A theoretical approach to the study of weak interactions in chemistry, biology and materials science

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"BIO-COMP-CHEM" Training School – September 2018 – Bansko (Bulgaria)

NONCOVALENT INTERACTIONS

Noncovalent interactions (NCIs) do not involve the sharing of electrons, but rather involve electrostatics, charge transfer, vdW forces between molecules…

Dykstra and Lisy, *Journal of Molecular Structure (Theochem)* 500 (2000) 375–390

NONCOVALENT INTERACTIONS

Key role in many chemical and biological processes

- Biomolecular function and activity
- Molecular reactivity
- Bulk properties of gases
- Crystal structure
- Macroscopic properties of condensed phases
- Nonlinear optical response of solid state polymers
- Reaction dynamics in liquids
- Solvation phenomena
- Surface and electrode chemistry
- Tribology and adherence of materials

Dykstra and Lisy, *Journal of Molecular Structure (Theochem)* 500 (2000) 375–390

NONCOVALENT INTERACTIONS

	Strength in kcal/mol
<u>Electrostatics</u>	
- Ionic (NaCl)	250 – 4000
- Hydrogen bonding (H_2O)	5 – 40
- Hole interactions (halogen, chalcogen, etc.)	1 – 20
<u>Van der Waals</u>	
- Debye forces (permanent- induced dipoles)	1 – 10
- London dispersion (alkanes)	
<u>π-effects</u>	
- π/π stacking (graphite)	1 – 20
- Cation and anion-π (Cl^-—C_6F_6)	

Computational tools

Electronic structure calculations

Post-HF CCSD(T) "Gold Standard"

MP2 Good but… tends to overestimate NCIs

DFT Periodic vdW description of surface

Gas phase B3LYP-D3 for dihydrogen bonds

LC-ωPBE-D3BJ for metallophilic interactions

M06-2X for halogen bonding

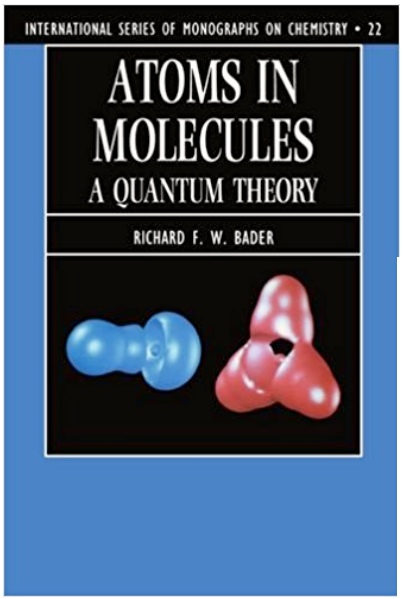
Basis sets Triple-ξ mandatory, polarization and diffuse recommended

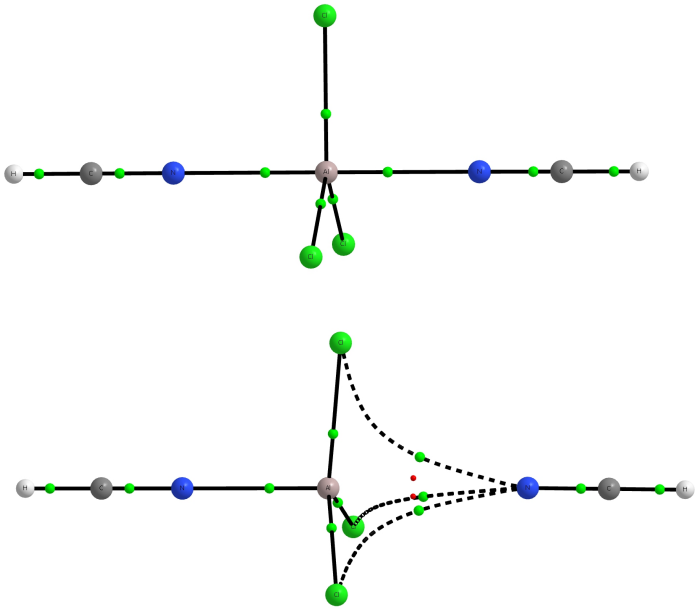
Benchmarking is usually the safest option!

Computational tools

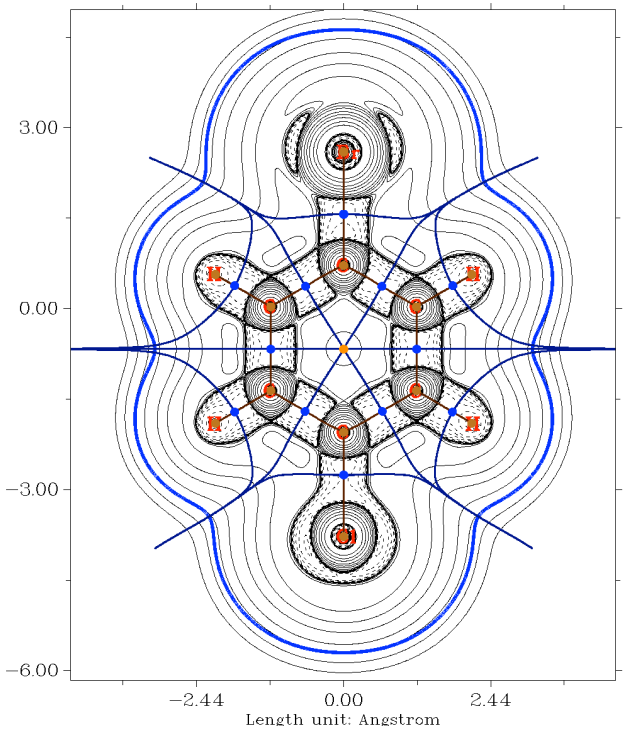
Quantum Theory of Atoms in Molecules – QTAIM (AIMAll)

Analyzes the topology of the electron density





$HCN\cdots AlCl_3\cdots NCH$

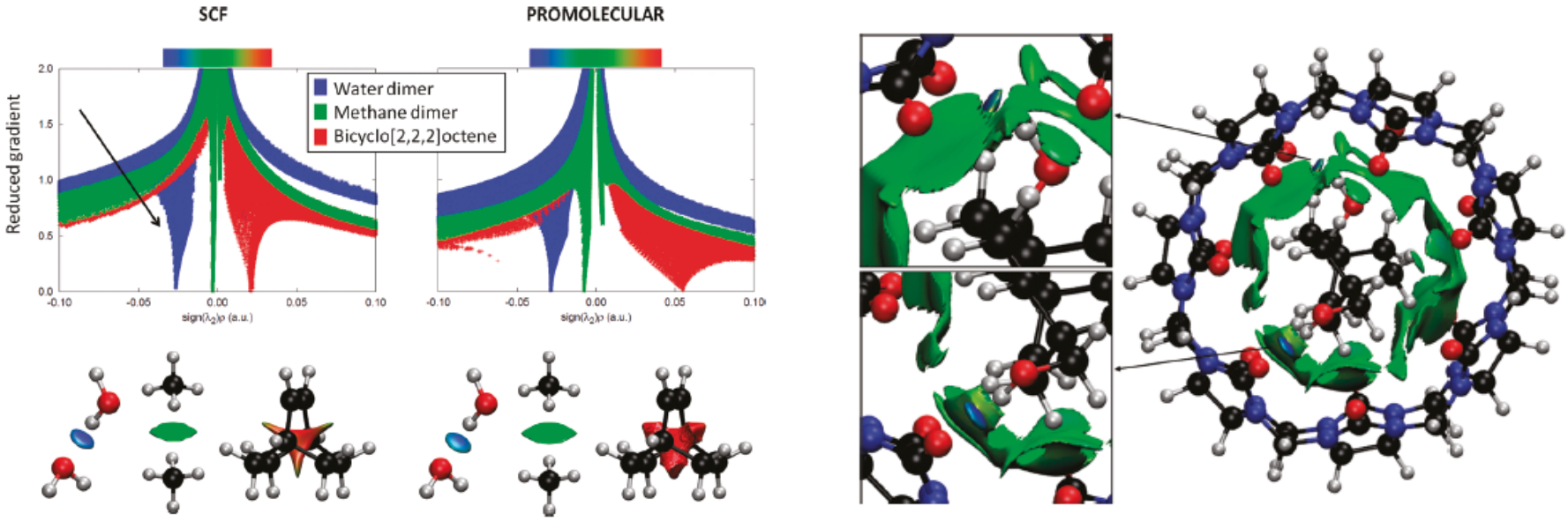


CH_4BrCl

R. Bader, *Atoms in Molecules: A Quantum Theory*. USA: Oxford University Press. (1994)

Computational tools

NCI index calculations (NCIPLOT)



