A Few Hidden Features in Q-CHEM for Geometry Optimization, Wavefunction Analysis, and QM/MM Calculations

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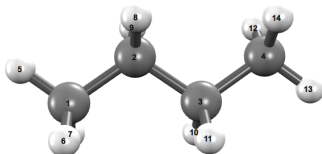
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Relaxed Potential Energy Scan

- A series of constrained geom opt

  - Initial angle: -180°
  - Final angle: 180°
  - Increment: 15°

- constraints: bond lengths, bond angles, torsional angles
- Initial value can be larger than the final value
- 2-d scan is allowed

```
$molecule
0 1
C       1.934574    -0.128781    -0.000151
C       0.556601     0.526657     0.000200
C      -0.556627    -0.526735     0.000173
C      -1.934557     0.128837     0.000138
H       2.720125     0.655980    -0.000236
H       2.061880    -0.759501    -0.905731
H       2.062283    -0.759765     0.905211
H       0.464285     1.168064    -0.903444
H       0.464481     1.167909     0.903924
H      -0.464539    -1.167976     0.903964
H      -0.464346    -1.168166    -0.903402
H      -2.062154     0.759848     0.905185
H      -2.720189    -0.655832    -0.000229
H      -2.061778     0.759577    -0.905748
$end

$rem
jobtype pes_scan
method hf
basis sto-3g
$end

$scan
tors 1 2 3 4 -180 180 15
$end
```
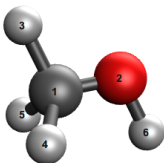
Relaxed Potential Energy Scan Results

- IQmol visualization of 1-d scan results
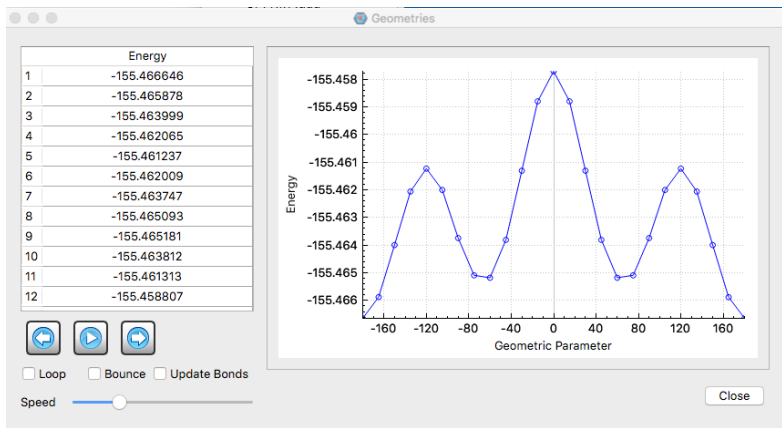
Frozen Potential Energy Scan

- A series of single-point energy calculations

- Initial bond length: 1.0Å
- Final bond length: 2.0 Å
- Increment: 0.5 Å

- No geometry optimization
- Input geometry must be z-matrix

```
$molecule
0   1
C
O   C  RCO
H1 C RCH1 O H1CO
X   C 1.0   O  XCO   H1  180.0
H2 C RCH2 X H2CX  H1   90.0
H3 C RCH2 X H2CX  H1  -90.0
H4 O ROH   C HOC   H1  180.0

RCO  = 1.421
RCH1 = 1.094
RCH2 = 1.094
ROH  = 0.963
H1CO = 107.2
XCO  = 129.9
H2CX = 54.25
HOC  = 108.0
$end

$rem
JOBTYPE           pes_scan
FROZEN_SCAN       TRUE
EXCHANGE          S
CORRELATION       VWN
BASIS             3-21G
$end

$scan
stre 1 2 1.0 2.0 0.5
$end
```
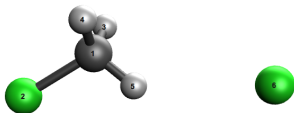
Restrained Potential Energy Scan

- A series of restrained geom opt

- Geometry restraints

$$k \left(R_{12} - R_{16} - R \right)^2$$

  - R_{min}: -2.0Å
  - R_{max}: 2.0 Å
  - Increment: 0.2 Å
  - Force constant (k): 1000.0

