

Modern2023
4-7 Sep 2023 Paris (France)



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EXERCISE BOOK

for MoDerm Hands On

Foreword. All the calculations performed in these sessions were designed for TopChem2 or ADF. Note that some of these calculations could also be performed using other softwares. Additionally, we would like to emphasize that, for practical reasons, most of these calculations have been conducted at a basic level of theory. If you decide to use these tools in your research, we strongly encourage you to employ more appropriate and advanced levels of theory for more accurate results.

All required input files for TopChem2 (wfn/wfx/cubes files) as well as ADF input files, along with useful articles, are provided on the local computers in the **Bureau/MODERM**. Do not hesitate to consult the “Practical Work” given at the end of this document.

Hands on Quantum Chemical Topology: Working Sessions I

I. Introductory QTAIM analysis with TopChem2: Exploring Chemical Structures and Their Interactions

Julien Pilmé

Some help can be found from the following resource: B. Silvi, R.J. Gillespie, C. Gatti, "Electron Density Analysis." In Book: *Comprehensive Inorganic Chemistry II*, Elsevier, 2013, pp. 187-226

A. Run a QTAIM analysis with Topchem2 for some molecules provided in the following list:

C-C bonds : C₂H₆, C₂H₄, C₂H₂, C₆H₆, Cubane C₈H₈
R-O bonds : H₂O, H₂CO, H₂O₂, CO, CO₂
R-BH₃ bonds : NH₃BH₃, B₂H₆
R-F bonds : LiF, F₂, ClF₃(C_{2v}), FCl
Intermolecular bonds : FH--CO, FH--OC

Command-line for performing your QTAIM analysis

```
> topchem2 wfn:your_file.wfn (wfx:your_file.wfx) function:rho cp:y proc:4 refine:f vmd  
output:your_file.pop pop:cov
```

B. Check the integration of total number of electrons in the output (file.pop), this corresponds to the total number of electrons in the system. This should be done each time to check the accuracy of the integration.

C. **Analysis of Results.** We recall the QTAIM classification (Bianchi et al ¹):

	Scheme	ρ_{bcp}	$\nabla^2\rho_{\text{bcp}}$	$ V_{\text{bcp}} /G_{\text{bcp}}$	H_{bcp}
Closed-Shell	Van der Waals	Low	> 0	≈ 1	> 0
	ionic	Low	> 0	≈ 1	> 0
	donor-acceptor	Low	> 0	≈ 1	< 0
Shared -Shell	polarcovalent	High	< 0	> 1	< 0
	covalent	High	< 0	> 1	< 0

Reminder. if the electron density is high at the BCP and its Laplacian $\nabla^2\rho_{\text{b}}$ is negative, the local concentration of charge indicates a **shared-shell** bonding. In contrast, if $\nabla^2\rho_{\text{b}}$ is positive there is a depletion of charge which characterizes **closed-shell interactions**. Energetic local descriptors are also often used to differentiate two categories of

closed-shell bonding: the $|V_{\text{b}}|/G_{\text{b}}$ ratio that reflects the covalency magnitude of the interaction. If the latter ratio is smaller than 1, the kinetic energy density is the leading term and electrons are destabilized close to the BCP, no covalency is expected (for example pure ionic or van der Waals bonding). $H_{\text{bcp}} = G_{\text{bcp}} + V_{\text{bcp}}$ is the total energy.

- i. The main output file (file.pop) contains all the compiled results. Find all the critical points: bond (bcp), cage (ccp) and ring (rcp). How many of each type are there? In each case, check that the Poincaré-Hopf theorem holds. Use molden to visualize their spatial distribution within the molecular structure (file_cprho.xyz).
- ii. From your result file 'xxx.pop', extract the values of some local descriptors (listed in the table below) computed at the bond critical points (BCP) locations. You can find the index of a BCP by visualizing them either with VMD (file xxx_rho.vmd) or Molden (file xxx_rho_cprho.xyz). Also extract the QTAIM charges and the delocalization index δ_{AB} . Use Lewis structures to aid in determining the nature (shared-shell or closed-shell) of the chemical interaction under investigation.

¹ R. Bianchi, G. Gervasio, D. Marabello. Experimental Electron Density Analysis of Mn₂(CO)₁₀: Metal–Metal and Metal–Ligand Bond Characterization. *Inorg. Chem.* **39** (2000), 2360.

- iii. Assuming that the formal bond orders for C–C bonds are 1, 2, and 3 for ethane, ethylene, and acetylene respectively, fit the densities at the C-C BCP to a linear regression model. Then, calculate the expected bond order for benzene and cubane based on its density. Compare these results with the bond orders obtained from the delocalization indices.

	Selected QTAIM descriptors computed at bcp				QTAIM charges		Delocalization Index	bonding scheme?
	ρ_{bcp}	$\nabla^2\rho_{\text{bcp}}$	$ \mathbf{V}_{\text{bcp}} /G_{\text{bcp}}$	H_{bcp}	Q(A)	Q(B)	δ_{AB}	
C-C bond								
H ₃ C-CH ₃								
H ₂ C-CH ₂								
HC-CH								
C ₆ H ₆								
C ₈ H ₈								
R-O bond								
H ₂ C-O								
C-O								
O-C-O								
H-O-H								
HO-OH								
R-BH₃ bonds								
H ₃ N--BH ₃								
H ₃ B--BH ₃								
R-F bonds								
LiF								
F ₂								
F-Cl								
Intermolecular bonds								
FH···CO								
FH···OC								

II. QTAIM descriptors and IQA energy decomposition with ADF.

Laurent Joubert and Vincent Tognetti

Practical Work with AMS 2023

Launch of the program

AMS is a suite of softwares² organized in **modules**. We will first "launch" the main module, "AMSJobs" which corresponds to the AMS file explorer. It is not recommended, for the beginner, to use both the file explorer of the operating system and that of AMS. We only need AMS here. If there is no shortcut on your desktop, you will have to open a terminal and type the command: `$AMSBIN/amsjobs`.

AMSJobs

You get a window containing all your AMS "jobs" (see Figure 1). Some "jobs" have been prepared for you and are visible in the default directory. A "job" is a set of files corresponding to a calculation that you launch with a given module (for example, geometry optimization of a molecule performed with the ADF molecular module). Everything is transparent via the GUI.

In the "AMSJobs" menu, choose "Preferences". We will now set an AMS option that will be very convenient for the future. In the "Module" tab, choose "AMSJobs" and then check the "Show Logfile" box. **Click "Save"**. Close the preferences window.

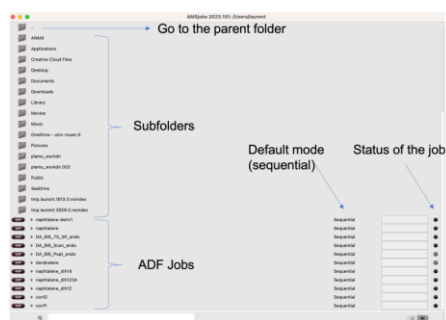


Figure 1: AMSJobs module (file explorer)

AMS modules

The various AMS modules (including AMSJobs) are accessible in the "SCM" menu of the software. Here are very briefly the most useful ones. You will discover them by following the tutorials:

- **AMSInput**: to build a molecule and prepare a calculation.
- **AMSView**: to visualize the results (calculation completed) in graphical form.
- **AMSMovie**: to follow the evolution of the calculation in the form of an animated film (changes in geometries, evolution of energy, a distance...).
- **AMSLevels**: to display an orbital energy diagram and also to allow easy visualization of orbitals.
- **AMSLogfile**: to display some information in real time (example: SCF cycles).
- **AMSOutput**: all results are collected in this file (useful if you are looking for details or details about the results).
- **AMSSpectra**: to allow you to visualize IR/Raman and UV-Visible calculated spectra.

² ADF 2023.1, SCM, Theoretical Chemistry, Vrije Universiteit, Amsterdam, The Netherlands, <http://www.scm.com>.

1. Local (molecular graph) and condensed (atomic) QTAIM descriptors

If not yet done, it is recommended to follow some tutorials specific to topological approaches. In the "Tutorial" menu (on the SCM Web Page), type "QTAIM" in the search window (on the left) and select the first link: "[QTAIM \(Bader\), localized orbitals and conceptual DFT](#)". Follow the instructions to perform an initial QTAIM analysis of C₆H₆.

2. Revealing electron delocalization through the Source Function (SF)

The source function (SF) introduced in late 90s by Bader and Gatti³ quantifies the influence of each atom in a system in determining the amount of electron density at a given point, regardless of the atom's remote or close location with respect to the point. The SF may thus be attractive for studying directly in the real space somewhat elusive molecular properties, such as "electron conjugation" and "aromaticity", that lack rigorous definitions as they are not directly associated to quantum-mechanical observables. In this exercise, based on reference⁴, we will see if the source function is able to reveal and measure the effects of electronic delocalization within model systems, namely the naphthalene molecule and some derivatives: 1,2-dihydronaphthalene, 1,4-dihydronaphthalene and 1,2,3,4-tetrahydronaphthalene (Figure 2).

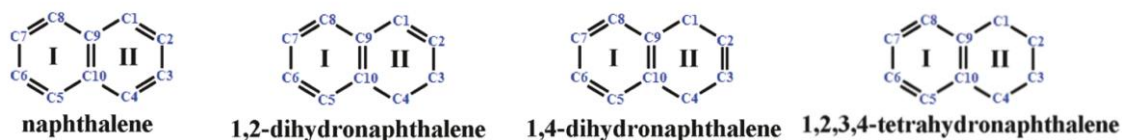


Figure 2: naphthalene molecule and some derivatives (hydrogens are omitted)

Build and **pre-optimize** the structures with the **GFNFF** force field (select "geometry optimization" as the task, and right click on the notched wheel at the bottom of the screen for the choice of the force field). **Optimize** all geometries at PBE/DZP/LC (large core) level with "normal" numerical quality (relativity: none). Starting from these optimized structures, **go to the 'Properties' menu, check the 'QTAIM analysis' box, select a 'Full' level analysis and check the 'Source Function' box.** Finally, perform **single point calculations** at the PBE/TZ2P/NFC (no frozen core) level with a "good" numerical quality (Relativity: none).