Identification of intermolecular interactions
based on the electron density and its derivatives

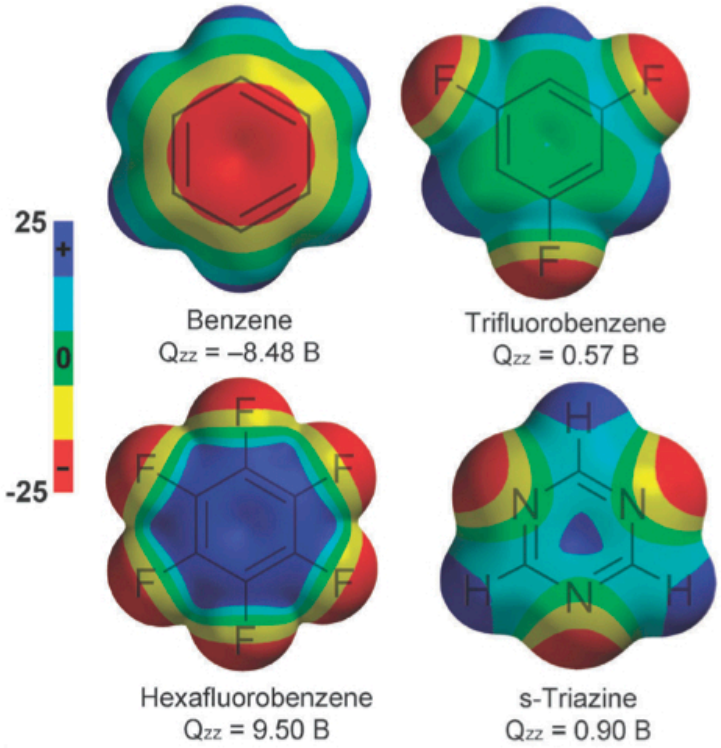
J. Am. Chem. Soc. 2010, **132**, 6498-6506; *J. Chem. Theory Comput*. 2011, **7**, 625-632

Computational tools

Molecular Electrostatic Potential– MEP (GaussView)

· Assesses the molecules reactivity towards positively or negatively charged reactants

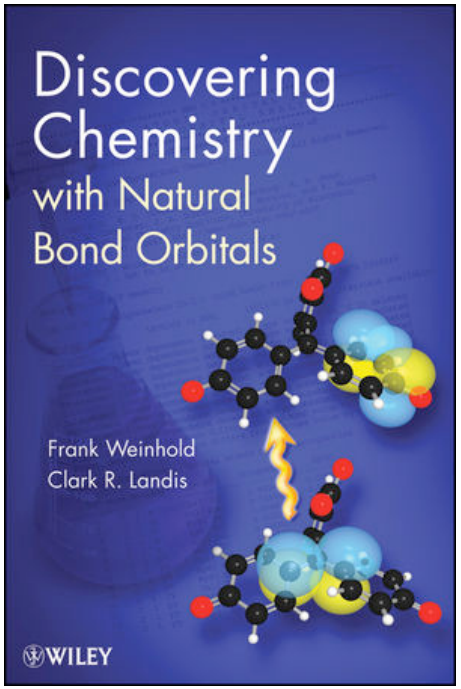
· Mapped onto a surface reflecting the molecules boundaries

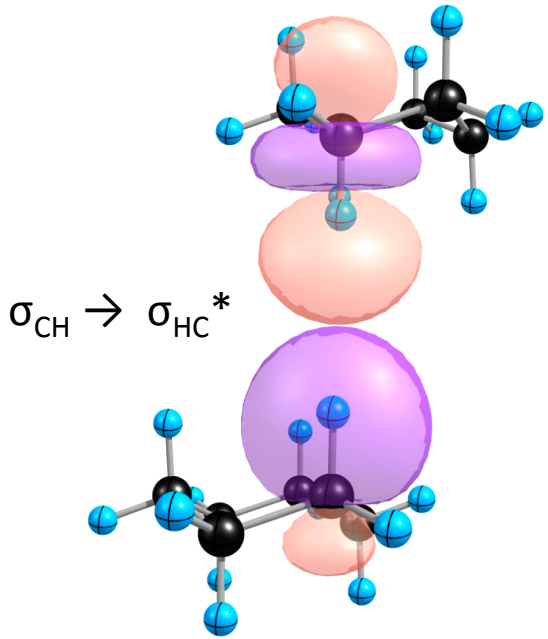


Computational tools

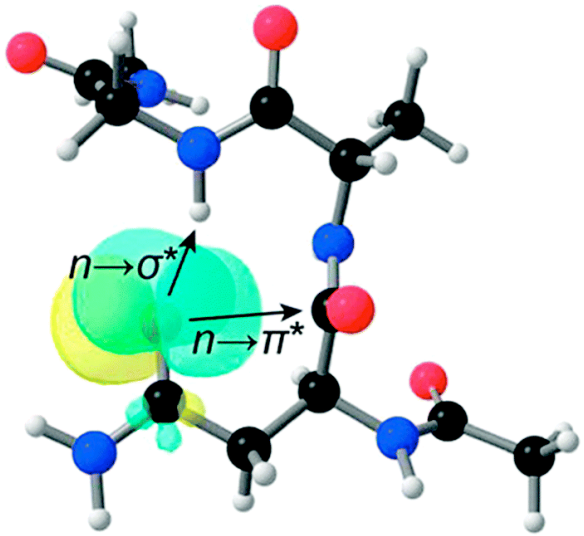
Natural Bond Orbitals – NBO Analysis (NBO6, Gaussian)

Atomic Orbital → NAO → NHO → **NBO** → NLMO → Molecular orbital





Intermolecular



Intramolecular

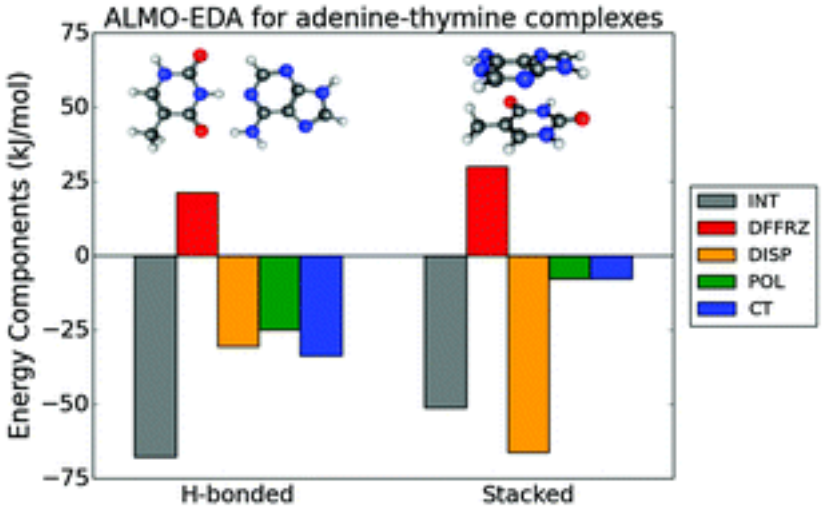
Computational tools

Energy Decomposition Analysis – EDA (Q-Chem, GAMESS, ADF, etc.)

