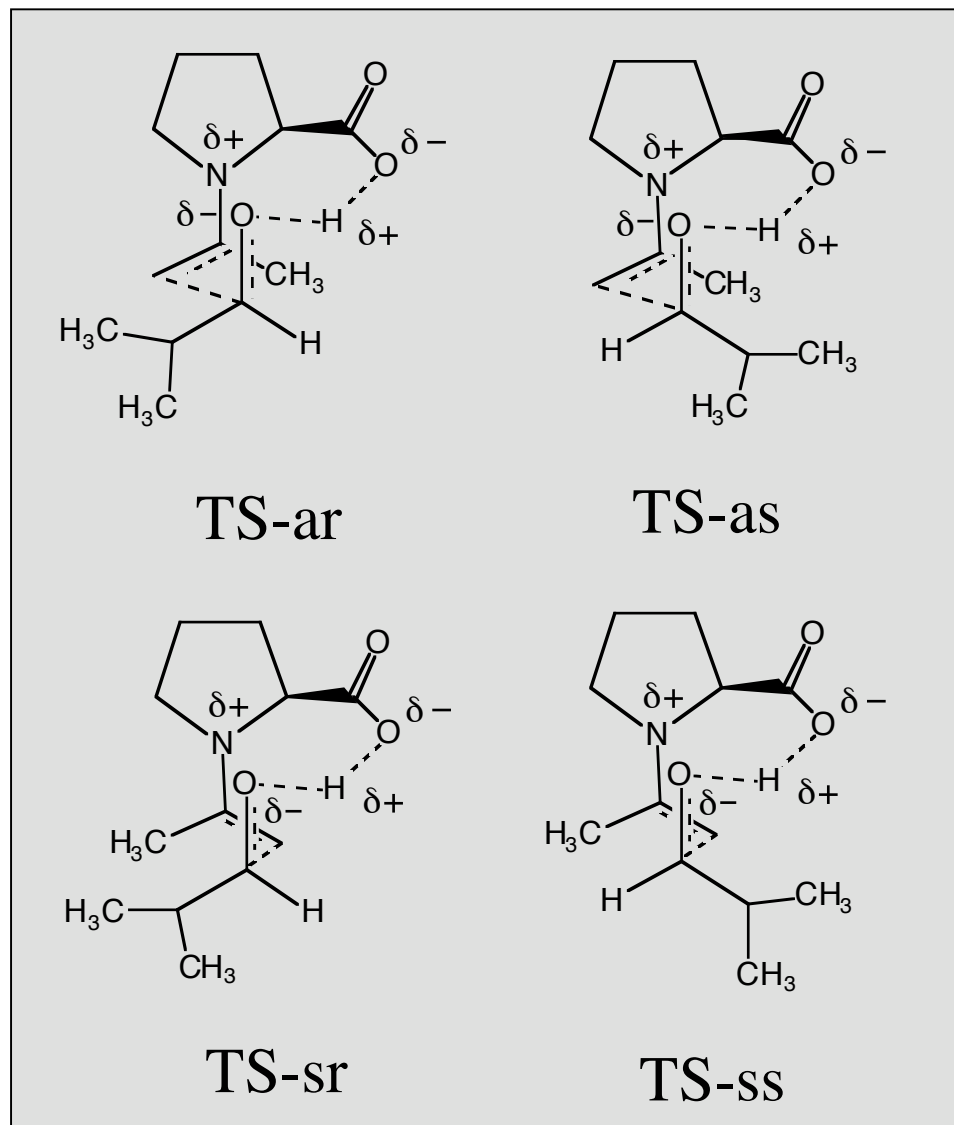
a) Case study

Adapted from

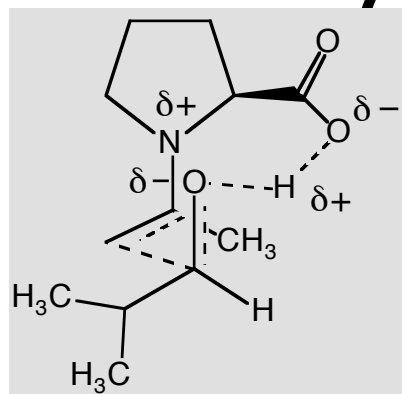
Arnó et al., *Theor. Chem. Acc.* (2002) 108:232-239



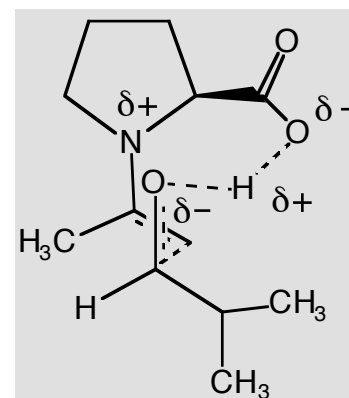
a) Case study



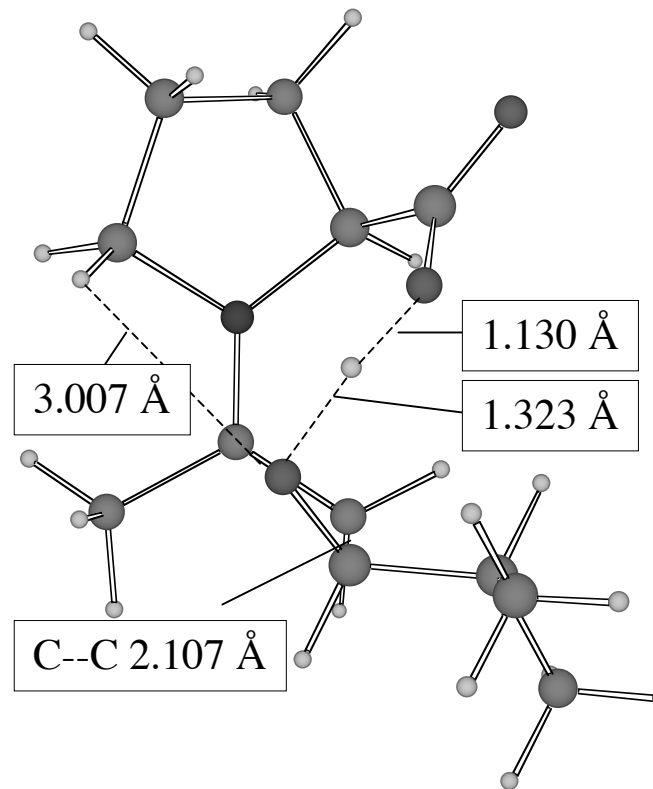
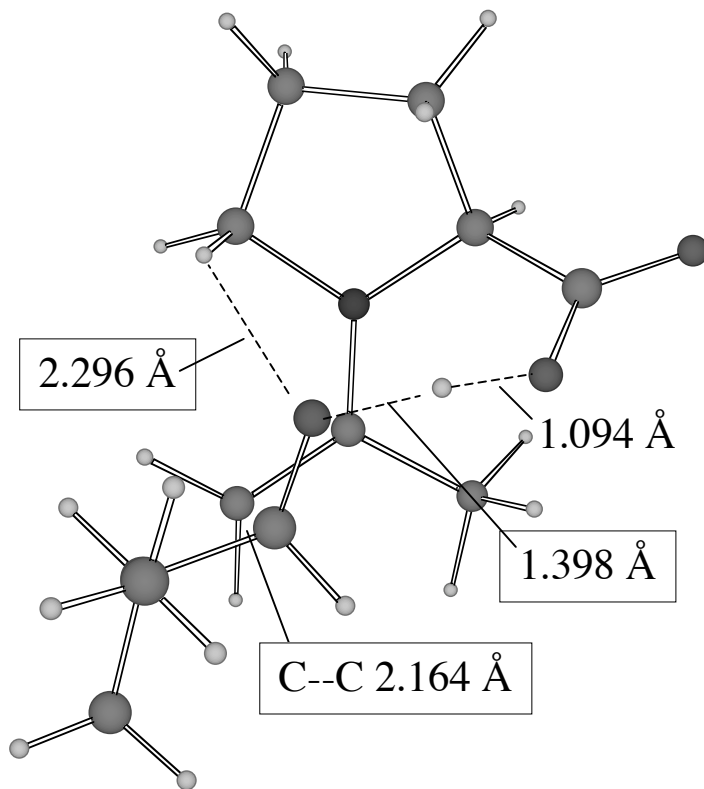
a) Case study