- 1-d scan only

- Can also use "r12pr34"

```
$molecule
-1   1
    C        0.418808    -1.240869     0.249048
    Cl      -0.775224    -1.495584     1.586668
    H        1.408172    -1.490565     0.631227
    H        0.147593    -1.907736    -0.568952
    H        0.413296    -0.199000    -0.092071
    Cl       1.947359     1.619163    -1.747832
$end

$rem
jobtype pes_scan
exchange b3lyp
basis 6-31G*
$end

$scan
r12mr34 1 2 1 6 -2.0 2.0 0.2 1000.0
$end
```
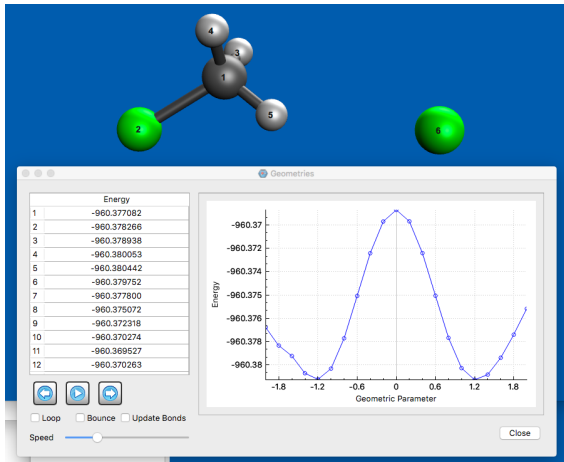
Restrained Potential Energy Scan Results

- IQmol visualization of 1-d scan results

Restrained Geometry Optimization

```
$molecule
-1  1
    C         0.4188082876   -1.2408695705    0.2490483370
    Cl       -0.7752244258   -1.4955845511    1.5866685479
    H         1.4081726568   -1.4905651530    0.6312274608
    H         0.1475935065   -1.9077368904   -0.5689527615
    H         0.4132963138   -0.1990006891   -0.0920715962
    Cl        1.9473593327    1.6191631608   -1.7478328574
$end

$rem
jobtype opt
exchange b3lyp
basis 6-31G*
$end


$opt2
r12mr34 1 2 1 6 0.0 1000.0
$end
```

# Charge Populations in Q-CHEM

- Mulliken charges
  - Can be non-physical with larger basis sets

- NBO charges

- CHELPG charges (CHELPG = TRUE)
  - Well reproduce the dipole moment

- Hirshfeld charges (HIRSHFELD = TRUE)
  - Usually too small

- CM5 charges (CM5 = TRUE)
  - Improvement by Don Truhlar

- Iterative Hirshfeld charges (HIRSHITER = TRUE)
  - Much better than Hirshfeld charges

# ESP/RESP charge calculations

- ESP Grid Options:
  - 1: Spherical harmonics
  - 2: Lebedev
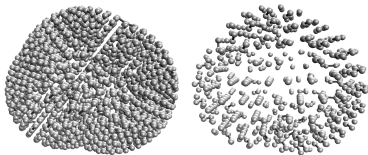


- RESP_CHARGES = TRUE

```
$molecule
0 1
    C      1.22227    -0.2466     0.0178
    H      2.09272     0.3971    -0.0423
    H      1.27594    -0.9548    -0.8023
    H      1.26663    -0.7997     0.9461
    C     -0.07041     0.5616    -0.0459
    H     -0.12063     1.1336    -0.9663
    H     -0.12012     1.2567     0.7739
    O     -1.24418    -0.2540     0.1065
    H     -1.35216    -0.8912    -0.5924
$end

$rem
   BASIS      = 6-31G*
   METHOD     = B3LYP
   JOBTYPE    = SP
   ESP_CHARGES  = 1      # or 2
$end
```

ESP charges with different grids

- Dipole moment: X 1.0606; Y -0.2250; Z -1.2090; Tot 1.6239

- ESP_Charges = 1

- ESP_Charges = 2

```
    Merz-Kollman ESP Net Atomic Charges

   Atom                    Charge (a.u.)
--------------------------------------------
   1 C                       -0.359692
   2 H                        0.075218
   3 H                        0.088502
   4 H                        0.105036
   5 C                        0.356774
   6 H                       -0.035130
   7 H                        0.032457
   8 O                       -0.673003
   9 H                        0.409839
--------------------------------------------
Sum of atomic charges =      0.000000

Related Dipole Moment =      1.6305
(X  1.0669 Y -0.2059 Z -1.2157)
```

```
    Merz-Kollman ESP Net Atomic Charges

   Atom                    Charge (a.u.)
--------------------------------------------
   1 C                       -0.362941
   2 H                        0.076361
   3 H                        0.090774
   4 H                        0.107454
   5 C                        0.338283
   6 H                       -0.028913
   7 H                        0.038096
   8 O                       -0.669108
   9 H                        0.409994
--------------------------------------------
Sum of atomic charges =      0.000000

Related Dipole Moment =      1.6285
(X  1.0631 Y -0.2069 Z -1.2162)
```