· There are in fact many EDAs… ALMO-EDA, EDA-NOCV, SAPT(DFT)…

· Decomposes total interaction energy in a supermolecule into several energetic terms that are chemically meaningful

$$\Delta E_{int} = \Delta E_{Pauli} + \Delta E_{elect} + \Delta E_{disp} + \Delta E_{pol} + \Delta E_{CT}$$



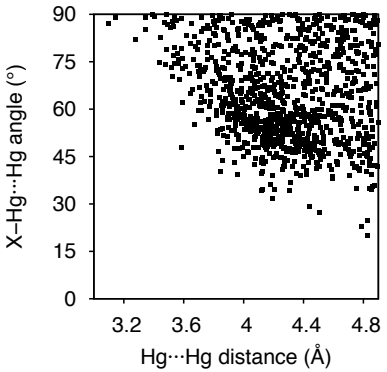
Head-Gordon et al. *Phys. Chem. Chem. Phys*. 2016, **18**, 23067

Computational tools

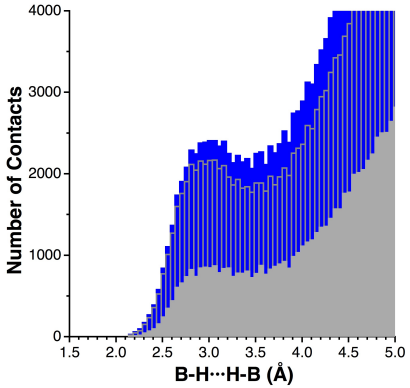
Structural database mining

Access to millions of crystal structures: CSD, PDB, ICSD, Mogadoc…

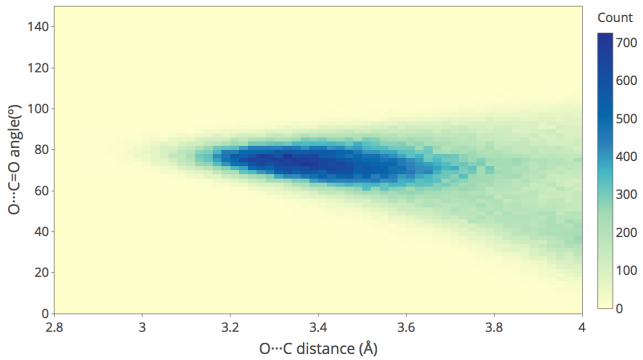
Angular dependence



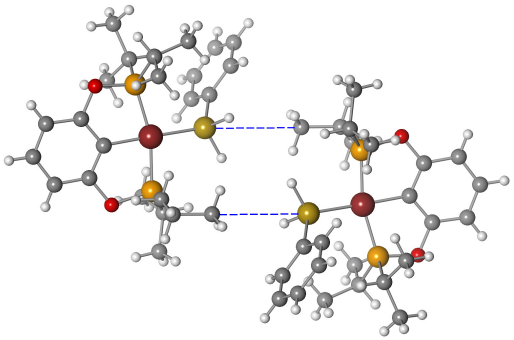
Occurrence



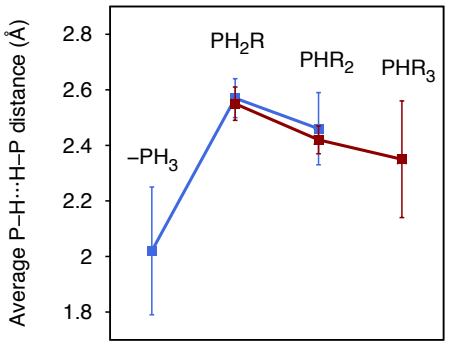
2D histrogram (Heat maps)



Specific examples



General trends



The Cambridge Structural Database

What is the CSD?

The CSD is a molecular repository operated by the CCDC

Initially (1965) part of the University of Cambridge ,
today an independent non-profit organisation.

The Cambridge Structural Database

What's in the CSD?

The CSD contains X-ray and neutron diffraction analyses of carbon-containing molecules up to 1000 atoms including:

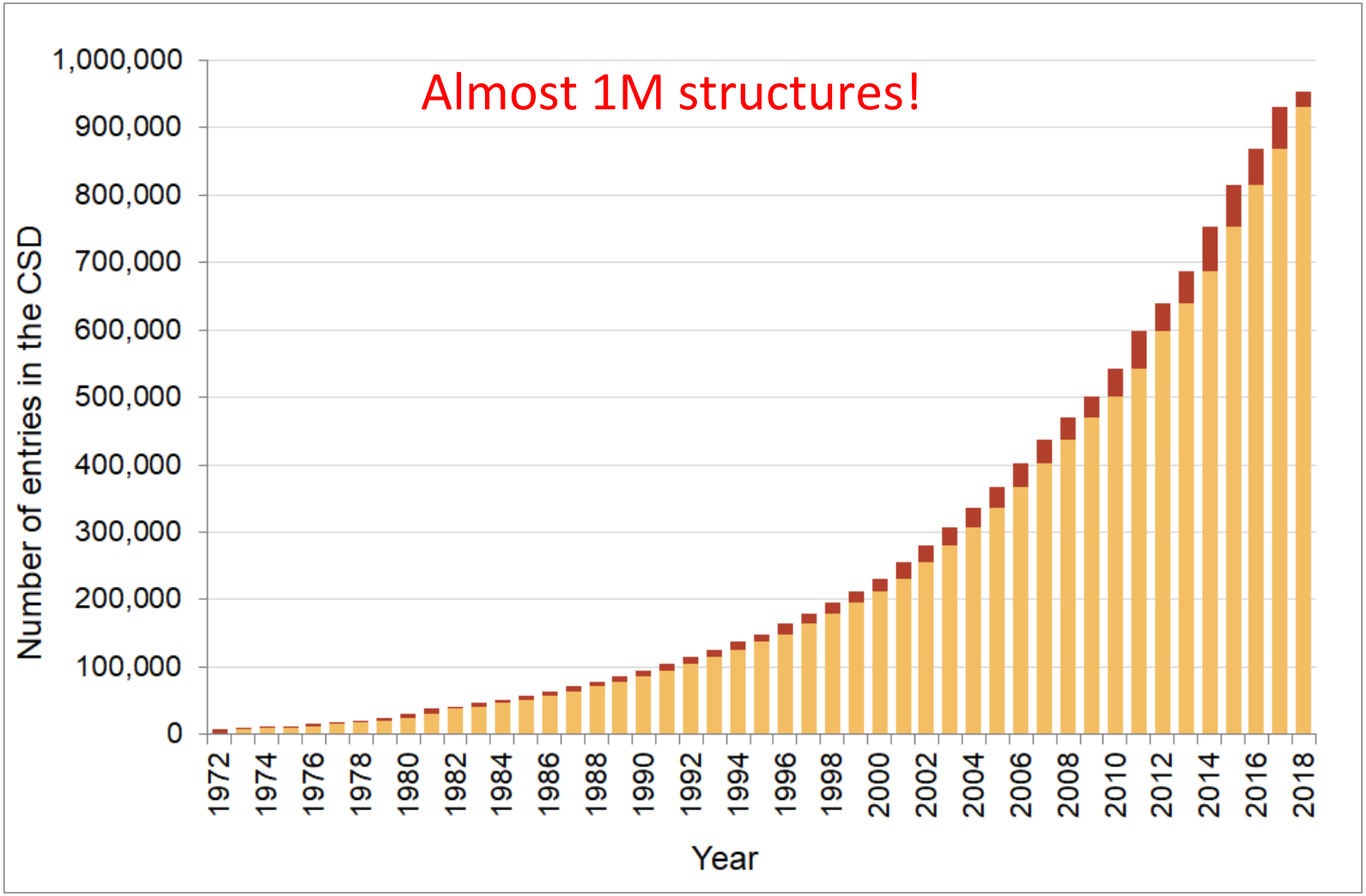
- Organics
- Compounds of the main group elements
- Organometallics
- Metal complexes

The CSD covers peptides of up to 24 residues;

higher oligomers are covered by the Protein Data Bank (see Dr. Cirera´s tutorial).