TS-ar



TS-ss

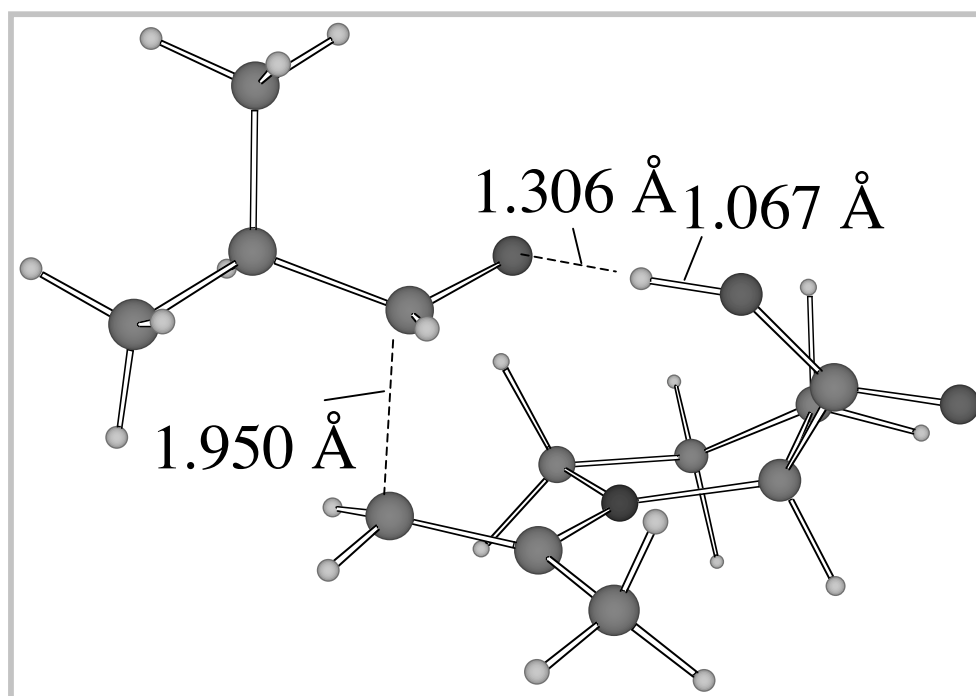


b) Steps of the exercise:

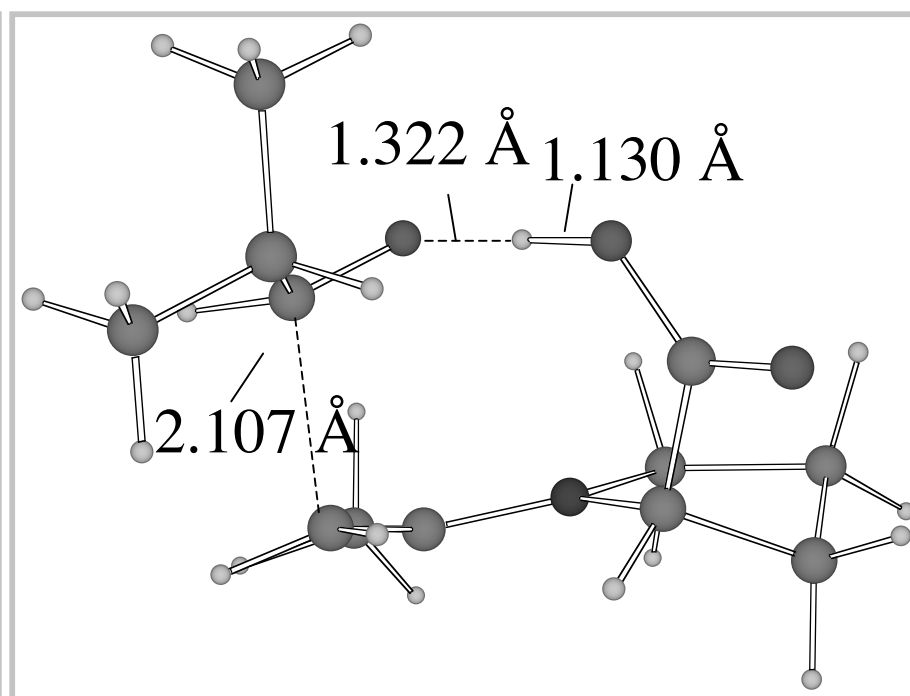
1. Create an initial geometry for transition states

1.a Draw your molecules

Initial guess structure for TS-1 (TS-ar) and TS-2 (TS-ss)

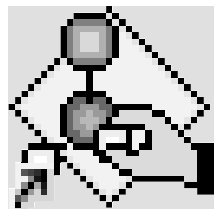


TS-1 (TS-ar)



TS-2 (TS-ss)

1.a Draw your molecules with Chem3D



CS Chem3D Pro™

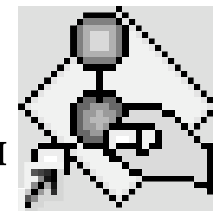
CambridgeSoft Corporation

<http://www.cambridgesoft.com>

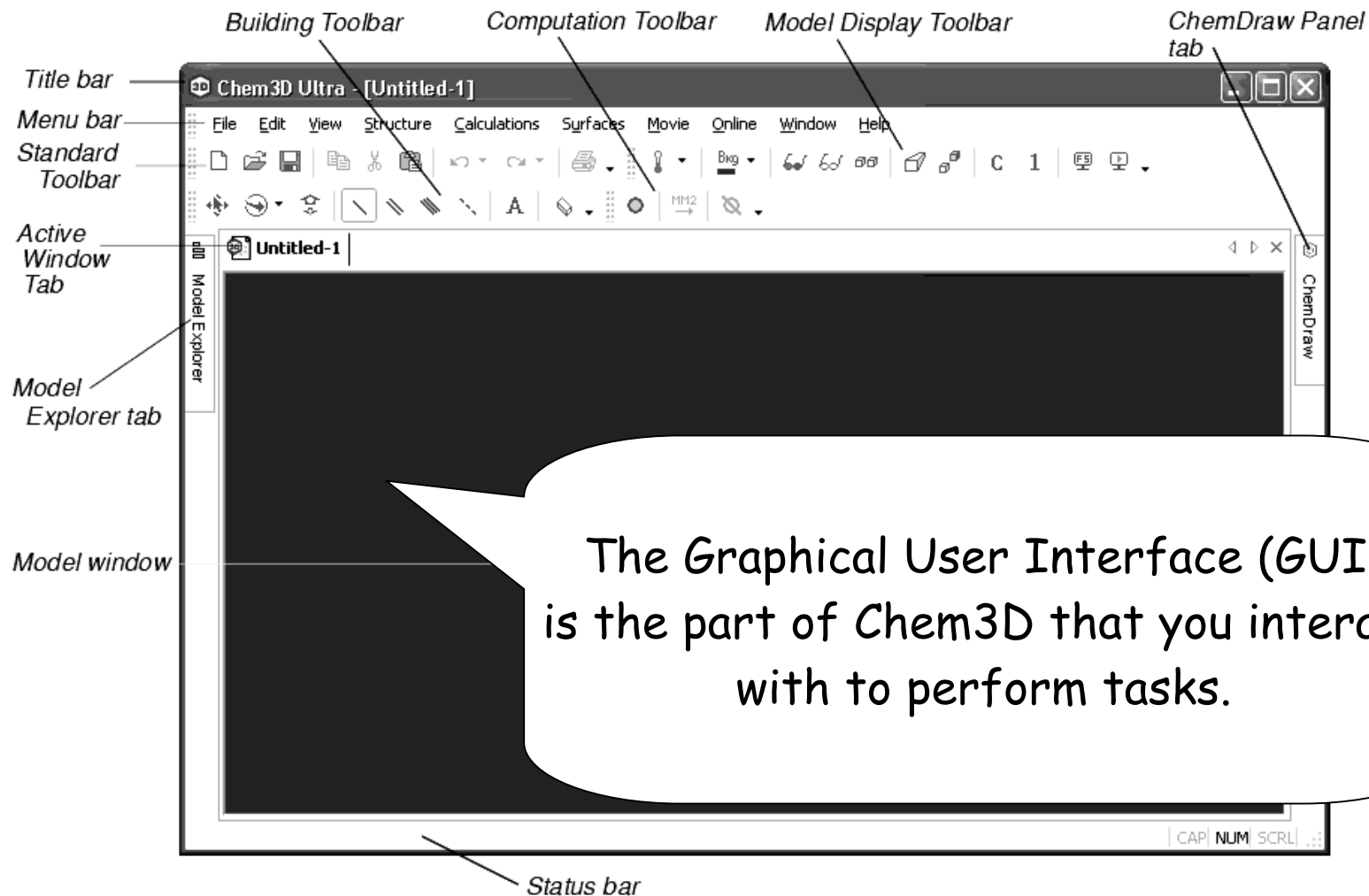
Chem3D is an application designed to enable scientists to model chemicals. It combines powerful building, analysis, and computational tools with a easy-to-use graphical user interface, and a powerful scripting interface. It combines powerful building, analysis, and computational tools with a easy-to-use graphical user interface, and a powerful scripting interface.