ESP and RESP charges

- Dipole moment: X 1.0606; Y -0.2250; Z -1.2090; Tot 1.6239

- ESP_Charges = 1

- RESP_Charges = 1

```
    Merz-Kollman ESP Net Atomic Charges

  Atom                    Charge (a.u.)
----------------------------------------
   1 C                     -0.359692
   2 H                      0.075218
   3 H                      0.088502
   4 H                      0.105036
   5 C                      0.356774
   6 H                     -0.035130
   7 H                      0.032457
   8 O                     -0.673003
   9 H                      0.409839
----------------------------------------
Sum of atomic charges =     0.000000

Related Dipole Moment =     1.6305
(X  1.0669 Y -0.2059 Z -1.2157)
```

```
    Merz-Kollman RESP Net Atomic Charges

  Atom                    Charge (a.u.)
----------------------------------------
   1 C                     -0.272946
   2 H                      0.067338
   3 H                      0.067338
   4 H                      0.067338
   5 C                      0.346165
   6 H                     -0.015626
   7 H                     -0.015626
   8 O                     -0.608147
   9 H                      0.364167
----------------------------------------
Sum of atomic charges =     0.000000

Related Dipole Moment =     1.7694
(X  1.0670 Y -0.1781 Z -1.4002)
```

ESP charges for TDDFT excited states

```
$molecule
0 1
    O      -0.00000     0.00000      0.7625
    C       0.00000     0.00000     -0.6375
    H       0.86602    -0.00000     -1.1375
    H      -0.86602     0.00000     -1.1375
$end

$rem
   BASIS        = 6-31G*
   METHOD       = B3LYP
   JOBTYPE      = SP
   CIS_N_ROOTS  = 3
   SET_TRIP     = FALSE
   RPA          = 2          # No TDA
   POP_MULLIKEN = -1         # Mulliken charges for all states
   ESP_CHARGES  = 1          # ESP charges for all states
   CIS_RLX_DNS  = 1          # We should use the relaxed density
$end
```

ESP and RESP charges

- CIS_RLX_DNS = 0

```
    Merz-Kollman ESP Net Atomic Charges

  Atom                      Charge (a.u.)
----------------------------------------
    1 O                       -0.365648
    2 C                        0.185380
    3 H                        0.090134
    4 H                        0.090134
----------------------------------------
Sum of atomic charges =       0.000000

Related Dipole Moment =       2.8917
(X   0.0000 Y   0.0000 Z  -2.8917)
```

ESP charges for excited states

	1	2	3
1	0.2938661	0.2277436	-0.0598282
2	-0.8473374	-0.8761796	0.0035142
3	0.2767357	0.3242180	0.0281570
4	0.2767357	0.3242180	0.0281570

- CIS_RLX_DNS = 1

```
    Merz-Kollman ESP Net Atomic Charges

  Atom                      Charge (a.u.)
----------------------------------------
    1 O                       -0.365648
    2 C                        0.185380
    3 H                        0.090134
    4 H                        0.090134
----------------------------------------
Sum of atomic charges =       0.000000

Related Dipole Moment =       2.8917
(X   0.0000 Y   0.0000 Z  -2.8917)
```

ESP charges for excited states

	1	2	3
1	-0.0914159	-0.0518477	-0.3150189
2	-0.3737757	-0.5369765	0.2755906
3	0.2325958	0.2944121	0.0197142
4	0.2325958	0.2944121	0.0197141

TDDFT excitation energies

- TDDFT working equation is

$$\begin{pmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{B} & \mathbf{A} \end{pmatrix} \begin{pmatrix} \mathbf{X} \\ \mathbf{Y} \end{pmatrix} = \Delta E \begin{pmatrix} \mathbf{X} \\ -\mathbf{Y} \end{pmatrix}$$

Hirata and Head-Gordon, Chem. Phys. Lett. 302, 375 (1999);

TDDFT excitation energies

- TDDFT working equation is

$$\begin{pmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{B} & \mathbf{A} \end{pmatrix} \begin{pmatrix} \mathbf{X} \\ \mathbf{Y} \end{pmatrix} = \Delta E \begin{pmatrix} \mathbf{X} \\ -\mathbf{Y} \end{pmatrix}$$

- We can write the vertical excitation energy (VEE) as

$$\begin{aligned} \Delta E &= \Delta E_1 + \Delta E_2 \\ \Delta E_1 &= \sum_{ai} \left(X_{ai}^2 + Y_{ai}^2 \right) \left(\varepsilon_a - \varepsilon_i \right) \\ \Delta E_2 &= \Delta E_{2,J} + \Delta E_{2,K} + \Delta E_{2,XC} \end{aligned}$$

Hirata and Head-Gordon, Chem. Phys. Lett. 302, 375 (1999);
Mol. Phys. 108, 2791 (2010).