In the first output file (naphthalene), find the results section concerning the source function (non-local QTAIM properties) and analyze the decomposition of the BCP electron density of the C9-C10 central bond (see Figure 1). Note the contribution (%) of the C9 and C10 bonded atoms, then the nearest neighboring atoms for one of the two rings (C8 and C5 for example) and finally the most distant carbon atoms (C6 and C7 for example). By symmetry, the contributions are identical for the other cycle.

Repeat the same procedure for the three naphthalene derivatives and analyze the results of the SF analysis for the C9-C10 bond in the same way, this time distinguishing between the left and right cycles. Are the results in line with your expectations?

³ R.F.W. Bader, C. Gatti. A Green's function for the density. *Chem. Phys. Lett.* **287** (1998), 233.

⁴ E. Monza, C. Gatti, L. Lo Presti, E. Ortoleva. Revealing electron delocalization through the source function. *J. Phys. Chem. A* **115** (2011), 12864.

3. IQA/QTAIM energy decomposition⁵

In the "Tutorial" menu, search for "IQA" and then select the link "[Interacting Quantum Atoms \(IQA\)](#)". Two mini-tutorials will teach you the basics of IQA/QTAIM analysis.

4. Analyzing hydrogen bonded complexes

In 2006, Fonseca Guerra and Bickelhaupt showed with state-of-the-art calculations that the hydrogen bonds in DNA Watson–Crick base pairs were not predominantly electrostatic phenomena and that electrostatic interactions and covalent contributions in these hydrogen bonds are in fact of the same order of magnitude⁶. This old debate is still a subject of controversy.

More recently, Galbraith et al.⁷ used a valence bond (VB) theory-based EDA and concluded that the HBs in F–H···FH, F–H···OH₂, F–H···NH₃, HO–H···OH₂, HO–H···NH₃ and H₂N–H···NH₃ are predominantly covalent in nature.

We propose to study the last six hydrogen-bonded systems in DFT, for example by optimizing them at the **B3LYP-D3/TZ2P/NFC** calculation level with a "Good" numerical quality and without taking relativistic effects into account. We will activate the **QTAIM** option in the "Properties" menu (**Full** level) as well as the **IQA** option (the source function may be interesting as well).

To analyze hydrogen bonds, the *local QTAIM properties* at *bond critical points* (BCPs) should first be examined. In practice, we have to locate the two atoms linked by a BCP in the "**Bond Paths**" section of the *QTAIM local properties*. After noting the **number** of the corresponding critical point (CP), you will have to search it in the list of CPs. Finally, the values of the most relevant *local descriptors* to characterize these hydrogen bonds will then be noted (see the corresponding **QTAIM course** to learn more about them).

In a second step, we will note the values of *relevant non-local descriptors* and then we will examine the *hydrogen bond inter-atomic interaction energies* (and their *covalent* and *non-covalent* contributions) in the **IQA** section. Do these results seem to be consistent with Galbraith et al.'s study? Are *dispersion effects* relevant?

Finally, we can study a **DNA base pair**. To do this, select "**GC_WC**" it in the **AMSJobs** file explorer and choose "**Output**" in the **SCM** menu. Or, if you prefer to run the calculation by yourself (approx. 45 minutes), choose the aromatic core at the bottom of the screen and **make just one energy point** from this pre-optimized structure using the level of theory used for the small hydrogen-bonded systems. Are the results in agreement with the findings of Fonseca Guerra and Bickelhaupt (use the same analysis tools)?

⁵ J.M. Guevara-Vela, E. Francisco, T. Rocha-Rinza, Á. Martín Pendás. Interacting quantum atoms—a review. *Molecules* **25** (2020), 4028.

⁶ C. Fonseca Guerra, F. M. Bickelhaupt in "Modern Methods for Theoretical Physical Chemistry of Biopolymers", Chapter 4 (2006), pp. 79-97, Elsevier Ed.

⁷ C. T. Nemes, C. J. Laconsay, J. M. Galbraith. Hydrogen bonding from a valence bond theory perspective: the role of covalency. *Phys. Chem. Chem. Phys.* **20** (2018), 20963.

5. REG/IQA analysis⁸

As before, look for the "REG" tutorial via the graphical interface (GUI) and then select the first [link](#) that appears (*A relative energy gradient (REG) analysis along a PES Scan (1D)*). This tutorial requires both the use of the AMS GUI but also a *command terminal*. Indeed, it is a post-processing of data via a Python script (see the tutorial for more information). This last part is a little more "technical" and requires mastering some basic Linux commands (if needed, refer to "[Working sessions on Linux](#)" document).

Concerning the script part, you will have to "type it" in a terminal/command-line. Here is how you must open the terminal:

- **Windows:** Help → Command-line, type `bash` and hit Enter.
- **MacOS:** Help → Terminal.
- **Linux :** Open a terminal and run: `source /path/to/ams/amsbashrc.sh`

6. Studying a Diels-Alder reaction with an IQA/QTAIM energetic decomposition

In this section, we will use an **IQA/QTAIM energy decomposition** to study the well-known Diels-Alder reaction between cyclopentadiene and maleic anhydride, leading mainly to the *endo* product (Figure 3).

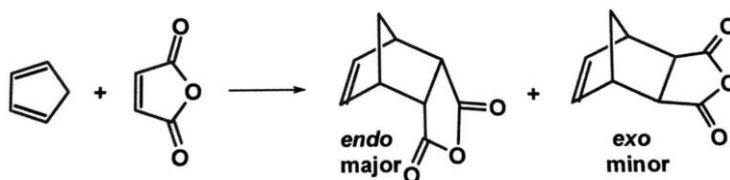


Figure 3: Diels-Alder reaction between cyclopentadiene and maleic anhydride

a) Study of the *endo* transition state

The majority of the *endo* form is generally explained by the role of secondary orbital interactions at the transition state. They are absent during the formation of the *exo* form.

The optimized Cartesian coordinates of the transition state (B3LYP-D3/TZP/NFC/Good) are provided to avoid the somewhat long study of the complete reaction path. This is the "DA_TS_endo.xyz" file. Create a **new AMS input** and import these coordinates via the "**File**" menu then "**Import Coordinates**". Perform a *simple point calculation* at the calculation level indicated above (Relativity: None). **Do not forget to activate the QTAIM (Properties) option as well as IQA.**

Scan the **IQA section** of the output file. Note the values corresponding to the primary interactions (total energy, covalent and non-covalent contributions for each interaction). Next, examine the *secondary* interactions between the other two sp^2 carbons of diene and the carbons of the ketone functions of the dienophile. Compare them to primary interactions. Are they the only *secondary* interactions favoring the *endo product*?

⁸ J.C.R. Thacker, P.L.A. Popelier . The ANANKE relative energy gradient (REG) method to automate IQA analysis over configurational change. *Theor. Chem. Acc.* **136** (2017), 86.

b) REG/IQA study of the reaction path

For this part, it is essential to have made the REG tutorial accessible in the "Tutorial" section of the AMS documentation.

To go further in the analysis, we also provide the results of the "IRC" (Intrinsic Reaction Coordinate) path corresponding to this Diels-Alder reaction. For this purpose, it is advisable (but not mandatory) to open the "DA_IRC_endo.ams" job in **AMSJobs**. The AMS "**Movie**" module (accessible via the **SCM menu**) makes it possible to visualize the entire reaction path for the reaction studied.

Now open a *terminal window* and run the **new ADFREG.py** script (**an updated version of the original REGScan.py script**) using the following command line:

```
$AMSBIN/plams ADFREG.py -v resultsdir=./DA_IRC_endo.results
```

After the script is complete (choose the **default values**), open the results file **DA_IRC_endo.txt** with a text editor. What are the interactions that promote the stability of the product **after** the transition state? Which ones go against the stabilization of this product on this same segment of the path?

It is also possible to examine the other segment, leading from a reaction intermediate to the transition state. What are the interactions responsible for the kinetic barrier? Which ones go against this barrier?

Hands on Quantum Chemical Topology: Working Sessions II

Julien Pilmé and Vanessa Labet

This session will be only performed with Gaussian and TopChem2. We provide most of wfn/wfx or cube files needed for this session. Geometries have been optimized at the B3LYP/6-31G(d, p) or B3LYP/6-31+G(d, p) level of theory.

Essential exercises

I. Nature of the chemical bond with ELF

The objective of this exercise is to determine and analyse the characteristics of specific bonds by using two approaches: visualizing the ELF localization domains and conducting the population analysis of basins.

A. Carbon-Carbon bonding scheme

Choose some molecules in the following list:

- $\text{H}_3\text{C}-\text{CH}_3$; $\text{H}_2\text{C}=\text{CH}_2$; buta-1,3-diène; cubane C_8H_8 ; carbene C_3H_2 ; acetylene $\text{HC}\equiv\text{CH}$; epoxy acetylene C_2O , benzene C_6H_6 , cyclobutadiene C_4H_4
- **The exotic octatetraynyl radical C_8H** (file [c8h.wfx](#)) was detected in 1996 inside the carbon star envelope IRC+10216.⁹
(As C_8H is an open-shell system, add the option **level:roh** to the command-line)
- **The controversial nature of the bonding bridgehead carbon atoms** in propellane C_5H_6 .¹⁰
(to identify all the attractors, add the option **th_cp :0.1** to the command-line)
- **The C_2 controversial quadruple bond.** There are diatomic molecules such as C_2 and CN^+ (cyonium cation), which, by having eight valence electrons, could at least formally express quadruple bonding between the two atoms.^{11,12}

Using the provided wfn/wfx files, run the Topchem2 software to process the ELF analysis ("function:elf" command), and answer the following questions:

- Draw Lewis (resonant) structure(s) of the compound. Identify the ELF attractors, as well as the core and valence basins. With the help of your Lewis scheme, explain the ELF notation of each attractor and basins.