Chem3D provides computational tools based on molecular mechanics for optimizing models, conformational searching, molecular dynamics, and calculating single point energies for molecules.

1.a Draw your molecules with Chem3D (section 4.b.1)

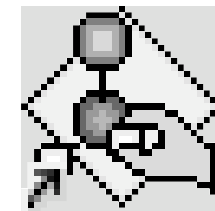


CS Chem3D Pro™



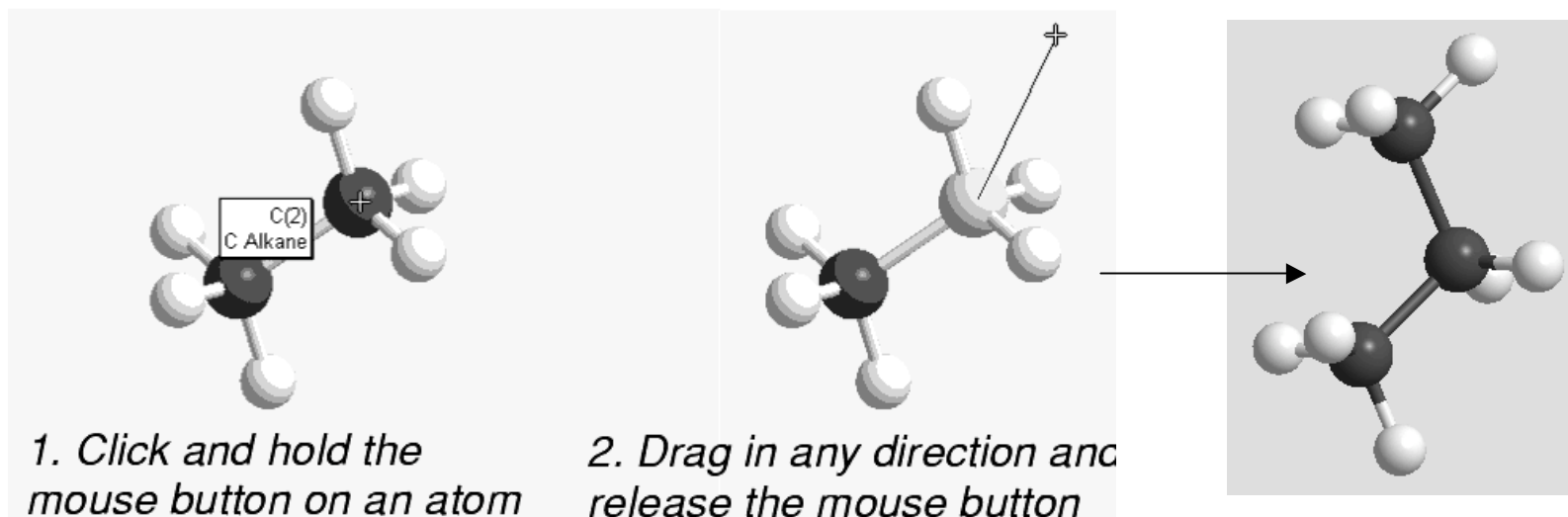
1.a Draw your molecules with Chem3D (section 4.b.1)

CS Chem3D Pro™



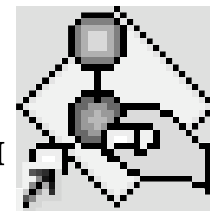
Building Molecules With the Bond Tools

- 1. Choose a bond tool. The Single Bond tool is used in this example.
- 2. Point in the model window, and drag in the direction you want the bond to be oriented.
- 3. Release the mouse button to complete the bond.



1.a Draw your molecules with Chem3D (section 4.b.1)

CS Chem3D Pro™



Building Molecules With the Bond Tools

5. Repeat adding bonds until you have the model you want.

After you have the backbone, you can change the carbons to different heteroatoms.

To change one element into another (for example an H to C):

1. Click the Text Building tool 

2. Click a hydrogen atom attached to C(1).

A text box appears.

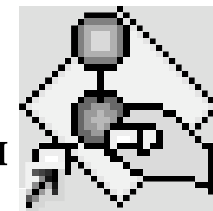
3. Type C.

NOTE: Element symbols and substructure names are case sensitive. You must type an uppercase C to create a carbon atom.

4. Press the Enter key.

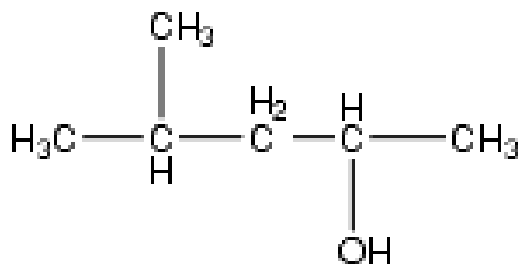
1.a Draw your molecules with Chem3D (section 4.b.1)

CS Chem3D Pro™



Using Labels to Create Models

For example, to build the model of 4-methyl-2-pentanol



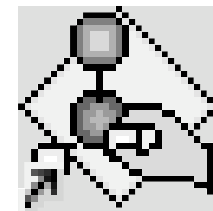
1. From the **File menu**, choose **New**, or click the new file tool on the Standard toolbar.
2. Click the Text Building tool .
3. Click in the empty space in the model window.
A text box appears where you clicked.
4. In the text box, type CH3CH(CH3)CH2CH(OH)CH3.

You type labels as if you were naming the structure: pick the longest chain of carbons as the backbone, and specify other groups as substituents. Enclose substituents in parentheses after the atom to which they are attached.

5. Press the Enter key.

b) Steps of the exercise:

CS Chem3D Pro™



- 1. Create an initial geometry for transition states**
 - 1.b Create the Gaussian Input File with Chem3D**

1.b.1 From the Calculations menu, point to Gaussian submenu, choose Create Input File.

The Create Input File dialog box appears.

Important: we will not choose any properties or methods here! We will edit our input file separately using any text editor (such as word or blocco note, etc...).

1.b.2. Click Create.

An input file saves in Gaussian's native .GJF format.

b) Steps of the exercise:

2. Prepare the approximate Hessian

The Gaussian program will be used to perform the TS search calculations

Gaussian is a computational chemistry software capable of predicting many properties of molecules and reactions, including the following:



Gaussian 03

<http://www.gaussian.com/>

- ✓ **Energies and structures**
- ✓ **Bond and reaction energies**
- ✓ **Molecular orbitals**
- ✓ **Multipole moments**
- ✓ **Atomic charges and electrostatic potential**
- ✓ **Vibrational frequencies**
- ✓ **NMR and EPR properties**
- ✓ **Reaction pathways**

b) Steps of the exercise:



2. Prepare the approximate Hessian

2.a Editing the Gaussian Input File

```
%chk=filename.chk  
#p rhf sto-3g ginput pop=full  
freq
```

Estimating the Hessian for TS-1

```
0 1  
6      2.684531      -0.638608      -2.084797  
6      -1.098009      -1.385873       0.589539  
...
```

b) Steps of the exercise:



2. Prepare the approximate Hessian

2.a Editing the Gaussian Input File

```
*****
%chk=filename.chk
#p rhf sto-3g ginput pop=full
  freq

Estimating Hessian for TS-1
0
6      2.684531      -0.638608      -2.084797
6      -1.098009      -1.385873       0.589539
...
*****
```

"Link 0 commands".

b) Steps of the exercise:



2. Prepare the approximate Hessian

2.a Editing the Gaussian Input File

```
%chk=filename.chk
```

```
#p rhf sto-3g ginput pop=full  
freq
```

```
Estimating the Hessian for
```

```
0 1
```

```
6 0.038608 -2.084797
```

```
6 0.0009 -1.385873 0.589539
```

```
...
```

The "Route Section"

b) Steps of the exercise:



2. Prepare the approximate Hessian

2.a Editing the Gaussian Input File

```
%chk=filename.chk  
#p rhf sto-3g ginput pop=full  
freq
```

Title Section

```
Estimating the Hessian for TS-1
```

```
0 1  
6 684531 -0.638608 -2.084797  
6 6 589539  
...
```

The Molecular Charge and Spin Section.

b) Steps of the exercise:



2. Prepare the approximate Hessian

2.a Editing the Gaussian Input File

```
%chk=filename.chk
```

```
#p rhf sto-3g ginput pop=full
```

```
freq
```

```
Estimating the Hessian
```

```
0 1
```

```
6      2.684531    -0.638608    -2.084797
```

```
6      -1.098009    -1.385873     0.500000
```

```
...
```

Geometry Specification Section

Remember that there should be **three** blank lines, one before and one after the title section, and one after the geometry

b) Steps of the exercise:

2. Prepare the approximate Hessian

2.b Saving the filename.com, logging and transferring on Unix and Running the calculation