TDDFT excitation energies

- TDDFT working equation is

$$\begin{pmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{B} & \mathbf{A} \end{pmatrix} \begin{pmatrix} \mathbf{X} \\ \mathbf{Y} \end{pmatrix} = \Delta E \begin{pmatrix} \mathbf{X} \\ -\mathbf{Y} \end{pmatrix}$$

- We can write the vertical excitation energy (VEE) as

$$\begin{aligned} \Delta E &= \Delta E_1 + \Delta E_2 \\ \Delta E_1 &= \sum_{ai} \left(X_{ai}^2 + Y_{ai}^2 \right) (\varepsilon_a - \varepsilon_i) \\ \Delta E_2 &= \Delta E_{2,J} + \Delta E_{2,K} + \Delta E_{2,XC} \end{aligned}$$

- VEE can be decomposed for
  - pure and hybrid functionals
  - two range-separated functionals: ωB97X-D and LRC-ωPBEh
  - Results are slightly off for pure basis sets

Hirata and Head-Gordon, Chem. Phys. Lett. 302, 375 (1999);
Mol. Phys. 108, 2791 (2010).

Sample Input: H_2CO

```
$molecule
0 1
O
C,1,R1
H,2,R2,1,A
H,2,R2,1,A,3,180.

R1=1.4
R2=1.0
A=120.
$end


$rem
method                      wB97X-D
basis                       6-31++G**
cis_n_roots                 5
rpa                         2
cis_dynamic_mem             false       #use old TDDFT implementation
excit_energy_components     true
$end
```

- HOMO: -0.369; LUMO: -0.028; **Gap: 9.279 eV**

- Output file:

```
Excited state   1: excitation energy (eV) =    2.1475
 Total energy for state  1:                    -114.33552540 au
    Multiplicity: Triplet
    Trans. Mom.:  0.0000 X   0.0000 Y   0.0000 Z
    Strength   :      0.0000000000
    X: D(  8) --> V(  1) amplitude =  0.9968
    Details  -- H:   26.7523 J1:  -28.3251  K1:   8.1581   XC1:   3.0430
             J2:    0.0000 K2:  -7.1299 XC2:  -0.3510 Total:   2.1475

    dE1 = 9.6283 eV;   dE2 = -7.4809 eV   #not shown in output

Excited state   3: excitation energy (eV) =    2.8774
 Total energy for state  3:                    -114.30870220 au
    Multiplicity: Singlet
    Trans. Mom.: -0.0000 X  -0.0000 Y  -0.0000 Z
    Strength   :      0.0000000000
    X: D(  8) --> V(  1) amplitude =  0.9963
    Details  -- H:   28.4549 J1:  -30.3332  K1:   8.1053   XC1:   3.2048
             J2:    0.6325 K2:  -6.9064 XC2:  -0.2806 Total:   2.8774

    dE1 = 9.4318 eV;   dE2 = -6.5545 eV   #not shown in output
```

- HOMO: -0.369; LUMO: -0.028; **Gap: 9.279 eV**

- Output file:

```
Excited state   1: excitation energy (eV) =    2.1475
 Total energy for state  1:                   -114.33552540 au
    Multiplicity: Triplet
    Trans. Mom.:  0.0000 X   0.0000 Y   0.0000 Z
    Strength   :    0.0000000000
    X: D(  8) --> V(  1) amplitude = 0.9968
    Details  -- H:  26.7523 J1:  -28.3251  K1:   8.1581   XC1:   3.0430
                  J2:   0.0000 K2:   -7.1299 XC2:   -0.3510 Total:   2.1475

    dE1 = 9.6283 eV;   dE2 = -7.4809 eV   #not shown in output

 Excited state   3: excitation energy (eV) =    2.8774
 Total energy for state  3:                   -114.30870220 au
    Multiplicity: Singlet
    Trans. Mom.: -0.0000 X  -0.0000 Y  -0.0000 Z
    Strength   :    0.0000000000
    X: D(  8) --> V(  1) amplitude = 0.9963
    Details  -- H:  28.4549 J1:  -30.3332  K1:   8.1053   XC1:   3.2048
                  J2:   0.6325 K2:   -6.9064 XC2:   -0.2806 Total:   2.8774

    dE1 = 9.4318 eV;   dE2 = -6.5545 eV   #not shown in output
```

