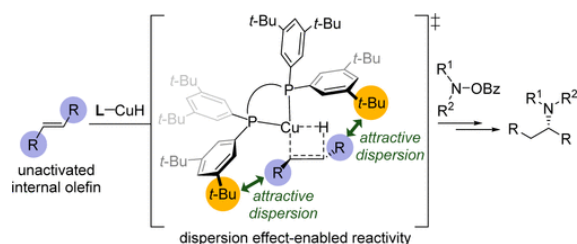


Energy Decomposition Analysis

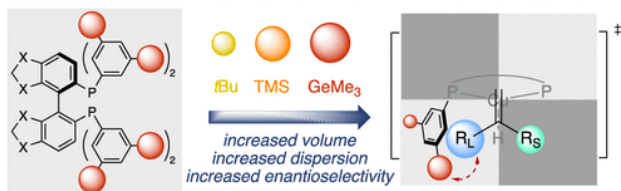
Yuezhi Mao

San Diego State University

- Non-covalent interactions (NCIs) are ubiquitous and play an important role in modern chemistry

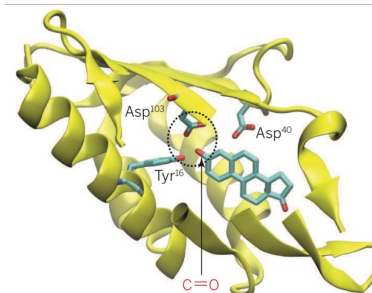


G. Lu, R. Y. Liu, Y. Yang et al. JACS (2017)

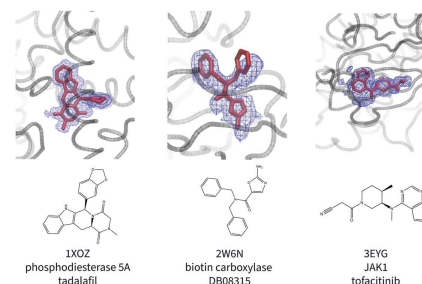


Y. Xi, B. Su, X. Qi et al. JACS (2020)

Design of ligands for
organometallic catalysis



S. D. Fried, S. Bagchi, S. G. Boxer, Science (2014)



S. Lahey, C. N. Rowley, Chem. Sci. (2020)

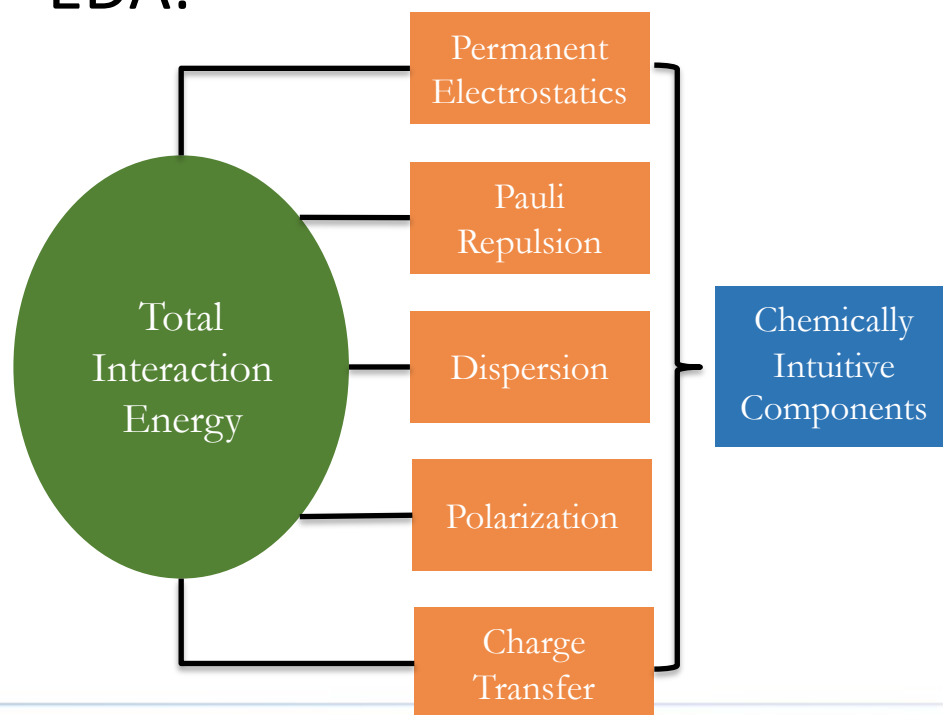
Enzyme catalysis and drug-
protein binding

Energy decomposition analysis



- Components not uniquely defined, but **physically meaningful** and **chemically intuitive**

EDA:



- Useful in
 - Unraveling the nature of specific NCIs (e.g., hydrogen/halogen bonds, π -stacking)
 - Characterizing the role of NCIs in chemical processes (e.g., how each energy component helps stabilize a specific TS structure)
 - Guiding the development of other theoretical models (e.g., force fields, machine-learning potential)

- **ALMO-EDA (Head-Gordon group @Berkeley):**
 - DFT-based EDA for non-covalent interactions
 - Adiabatic EDA: decomposition of molecular properties
 - EDA for bonded interactions
 - MP2-EDA for non-covalent interactions
 - TDDFT-based EDA for interactions involving excited states
- **SAPT/cDFT-EDA (Herbert group @Ohio State):**
 - SAPT calculation provides both the total interaction energy and its decomposition
 - Employing cDFT to separate CT from SAPT induction

EDA based on **Absolutely Localized Molecular Orbitals (ALMOs)**:



$$\Delta E_{\text{INT}} = \Delta E_{\text{FRZ}} + \Delta E_{\text{POL}} + \Delta E_{\text{CT}}$$

- **Frozen interaction (FRZ)**: energy change upon moving the isolated fragments into their positions in the complex while keeping their own electronic structure unchanged
- **Polarization (POL)**: energy lowering arising from the intramolecular relaxation of each fragment's electronic structure at the presence of other fragments; inter-fragment orbital mixings are forbidden by enforcing the ALMO constraint
- **Charge transfer (CT)**: energy lowering due to electron delocalization between fragments

Besides these 3 terms, the **geometry distortion (GD)** term needs to be reported when decomposing the total binding energy, i.e., the energy difference between the *full complex* and *fully relaxed monomers*

The second-generation ALMO-EDA (ALMO-EDA-II):^[1]

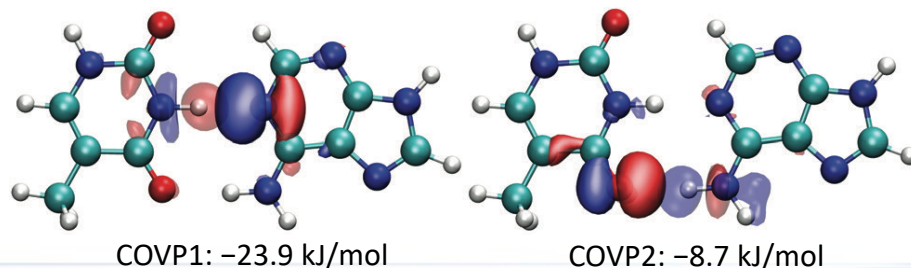
$$\Delta E_{\text{INT}} = \Delta E_{\text{ELEC}} + \Delta E_{\text{PAULI}} + \Delta E_{\text{DISP}} + \Delta E_{\text{POL}} + \Delta E_{\text{CT}}$$

Advances:

1. Further decomposition of the frozen interaction into contributions from **permanent electrostatics**, **Pauli repulsion**, and **dispersion**^[2] (two flavors: “quasiclassical” and “orthogonal” frozen decompositions)
2. The fragment electric response function (FERF) approach: a more robust scheme to separate POL and CT with a well-behaved basis set limit^[3]
3. Non-perturbative charge-transfer analysis (CTA) and polarization analysis (more to come in 6.1)^[4]

$$\Delta E_{\text{POL}} = \sum_A \Delta E_{\text{POL}}^{(A)}$$

$$\Delta E_{\text{CT}} = \sum_{A \neq B} \Delta E_{\text{CT}}^{A \rightarrow B} + \Delta E_{\text{CT}}^{B \rightarrow A}$$

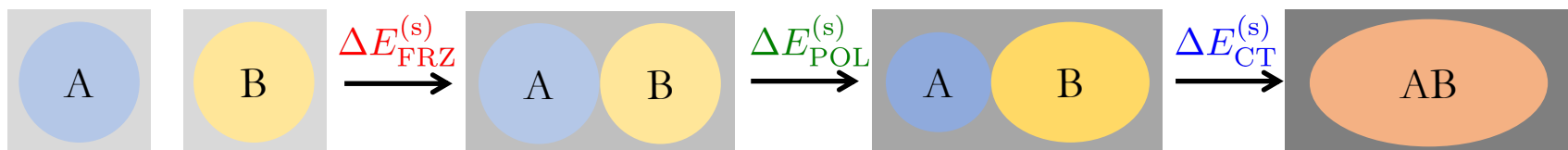


[1] Horn, Mao, Head-Gordon, PCCP **18**, 23067 (2016); Mao et al. Annu. Rev. Phys. Chem. **72**, 641 (2021)