The Cambridge Structural Database

How big is the CSD?



The Cambridge Structural Database

CSD Refcodes (Entry identifiers)

- Six letters, e.g. ABACOF
- Two digits additional structure determinations, e.g. ABACOF03

For each entry (when possible):

- Bibliographic info. (Author, journal, DOI …)
- Chemical info. (formula, diagram …)
- Crystallographic info. (space group, R-factor …)
- Extra text info. (disorder, polymorphism …)

The Cambridge Structural Database

A typical CSD entry

Refcode: ACACCS

Author(s): F.A.Cotton, C.E.Rice, G.W.Rice

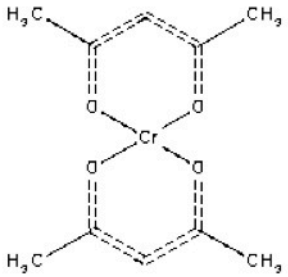
Journal: Inorg.Chim.Acta
Volume: 24
Page: 231
Year: 1977

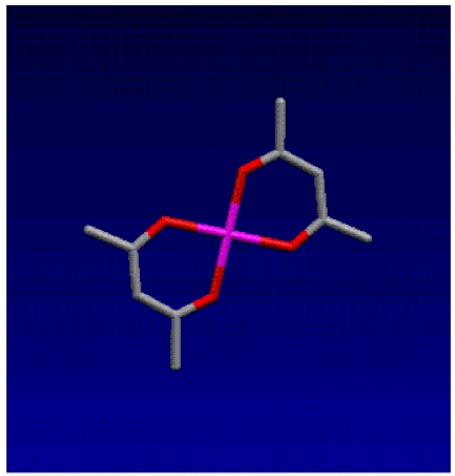
Formula: C10 H14 Cr1 O4
Name: bis(2,4-Pentanedionato) chromium

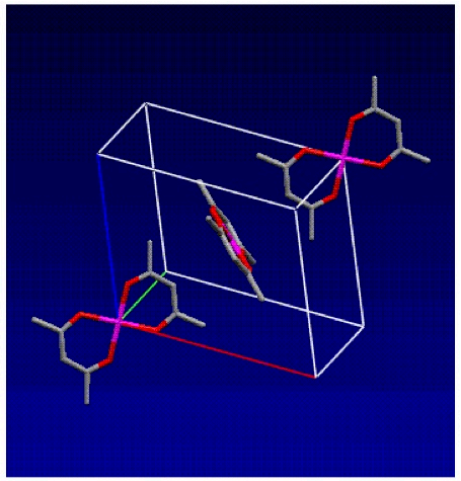
Spacegroup
Name: P21/n **Number:** 14

Cell Parameters
a: 11.445 **b:** 4.748 **c:** 10.325
alpha: 90.00 **beta:** 91.60 **gamma:** 90.00
Volume: 560.851

Reduced Cell Parameters
a: 4.748 **b:** 10.325 **c:** 11.445
alpha: 91.60 **beta:** 90.00 **gamma:** 90.00
Volume: 560.848