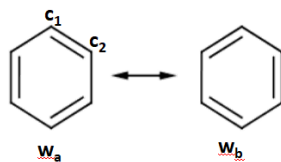
⁹ <https://ui.adsabs.harvard.edu/abs/1996A%26A...309L..27C/abstract>

¹⁰ Polo, V., Andres, J. and Silvi, B. New insights on the bridge carbon-carbon bond in propellanes: A theoretical study based on the analysis of the electron localization function. *J. Comput. Chem.* **28** (2007), 857.
<https://doi.org/10.1002/jcc.20615>

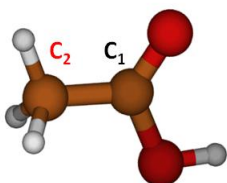
¹¹ <https://www.ch.imperial.ac.uk/rzepa/blog/?p=3065>

¹² Shaik, S., Danovich, D., Wu, W. *et al.* Quadruple bonding in C_2 and analogous eight-valence electron species. *Nature Chem* **4** (2012). 195 <https://doi.org/10.1038/nchem.1263>

- ii. Look at the $V(C, C)$ bonding basins and their corresponding populations: How many electrons are there in each case? What are the populations for the single, double and triple bonds according to the TopChem2 output? Does it agree with what you expected?
- iii. Calculate the weights w_a and w_b of the resonant structures for Benzene using only the $V(C_1, C_2)$ basin population.



- B. Polar A-B covalent systems and inductive effect.** The inductive effect relates to the through-bond transmission by successive polarization of the bonds between a dipolar or charged substituent and the reaction site. A quantitative assessment of the inductive effects of groups (substituents) **should be correlated with the pKa**. For example, we can predict the acidity of a carboxylic acid with the bond polarity index (bpi) of the basin $V(C_1, C_2)$ defined as :
- $$\text{bpi}(C_1, C_2) = \frac{\bar{N}[V(C_1, C_2)|C_1] - \bar{N}[V(C_1, C_2)|C_2]}{\bar{N}[V(C_1, C_2)]}$$



Reminder : the bond polarity index (bpi). The combination of ELF and QTAIM topologies has led Raub and Jansen¹³ to propose a bond polarity index designed for a disynaptic basin $V(X, Y)$: $\text{bpi}(X, Y) = \frac{\bar{N}[V(X, Y)|X] - \bar{N}[V(X, Y)|Y]}{\bar{N}[V(X, Y)]}$, in which $\bar{N}[V(X, Y)]$ is the total population of the $V(X, Y)$ basin, $\bar{N}[V(X, Y)|X]$ and $\bar{N}[V(X, Y)|Y]$ give the respective contributions of X and Y QTAIM basins to $\bar{N}[V(X, Y)]$. By definition, a strongly polarized bond yields an index close to -1 or +1.

➤ topchem2 wfn:file.wfn function:elf proc:4 refine:f vmd contrib:y

Please fill in the following table and draw conclusions about the inductive effect related to the substituent R of the carboxylic acid **RC-COOH**.

Group R	bpi (C ₁ , C ₂)	pKa
CH ₂ CH ₃ (propionic)		4.87
CH ₃ (acetic)		4.76
CH ₂ OH (glycolic)		3.82
CH ₂ NH ₃ ⁺ (protonated glycine)		2.40
COOH (oxalic)		1.25
CF ₃ (trifluoroacetic)		0.25

- C. A more difficult exercise, for a more in-depth analysis.** Classify the following compounds in the appropriate category according to their ELF signatures: covalent, dative, ionic or charge-shift signature.

Some charge-shift (CSB) systems are gathered in the following source:

Charge-Shift Bonding—A Class of Electron-Pair Bonds That Emerges from Valence Bond Theory and Is Supported by the Electron Localization Function Approach. Chem. Eur. J., S. Shaik et al, 2005.

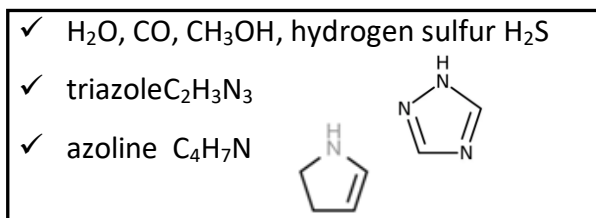
¹³ Raub and Jansen, Th. Chem. Acc. **106**, 2001

If you suspect a dative bond, verify the topological changes (number of basins) occurring along the reaction path when the equilibrium structure is stretched (**the stretched structure was optimized in an open-shell formalism, add the following option to the command-line: level :uhf th_cp : 0.1**)

Molecules	pop. V(A, B)	Stretched structure (if available)		Category
		V(A) or V(B) ?	V(A) and V(B) ?	
H ₃ B-NH ₃				
H ₃ C-CH ₃				
H ₃ B-BH ₃				
HO-OH				
N-F ₃				
S-F ₄				
H ₂ N-NH ₂				

II. Hydrogen bonds

Hydrogen bonds are intermolecular interactions of the A-H...B where B has lone pairs. In this exercise, we try to correlate and predict the intermolecular interaction energies of FH.....B systems by the value of the molecular electrostatic potential (MESP, also reported in the literature as MEP) computed at the location of the (3, 3) critical point, so-called V_{\min} .¹⁴ The interaction energies should be also correlated with the core-valence bifurcation index (CVB). CVB is related to the ELF value computed at the FH.....B (3, -1) critical point.¹⁵ We selected a small panel of molecules for the **B group**:



¹⁴ Gadre, S.R.; Suresh, C.H.; Mohan, N. Electrostatic Potential Topology for Probing Molecular Structure, Bonding and Reactivity. *Molecules* **26**(2021), 3289. <https://doi.org/10.3390/molecules26113289>

¹⁵ Alikhani, M.E., Fuster, F., Silvi, B. What Can Tell the Topological Analysis of ELF on Hydrogen Bonding? *Struct Chem* **16** (2005), 203. <https://doi.org/10.1007/s11224-005-4451-z>

- A. The **intermolecular interaction energy** (E_{int}) FH·····B has been computed at the B3LYP-D3/6-31G(d,p) level of theory for several B molecules (see table below). From the provided **cubes files**, find the location of the MESP (3, +3) critical points (minima) and identify the corresponding V_{min} (**global minimal**) for each B molecule.

➤ topchem2 **input:**file_mep.cube **rho_file:**file_rho.cube **function:**mep **proc:**4 **vmd**

	MESP V_{min}	E_{int} (kcal/mol)
OC		-2.89
CO		-5.27
SH ₂		-5.89
OH ₂		-11.97
Methanol		-12.35
triazole C ₂ H ₃ N ₃		-13.98
azoline C ₄ H ₇ N		-18.29

- B. Display the MESP surfaces mapped onto the electron density isosurface using VMD:

vmd -e file_mep.cube.vmd

What kind of domains do you see?

- C. Use excel in order to analyse the correlation between the interaction energy and V_{min} and compute the parameters of the linear regression. Could you find nice correlations?
- D. Optimize the geometry at the B3LYP-D3/6-31G(d,p) level of theory and generate the wfn files for two new B molecules : NH₃ and formaldehyde (CH₂=O). Alternatively, you can also directly use the provided wfn/wfx files. Compute MESP V_{min} ; can you predict their intermolecular interaction energies with HF? (**reference values**: interaction energies CH₂=O: -9.06 kcal/mol, NH₃: -15.36 kcal/mol)

Reminder: The core-valence bifurcation index (CVB) is an ELF criterion designed to classify the hydrogen bonds¹⁵. It is directly connected the ELF value computed at the (3, -1) critical point which splits $V(\text{H}, \text{F})$ and $V(\text{B})$. It has been shown, in particular, that this latter value is roughly linked to the interaction energy between FH and B.

- E. Calculate the the ELF value computed at the (3, -1) critical point which splits $V(\text{H}, \text{F})$ and $V(\text{B})$ for each FH···B molecule and fill the following Table.

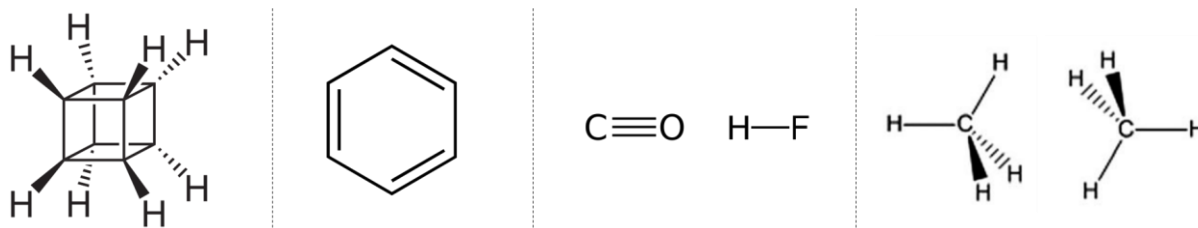
➤ topchem2 **wfn:**file.wfn **function:**cvb **proc:**4

molecule	ELF _(3,-1)	E _{int} (kcal/mol)
FH...OC		-2.89
FH ...CO		-5.27
FH ...H ₂ S		-5.89
FH ... H ₂ O		-11.97
FH ... methanol		-12.35
FH ... triazole C ₂ H ₃ N ₃		-13.98
FH ... azoline C ₄ H ₇ N		-18.29

Visualizing non covalent interactions with the NCI Index

III. Comparing NCI and QTAIM analysis

A. Getting started with simple examples



- ✓ Perform an NCI analysis on the following systems already studied in the previous QTAIM session: **C₆H₆**, **cubane**, **FH...OC**, **CH₄...CH₄**

➤ topchem2 **wfn**:file.wfn **function**:nci **vmd output**:file_nci.pop **proc**:4
 ➤ Visualize the corresponding 3D NCI plots: > vmd -e file.vmd

- ✓ The NCI regions seem to correspond to some QTAIM critical points: which ones? (If needed you can superimpose the QTAIM critical points by loading the file_rho_cprho.xyz file on top of the NCI file in VDM)
- ✓ Display the 2D NCI plot and check that the results are consistent with the QTAIM analysis performed previously (position of the electron density critical points, value of the electron density at these points).

➤ gnuplot file.gnu

What about the sign of λ_2 ? Is it in agreement with the chemical intuition?