[2] Horn, Mao, Head-Gordon JCP **114**, 114107 (2016); [3] Horn, Head-Gordon, JCP **143**, 114111 (2015)

[4] Veccham et al. PCCP **23**, 928 (2021); Shen, Wang, Head-Gordon, JCTC, **18**, 7428 (2022); Shen et al. *in preparation*

- A unique feature of ALMO-EDA-II: **incorporate solvation effects** throughout the entire procedure via **implicit solvent models** such as PCM, SMD, etc.



$$\Delta E_{\text{INT}}^{(s)} = E_{\text{Full}}^{(s)} - \sum_A E_A^{(s)} = \Delta E_{\text{FRZ}}^{(s)} + \Delta E_{\text{POL}}^{(s)} + \Delta E_{\text{CT}}^{(s)}$$

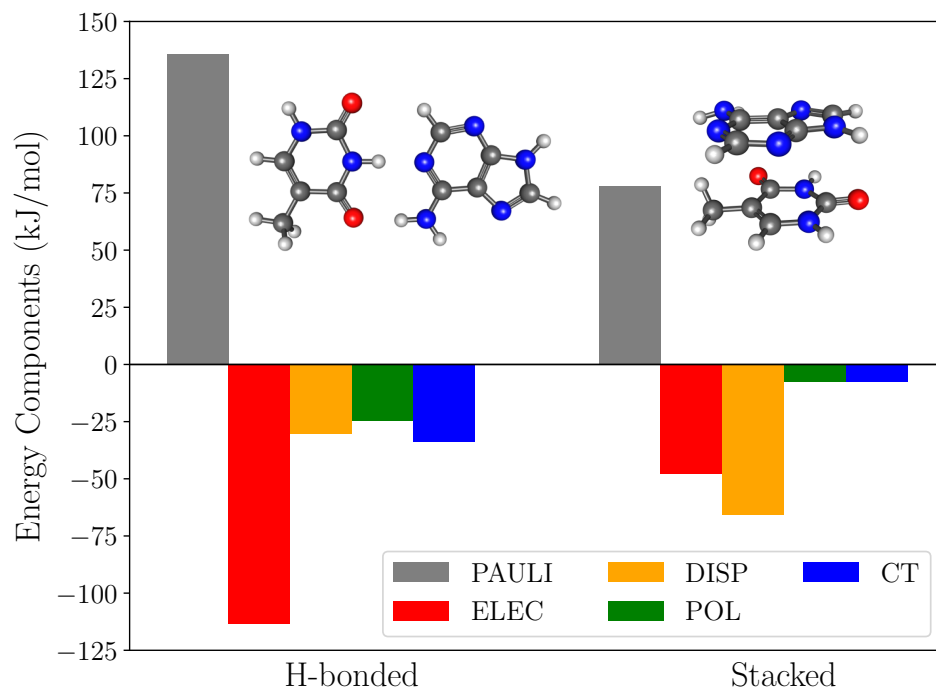
$$\Delta E_{\text{FRZ}}^{(s)} = E_{\text{FRZ}}^{(s)} - \sum_A E_A^{(s)}$$

$$= \Delta E_{\text{ELEC}}^{(s)} + \Delta E_{\text{PAULI}}^{(s)} + \Delta E_{\text{DISP}}^{(s)}$$

$$\Delta E_{\text{POL}}^{(s)} = E_{\text{POL}}^{(s)} - E_{\text{FRZ}}^{(s)}, \quad \Delta E_{\text{CT}}^{(s)} = E_{\text{Full}}^{(s)} - E_{\text{POL}}^{(s)}$$