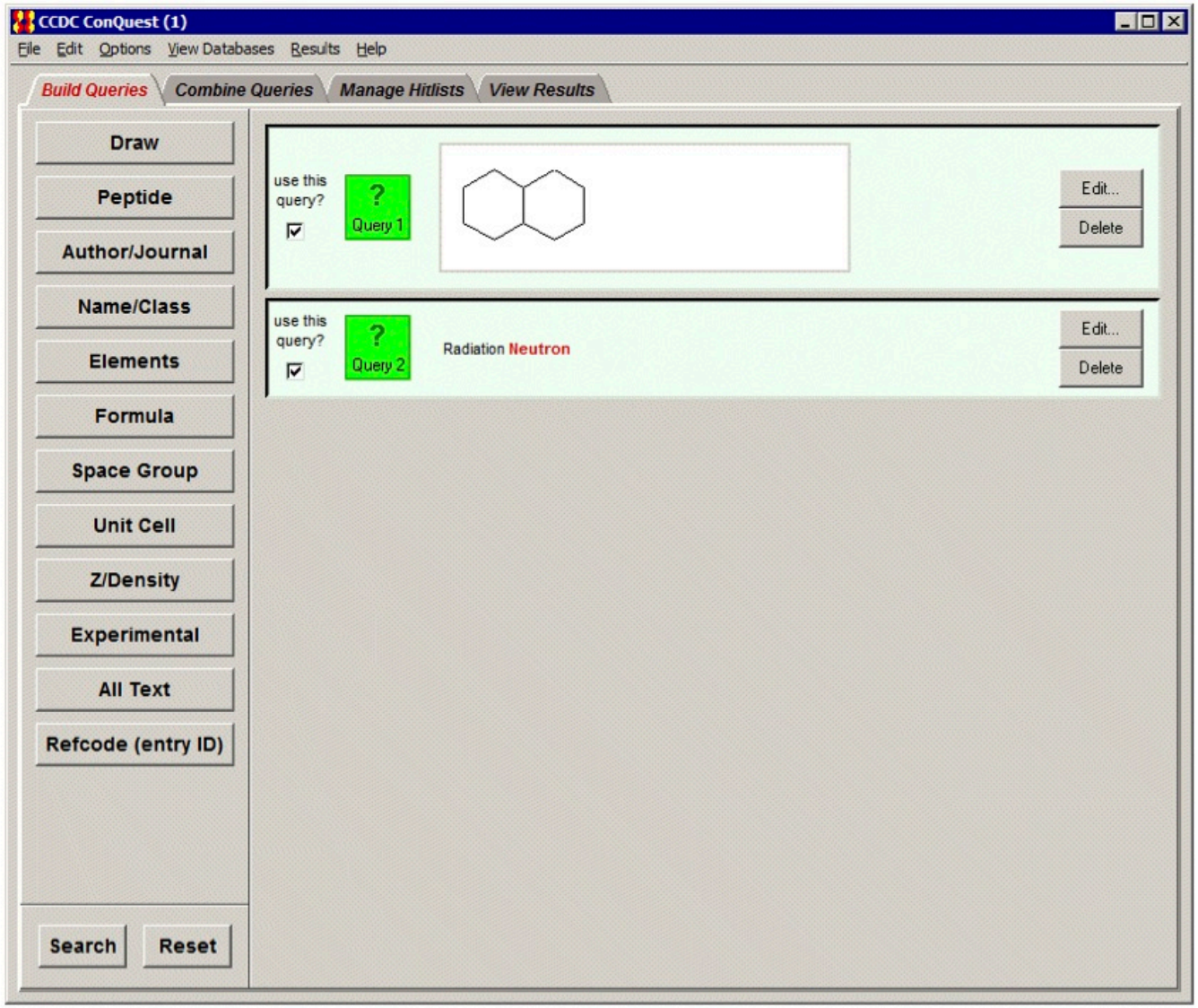






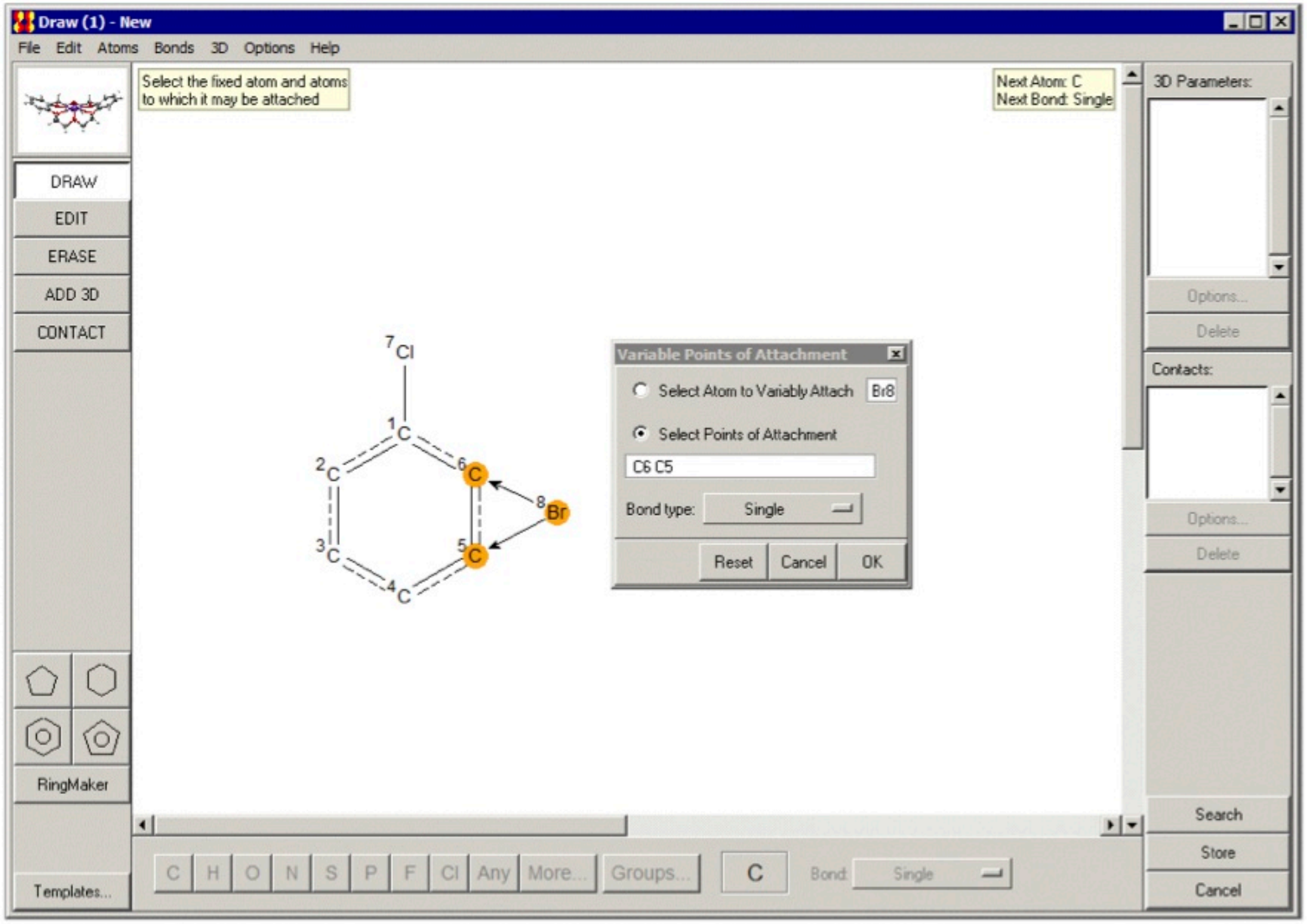
The Cambridge Structural Database

Searching the CSD: **ConQuest**



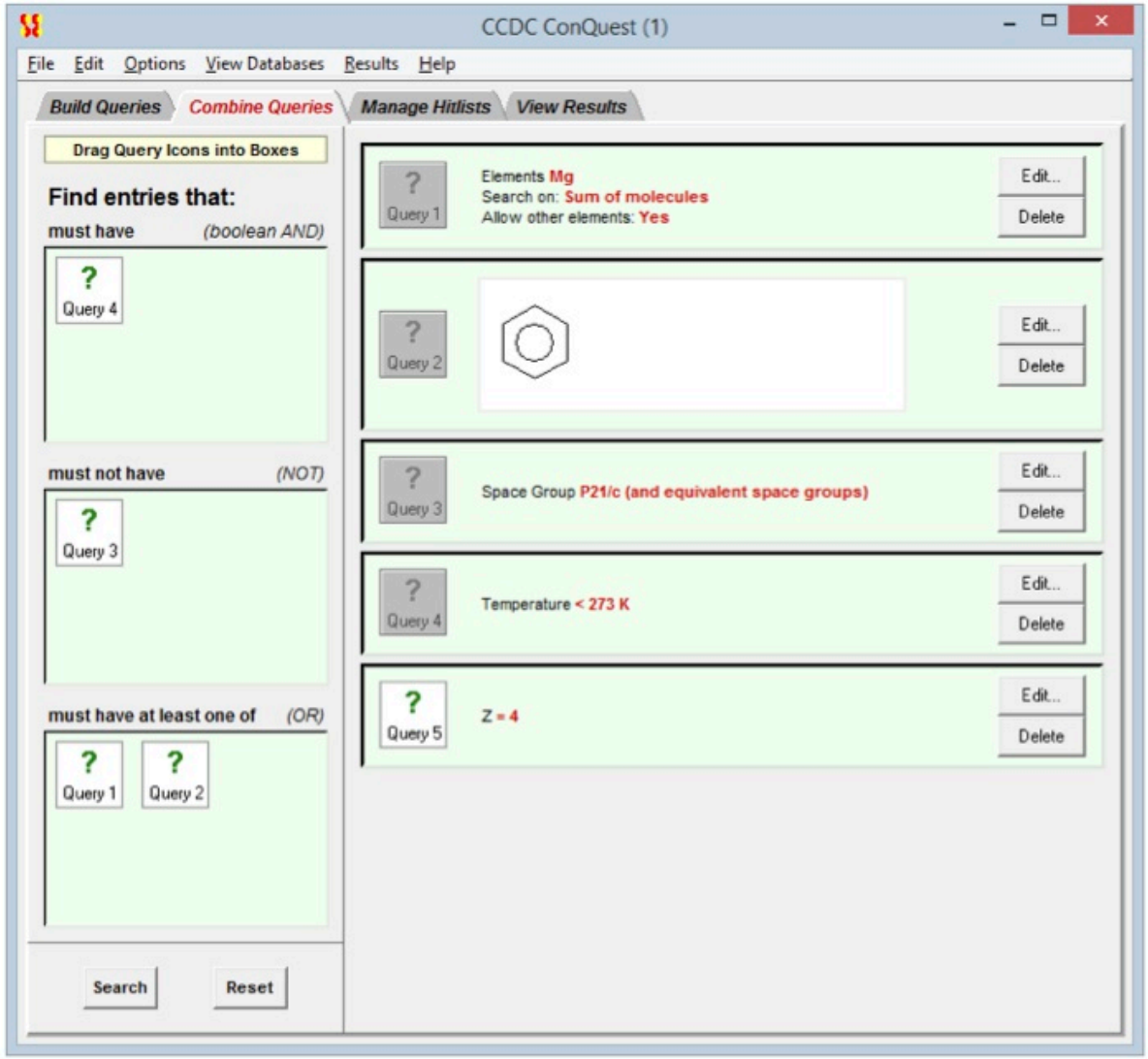
The Cambridge Structural Database

Searching the CSD: **ConQuest**



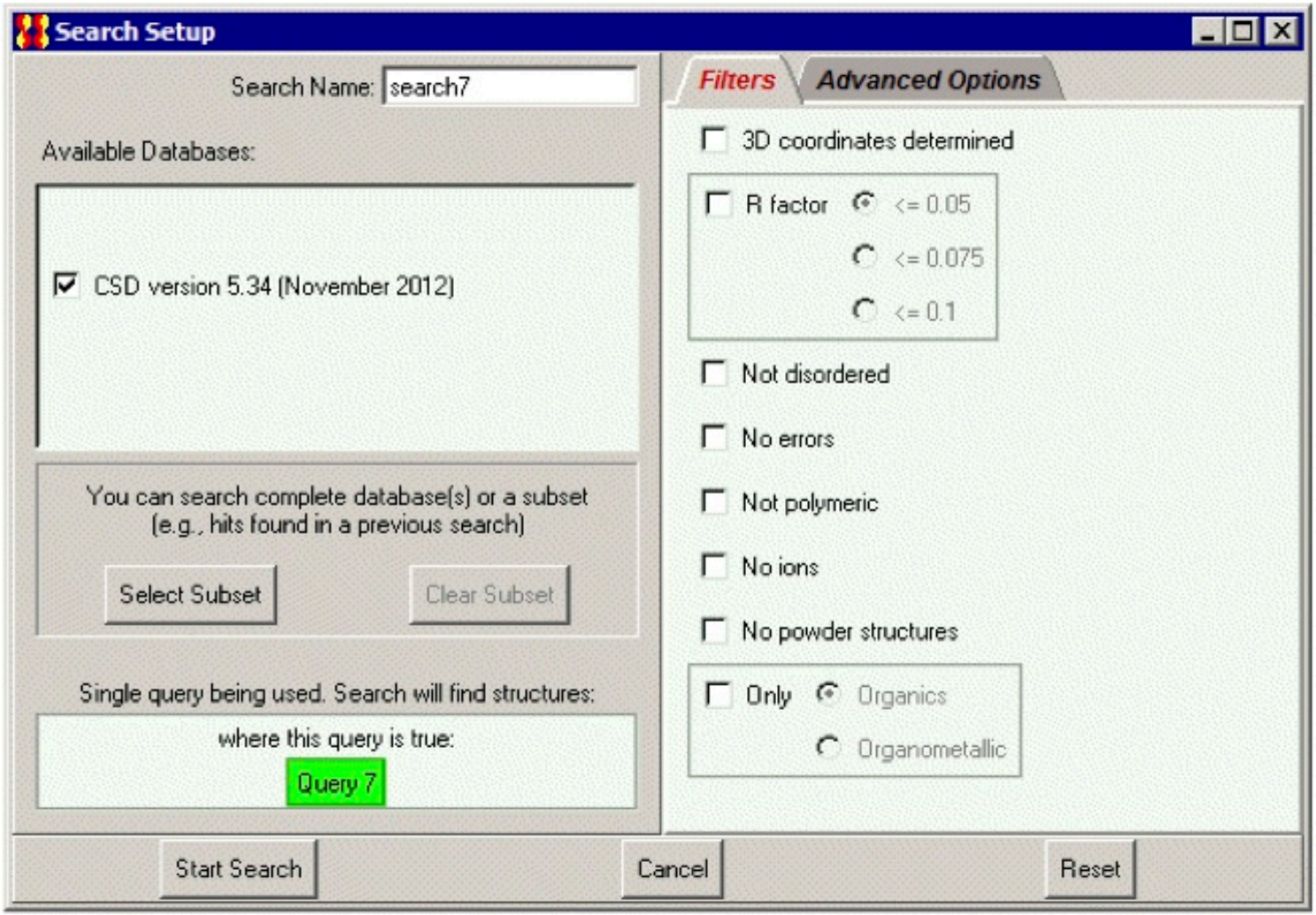
The Cambridge Structural Database

Combine queries



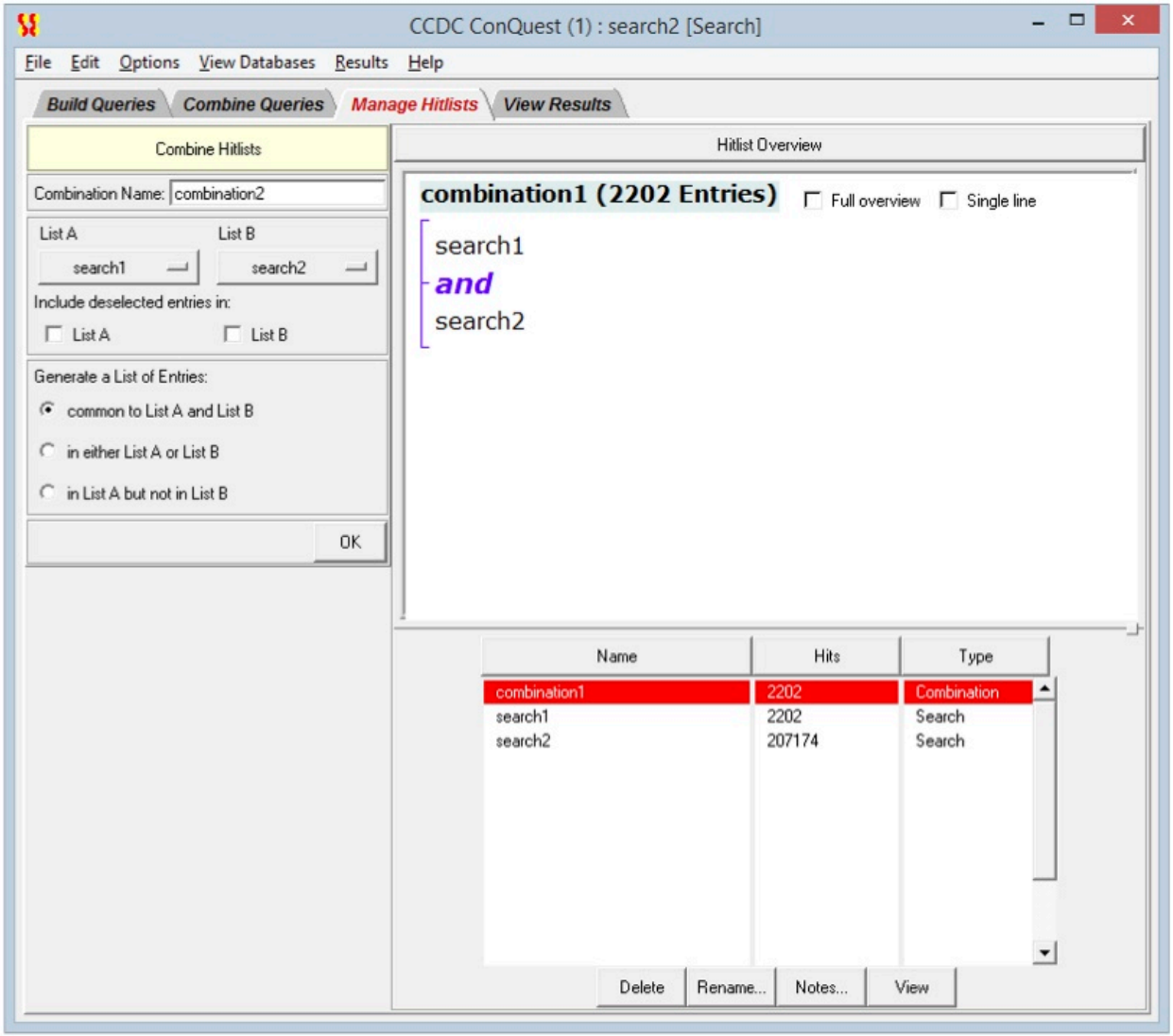
The Cambridge Structural Database

Start searches



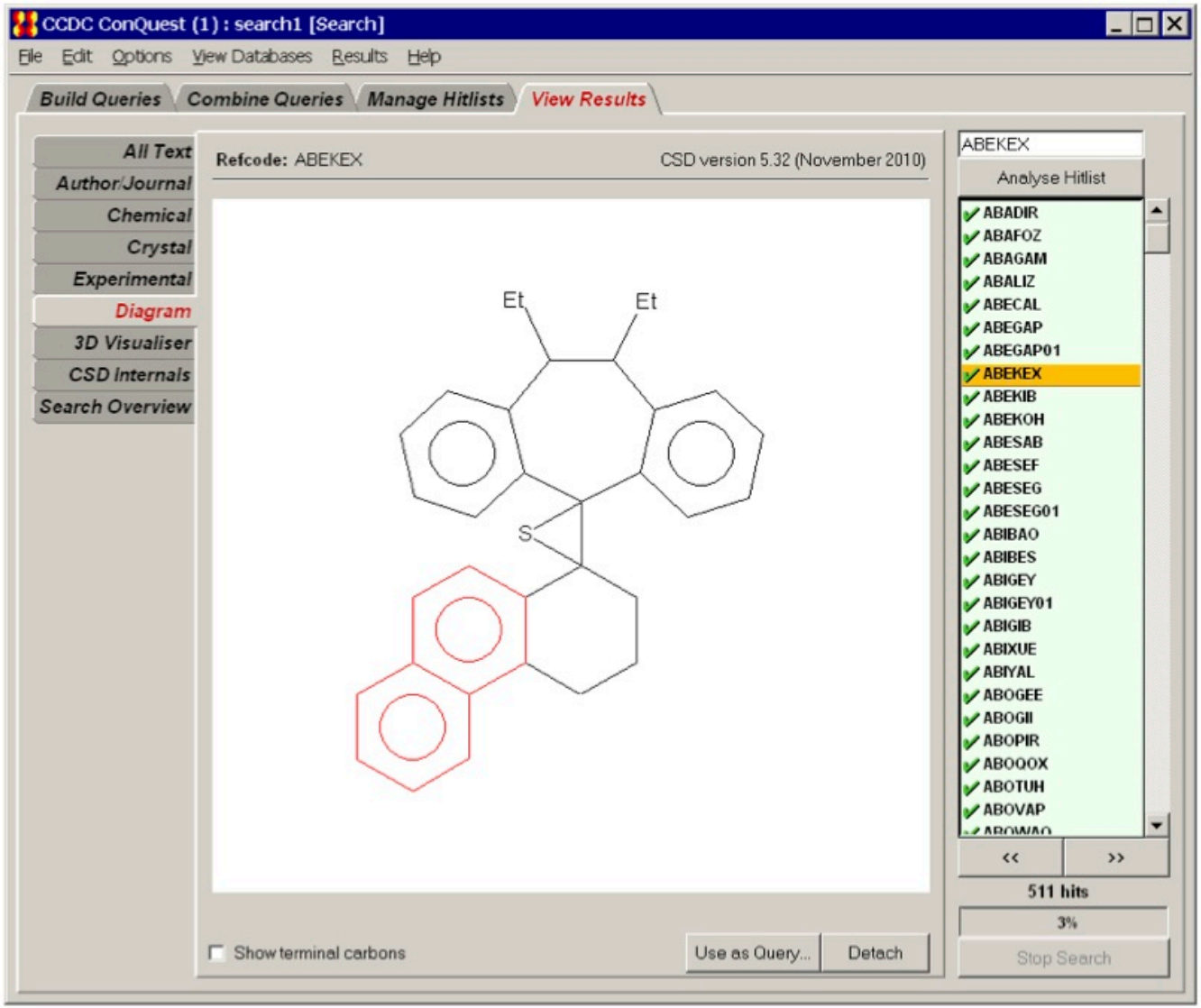
The Cambridge Structural Database

Manage hitlists



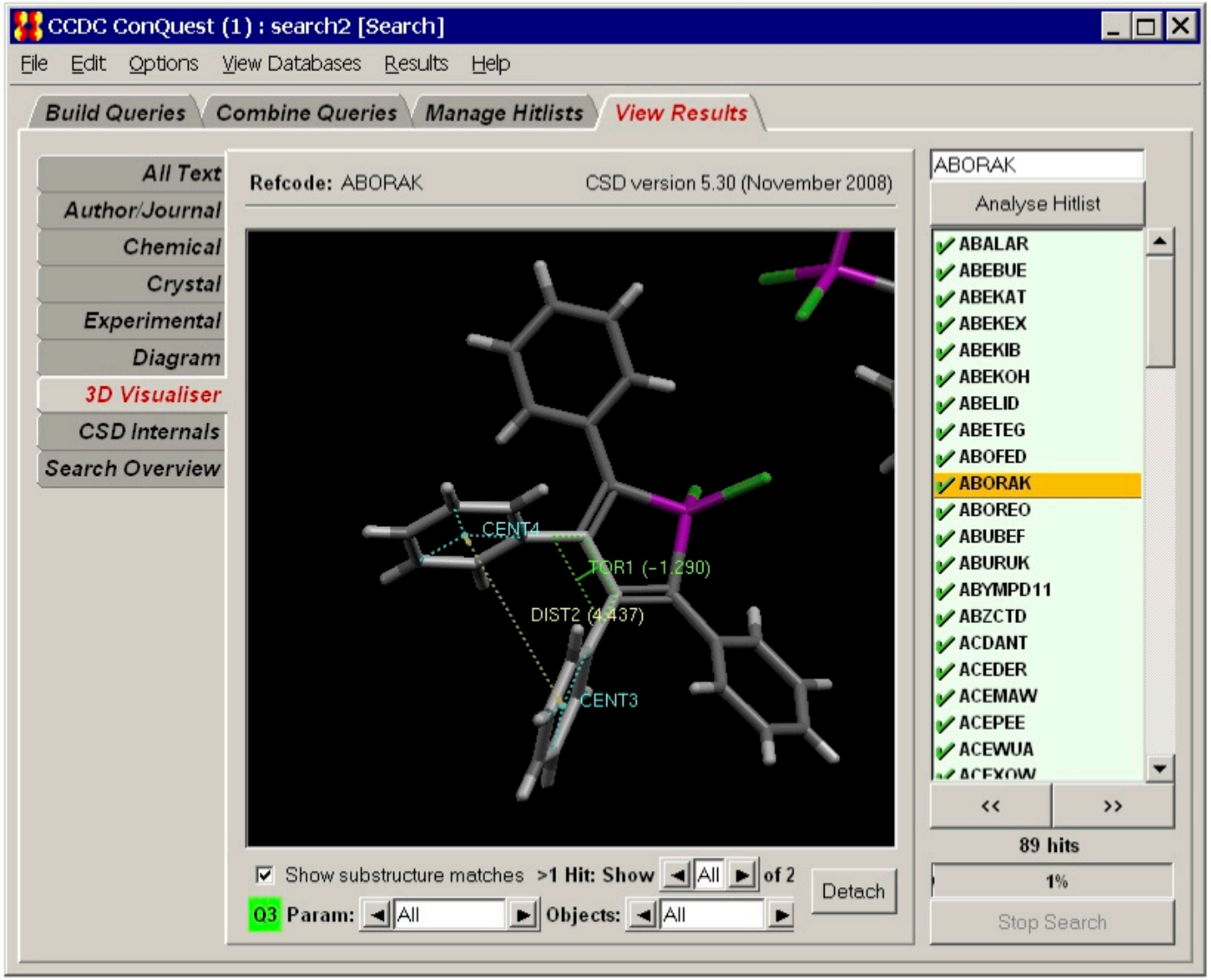
The Cambridge Structural Database

View results



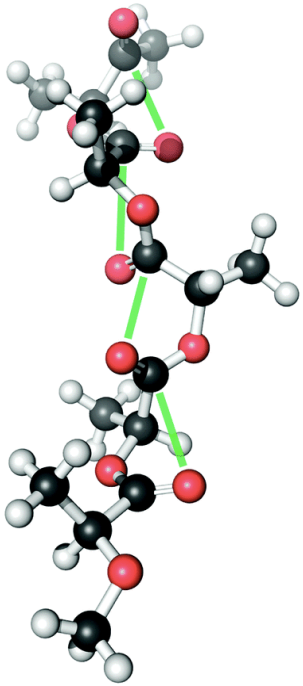
The Cambridge Structural Database

3D visualizer

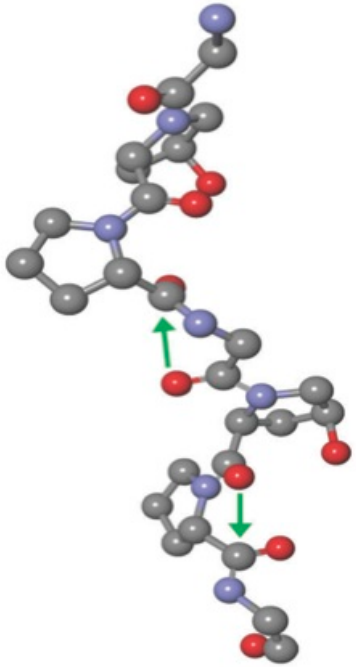


A case study

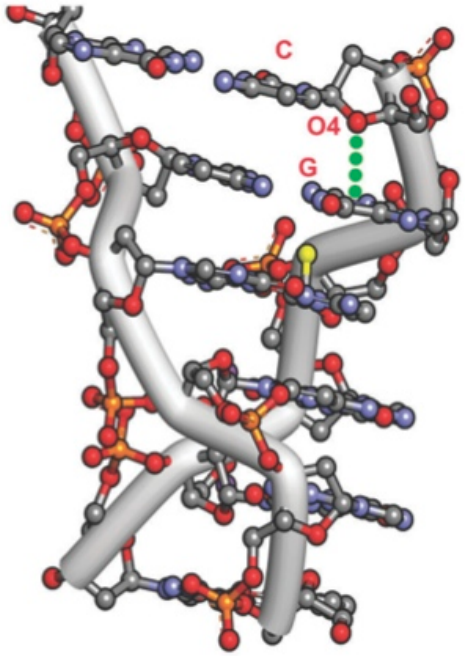
The n → π* interaction



Poly-Lactic Acid