2.b Saving the filename.com

On the Unix machine the input files need to have the extension ".com". Thus the first step after the editing of your input is to:

save it as "filename.com"

***** WARNING:** Be sure that your file is a text file. This warning is particularly important if you have used Word as text editor because it save files as word document by default. We need to save it as "text only" to be readable in the Unix environment*******

2.b Logging on Unix using "PuTTY" (see also section 4.b.4)

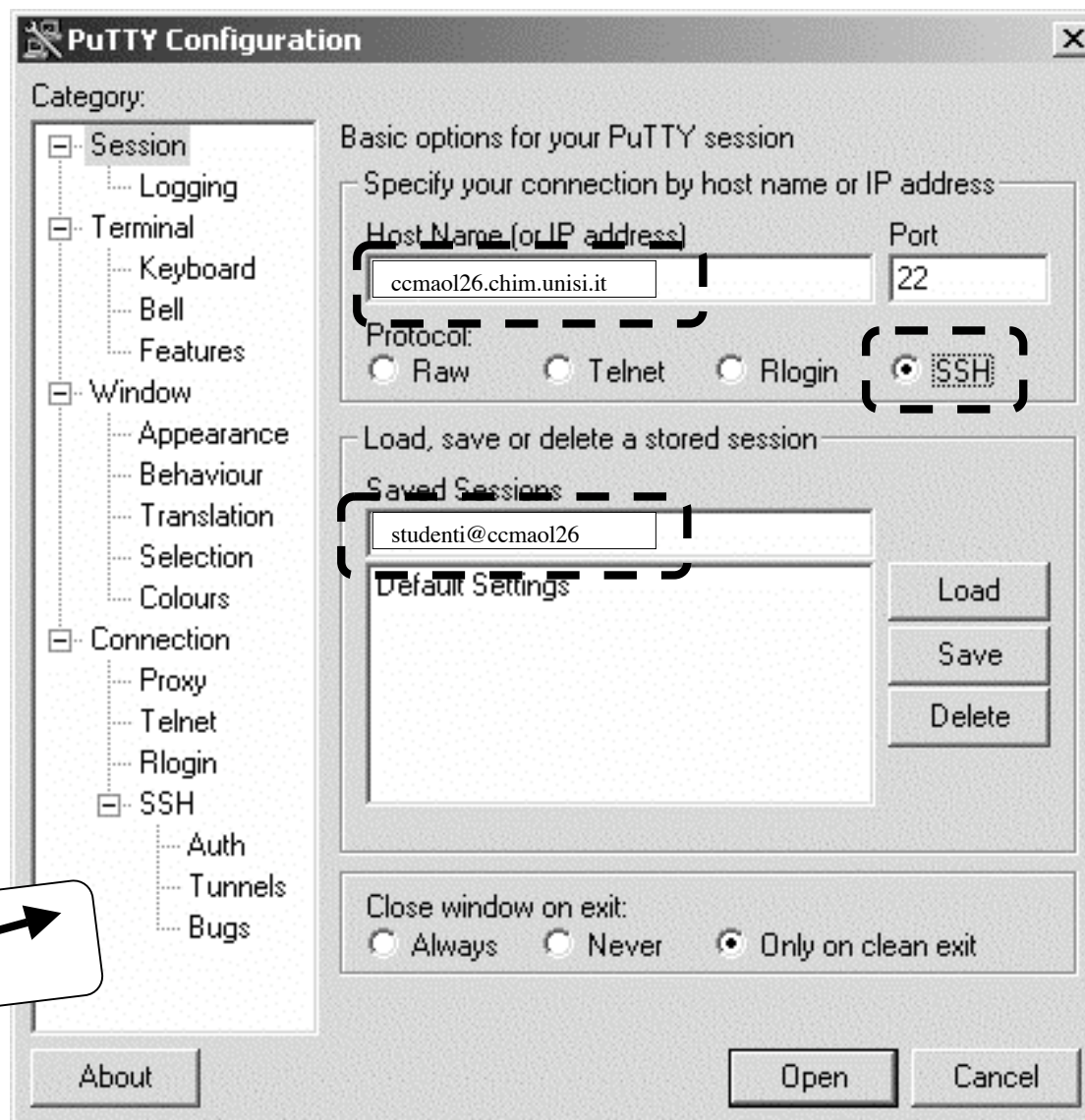
Most computational chemistry software has been written to run under Unix. You will use Gaussian on a Unix-based environment here. Part of the work you will be doing will be done on a Unix computer called

"ccmaol26.chim.unisi.it"

which belongs to the group of Computational Chemistry and Photochemistry of Siena.

To log on to ccmaol26, you will use the Windows program called

"PuTTY" →



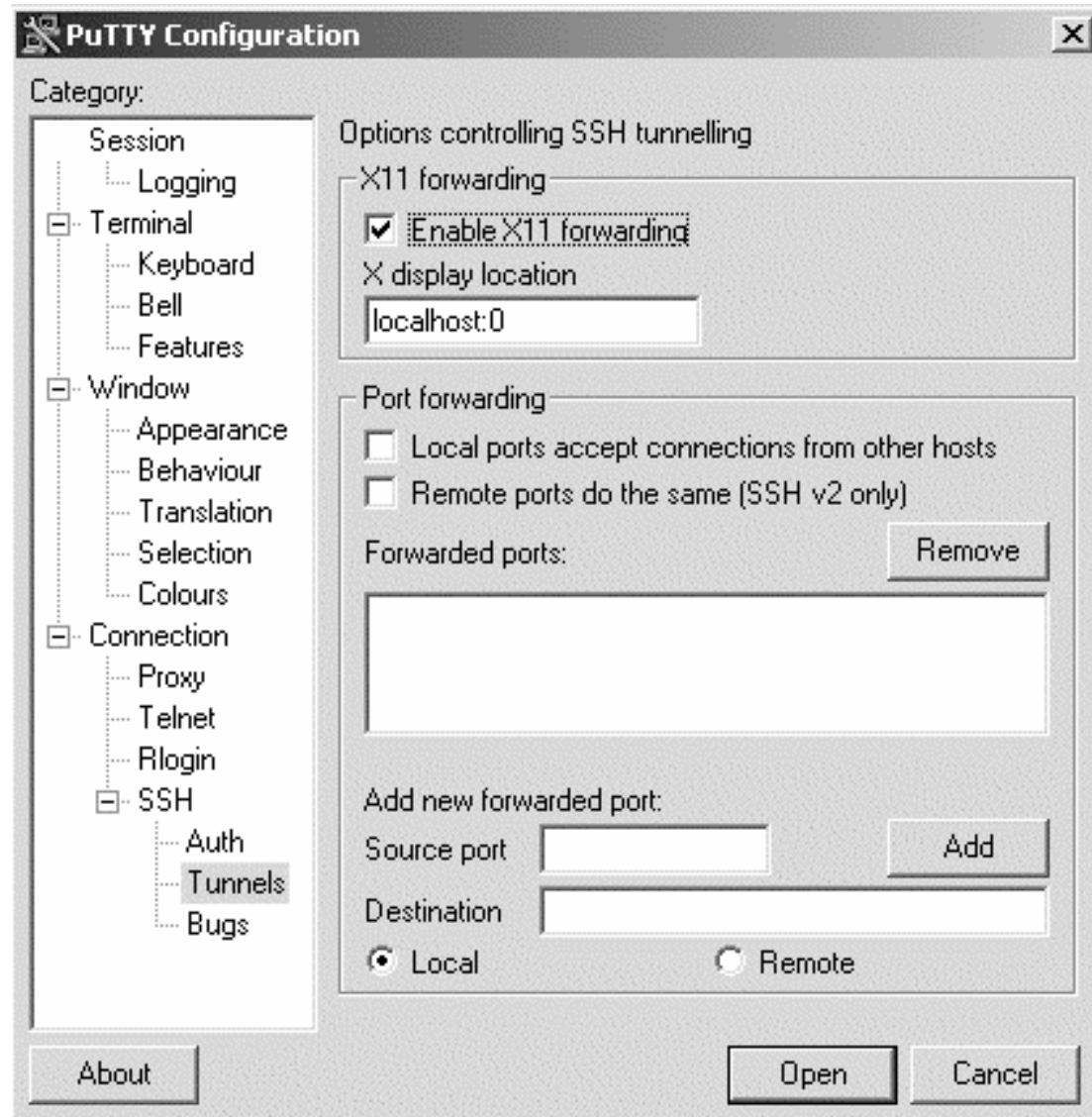
2.b Logging on Unix using "PuTTY" (see also section 4.b.4)

Inside the Connection/SSH menu on the left, click on X11 and choose

"Enable X11 forwarding"

on the right side of the window.

This setting is needed to display graphical windows as you will need to later on. By selecting Enable X11 Forwarding, in fact, you can allow graphical programs on the UNIX machines to be displayed on your windows X Server, provided you have installed an X Server for your system (in our lab. we will use Xming).