The primary effect of
continuum solvent:
Damping the electrostatics

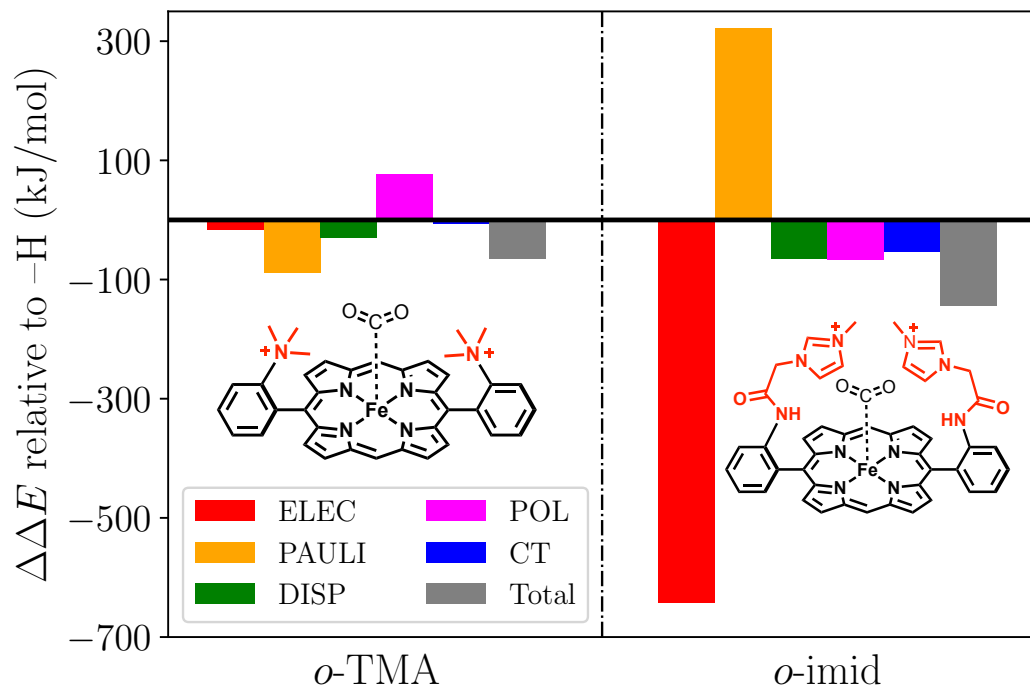
- Identifying the “fingerprints” of non-covalent interactions



The adenine-thymine complex:

- H-bonded:** dominated by ELEC, with non-trivial DISP, POL, and CT contributions
- Stacked:** dominated by DISP, followed by also significant ELEC

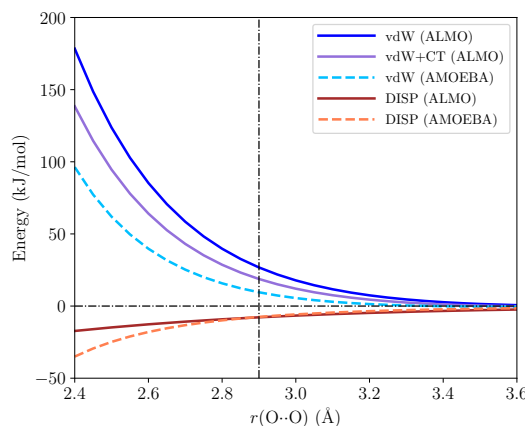
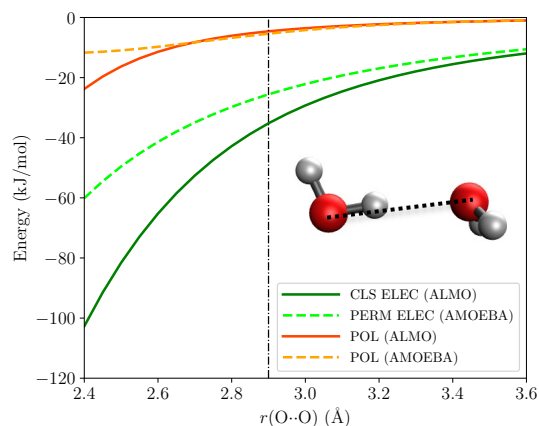
- Identifying the “fingerprints” of non-covalent interactions



Substituent group effects on the binding of $\text{CO}_2^{\bullet-}$ at the catalytic site of the FeTPP complex:

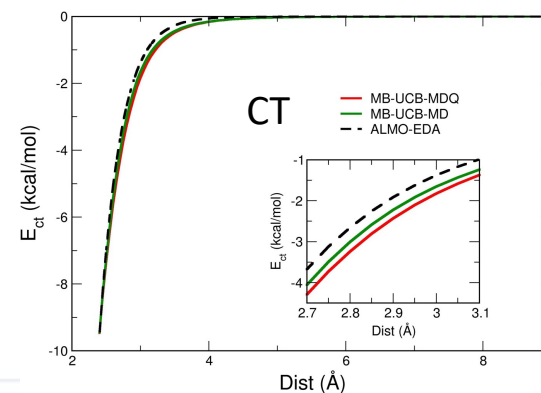
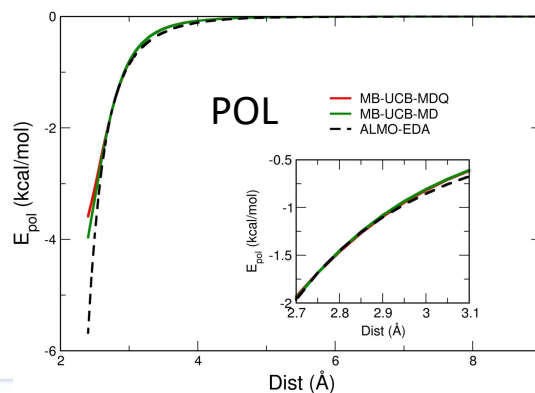
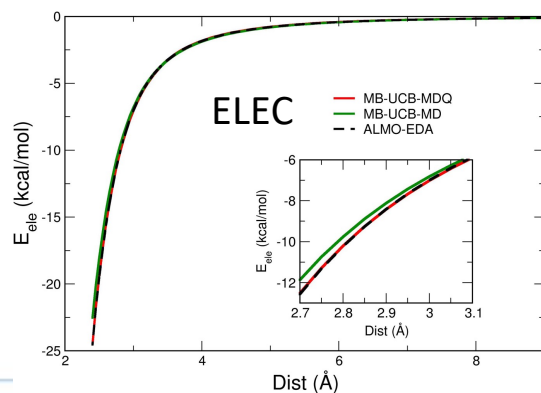
- o*-TMA:** primarily arising from reduction of Pauli repulsion
- o*-imid:** dominated by electrostatic stabilization