- HOMO-LUMO gap $\gg$ lowest singlet/triplet excitation energies

● Why is the triplet state lower in energy?

```
Excited state   1: excitation energy (eV) =    2.1475
 Total energy for state  1:                     -114.33552540 au
    Multiplicity: Triplet
    Trans. Mom.:  0.0000 X   0.0000 Y   0.0000 Z
    Strength   :    0.0000000000
    X: D(  8) --> V(  1) amplitude =  0.9968
    Details  -- H:   26.7523 J1:  -28.3251  K1:    8.1581   XC1:    3.0430
                J2:    0.0000 K2:   -7.1299 XC2:   -0.3510 Total:    2.1475
    dE1 = 9.6283 eV;    dE2 = -7.4809 eV   #not shown in output

 Excited state   3: excitation energy (eV) =    2.8774
 Total energy for state  3:                     -114.30870220 au
    Multiplicity: Singlet
    Trans. Mom.: -0.0000 X  -0.0000 Y  -0.0000 Z
    Strength   :    0.0000000000
    X: D(  8) --> V(  1) amplitude =  0.9963
    Details  -- H:   28.4549 J1:  -30.3332  K1:    8.1053   XC1:    3.2048
                J2:    0.6325 K2:   -6.9064 XC2:   -0.2806 Total:    2.8774
    dE1 = 9.4318 eV;    dE2 = -6.5545 eV   #not shown in output
```

- ## Why is the triplet state lower in energy?

```
Excited state    1: excitation energy (eV) =    2.1475
 Total energy for state  1:                    -114.33552540 au
     Multiplicity: Triplet
     Trans. Mom.:  0.0000 X   0.0000 Y   0.0000 Z
     Strength   :    0.0000000000
     X: D(  8) --> V(  1) amplitude =  0.9968
     Details -- H:   26.7523 J1:  -28.3251  K1:    8.1581   XC1:   3.0430
                J2:    0.0000 K2:   -7.1299  XC2:  -0.3510  Total:   2.1475
     dE1 = 9.6283 eV;    dE2 = -7.4809 eV   #not shown in output

 Excited state    3: excitation energy (eV) =    2.8774
 Total energy for state  3:                    -114.30870220 au
     Multiplicity: Singlet
     Trans. Mom.: -0.0000 X  -0.0000 Y  -0.0000 Z
     Strength   :    0.0000000000
     X: D(  8) --> V(  1) amplitude =  0.9963
     Details -- H:   28.4549 J1:  -30.3332  K1:    8.1053   XC1:   3.2048
                J2:    0.6325 K2:   -6.9064  XC2:  -0.2806  Total:   2.8774
     dE1 = 9.4318 eV;    dE2 = -6.5545 eV   #not shown in output
```

- The J2 tem is

$$\Delta E_{2,J} = \int \int \rho_{\text{trans}}(\mathbf{r}_1) \frac{1}{r_{12}} \rho_{\text{trans}}(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2$$

- **Why is the triplet state lower in energy?**

```
Excited state   1: excitation energy (eV) =    2.1475
 Total energy for state  1:                  -114.33552540 au
    Multiplicity: Triplet
    Trans. Mom.:  0.0000 X   0.0000 Y   0.0000 Z
    Strength   :    0.0000000000
    X: D(  8) --> V(  1) amplitude =  0.9968
    Details  -- H:   26.7523 J1:  -28.3251  K1:    8.1581  XC1:   3.0430
             J2:     0.0000  K2:   -7.1299  XC2:   -0.3510 Total:   2.1475
    dE1 = 9.6283 eV;    dE2 = -7.4809 eV   #not shown in output

 Excited state   3: excitation energy (eV) =    2.8774
 Total energy for state  3:                  -114.30870220 au
    Multiplicity: Singlet
    Trans. Mom.: -0.0000 X  -0.0000 Y  -0.0000 Z
    Strength   :    0.0000000000
    X: D(  8) --> V(  1) amplitude =  0.9963
    Details  -- H:   28.4549 J1:  -30.3332  K1:    8.1053  XC1:   3.2048
             J2:     0.6325 K2:   -6.9064  XC2:   -0.2806 Total:   2.8774
    dE1 = 9.4318 eV;    dE2 = -6.5545 eV   #not shown in output
```

- The J2 tem is

$$\Delta E_{2,J} = \int \int \rho_{\text{trans}}(\mathbf{r}_1) \frac{1}{r_{12}} \rho_{\text{trans}}(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2$$

- The transition density, $\rho_{\text{trans}}(\mathbf{r})$, is zero for triplet excitations.