Reminder: It is established that there is a correlation between the shape of the NCI region and the type of the QTAIM critical points:

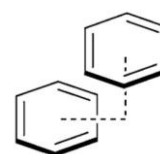
SHAPE OF THE NCI REGION	TYPE OF QTAIM CP
Planar	BCP (closed-shell)
Cylindrical	RCP, BCP (shared interaction)
Spheroidal	CCP, BCP (shared interaction), ACP

- ✓ Is it verified for these systems? Check it for other systems on which you performed a QTAIM analysis in the previous session.

B. More complicated cases

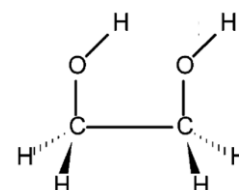
Benzene dimer

- ✓ Follow the same procedure as above for the benzene dimer.
- ✓ What conclusion can you draw from the confrontation of the QTAIM and NCI analysis? How can you explain this?

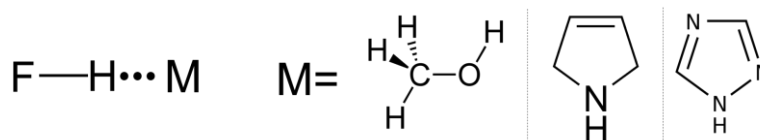


1,2-ethanediol

- ✓ Visualize the optimized geometry of 1,2-ethanediol.
- ✓ What are the H---O distances? Would you say that there is an intramolecular hydrogen bond?
- ✓ Perform a QTAIM analysis. Is there BCP for non covalent interactions?
- ✓ Perform a NCI analysis. Is there a NCI domain?
- ✓ What conclusion can you draw from the confrontation of both QTAIM and NCI analyses?



IV. Systems with multiple non-covalent interactions



A. Perform an NCI analysis for $FH \cdots CH_3OH$.

- ✓ How many peaks do you see on the 2D NCI plot?
- ✓ How many NCI regions do you see on the 3D NCI plot?
- ✓ Try to associate each 2D peak with a NCI domain by modifying parameters in VMD.

How to modify the VMD parameters?

To change the RDG isovalue: In the VMD main window, click on *Graphics*, then *Representations*. In the *Draw Style* tab, you can change the value in the *Isovalue* section.

To change the color scale: In the main window, click on *Graphics*, then *Representations*. In the *Trajectory* tab, you can change the two values in the *Color Scale Data Range* section.

Be careful ! you may want to perform a QTAIM on this system. If you keep the default parameters, you will see in the output file that one critical point is missing (the Poincaré-Hopf relation does not hold!). To recover it you have to authorize the search for a critical point at a smaller minimal distance from atomic attractors. The default minimal value is 0.3 bohr. Decrease it at 0.2 bohr by typing:

```
➤ topchem2 wfn:file.wfn function:rho cp:y atom_dist:0.2 output:file_rho.pop proc:4
```

B. Follow the same procedure for FH...azoline and FH...triazole.

- ✓ In the case of the FH ...azoline, why don't you see the NCI domain associated to the hydrogen bond? *Tips: Confront the 2D NCI plot and the QTAIM analysis.*

Tip : In some cases, you may want to obtain an image of the 2D NCI plot for a smaller range than $[-0.05 ; 0.05]$ for $\text{sign}(\lambda_2) \cdot \rho$. This is possible by using additional options in the command line of Topchem:

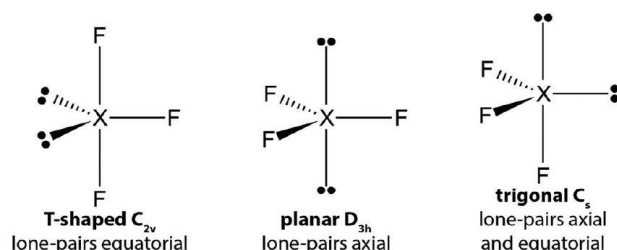
```
➤ topchem2 wfn:file.wfn function:nci vmd output:file_nci.pop proc:4 lambda_min:-0.01  
lambda_max:0.01
```

- ✓ Create images of the 2D NCI plots of FH...CH₃OH, FH...azoline et FH...triazole for which peaks associated to hydrogen bonds do not appear.

Supplementary Exercises

V. ELF and VSEPR

The geometry of trifluoride chlorine ClF_3 can be simply rationalized by a VSEPR-type AX_3E_2 structures. In principle, there exist a one-to-one correspondence between the VSEPR domains and the localization basins of ELF.¹⁶ This exercise serves as an illustration of how the ELF topology can effectively help in the rationalization of both VSEPR and non-VSEPR structures.



- A. Optimize the geometry and generate the wfn files for each structure at the B3LYP/6-31+G(d) level. For the T-shaped structure, you can constrain the axial F-X-F angle to 87° . Alternatively, you can also directly use the provided wfn/wfx files. What structure is expected for the ground state of ClF_3 ? Is it consistent with VSEPR?
- B. Compute and display with VMD the ELF localization domains of the T-shaped C_{2v} and the planar D_{3h} type. Then, characterize the nature of Cl-F interactions for each case.

➤ topchem2 wfn:file.wfn function:elf proc:4 refine:f vmd contrib:y th_cp:0.2

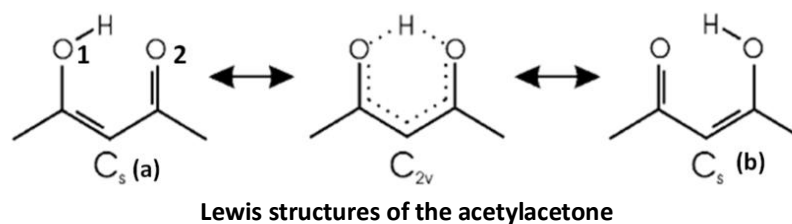
- C. In principle the electronic structure of the ground state is expected to be associated with **five** VSEPR domains around the central atom (3 Cl-F bonds, 2 Cl lone-pairs). Is it consistent with a T-shaped C_{2v} or a D_{3h} structure?

Chemical Reactivity with ELF

VI. Charge-transfer-assisted Hydrogen Bonds.

While the strength of the “classical hydrogen bond” $\text{A-H}\cdots\text{B}$ is typically lower than 15 kcal/mol, strong hydrogen bonds span more than 2 orders of magnitude and can result from charge-transfer-assisted HBs in polarizable systems. For a symmetric $\text{O}\cdots\text{H}\cdots\text{O}$ scheme, the H-atom is equally shared and no clear distinction can then be made between the donor and acceptor. Such a pattern could be evidenced for the enolic acetylacetone which contains a neutral donor and acceptor oxygen atoms connected by a system of conjugated double bonds (C_s structure). However, reinforcement of H-bonding and π -delocalization could lead to a symmetric C_{2v} intramolecular resonance-assisted where for example, the C-C and C=C bonds become equivalent.

¹⁶ Amaouch, M., Sergentu, D.-C., Steinmetz, D., Maurice, R., Galland, N., Pilmé, J. The bonding picture in hypervalent XF_3 (X= Cl, Br, I, At) fluorides revisited with quantum chemical topology.. *J. Comput. Chem.* **38** (2017), 2753– 2762



This exercise aims to elucidate the nature of the intramolecular HB pattern for the enol optimized structure and target to propose a resonant scheme between the asymmetric formal C_s structure and the symmetric resonance-assisted C_{2v} structure.

You can find help from the following sources:

- Srinivasan, R., Feenstra, J. S., Park, S. T., Xu, S., Zewail, A. H. Direct determination of hydrogen-bonded structures in resonant and tautomeric reactions using ultrafast electron diffraction. *JACS* **126** (2004), 2266
- Fuster, F., Silvi, B. Does the topological approach characterize the hydrogen bond? *Theor. Chem. Acc.* **104** (2000), 13

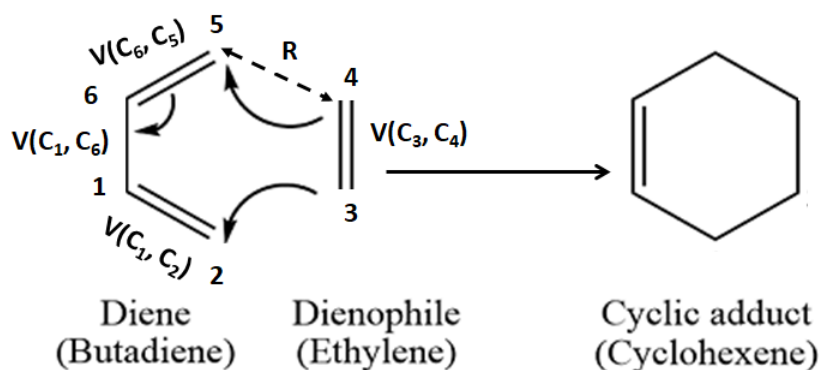
- A. Obtain and visualize the ELF basins for enol the *prototypical* constrained C_{2v} symmetric structure. Identify the ELF attractors and the basins populations with the help of Figure 1. What ELF topology do you see for enol and the C_{2v} structure?
- B. The bond polarity index $bpi(O_1, H)$ can be here related to resonant weights of the Lewis structures between the C_s (a) and C_{2v} structures according to a small linear system :

$$\begin{cases} 0.5 \omega_{C_s} + \omega_{C_{2v}} = |bpi(O_1, H)| \\ \omega_{C_s} + \omega_{C_{2v}} = 1 \end{cases}$$

Explain the construction of the proposed linear system. Solve the system for the optimized enol and comment your results.

VII. Forming & breaking bonds along reaction paths.

The ELF topology can be used for monitoring the evolution of electronic structure of reactants and transition states along the intrinsic reaction coordinate associated with the chemical pathway. The Diels-Alder reaction pathway between ethylene and 1,3-butadiene is here selected as an example.



You can find help from the following paper: *S. Berski, J. Andrés, B. Silvi, and L. R. Domingo* The joint use of catastrophe theory and electron localization function to characterize molecular mechanisms. A density functional study of the diels– alder reaction between ethylene and 1, 3-butadiene. *J. Phys. Chem. A* **107** (2003), 6014-6024

Some illustrative videos of different mechanisms are also available here:
<https://www.lct.jussieu.fr/pagesperso/silvi/recherche.html>

The geometries have been optimized at the B3LYP/6-31G(d,p) level of theory along the reaction path. Some wfn files (**diels_xx.wfn**) have been obtained.