- Development and assessment of force fields



Comparison between **AMOEBA** force field and **ALMO-EDA**:^[1] the agreement at the level of individual terms is poor

MB-UCB:^[2] component-wise agreement with ALMO-EDA results

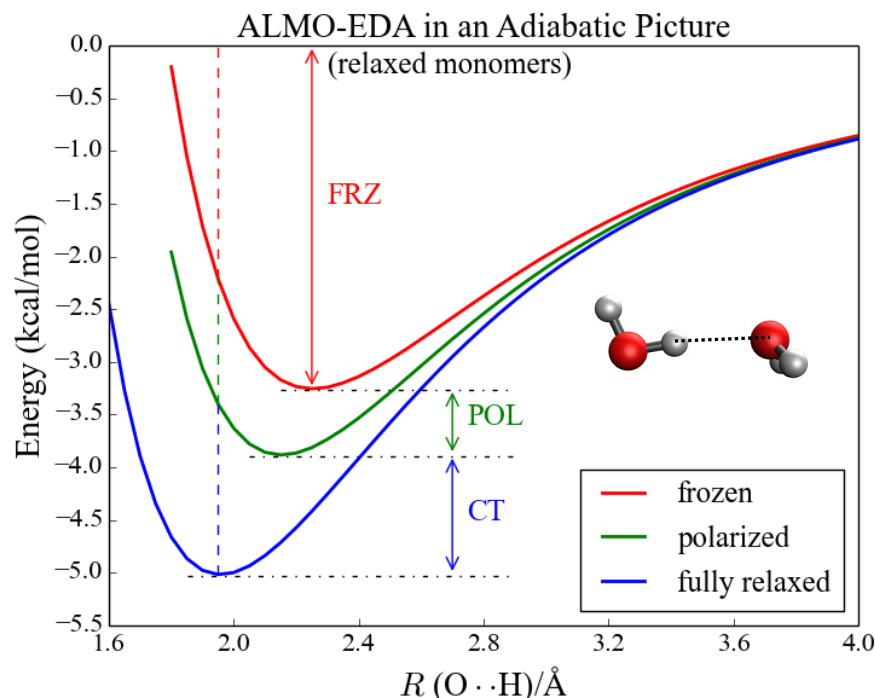


[1] Mao et al. JCTC **12**, 5422 (2016)

[2] Das et al. JCTC **15**, 5001 (2019); JCTC **18**, 953 (2022)

The adiabatic EDA scheme:

- Relax the complex geometry on each intermediate potential energy surface (PES)
- Partition shifts in molecular properties into FRZ, POL, and CT contributions



Interaction components defined as the energy differences between the stationary points on two neighboring PESs:

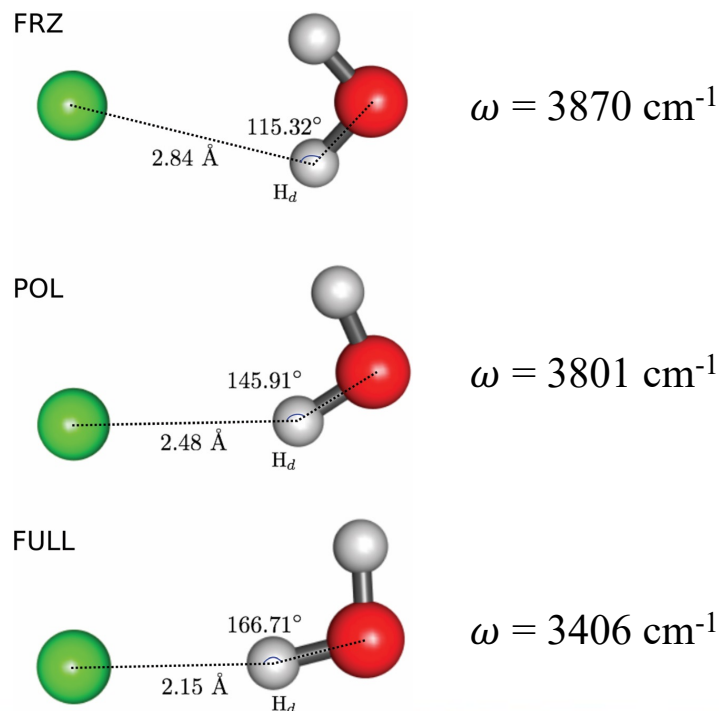
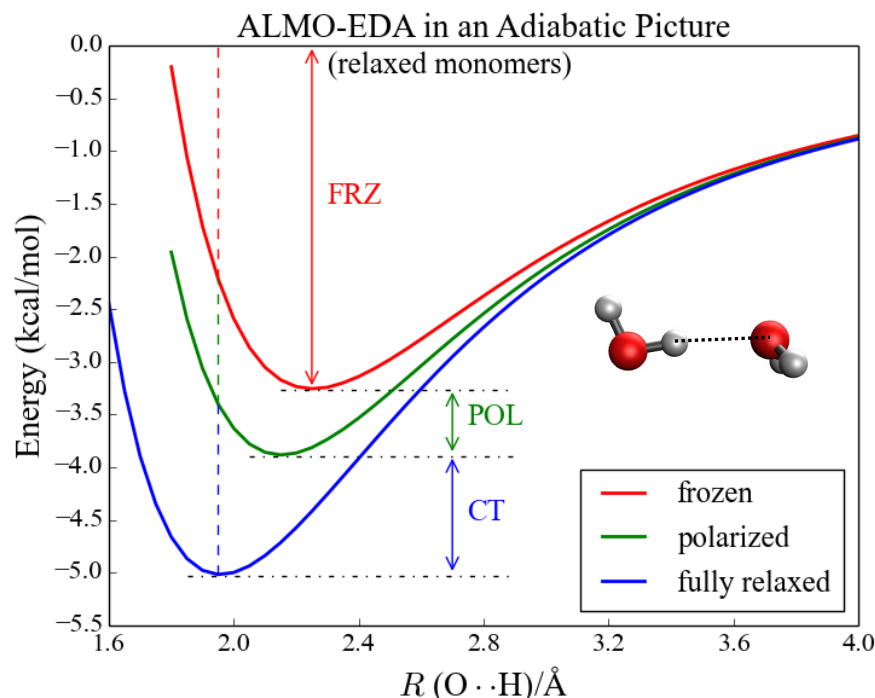
$$\Delta E_{\text{FRZ}}^{(\text{ad})} = E_{\text{FRZ}}^{(0)} - \sum_{A=1}^{N_{\text{frag}}} E_A^{(0)}$$

$$\Delta E_{\text{POL}}^{(\text{ad})} = E_{\text{POL}}^{(0)} - E_{\text{FRZ}}^{(0)}$$

$$\Delta E_{\text{CT}}^{(\text{ad})} = E_{\text{Full}}^{(0)} - E_{\text{POL}}^{(0)}$$

The adiabatic EDA scheme:

- Relax the complex geometry on each intermediate potential energy surface (PES)
- Partition shifts in molecular properties into FRZ, POL, and CT contributions



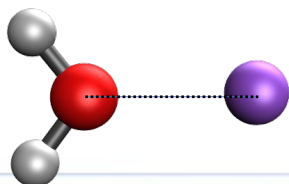
- Option sets are available:
 - **EDA2 = 1**: Frozen decomposition + FERF-DQ for polarization
 - **EDA2 = 2**: Frozen decomposition + original ALMO polarization
- General recommendations:
 - Always use **dispersion-corrected DFT** (otherwise DISP term not meaningful)
 - Use **option 1** for small-to-medium systems with a large basis set; use **option 2** for large systems for which only double-zeta basis sets are affordable
- Other useful job control keywords:
 - EDA_PCT_A = True: Perform perturbative CTA analysis (non-perturbative CTA also available in Q-Chem 6.0)
 - EDA_BSSE = True: Perform counterpoise correction for BSSE (needed for small basis)
 - EDA_CLS_DISP = True: Evaluate dispersion energy using unmodified fragment densities (automatically turned on when there is ECP)
 - SOLVENT_METHOD = PCM or SMD: Specify the solvation model in ALMO-EDA(solv)
 - **Visualization tools**: COVP, NOCV, electron density difference (EDD), etc.