2.b Logging on Unix using "PuTTY" (see also section 4.b.4)

After selecting your host, protocol and X11 setting click on **Open**. This will connect you to the server and ask if you want to accept the RSA key of the server. You will want to select **yes**.

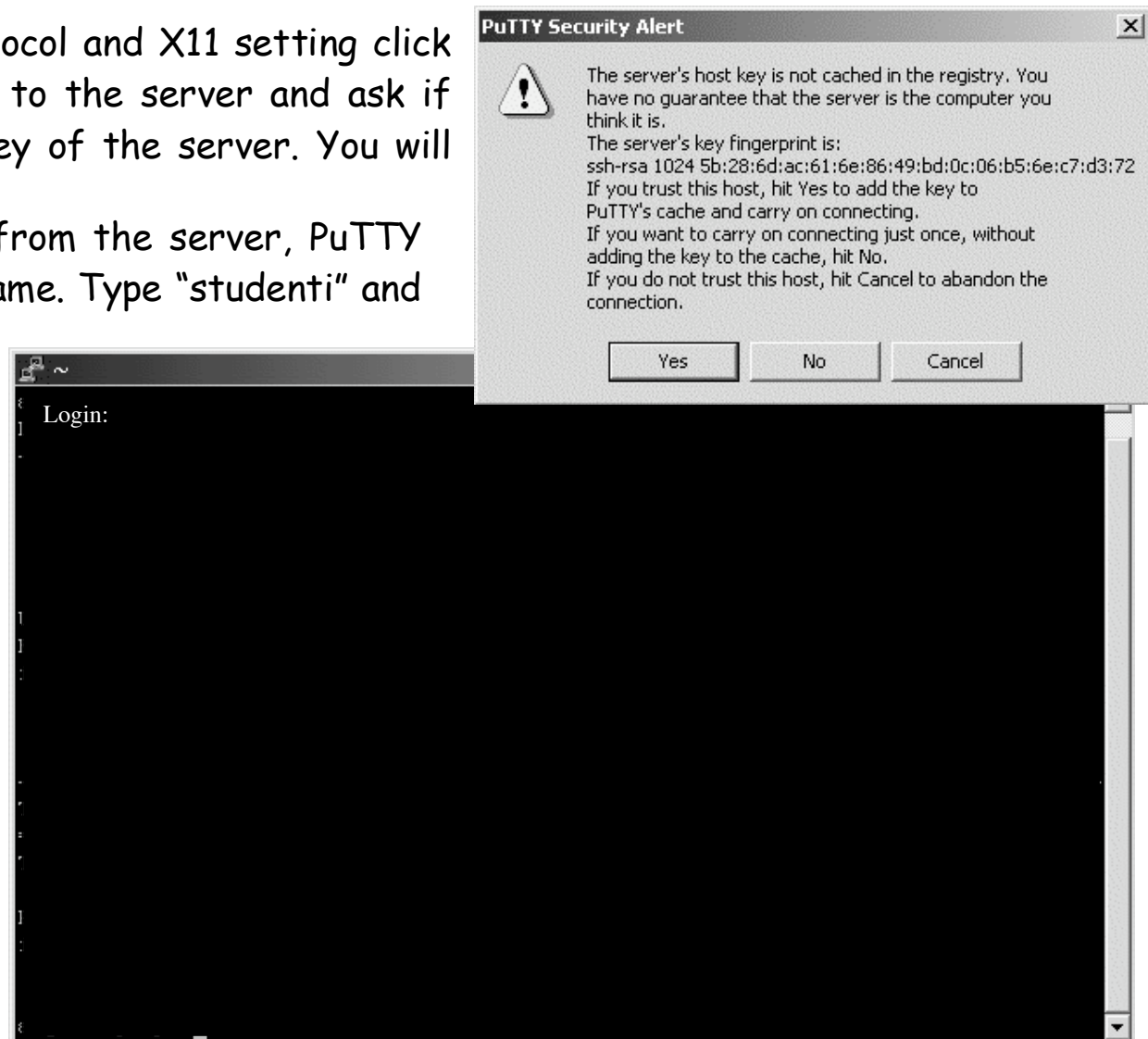
After accepting the RSA key from the server, PuTTY will ask you to input your username. Type "studenti" and press the "enter" key.

Then you will be asked for a password - this will be given to you by the demonstrator.

Type that in and press the "enter" key.

If you have done all this correctly, you are now connected to ccmaol26, and have an active Unix window.

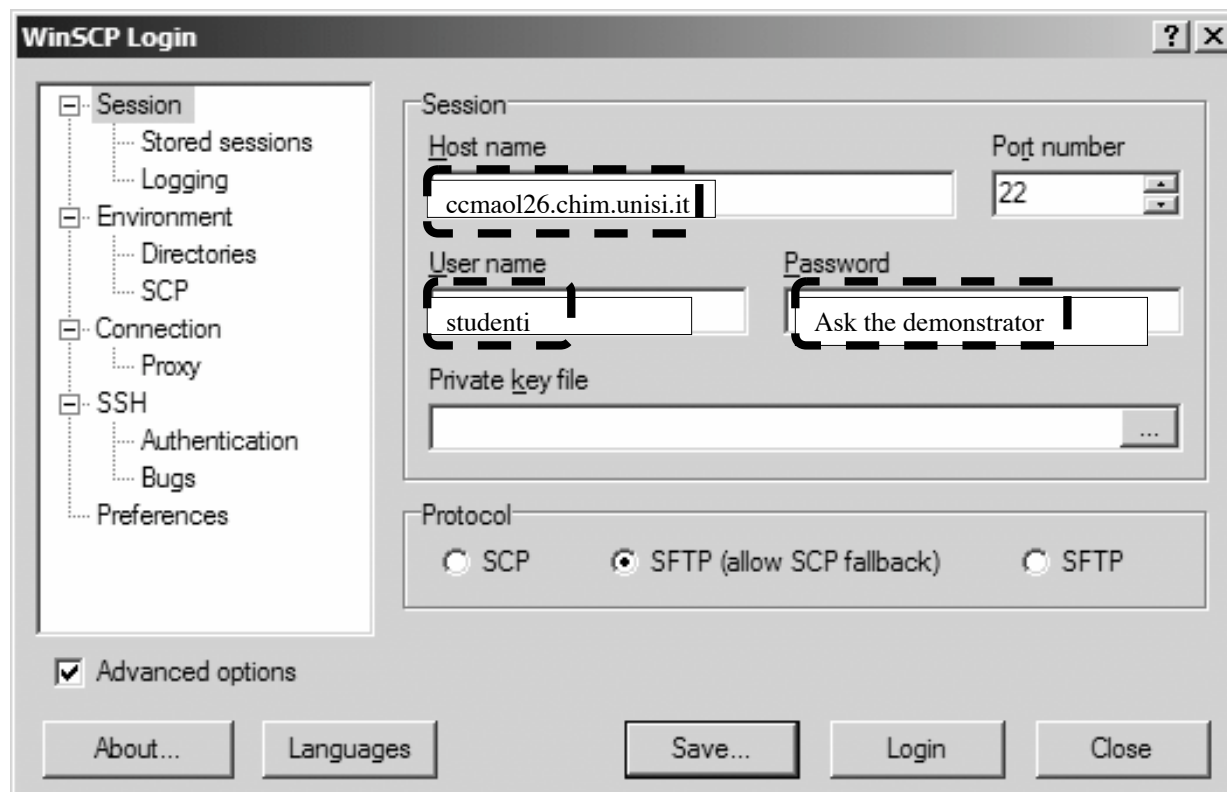
In this window, you can carry out any text-based commands: list files, edit files.