- A. For each file, identify the ELF attractors and basins with help of the Lewis schemes (be careful, the basin numbering can differ from above Lewis Figure).
- B. Look at the $V(C, C)$ and $V(C)$ basins and their corresponding populations. How many are there in each case? To help you, you can fill in the following table (the last column corresponds to the next question):

R (Å)	Total Energy	$V(C_3, C_4)$	$V(C_1, C_6)$	$V(C_3)$	$V(C_4)$	$V(C_2)$	$V(C_5)$	$V(C_2, C_3)$	$V(C_4, C_5)$	BET phase
2.75										
2.50										
2.27										
2.18										
2.10										
2.00										
1.55										

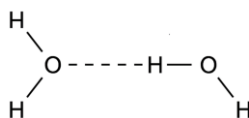
- A. The chemical path can be split into several phases expected by **the Bond Evolution Theory (BET)**. Identify and classify these phases predicted by BET and provide a description of the mechanism in terms of “curly arrows”. Do they align with your first expectations ?

VIII. Visualizing non covalent interactions with the NCI Index

1. Approaching water molecules

Source : Contreras-García, J., Yang, W., Johnson, E. R. Analysis of hydrogen-bond interaction potentials from the electron density: integration of noncovalent interaction regions. *The J. Phys. Chem. A*, **115** (2011), 12983. <https://pubs.acs.org/doi/pdf/10.1021/jp204278k>

Perform an NCI analysis for two water molecules approaching each other.



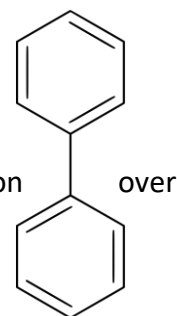
Various intermolecular distances O·····H have been selected: 3.5 Å, 3.0 Å, 2.5 Å, 2.2 Å, 1.9 Å, 1.6 Å.

- ✓ 2D NCI plots: How do the number of peaks and the corresponding $\text{sign}(\lambda_2) \cdot \rho$ values change as the intermolecular distance decreases?
- ✓ 3D NCI plots: How do the spatial extension of the NCI domain and its color(s) change as the intermolecular distance decreases?
- ✓ Try to summarize your observations to describe and analyze the change in the NCI signature as the intermolecular interaction evolves from no interaction to short-range repulsion.

2. Steric clash

Source : Laplaza, R., Boto, R. A., Contreras-García, J., Montero-Campillo, M. M. Steric clash in real space: biphenyl revisited. *Phys. Chem. Chem. Phys.* **22** (2020), 21251. <https://pubs.rsc.org/en/content/articlepdf/2020/cp/d0cp03359f>

In the biphenyl molecule the two phenyl rings are twisted (torsional angle of 44°). The reason generally given for this is a compromise between allowing π -delocalisation the rings (maximized stabilisation in the planar structure) and avoiding steric repulsion between ortho hydrogens (minimized destabilisation when the rings are perpendicular).



A. Planar structure for biphenyl

- ✓ How many QTAIM critical points of each type can you anticipate? Is it consistent with the Poincaré-Hopf theorem?
- ✓ Check your prediction by performing a QTAIM analysis (**biphenyl_0.wfx**).
- ✓ How can you characterize the H·····H interaction? Attractive or repulsive? Support your conclusion by an NCI analysis.
- ✓ Perform an ELF analysis. Compare the shape and volume of the ELF basins around hydrogen atoms.

B. Optimal twisted structure

- ✓ Which modification in the number and type of QTAIM critical point can you anticipate when phenyl rings are twisted with an angle of 44°? (Be careful to the Poincaré-Hopf theorem!)
- ✓ Check your prediction by performing a QTAIM analysis (**biphenyl_opt.wfx**).
- ✓ In this optimal geometry, is the H·····H interaction associated with an NCI domain?
- ✓ How do the shape and volume of the ELF basins around hydrogen atoms change with respect to the planar structure?

C. Varying the torsional angle

Perform QTAIM and NCI analysis of twisted biphenyl structures with varying torsional angles (**all the .wfx files are provided**).

- ✓ For which value of the torsional angle does the QTAIM critical points in the C-H·····C-H region disappear?
- ✓ What about the NCI domain?
- ✓ Reconstruct Fig. 4 of the above reference (see below)

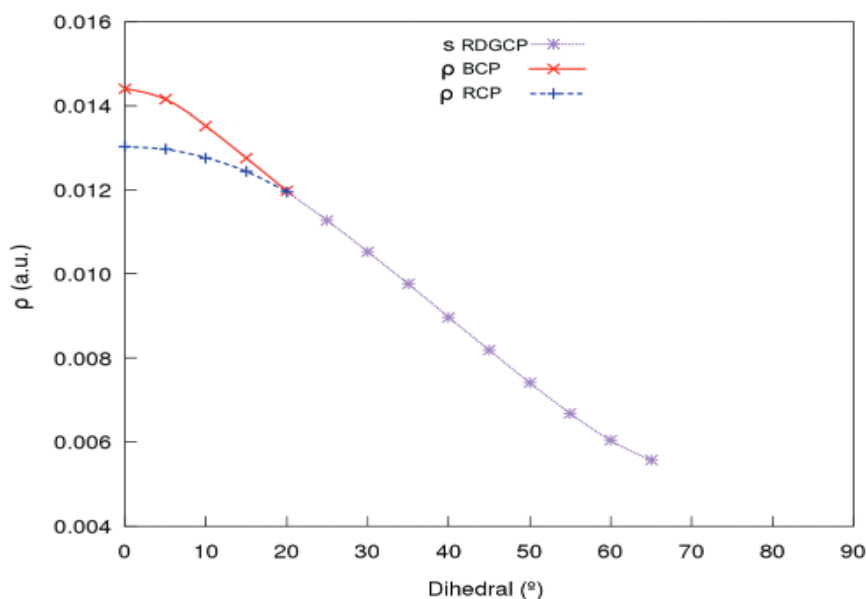


Figure 4: Representation of the density on the BCP (red x marks), RCP (blue cross marks) and RDGCP (reduced density gradient critical point, lilac star marks) between phenyl rings versus the dihedral angle for the biphenyl molecule. Results at the B3LYP/def2-TZVP level of theory. (From Laplaza et al, *Phys. Chem. Chem. Phys.* **22** (2020), 21251)

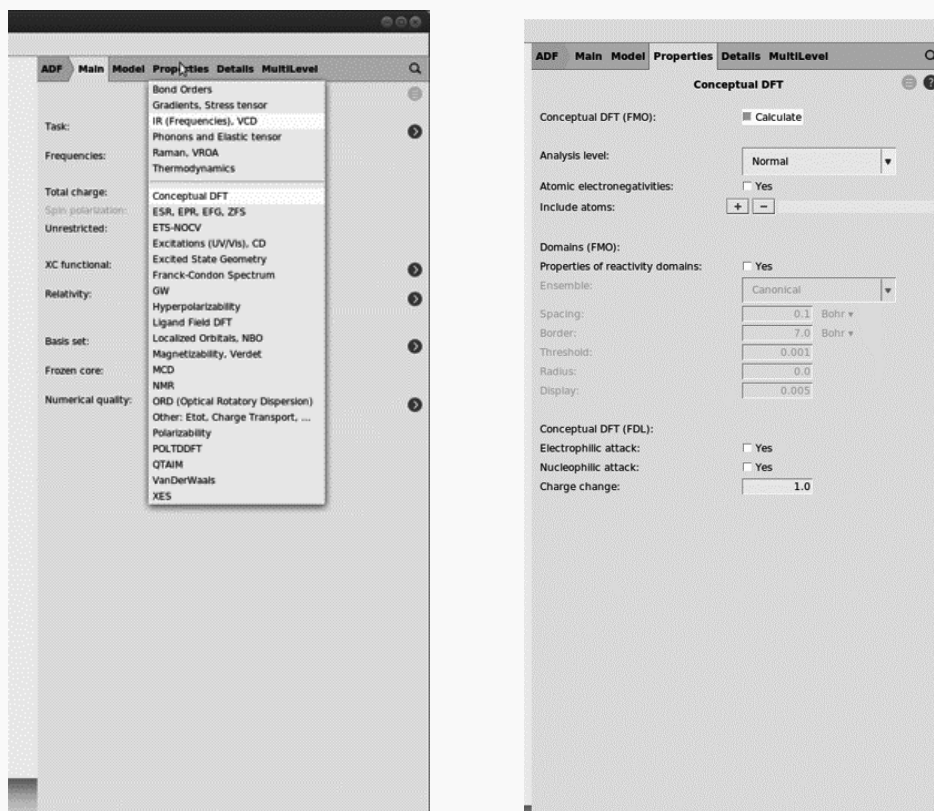
Hands on Conceptual DFT : Working Sessions III

Frédéric Guégan, Vanessa Labet, Christophe Morell

1 Exercises with ADF

Quick start:

In ADF, every calculation options can be given through the graphical interface. Conceptual DFT calculations may be invoked from the input maker, in the dedicated section of the properties panel. The menu is quite self explanatory.



1.1 Global descriptors

1.1.1 Global electrophilicity

1. Optimise the geometry of the HCOX carbonyl derivatives with X = H, CH₃, Cl, OCH₃, at the BLYP/DZP level.
2. Extract the energy of the HOMO and LUMO for all these molecules, and calculate their electrophilicity index ($\omega = \mu^2/2\eta$). Check that the values you computed match those computed by ADF. How do these molecule order with respect to ω ? Does this meet your expectations?

1.1.2 Diels Alder reactions

Diels Alder cycloaddition reactions can usually be divided in two classes, depending on the nature of the substituting groups on the diene and dienophile. In the so-called *normal electronic demand*, the diene can be categorised as nucleophilic, and the reaction starts by a formal electron transfer from the diene to the dienophile.¹ In the case of the *inverse electronic demand*, the electron transfers are reversed: formally, electrons first flow from the dienophile to the diene.