- TDDFT with B3LYP functional:

```
Excited state   3: excitation energy (eV) =     2.8422
Total energy for state  3:                      -114.21958212 au
   Multiplicity: Singlet
   Trans. Mom.:  0.0000 X  -0.0000 Y  -0.0000 Z
   Strength   :     0.0000000000
   X: D(  8) --> V(  1) amplitude =  0.9998
   Details  -- H:  28.8102 J1: -30.6356  K1:    4.2395  XC1:   3.0889
               J2:   0.6445  K2:  -3.0329 XC2:  -0.2723 Total:   2.8422
   dE1 = 5.5030 eV;   dE2 = -2.6607 eV       #not shown in output
   HOMO: -0.297; LUMO: -0.098; Gap: 5.415 eV   #not shown in output
```

- TDDFT with ωB97X-D functional:

```
Excited state   3: excitation energy (eV) =     2.8774
Total energy for state  3:                      -114.30870220 au
   Multiplicity: Singlet
   Trans. Mom.: -0.0000 X  -0.0000 Y  -0.0000 Z
   Strength   :     0.0000000000
   X: D(  8) --> V(  1) amplitude =  0.9963
   Details  -- H:  28.4549 J1: -30.3332  K1:    8.1053  XC1:   3.2048
               J2:   0.6325  K2:  -6.9064 XC2:  -0.2806 Total:   2.8774
   dE1 = 9.4318 eV;   dE2 = -6.5545 eV       #not shown in output
   HOMO: -0.369; LUMO: -0.028; Gap: 9.279 eV   #not shown in output
```

- TDDFT with B3LYP functional:

```
Excited state   3: excitation energy (eV) =    2.8422
Total energy for state  3:                     -114.21958212 au
    Multiplicity: Singlet
    Trans. Mom.:  0.0000 X  -0.0000 Y  -0.0000 Z
    Strength   :    0.0000000000
    X: D(  8) --> V(  1) amplitude =  0.9998
    Details  -- H:   28.8102 J1:  -30.6356  K1:    4.2395  XC1:   3.0889
                J2:    0.6445  K2:   -3.0329 XC2:  -0.2723 Total:   2.8422
    dE1 = 5.5030 eV;   dE2 = -2.6607 eV       #not shown in output
    HOMO: -0.297; LUMO: -0.098; Gap: 5.415 eV   #not shown in output
```

- TDDFT with ωB97X-D functional:

```
Excited state   3: excitation energy (eV) =    2.8774
Total energy for state  3:                     -114.30870220 au
    Multiplicity: Singlet
    Trans. Mom.: -0.0000 X  -0.0000 Y  -0.0000 Z
    Strength   :    0.0000000000
    X: D(  8) --> V(  1) amplitude =  0.9963
    Details  -- H:   28.4549 J1:  -30.3332  K1:    8.1053  XC1:   3.2048
                J2:    0.6325  K2:   -6.9064 XC2:  -0.2806 Total:   2.8774
    dE1 = 9.4318 eV;   dE2 = -6.5545 eV       #not shown in output
    HOMO: -0.369; LUMO: -0.028; Gap: 9.279 eV   #not shown in output
```

- The **K2** term is

$$\Delta E_{2,K}(\text{PBE0}) = -\int \int \rho_{\text{detach}}(\mathbf{r}_1) \frac{0.25}{r_{12}} \rho_{\text{attach}}(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2$$

$$\Delta E_{2,K}(\omega\text{B97X} - \text{D}) = -\int \int \rho_{\text{detach}}(\mathbf{r}_1) \frac{0.22 \, \text{erfc}(\omega r_{12}) + \text{erf}(\omega r_{12})}{r_{12}} \rho_{\text{attach}}(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2$$