2.b Transferring files from PC to Unix and viceversa using "WinSCP" (see also section 4.b.4)

WinSCP is a secure file copying program for Windows

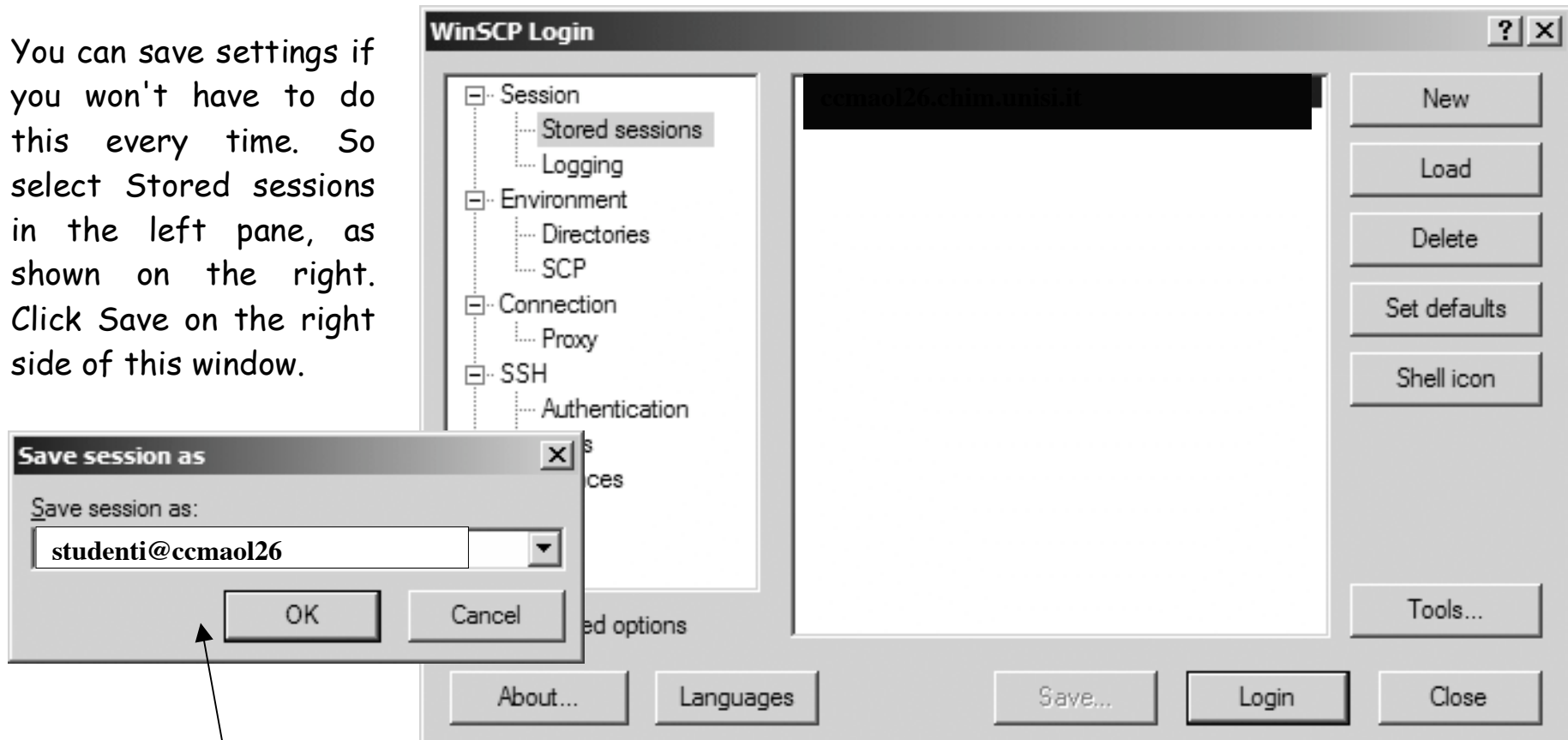
You should see the screen on the right when WinSCP first starts up.



Fill in the text fields on the Session screen as shown. You do not need to change the Port number, and you do not need a Private key file.

2.b Transferring files from PC to Unix and viceversa using "WinSCP" (see also section 4.b.4)

You can save settings if you won't have to do this every time. So select **Stored sessions** in the left pane, as shown on the right. Click **Save** on the right side of this window.



In the "Save session as", enter "studenti@ccmaol26" and click OK. To connect to ccmaol26, simply select **Stored sessions** in the left pane of the WinSCP window, then select your connection in the right side and, finally, hit the **Login** button at the bottom. Accept the RSA key of the server selecting **yes**. You might be prompted for your password again; if so, enter it

2.b Transferring files from PC to Unix and viceversa using "WinSCP" (see also section 4.b.4)

Once connected to ccmaol26, WinSCP will present you a window where on the right side you can find the files present in your home directory on the Unix machine (this is often referred to as the remote file listing). On the left side you have your windows folders. Select the folder where you want to transfer (to or from) files. Transferring files with WinSCP is very simple. You only need to drag the file from your computer (left side) into the Unix machine (right side), or viceversa. When you're finished just close WinSCP.

PC

Name	Rights	Owner	Group
.ssh	rwX----	gtg326a	gtpsa
.tin	rwX----	gtg326a	gtpsa
.trn	rwX----	gtg326a	gtpsa

ccmaol26

Name	Rights	Owner	Group
.ssh	rwX----	gtg326a	gtpsa
.tin	rwX----	gtg326a	gtpsa
.trn	rwX----	gtg326a	gtpsa

WARNING: after dragging the file you will be asked to copy it. Choose More and select text file option.

2.b Running Programs on ccmaol26

Unix programs are usually started by issuing a command at the prompt.

Some programs automatically open a new window, whereas some give output to the same window. In either case, you will often need to add an "&" character after the command to make the program run "in the background". This means that while the program runs, you are still able to continue issuing other commands. For example, to run Gaussian 03 on the input file "filename.com" you should type:

"g03 filename.com &"

WARNING: Our ccmaol26 workstation is actually a cluster of several machines and is composed of a master (ccmaol26 itself) and pure compute nodes. To make our calculations running we will access directly the node and run the calculations there. To do this:

Type in the putty window

"ssh nodename"

Then move to you directory containing your input file **"cd surname"**

For the nodename ask the demonstrator. The calculation will run for about 5 minutes.

2.c Interpreting the Gaussian Output

```
%chk=TS-1-hess
```

```
%mem=250Mb
```

```
-----  
#p rhf sto-3g ginput pop=full freq  
-----
```

**"Route
Section"**

```
1/10=4,30=1,38=1/1,3;
```

```
2/15=1,17=6,18=5,40=1/2;
```

```
3/6=3,11=1,16=1,24=10,25=1,30=1/1,2,3;
```

```
...
```

```
1/10=4,30=1/3;
```

```
99/99;
```

```
Leave Link 1 at Wed Sep 6 18:41:10 2006, MaxMem= 32768000 cpu: 0.2  
warning: Initializing libguide.a, and found libguide.a already initialized, ..
```

```
(Enter /usr/local/g03/l101.exe)
```

```
-----  
Estimating the Hessian for TS-1  
-----
```

"Title Section"

```
Symbolic Z-matrix:
```

```
Charge = 0 Multiplicity = 1
```

```
6          2.68453   -0.63861   -2.0848
```

```
6          -1.09801  -1.38587    0.58954
```

```
...
```

```
1          -3.55027  -0.57012    1.41577
```

**"Geometry
Specification
Section"**

2.c Interpreting the Gaussian Output

Then the calculation will start:

...

```
SCF Done:  E(RHF) = -736.288020069      A.U. after 16 cycles
             Convrg = 0.6531D-08          -V/T = 2.0085
             S**2  = 0.0000
```

**"SCF
Results"**

```
KE= 7.300821293264D+02 PE=-4.206736100217D+03 EE= 1.499555568751D+03
Leave Link 502 at Wed Sep 6 18:41:19 2006, MaxMem= 32768000 cpu: 5.1
warning: Initializing libguide.a, and found libguide.a already initialized, but
```

...

```
*****
```

Population analysis using the SCF density.

```
*****
```

Molecular Orbital Coefficients

			1	2	3	4	5
			0	0	0	0	0
EIGENVALUES	--		-20.18564	-20.16774	-20.14409	-15.42362	-11.15896
1	1	C 1S	-0.00001	-0.00000	-0.00000	-0.00000	-0.00002
2		2S	0.00003	-0.00002	-0.00001	0.00027	-0.00006

"MO energies and coefficients"

...

2.c Interpreting the Gaussian Output

The frequency calculation will start:

...

(Enter /usr/local/g03/l701.exe)

Compute integral second derivatives.

... and contract with generalized density number 0.

...

Full mass-weighted force constant matrix:

Low frequencies -748.4009 -0.7464 -0.4355 -0.1681 -0.0002 0.0003

Low frequencies 0.0005 43.7044 50.8752

***** 1 imaginary frequencies (negative Signs) *****

incident light, reduced masses (AMU), force constants (mDyne/A),
and normal coordinates:

	1	2	3
	A	A	A
Frequencies --	-748.4009	43.7044	50.8752
Red. masses --	6.7239	4.1635	4.1732
Frc consts --	2.2189	0.0047	0.0064
IR Inten --	964.2845	0.2838	0.5800
Raman Activ --	17.4645	0.6980	0.2108
Depolar (P) --	0.3400	0.7136	0.6880
Depolar (U) --	0.5075	0.8328	0.8151

**"Low
Frequencies"**

2.c Interpreting the Gaussian Output

...

Item	Value	Threshold	Converged?
Maximum Force	0.000017	0.000450	YES
RMS Force	0.000003	0.000300	YES
Maximum Displacement	0.001726	0.001800	YES
RMS Displacement	0.000452	0.001200	YES

Predicted change in Energy=-9.795718D-09
Optimization completed.
-- Stationary point found.