¹Although a back transfer will occur at some point to allow the formation of both C-C bonds.

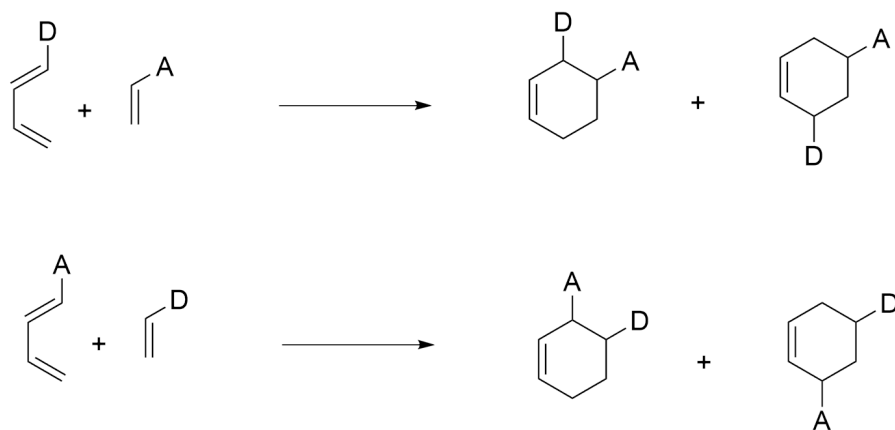


Figure 1: Diels Alder reaction with substitution on the diene and dienophile by electron accepting (A) or donating (D) groups.

We propose in this exercise to show that a simple calculation of chemical potential allows to evaluate the type of electronic demand two Diels-Alder reagents are likely to follow.

1. Optimise the geometries of a butadiene molecule substituted by an electron donating group (for instance 1-aminobutadiene), at the BLYP double-zeta level of theory, then evaluate its chemical potential in the FMO approximation.
2. Run the same calculation in the case of an accepting group (for instance 1-cyanobutadiene).
3. Run similar calculations in the case of an ethylene molecule, with the same kind of substitutions.
4. Do the results match your expectations?

1.2 Local descriptors

1.2.1 Qualitative approaches

1. Optimise the geometry of an ethylene molecule, at a BLYP/double-zeta level of theory. Then, run a single point calculation on the optimised geometry using the same functional, with a triple-zeta + polarisation basis set. Open the AMS View panel. In the "Fields" section, modify the grid quality to medium. Then, still in the "Fields" section, select "Calculated". In the banner that should appear at the bottom of the window, click on the first instance of "Select Field"; click "Orbitals (occupied)", and select the HOMO. Do the same thing in the second "Select Field" menu, and change the "-" option in the middle pane by "*". This computes the HOMO density (FMO approximation of the f^- Fukui function). To represent this field as an isosurface, click on "Add" (top banner) and select "Isosurface with phase". In the "Select Field" menu, click on "Other" and select the Field you just computed. You may change the default isovalue to 0.01 a.u. Does the result meet your expectations?
2. Do the same operations for the f^+ function (LUMO density). Same question.
3. Run another single point calculation, at the same level of theory, but additionally asking for the computation of CDFT descriptors in the finite difference scheme (FDL). Once these calculations are done, open the View menu. Change the grid quality to medium, and add

an isosurface with phase. In the Select Field menu, click on the second "Properties" pane, and select "Fukui minus". A pop-up window should open asking you to provide the data file for the anion single point. Selecting it triggers the computation of f^- in the FDL. Represent the 0.01 isosurface. What differences do you notice?

4. Same question for the f^+ function.
5. Using the same menus, you can also ask for the graphical representation of the Dual descriptor, both in FMO approximation and FDL. Represent both and compare them.
6. The DD is a powerful tool, highlight in a single shot places that are likely to cede away electrons (basis Lewis sites) and those likely to gain (acidic Lewis sites). It noticeably allows to properly characterise ambiphilic species, such as carbenes. To illustrate this, optimise the structure of the linear fluoro zinc dimethylcarbene $\text{FZnC}(\text{CH}_3)_2^+$, at the PW91/double-zeta level of theory. Then conduct a single point calculation with the same functional, using a polarised triple-zeta basis set (and no frozen core). Ask for the calculation of C-DFT descriptors in the FDL limit. Represent the DD in the FDL approximation. Are the results in line with your expectations?

1.2.2 Quantitative approaches

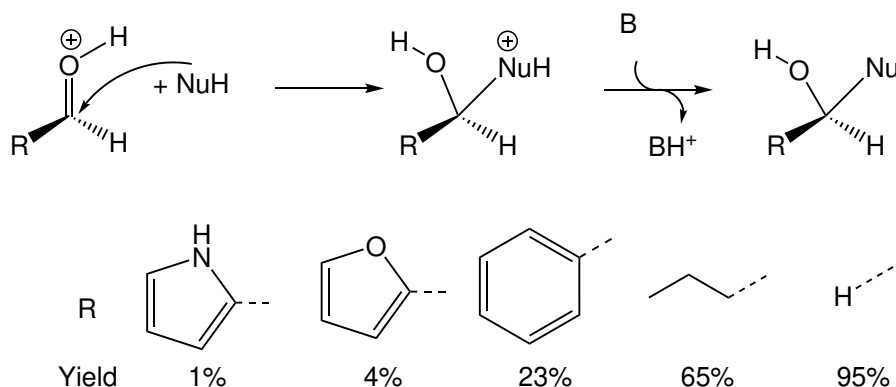


Figure 2: Structures and experimental yields observed for a series of reaction between a model nucleophile and various electrophiles, under acidic catalysis.

1. We provide in Figure 2 the structures and experimental yields observed in a series of experiments involving electrophiles (here aldehydes) reacting with the same nucleophile, under an acidic catalysis. Experimental evidences were brought forward that the first reaction step, that is the nucleophilic addition on the electrophile, is the rate limiting step, hence dictates the reactivity (yields). DFT reaction profile calculations furthermore showed protonation of the carbonyl function occurs when moving from the reagent to the first transition state. Altogether, this leads to propose that activation energies (hence, reactivity) could be linked to the properties of the protonated electrophiles, here likely electrophilicity.

Optimise the structures of all the protonated electrophiles in Figure 2, at a GGA/DZP level of theory. Then, conduct a CDFT analysis in the finite difference limit, using the hybrid B3LYP functional but with a TZP basis set. Extract the global electrophilicity

ω and the local electroaccepting power, computed using the QTAIM partitioning.² Your results should show a decent correlation between the experimental yields and the local electrophilicity on the carbonyl carbon atom, but not with the global electrophilicity.

2. For the curious ones: using the tools we saw in the previous subsection, you can plot the isosurface of local electroaccepting power and compare it to the Dual Descriptor. As you may notice, the results differ; $\Delta\rho_{elec}$ emphasize electrophilic domains, while the DD (by construction) puts electrophilic and nucleophilic domains on the same foot.

1.3 A word of caution

In the previous examples we saw how descriptors can be computed and used to get a more quantitative insight on chemical properties. This is particularly true of the FDL versions. However the need to compute the associated ions can be problematic in some cases:

- the spin multiplicities of the ions can be non obvious, especially if a metal center is present;
- the electronic state of the ions can in fact be degenerate, and single reference methods are thus expected to fail;
- it is not always possible to attach an additional electron to the molecule, so the anion state cannot be computed (or is physically irrelevant).

This last point can be tricky to notice at first: because the basis sets are of finite size, it is sometimes possible to converge a numerical solution of the Kohn-Sham equations, with a non-bound electron. No error will be raised by the computer but the computed quantities will have no sense. We propose to show this on a simple example: methylfuran.

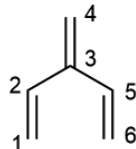
Optimise the geometry of 2-methylfuran, at the BLYP/DZ level. Then ask for a FDL-CDFT calculation at the BLYP/TZP level. In principle no error arises, but if you look at the right hand-side chemical potential μ^+ (which is equal to the electron affinity) you may note it is positive: the anion should spontaneously release an electron. The problem of the electronic state is also obvious by the aspect of the f^+ function: at 0.03 a.u., no surface is produced, and lowering the isovalue to 0.001 a.u. clearly shows the electron is mostly located outside of the molecular volume.

1.4 Non-local descriptors - ADF only

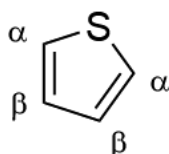
1. Optimise the structure of the butadiene molecule, at a GGA/DZP level of theory. Then run a single point calculation with the same functional and a TZP basis set, asking for a FMO CDFT analysis (Analysis level: full).
2. Run the same calculations for the n-butane molecule.
3. Search for the Linear Response Function (LRF) interatomic matrices in the outputs. Can you understand the differences and similarities in the $\chi(C_i, C_j)$ elements? It can be useful to draw resonance structures (remind the LRF translates the response of electron density at an atom C_i when the potential is changed on another atom C_j).

²Caution: while preparing these exercises we noticed a slight issue with the implementation of the QTAIM condensation in ADF: ordering of atom is done following ADF internal numbering, but the assignation of symbols is bogus. To find the correct numbering, in the View Panel, select Atom Info.

4. Optimise the structure of vinylbutadiene (also called [3]dendralene, see structure below) at a GGA/DZ level of theory, and then compute the LRF matrix at the GGA/TZP level. Dendralenes are molecules known to present so-called "cross-conjugation": they present three π electron systems that are only pair-wise conjugated (no full conjugation). Is this visible in the LRF matrix?



5. By construction, the LRF integral over one set of coordinates is zero. This means that the sum of all LRF matrix elements for a given atoms are zero. This then further implies that the diagonal elements already bear a lot of meaning: they translate how much of electron density a given site is likely to spread away under a perturbation in the external potential on this site. Said otherwise, $\chi(X, X)$ allows to assess the polarisability of atom X, which can be instrumental in reactivity (for any process being usually explained with mesomeric forms, for instance). Here we propose to evaluate this in the case of electrophilic aromatic substitution. Optimise the geometry of thiophene at a GGA/DZP level of theory, and then compute the LRF at GGA/TZP level. Extract the diagonal LRF elements for the carbon atoms. Experimentally, SEAr occurs principally at the α position with respect to sulfur. Are your computed values in line with this result?