Q-Chem input:

```
$molecule
1 1
--
1 1
Na 0.00000 0.00000 -0.99709
--
0 1
O 0.00000 0.00000 1.10291
H -0.76356 0.00000 1.68914
H 0.76356 0.00000 1.68914
$end
```

```
$rem
JOBTYPE EDA
EDA2 1
METHOD wB97X-V
BASIS def2-TZVPPD
SCF_CONVERGENCE 8
SOLVENT_METHOD SMD
$end
```

```
$smx
solvent water
$end
```



Output:

```
=====
Results of EDA2
=====
Basic EDA Quantities
...
-----
E_prp (kJ/mol) = 0.0000
E_sol (kJ/mol) = 44.0123
E_frz (kJ/mol) = -93.3331 (unscreened)
[E_frz(solv) = -49.3208 kJ/mol (unscreened FRZ + SOL)]
E_pol (kJ/mol) = -10.6879
E_vct (kJ/mol) = -3.3989
E_int (kJ/mol) = -63.4076
-----
```

The basic 3 terms (FRZ, POL, CT) with solvation incorporated

[E_frz(solv) = -49.3208 kJ/mol (unscreened FRZ + SOL)]

Plan to further simplify the output format of ALMO-EDA(solv) for the 6.1 release

Decomposition of frozen interaction energy

```
-----
Classical Frozen Decomposition (unscreened):
-----
E_cls_elec (CLS ELEC) (kJ/mol) = -157.7515
E_mod_pauli (MOD PAULI) (kJ/mol) = 71.5263 (FRZ - CLS ELEC - DISP)
→ E_disp (DISP) (kJ/mol) = -7.1079
-----
```

Focusing on the classical frozen decomposition results (the orthogonal decomposition results are similarly arranged)

Classical Decomposition Terms with Solvent Contributions:

```
-----
E_sol_elec (kJ/mol) = 44.2388
→ E_cls_elec(solv) (kJ/mol) = -113.5127 (CLS ELEC + SOL ELEC)
E_sol_nonelec (kJ/mol) = -0.2265
→ E_mod_pauli(solv) (kJ/mol) = 71.2998 (MOD PAULI + SOL non-ELEC)
-----
```


Adiabatic EDA job control and example

- Analytic gradients** on the FRZ and POL surfaces are employed to optimize the structures on those two surfaces (set `FRZ_GEOM/POL_GEOM = True`)
- Vibrational frequencies in the FRZ/POL states are calculated using the **finite-difference method** (analytic Hessian not yet available)
- In general, it is recommended to start from optimizing the fully relaxed structure
- Example:** Calculating the equilibrium structure and harmonic frequencies of $\text{OC}\cdots\text{BeO}$ in the frozen state



Q-Chem input:

```
$molecule
0 1
--
0 1
Be      0.00000      0.00000      1.08786
O       0.00000      0.00000      2.40495
--
0 1
C       0.00000      0.00000     -1.08826
O       0.00000      0.00000     -2.20075
$end
```

```
$rem
JOBTYP  OPT
FRZ_GEOM TRUE
METHOD  B3LYP
DFT_D   D3_BJ
BASIS   DEF2-TZVPP
SCF_CONVERGENCE 9
$end
```

Forces on the frozen surface will be calculated

@@@

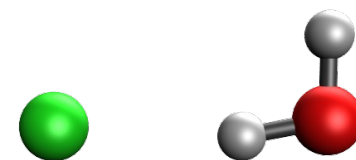
```
$molecule
read
$end
```

Read in the optimized structure for harmonic frequency calculation

```
$rem
JOBTYP  FREQ
FRZ_GEOM TRUE
METHOD  B3LYP
DFT_D   D3_BJ
BASIS   DEF2-TZVPP
SCF_CONVERGENCE 9
$end
```

- ALMO-EDA-II for water...Cl⁻ at equilibrium structure:
 - At the ω B97X-V/def2-SVPD level of theory
 - Because of the use of a relatively small basis set, we choose **EDA2 = 2** (ALMO polarization + decomposition of the frozen interaction)
 - Counterpoise correction for BSSE will be performed (**EDA_BSSE = TRUE**)
 - Perform the EDA calculation (i) in vacuum and (ii) in solvent water described by the SMD model. Report the results for the ELEC, PAULI, DISP, POL, CT terms (focusing on the results of “quasiclassical” decomposition) as well as the total interaction energies

	ELEC	PAULI	DISP	POL	CT	Total
vacuum						
SMD water						



- **Note:** IQmol doesn't provide a full support for ALMO-EDA-II jobs yet so the input file needs to be manually edited
- **Procedure for job setup:**
 - Open the XYZ file “water_cl.xyz” using IQmol
 - Change the charge to “-1” (the multiplicity should then automatically update to “1”). Under the dropdown menu of “Calculate” select “Energy Decompose”, and set “Method” to “Omega-B97X-V”
 - We then need to **manually edit** the generated input file on the right of job setup panel: (i) set “BASIS = def2-SVPD” and “GUI = 0” (since we are not doing any visualization here); (ii) add the following two lines under “JOB_TYPE = EDA”: EDA2 = 2, and EDA_BSSE = TRUE
 - As the last step, we need to edit the \$molecule section to specify the fragments: frag 1: -1 1; frag 2: 0 1
 - The generated input is shown on the right. It's ready to submit!