**"Convergence
Criteria"**

...

IN NATURE THERE ARE NEITHER REWARDS OR
PUNISHMENTS -- THERE ARE CONSEQUENCES.

-- ROBERT GREEN INGERSOLL

Job cpu time: 0 days 0 hours 4 minutes 23.6 seconds.

Normal termination of Gaussian 03 at Wed Sep 6 18:47:51 2006.

**All the Gaussian job
terminate with a
phrase and if the job
has finished
correctly with the
phrase "Normal
termination"**

b) Steps of the exercise:



2. Prepare the approximate Hessian

2.d Displaying the normal mode using MOLDEN

Before starting the TS search, it is advisable to plot the mode corresponding to the imaginary frequency in order to verify that this mode reasonably describes our reaction coordinate. To display the normal mode corresponding to the frequency we will use the Molden program under the windows environment.

Molden will be used to analyze Gaussian output

Molden is a package for displaying molecular density. It can read all the information it needs from a GAUSSIAN output file. Thus, you can obtain information about the molecule without having to sort through the long output file (as well as animating the vibrational frequencies, for instance.)

General Molden website: <http://www.cmbi.ru.nl/molden/molden.html>

2.d Displaying the normal mode using MOLDEN



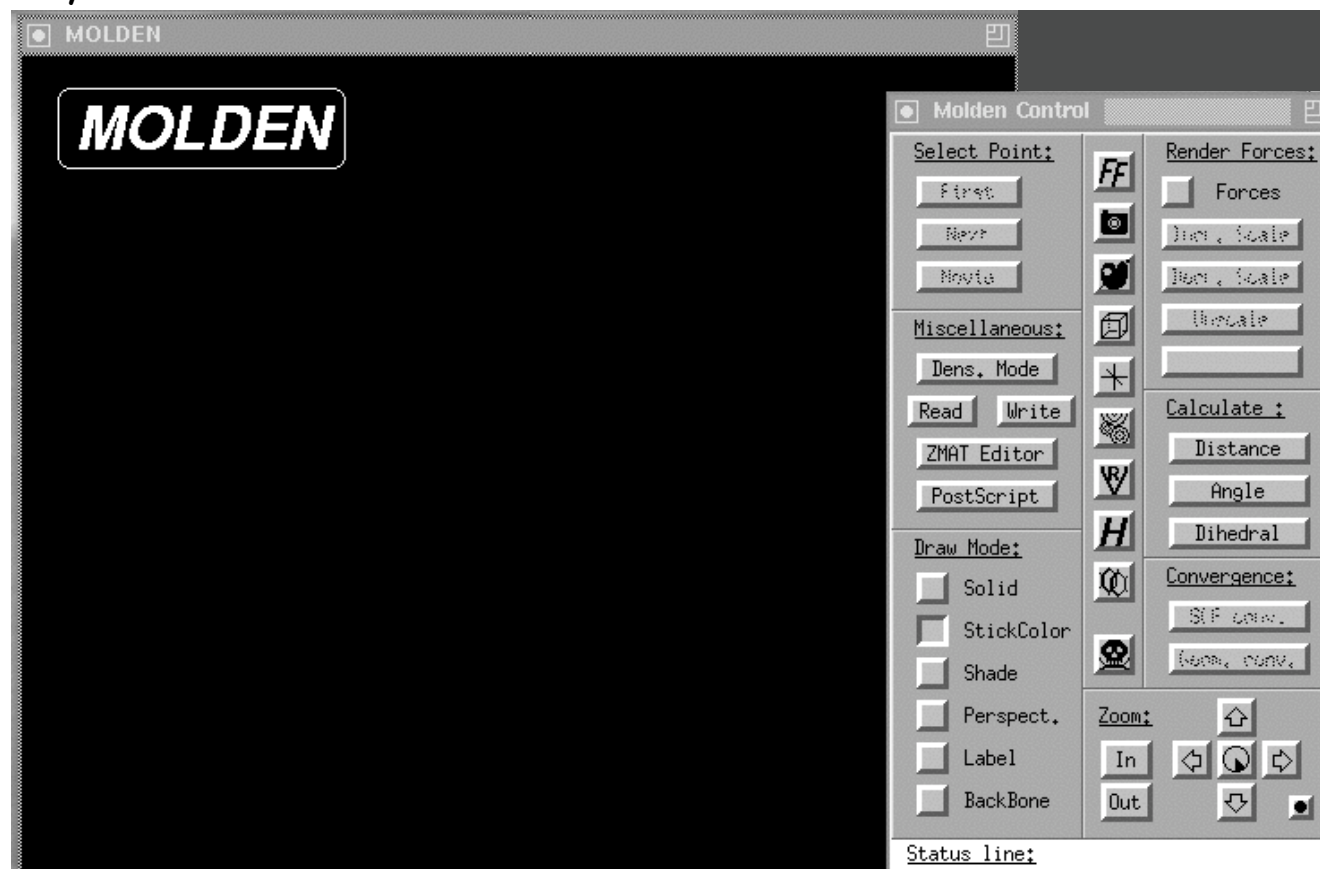
* First of all you have to transfer back on your PC the "filename.log" file using WinSCP.



* Start "Xming" from the "Start" menu. Xming is a port of the X Window System server to Windows. The icon of the program (shown below) will hopefully appear in your ruler.

Now you can start Molden.

It will appear a Model Window and Molden Control Panel.



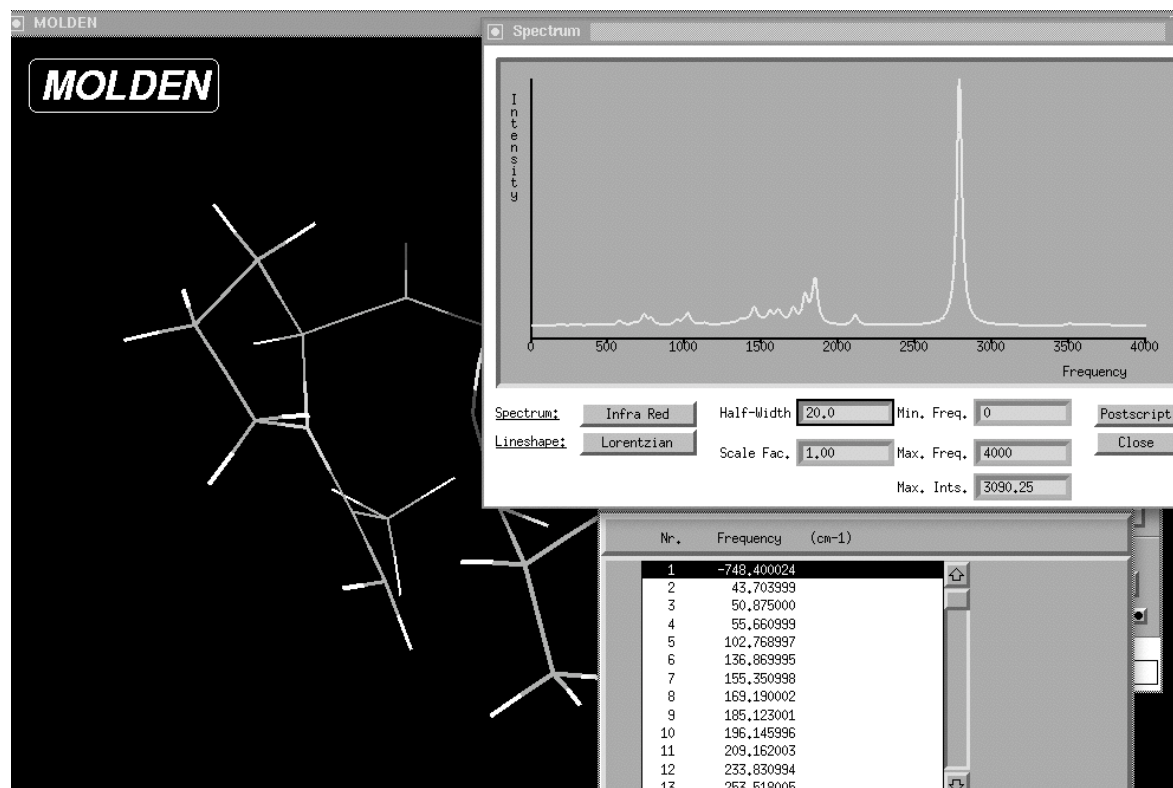
2.d Displaying the normal mode using MOLDEN