2 Exercises with Gaussian/GaussView and TopChem

TopChem can compute several CDFT descriptors from a wavefunction file (.wfn or .wfx) produced by Gaussian. To produce the wavefunction file : (1) add `output=wfx` in the route section of the Gaussian input file, (2) don't forget to give a **name for your .wfx file** after the blank line following the molecule specifications.

By default, only occupied orbitals are printed out in the wavefunction file. To include some virtual orbitals, add `iop(99/18=n)` in the route section (n being the number of virtual orbitals included in the .wfx file. For example, you can choose n=1 to include only the LUMO).

Quick start command line :

- To compute global descriptors only :

```
topchem2 wfx:filename.wfx function:fwv output:filename.top proc:2
```

- To visualize local descriptors :

```
topchem2 wfx:filename.wfx function:fp output:filename_fp.top proc:2  
for the  $f^+$  Fukui function
```

```
topchem2 wfx:filename.wfx function:fm output:filename_fm.top proc:2  
for the  $f^-$  Fukui function
```

```
topchem2 wfx:filename.wfx function:dld output:filename_dd.top proc:2  
vmd for the  $\Delta f$  dual descriptor, and then vmd -e file.vmd to visualize the dual  
descriptor with VMD
```

- To condense local descriptors on atoms using the QTAIM partition :

```
topchem2 wfx:filename.wfx function:rho fukui:XX proc:2 with XX=fp, fm  
or dd depending on the function you want to condense (XX=fp for  $f^+$ , XX=fm for  
 $f^-$ , XX=dd for  $\Delta f$ .)
```

2.1 Global descriptors

2.1.1 Global electrophilicity

1. Optimise the geometry of the HCOX carbonyl derivatives with X = H, CH₃, Cl, OCH₃, at the BLYP/6-31G level.
2. Extract the energy of the HOMO and LUMO for all these molecules, and calculate their electrophilicity index ($\omega = \mu^2/2\eta$). Check that the values you computed match those computed by TopChem. How do these molecule order with respect to ω ? Does this meet your expectations?

2.1.2 Diels Alder reactions

Diels Alder cycloaddition reactions can usually be divided in two classes, depending on the nature of the substituting groups on the diene and dienophile. In the so-called *normal electronic demand*, the diene can be categorised as nucleophilic, and the reaction starts by a formal electron transfer from the diene to the dienophile.³ In the case of the *inverse electronic demand*, the electron transfers are reversed: formally, electrons first flow from the dienophile to the diene.

³Although a back transfer will occur at some point to allow the formation of both C-C bonds.

We propose in this exercise to show that a simple calculation of chemical potential allows to evaluate the type of electronic demand two Diels-Alder reagents are likely to follow.

1. Optimise the geometries of a butadiene molecule substituted by an electron donating group (for instance 1-aminobutadiene), at the BLYP 6-31G level of theory, check that the frontier orbital are the expected π orbitals, then evaluate its chemical potential in the FMO approximation.
2. Run the same calculation in the case of an accepting group (for instance 1-cyanobutadiene).
3. Run similar calculations in the case of an ethylene molecule, with the same kind of substitutions.
4. Do the results match your expectations?

2.2 Local descriptors

2.2.1 Qualitative approaches

Optimise the geometry of ethylene at the BLYP/6-31+G(d) level. Then, conduct a single point calculation using the same functional with 6-311G(d), asking for a chk file and for a wfx file.

The dual descriptor - FMO approximation

Using Gaussian only

[Command line version ; see below for the graphical approach using GaussView]

1. Convert the chk file to a formatted fchk one, using the following command:

```
formchk filename.chk filename.fchk
```

2. Then, using the `cubegen` utility, build a cube file for the HOMO and LUMO, using the following commands:

```
cubegen 1 MO=LUMO filename.fchk filenameLU.cub -2 h
cubegen 1 MO=HOMO filename.fchk filenameHO.cub -1 h filenameLU.cub
```

(refer to the online manual for the explication of each keyword, <http://gaussian.com/cubegen/>).

3. Once you obtain both files, use the `cubman` utility to calculate the electron density associated with both orbitals, that is, the square of both HOMO and LUMO: in the terminal, type `cubman`, then type 'SQ' (square of the cube). A filename will be asked. Once provided, answer 'y' (formatted cube file). A second filename will be asked (for the output). We suggest you to simply add SQ at the original filename. Then answer 'y' again (output a formatted file). After a while, the calculation is complete, and you can proceed to the second MO.

- Then, use `cubman` to calculate the difference between the LUMO and HOMO electron densities (FMO approximation of the DD): type `cubman`, then 'SU'. Provide the filename for the LUMO density, 'y' (formatted), the filename for the HOMO density, 'y', the filename for the output, 'y'.

[Graphical approach using GaussView]

The previous operations can alternatively be piloted graphically by GaussView.

- Open the chk file⁴,
- Go to Results, Surfaces/Contours.
- In the pop-up window, click on "Cube Actions", and select New Cube. This opens a new window.
- Change "HOMO" to "HOMO,LUMO" so that both are computed. When the fields are ready, two cubes appear in the first window.
- Click again on "Cube Actions", "New Cube". Change the type to "Square a Cube", and select the first MO. Clicking on OK will produce the associated MO density. Do this for both MOs.
- Plot the obtained Fukui functions (isosurface at 0.01 a.u.). Do the results meet your expectations?
- Compute the difference between the LUMO and HOMO densities, and plot the 0.001 a.u. isosurface. Are the results in agreement with the previous ones?

Using Topchem

Use Topchem to compute the f^+ , f^- and Δf function, in the FMO approximation, from the .wfx file created by Gaussian for the ethylene molecule. Does this match the previous calculations ?

The dual descriptor - Finite differences approximation

- Perform two single point calculations using the optimised geometry, with the addition and subtraction of one electron (check the spin multiplicity!). Save the chk file in each case.
- Using either `cubegen` or GaussView, build the cube files for the electron densities of the anionic, cationic and neutral forms. Then, either use `cubman` or GaussView to compute the DD in the Finite difference approximation:

$$\Delta f(\mathbf{r}) = \rho_{N+1}(\mathbf{r}) + \rho_{N-1}(\mathbf{r}) - 2\rho_N(\mathbf{r})$$

Represent it as an isosurface. Does this match the previous calculations?

Optimise the structure of the linear fluoro dimethylcarbene zinc complex $\text{FZnC}(\text{CH}_3)_2^+$, at the PW91PW91/6-31G(d) level of theory. Then run three single point calculations at the PW91PW91/6-311G(d) level of theory, for the neutral, anionic and cationic forms. Compute the DD in the FDL, and represents it as a 0.001 a.u. isosurface. Do the result comply with your expectations?

⁴Note this only works if the chk file was produced on a computer with the same architecture; in the general case it is advised to first format it into a fchk file.

2.2.2 Diels Alder and charge transfer - Gaussian only

In 2013, an excited state expansion of the dual descriptor was proposed (PCCP 2013, 15, 14465-14475). In a nutshell, the idea is to develop the DD as a sum of electron density reorganisation under excitation,

$$\Delta f(\mathbf{r}) = \sum_i \alpha_i (\rho_i(\mathbf{r}) - \rho_0(\mathbf{r}))$$

with i the index of the excited state (0 meaning ground state). Although the analytical formula for the α weights is unknown, it is assumed they decrease with the excited state energy: the higher the ES, the less likely it is to contribute to the reactivity in the ground state.

In this exercise, we propose to revisit a concept that was then developed in a further publication (PCCP 2015, 17, 9359-9368): use one of the first electron density reorganisation, also coined first state-specific dual descriptors, to probe reactivity in a pre-reacting complex.

- (a) Compute the first 10 excited states⁵ for the following two geometries (xyz files should also be present on your computers), which correspond to the first geometry in an IRC file for the [4+2] Diels Alder reaction between cyanobutadiene and aminoethylene on one hand, cyanoethylene and aminobutadiene on the other hand. To do this, use the following keywords:

```
# M062X 6-31G(d,p) td=(nstates=10,root=1) density=current
```

and ask for a chk file. The option `root=1`, in addition to `density=current`, will allow to compute the 1st excited state electron density.

- (b) Format the checkpoint file with `formchk`, then build two cube files per fchk file, one for the excited state density,

```
cubegen 1 Density=CI [filename].fchk [filename]CI.cub -2 h
```

the other for the ground state density,

```
cubegen 1 Density=SCF [filename].fchk [filename]SCF.cub -1 h [filename]CI.cub
```

Note here that it is advised to read the grid details in the excited state density file: excited state densities usually spread further away from the molecule than the SCF density, and cubegen default grid for both files may be different.

- (c) Build a cube file corresponding to the first SSDD using cubman (subtract), for each molecule. Visualise the 0.004 a.u. isosurfaces.
- (d) Describe the electron density movement in both case: which reagent gives away electron density? Which gains? Does it match your expectations?

The first intermolecular SSDD indeed allows to map the easiest electron transfer between two reagents.

⁵There are cases for which the first excited state is not chemically relevant - for instance, involving only one reagent -, so in general it is better to consider a handful of excitations. If the electron density reorganisation appears uninteresting, then study the decomposition of the excited states wavefunctions over MOs to identify the adequate state to study. Then, re-run the calculation by modifying the `root` keyword.