Generated Input File:

```

$molecule
-1 1
--
-1 1
Cl   -1.1242249   0.0179827   0.0000000
--
0 1|
O     1.9940516  -0.0909265   0.0000000
H     1.0163933  -0.2184602   0.0000000
H     2.0588108   0.8652887   0.0000000
$end

$rem
BASIS  = def2-SVPD
GUI    = 0
JOB_TYPE = EDA
EDA2   = 2
EDA_BSSE = TRUE
METHOD = wB97XV
$end
  
```

Server: Q-Chem

Reset Cancel Submit

- After the job is finished, copy it back to your computer. Then under “Files” (in the “Model View” column on the left), double-click the output file; scroll down to find the section as shown on the right
- Starting from the output file we go ahead to set up a second EDA2 calculation with SMD water: click “Calculation → Q-Chem setup”, make sure that the generated input is the same as the previous job (you may need to set “GUI = 0” again); then click “Advanced → Solvent Model” and choose “SMD” and the solvent model and set solvent to “water”. Make sure that “SOLVENT_METHOD = SMD” appears in the \$rem section and a new \$smx section also appears:

```
$smx
      SOLVENT  WATER
$end
```

```
=====
                        Results of EDA2
=====
Basic EDA Quantities
=====
Fragment Energies (Ha):
1 -460.0529423442
2  -76.3470870124

E_prp (kJ/mol) = 0.0000
E_frz (kJ/mol) = -32.9000
E_pol (kJ/mol) = -15.0941
E_vct (kJ/mol) = -16.6774 (CP-corrected)
E_int (kJ/mol) = -64.6715 (CP-corrected)
=====

Decomposition of frozen interaction energy
-----
Orthogonal Frozen Decomposition:
-----
E_elec (ELEC) (kJ/mol) = -119.8483
E_pauli (PAULI) (kJ/mol) = 99.4947
E_disp (DISP) (kJ/mol) = -12.5464

Classical Frozen Decomposition:
-----
E_cls_elec (CLS ELEC) (kJ/mol) = -81.5197
E_mod_pauli (MOD PAULI) (kJ/mol) = 61.1661
E_disp (DISP) (kJ/mol) = -12.5464
=====
```

Submit the calculation and collect the EDA results from the output file.

EDA results in solvation environment: check out how each term differs from the results in vacuum

```

=====
Results of EDA2
=====
Basic EDA Quantities
=====
Fragment Energies (Ha):
1 -460.1558667113
2 -76.3591018936
=====
E_prp (kJ/mol) = 0.0000
E_sol (kJ/mol) = 43.6322
E_frz (kJ/mol) = -45.6542 (unscreened)
E_frz(solv) = -2.0220 kJ/mol (unscreened FRZ + SOL)
E_pol (kJ/mol) = -4.0923
E_vct (kJ/mol) = -15.3228 (CP-corrected)
E_int (kJ/mol) = -21.4370 (CP-corrected)

Decomposition of frozen interaction energy
=====
Classical Frozen Decomposition (unscreened):
=====
E_cls_elec (CLS ELEC) (kJ/mol) = -92.0390
E_mod_pauli (MOD PAULI) (kJ/mol) = 57.9297 (FRZ - CLS ELEC - DISP)
E_disp (DISP) (kJ/mol) = -11.5449

Classical Decomposition Terms with Solvent Contributions:
=====
E_sol_elec (kJ/mol) = 46.0173
E_cls_elec(solv) (kJ/mol) = -46.0217 (CLS ELEC + SOL ELEC)
E_sol_nonelec (kJ/mol) = -2.3851
E_mod_pauli(solv) (kJ/mol) = 55.5446 (MOD PAULI + SOL non-ELEC)
    
```

Collection of EDA results (in kJ/mol):

	ELEC	PAULI	DISP	POL	CT	Total
Vacuum	-81.5	61.2	-12.5	-15.1	-16.7	-64.7
SMD water	-46.0	55.5	-11.5	-4.1	-15.3	-21.4