Multiple-Environment Single-System QM/MM (MESS-QM/MM): QM/MM Calculations with a Fixed-Geometry QM Region
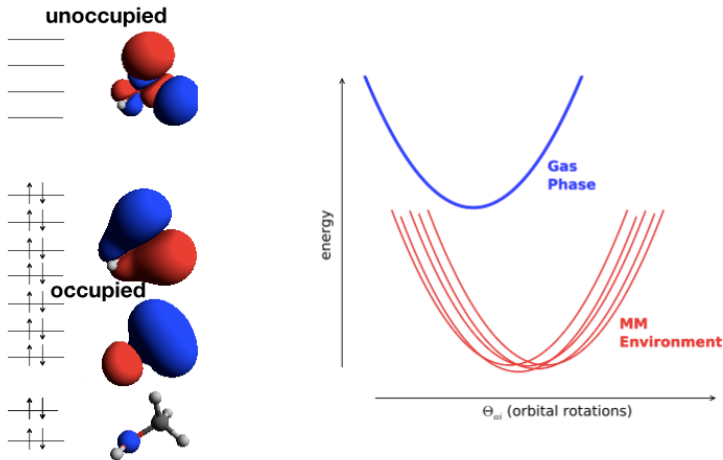
MESS-QM/MM: Fast Estimation of QM/MM Energy
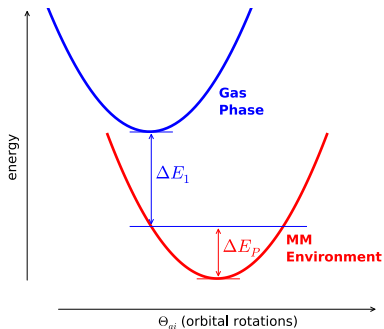
J. Phys. Chem. A, 119, 1511 (2015); J. Chem. Theory Comput., 12, 332 (2016); 13, 679 (2017).

MESS-QM/MM: Fast Estimation of QM/MM Energy

- Assume a quadratic surface
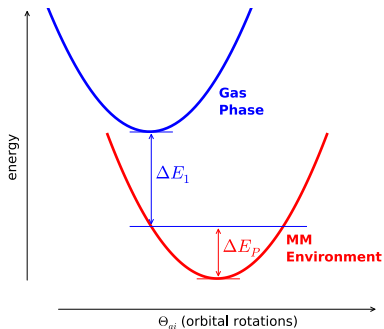
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MESS-QM/MM: Fast Estimation of QM/MM Energy

- Assume a quadratic surface
- Compute the Hessian for a reference environment
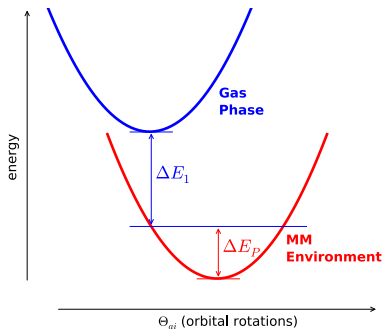
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MESS-QM/MM: Fast Estimation of QM/MM Energy

- Assume a quadratic surface

- Compute the Hessian for a reference environment

- For each MM environment
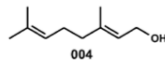 - Compute the gradient (g)
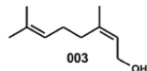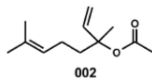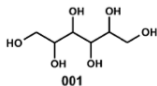 - Take a Newton step

$$\Delta\Theta = \mathbf{H}^{-1} \cdot g$$
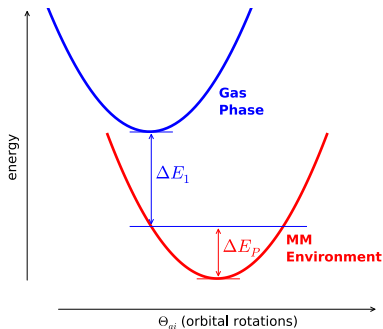
- Potential applications:
  - solvation free energies
  - enzymatic reaction free energy profiles
  - polarizable force-field development