Geometries :

Aminoethylene + cyanobutadiene

C	-1.42287300	-1.61016700	0.27043100
C	-0.31947000	-1.93053600	0.95540300
C	-1.84375800	1.49752300	0.83716700
H	-2.37827000	-1.51152200	0.78130600
C	1.02082600	0.81011200	0.32205900
H	0.64063600	-2.05649700	0.46319400
H	-0.37266200	-2.13683100	2.01663500
C	-1.18148700	1.75849600	-0.29485400
H	-1.42748200	0.85010400	1.60295000
H	-2.83014800	1.91112600	1.01656200
C	0.15674100	1.25003800	-0.60661000
H	0.78825600	0.85461400	1.38083600
H	-1.65306000	2.37153700	-1.05982300
H	0.45626000	1.23116900	-1.65199200
C	2.28873400	0.23788400	-0.01770000
N	3.31078700	-0.24750800	-0.26617600
N	-1.50853000	-1.43828400	-1.10427300
H	-0.61258800	-1.34232300	-1.56579300
H	-2.15883600	-0.72141400	-1.39622700

Cyanoethylene + aminobutadiene

C	1.10294700	-2.03910500	-0.15156300
C	-0.13604700	-1.94194300	-0.63410100
C	2.56520500	0.79472600	-0.32921500
H	1.92086100	-2.35843100	-0.78720100
H	1.33277400	-1.79065200	0.87763800
C	-0.37301700	1.56384500	-0.47066900
H	-0.37231300	-2.17487300	-1.66718300
C	1.77295100	1.16516700	0.68628900
H	2.15121900	0.49518900	-1.28838800
H	3.64535500	0.79677800	-0.23423800
C	0.31850100	1.26681100	0.64719900
H	0.16636000	1.81902400	-1.38108000
H	2.24157700	1.40092000	1.64158800
H	-0.22936200	1.10539200	1.57311700
C	-1.24201600	-1.52443300	0.18221400
N	-2.15522400	-1.19184900	0.81255800
N	-1.74406400	1.65920800	-0.56195100
H	-2.26552000	1.11004100	0.11040600
H	-2.13374300	1.62415300	-1.49024000

2.2.3 Quantitative analysis

- (a) We provide in Figure 2 the structures and experimental yields observed in a series of experiments involving electrophiles (here aldehydes) reacting with the same nucleophile, under an acidic catalysis. Experimental evidences were brought forward

that the first reaction step, that is the nucleophilic addition on the electrophile, is the rate limiting step, hence dictates the reactivity (yields). DFT reaction profile calculations furthermore showed protonation of the carbonyl function occurs when moving from the reagent to the first transition state. Altogether, this leads to propose that activation energies (hence, reactivity) could be linked to the properties of the protonated electrophiles, here likely electrophilicity.

Optimise the structures of all the protonated electrophiles in Figure 2, at BLYP/6-31G(d) level of theory. Then, conduct a CDFT analysis in the finite difference limit, using the same functional but with the 6-311G(d) basis set. For these calculations, ask for the computation of Hirshfeld atomic charges. Extract the SCF energies and the Hirshfeld atomic charges from all output files. They can be found after "Hirshfeld charges" (Q-H column). The electroaccepting power can be computed for each atom X using

$$\Delta\rho_{elec}(X) = -\left(\frac{\mu}{\eta}\right) f^+(X) + \frac{1}{2}\left(\frac{\mu}{\eta}\right)^2 (f^+(X) - f^-(X)), \quad (1)$$

with

$$\mu = \frac{1}{2}(E(N+1) - E(N-1)), \quad \eta = E(N+1) + E(N-1) - 2E(N) \quad (2)$$

$$f^+(X) = q_N(X) - q_{N+1}(X), \quad f^-(X) = q_{N-1}(X) - q_N(X) \quad (3)$$

Your results should show a decent correlation between the experimental yields and the local electrophilicity on the carbonyl carbon atom, but not with the global electrophilicity.

- (b) For the curious ones: using the tools we saw in the previous subsection, you can plot the isosurface of local electroaccepting power and compare it to the Dual Descriptor (if you asked for chk files). As you may notice, the results differ; $\Delta\rho_{elec}$ emphasize electrophilic domains, while the DD (by construction) puts electrophilic and nucleophilic domains on the same foot.

Practical Work with TopChem2: Summary of the main commands

TopChem2 is a comprehensive, standalone program that offers advanced quantum chemical topology studies of various properties, including the Electron Localization Function (ELF), the electron density (QTAIM), the Molecular ElectroStatic Potential (MESP), the Non Covalent Interactions Index (NCI). It can also compute some reactivity descriptors derived from Conceptual DFT. The input files can be either wfn/wfx Gaussian wavefunction files or cube volumetric data files (.cube files). It works in command-line.

See details, download and video tutorials on

<http://www.lct.jussieu.fr/pagesperso/pilme/topchempage.html>

The command-line of TopChem2 requires different arguments, some of which are mandatory while others are optional.

Mandatory Arguments:

✓ *input files:*

wfn/wfx: [string] input wfn/wfx gaussian file

input: [string] input volumetric cube data file

✓ *function*: [string]

rho (electron density)

elf (electron localization function)

cvb (core-valence bifurcation index)

mep (molecular electrostatic potential)

nci (non covalent interactions index)

fwv (global descriptors)/ *dld* (dual descriptor)/ *fm* (fukui f)/ *fp* (fukui f⁺)

Some optional arguments:

- *output*: [string] main results are provided in this output [string]
- *cp*: [y/n/o] y(enabled)/n(disabled) the search of critical points. "o" enables the search of critical points but both basin analysis and populations will be disabled.
- *th_cp*: [real] Below this threshold, all found critical points are dismissed.
- *atom_dist*: [real] Enforced minimal distance between non atomic critical points and atoms. Default: 0.3 bohr
- *contrib*: [y/n] QTAIM contributions to basin populations
- *level*: [rhf/uhf/roh/nat] level of theory of the wfn file. Default: rhf.
- *pop*: [cov] Compute variance and covariance analysis. For QTAIM, gives both localization and delocalization indexes.

Working Session I

Command-line for performing a QTAIM analysis.

✓ **To compute local descriptors, atomic charges and visualize critical points**

```
> topchem2 wfn:your_file.wfn (wfx:your_file.wfx) function:rho cp:y proc:4 refine:f vmd  
output:your_file.pop
```

✓ **To compute QTAIM delocalization/localization Indices**

```
> topchem2 wfn:your_file.wfn (wfx:your_file.wfx) function:rho cp:y proc:4 refine:f vmd  
output:your_file.pop pop:cov
```

The optional argument **atom_dist:0.2** can be used to enforce a minimal of 0.2 bohr distance between non atomic critical points and atoms. Your results are gathered in **your_file.pop**.

The **your_file_cprho.xyz** is also produced. It contains the Cartesian coordinates xyz (Å) of critical points and their numbering.

molden your_file_rho_cprho.xyz

You can also obtain a direct visualisation of the shape of the electron density (0.1 e.bohr^{-3}) and locations of critical points from the vmd file :

```
vmd -e your_file_rho.vmd  
and activate Mouse/Label/atoms
```

Working Session II

Command-line for performing a ELF analysis.

✓ **To compute ELF populations and visualize**

```
> topchem2 wfn:your_file.wfn (wfx:your_file.wfx) function:elf proc:4 refine:f contrib:y vmd  
output:your_file.pop
```

contrib: y # Enable the calculation of QTAIM contributions to ELF basins. Compute the bond polarity index (bpi).

✓ **ELF core-valence bifurcation index (CVB) analysis**

```
> topchem2 wfn:your_file.wfn (wfx: your_file.wfx) function:cvb proc:4 output:your_file.pop
```

Command-line for performing NCI 3D and 2D grids

```
> topchem2 wfn:your_file.wfn (wfx: your_file.wfx) function:nci proc:4 vmd output:your_file.pop  
you can change the visualization scale in the command-line with :  
lambda_min:[real] and lambda_max:[real]
```

Command-line for performing a MEP analysis

- ✓ **To compute its (3, +3) critical points and visualize the MESP onto the electron density isosurface from wfn**

```
> topchem2 wfn:your_file.wfn (wfx: your_file.wfx) function:mep proc:4 vmd output:your_file.pop
```

- ✓ **To compute its (3, +3) critical points and visualize the MESP onto the electron density isosurface from cube files**

```
> topchem2 input:your_file_mep.cube rho_file: your_file_rho.cube function:mep proc:4 vmd output:  
your_file.pop
```

All your numerical results are gathered in the **file.pop**. The **file_cp.xyz** files are also provided. It contains the Cartesian coordinates (Å) of critical points.

View 3D ELF, MEP or NCI domains with vmd :

```
> vmd -e file.vmd
```

How to modify the VMD parameters for MEP and NCI domains

For MEP, To change the density isovalue: In the VMD main window, click on *Graphics*, then *Representations*. In the *Draw Style* tab, you can change the value in the **Isovalue** section.

For NCI, To change the RDG isovalue: In the VMD main window, click on *Graphics*, then *Representations*. In the *Draw Style* tab, you can change the value in the **Isovalue** section.

For both, to change the color scale: In the main window, click on *Graphics*, then *Representations*. In the *Trajectory* tab, you can change the two values in the **Color Scale Data Range** section.

View 2D NCI peaks with gnuplot

```
> gnuplot file.gnu
```

Working Session III

By default, only occupied orbitals are printed out in the wavefunction file. To include some virtual orbitals, add `iop(99/18=n)` in the route section (n being the number of virtual orbitals included in the `your_file.wfx` (`your_file.wfn`) file. For example, you can choose `n=1` to include only the LUMO.

✓ To compute the global descriptors only

```
> topchem2 wfn:your_file.wfn (wfx: your_file.wfx) function:fwv proc:4 output:your_file.pop
```

✓ To visualize the local CDFT descriptors

- Dual Descriptor

```
> topchem2 wfn:your_file.wfn (wfx:your_file.wfx) function:dld proc:4 vmd  
output:your_file.pop
```

- f⁺ Fukui function

```
> topchem2 wfn:your_file.wfn (wfx: your_file.wfx) function:fp proc:4 vmd  
output:your_file.pop
```

- f Fukui function

```
> topchem2 wfn:your_file.wfn (wfx: your_file.wfx) function:fm proc:4 vmd  
output:your_file.pop
```

✓ To condense local descriptors on atoms using the QTAIM partition

```
> topchem2 wfn:your_file.wfn (wfx: your_file.wfx) function:rho cp:y proc:4 refine:f  
output:your_file.pop fukui:XX
```

XX depending on the function you want to condense : **XX=fp** for Fukui f⁺, **XX=fm** for Fukui f⁻, **XX=dd** for Dual Descriptor.