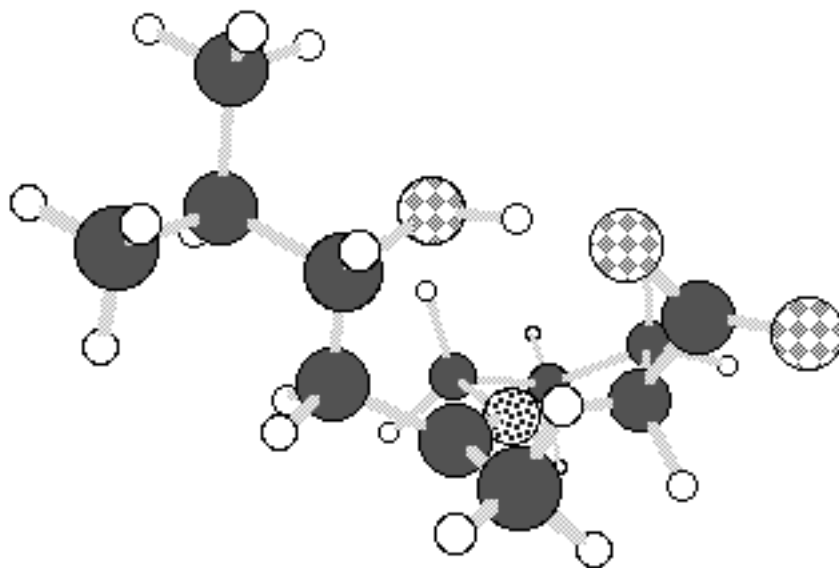
Proceed as follow:

- 1) Click "read" in the panel
- 2) Choose the file. Search for the output file in your directory.
- 3) Under the "Frequencies" menu, click "Norm. Mode". You will see the IR spectrum together with the Frequencies and related Eigenvalues.
- 4) Click on the negative Eigenvalues.
- 5) Check if the movement is the required one.
- 6) Exit clicking on the Skull.

If the movement correctly corresponds to the reaction coordinate under study go to step 3. Otherwise change the guess structure and re-compute the frequencies.



2.d Displaying the normal mode using MOLDEN



b) Steps of the exercise:

3. Search for the transition states

3.a Copying and Editing the previous Gaussian Input File

Make a copy of your previous "filename.com" in "filename_new.com" Open the text file and modify the settings such as method, basis set, calculation type etc. as follows:

```
*****  
%chk=TS-1-opt  
%mem=250Mb  
#p B3LYP 3-21G* gfinput p  
opt(TS,readfc,noeigen  
  
Search for TS-1  
  
0 1  
6      2.684531   -0.638608   -2.084797  
6     -1.098009   -1.385873    0.58953  
...  
  
1     -3.550267   -0.570119    1.41577  
*****
```

WARNING: if you want to save your old checkpoint file you need to change the name here. This requires also that you copy (on the Unix machine, i.e. using puTTY) the old "filename.chk" to "filename_new.chk" (cp). If you forget it the job will stop because it needs to read information from it!

N.B. Here you will have the same cartesian coordinates of your previous input! In fact, you have not optimized anything at this point!

3.a Copying and Editing the previous Gaussian Input File

```
*****  
%chk=TS-1-opt  
%mem=250Mb  
#p B3LYP 3-21G* ginput pop=full  
opt(TS,readfc,noeigentest)
```

B3LYP is one of the functionals of the DFT methods.

3-21G* is a split valence basis set. The standard basis set used for this kind of studies is the standard and well-tested **6-31G*** basis set. Here we will use the smaller **3-21G*** basis set thus sacrificing a bit of accuracy for speed and simplicity.

Opt keyword requests that a geometry optimization be performed. The geometry will be adjusted until a stationary point on the potential surface is found. Options: **Opt=TS** requests optimization to a transition state rather than a local minimum; **Opt=noEigentest** keyword avoids testing for eigenvalues. **Opt=readfc** keyword reads the Hessian computed at step 2.

b) Steps of the exercise:

3. Search for the transition states

3.b Saving the filename.com, logging and transferring on Unix and Running the calculation

See Step 2.b

The calculation will run for about 50 minutes. Use this time to setup the needed calculations for the other TS

b) Steps of the exercise:

3. Search for the transition states

3.c Interpreting the output

```
*****
Item                Value      Threshold  Converged?
Maximum Force       0.012664    0.000450    NO
RMS Force           0.001718    0.000300    NO
Maximum Displacement 0.108228    0.001800    NO
RMS Displacement    0.025875    0.001200    NO
*****
```

...

```
*****
Item                Value      Threshold  Converged?
Maximum Force       0.000030    0.000450    YES
RMS Force           0.000004    0.000300    YES
Maximum Displacement 0.001046    0.001800    YES
RMS Displacement    0.000238    0.001200    YES
Predicted change in Energy=-4.439922D-09
Optimization completed.
-- Stationary point found.
```

```
-----
!   Optimized Parameters   !
! (Angstroms and Degrees) !
```

```
-----
! Name  Definition          Value      Derivative Info!
-----
! R1    R(1,6)              1.5573    -DE/DX =    0.0    !
! ...
```

b) Steps of the exercise:

4. Calculating frequencies at transition states

4.a Copying and Editing the previous Gaussian Input File

If the TS search locates a stationary point, we need now to verify that it is indeed a saddle point with a subsequent Hessian calculation. Make a copy of your previous "filename_new.com" in "filename_new2.com" Open the text file and modify the settings as follows:

```
*****  
***same WARNING for checkpoint file as in section 3a***  
%chk=TS-1-freq  
%mem=350Mb  
#p B3LYP 3-21G* ginput pop=full  
freq geom=check
```

Calculating Frequencies at TS-1

0 1

```
*****
```

At this point you should know the meaning of all the keywords except one:

geom=check simply requests that the geometry is taken from the checkpoint file.

b) Steps of the exercise:

4. Calculating frequencies at transition states

4.b Saving the filename.com, logging and transferring on Unix and Running the calculation

See Step 2.b

The calculation will run for about 60 minutes. If you do not have much more time use the log file indicated in section 4.e

b) Steps of the exercise:

4. Calculating frequencies at transition states

4.c Interpreting the output

For a frequency job, as discussed earlier (see Step 2.c), there will be a section in the output summarising the results of the frequency run.

```
*****
Full mass-weighted force constant matrix:
Low frequencies --- -218.9253  -14.4074  -9.3989  -6.3363  -
0.0006
Low frequencies --- 0.0007  42.5760  48.2305
***** 1 imaginary frequencies (negative Signs) *****
Diagonal vibrational polarizability:
49.9223586 120.3780146 25.2210809
Harmonic frequencies (cm**-1), IR intensities (KM/Mole), Raman
scattering activities (A**4/AMU), depolarization ratios for plane
and unpolarized incident light, reduced masses (AMU), force
constants (mDyne/A), and normal coordinates:
          1              2              3
          A              A              A
Frequencies -- -218.9220  42.5108  48.1681
Red. masses  -- 6.3538  3.4809  4.0634
Frc consts  -- 0.1794  0.0037  0.0056
IR Inten    -- 139.0935  0.6129  0.8042
*****
```

b) Steps of the exercise:

4. Calculating frequencies at transition states
- 4.d Displaying the normal mode

See Step 2.d

Intrinsic reaction coordinate (IRC) paths should be traced in order to check that each transition structures actually connect the two associated minima of the proposed mechanism

b) Steps of the exercise:

5. Comparing results for TSs to confirm the expected stereoselectivity

The geometry of the two transition states **TS-1 (TS-ar)** and **TS-2 (TS-ss)** should resemble the ones showed before.

→ The total energy for TS-1 is -746.230934939 Hartrees
(Sum of electronic and thermal Enthalpies= -745.890899)

→ The total energy for TS-2 is -746.226851325 Hartrees
(Sum of electronic and thermal Enthalpies= -745.887248)

Thus, the transition state involving the re attack on the anti enamine (TS-ar) is about 2.5 kcal mol⁻¹ lower in energy than the transition state for the si attack on the syn enamine (to convert Hartrees to kcal mol⁻¹ multiply for 627.51). This energetic difference agrees well with the experimental results where the (R)-cetol (obtained if the C-C bond formation takes place along the anti arrangement of the enamine) is isolated in about 96% ee.

b) Steps of the exercise:

5. Comparing results for TSs to confirm the expected stereoselectivity

Houk et al. determined that for three reactions studied, the calculated gas-phase enthalpies of activation have the smallest error (standard deviation ± 0.4 kcal/mol) when compared with the experimental enantioselectivities (Bahmanyar, Houk et al., JACS, 2003, 125, 2475-2479).

The predicted product ratios from ΔH_{298} values (search for "Sum of electronic and thermal Energies" in the output), in our case confirm the stereoselectivity of the reaction:

Structure	Product Ratio	
	Calculated	Experimental
TS-ar	$\Delta H_{298}=0.0$	~96-99%
TS-ss	$\Delta H_{298}=2.3$	~4-1%