Collagen triple-helix



Z-DNA [PDB ID-131D]

The n→π* interaction

ACCOUNTS of chemical research

Article

pubs.acs.org/accounts

The *n*→*π** Interaction

Published as part of the Accounts of Chemical Research special issue "Chemical Biology of Peptides".

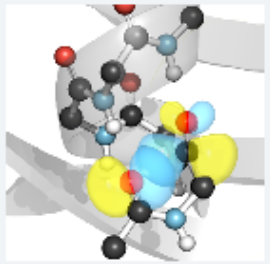
Robert W. Newberry[†] and Ronald T. Raines*[,†,‡]

[†]Department of Chemistry, University of Wisconsin–Madison, Madison, Wisconsin 53706, United States

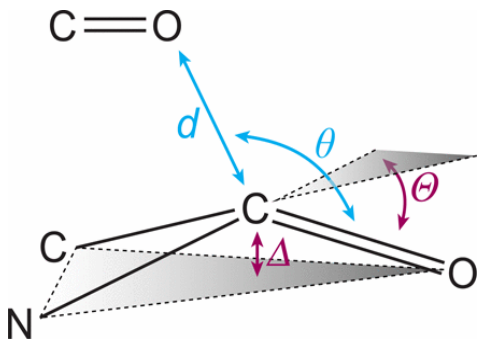
[‡]Department of Biochemistry, University of Wisconsin–Madison, Madison, Wisconsin 53706, United States

CONSPECTUS: The carbonyl group holds a prominent position in chemistry and biology not only because it allows diverse transformations but also because it supports key intermolecular interactions, including hydrogen bonding. More recently, carbonyl groups have been found to interact with a variety of