J. Phys. Chem. A, 119, 1511 (2015); J. Chem. Theory Comput., 12, 332 (2016); 13, 679 (2017).

Hydration Free Energy Calculations
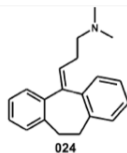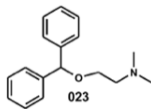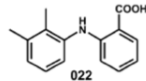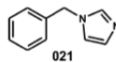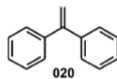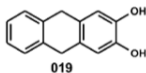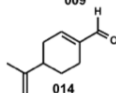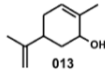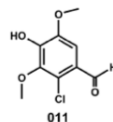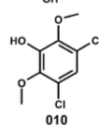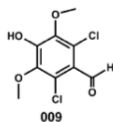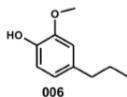
Computational Strategy
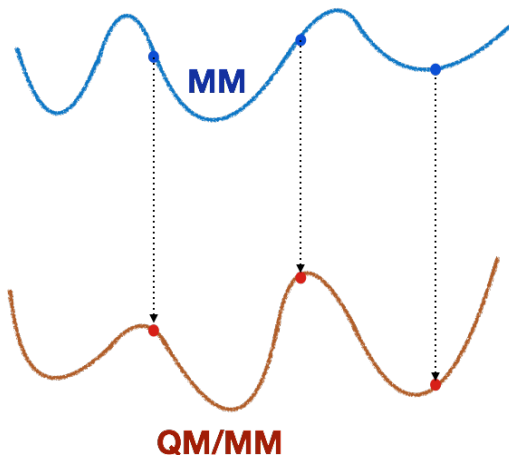
Step 1: Compute hydration free energy using MM energy functions. Solvent: >1500 TIP3P water

Step 2: Compute QM/MM energy on some MM configurations. Obtain QM/MM correction to the hydration free energy. QM region: solute

QM/MM Hydration Free Energy Calculations

- Computational Efficiency
  - MM: 100 CPU Hours
  - QM/MM correction: 400-2700 CPU Hours

J. Phys. Chem. A, 119, 1511 (2015); J. Chem. Theory Comput., 12, 332 (2016); 13, 679 (2017).

QM/MM Hydration Free Energy Calculations

- Computational Efficiency
  - MM: 100 CPU Hours
  - QM/MM correction: 400-2700 CPU Hours
  - Our accelerated QM/MM correction: 7-12 CPU Hours
    - Assumes a fixed geometry for the solute (QM region)
    - Difference in hydration free energy predictions: <0.2 kcal/mol

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- Computational Accuracy

Error	MM	After QM/MM correction	
(kcal/mol)		BLYP	
MSE	-1.15	-0.63	
RMSE	1.80	1.07	

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- Computational Accuracy

Error	MM	After QM/MM correction				
(kcal/mol)		BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
MSE	-1.15	-0.63	-1.42	-1.95	-1.97	-2.13
RMSE	1.80	1.07	1.70	2.18	2.22	2.37

J. Phys. Chem. A, 119, 1511 (2015); J. Chem. Theory Comput., 12, 332 (2016); 13, 679 (2017).

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- More sophisticated functionals yielded worse results.

J. Phys. Chem. A, 119, 1511 (2015); J. Chem. Theory Comput., 12, 332 (2016); 13, 679 (2017).

QM/MM Hydration Free Energy Calculations

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- More sophisticated functionals yielded worse results.
- We also need to improve QM/MM vdW interactions.

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Computational Chemistry: Applications, Theory and Software
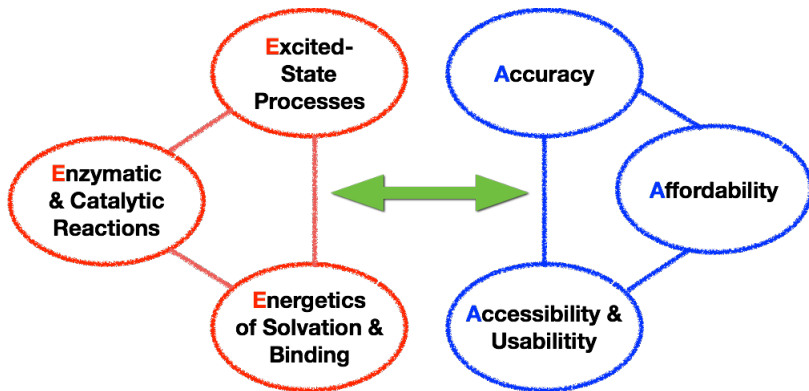
Main Topics

- Fluorescence/bioluminescence, reaction rates, binding affinity
- Chemical, solvent, macromolecular, methodological perturbations

Acknoweldgements

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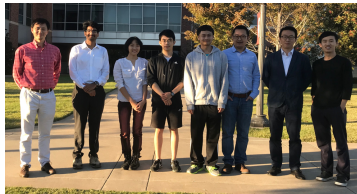 - Samarjeet Prasad and Qiao Zeng, *NHLBI, NIH*

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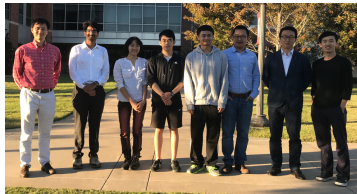   - Samarjeet Prasad and Qiao Zeng, *NHLBI, NIH*

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    - NIH, *SBIR Phase II*
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    - University of Oklahoma