nucleophiles, including other carbonyl groups, in what we have termed an *n*→*π** interaction. In an *n*→*π** interaction, a nucleophile donates lone-pair (*n*) electron density into the empty *π** orbital of a nearby carbonyl group. Mixing of these orbitals releases energy, resulting in an attractive interaction. Hints of such interactions were evident in small-molecule crystal structures as early as the 1970s, but not until 2001 was the role of such interactions articulated clearly.

These non-covalent interactions were first discovered during investigations into the thermostability of the proline-rich protein collagen, which achieves a robust structure despite a relatively low potential for hydrogen bonding. It was found that by modulating the distance between two carbonyl groups in the peptide backbone, one could alter the conformational preferences of a peptide bond to proline. Specifically, only the trans conformation of a peptide bond to proline allows for an attractive interaction with an adjacent carbonyl group, so when one increases the proximity of the two carbonyl groups, one enhances their interaction and promotes the trans conformation of the peptide bond, which increases the thermostability of collagen.



- Most common C=O···C=O



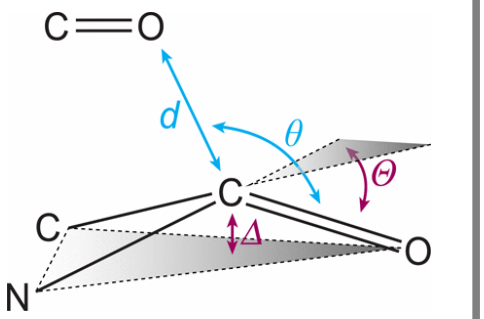
- Dictates protein structure and function

- Present in polymers (PLA), aminoacids and drugs.

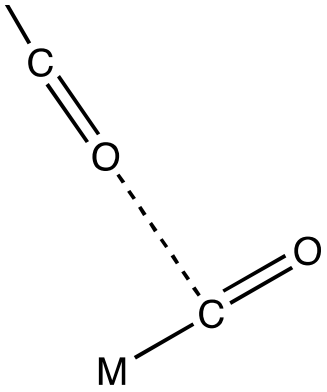
"We anticipate that the n→π interaction will be found in an ever-expanding array of molecules, particularly those with a high density of carbonyl groups. Revealing their impact will provoke clever experiments, and interpretation will be guided by computational methodology."*

Newberry and Raines, Acc. Chem. Res. **2017**, *50,* 1838-1846

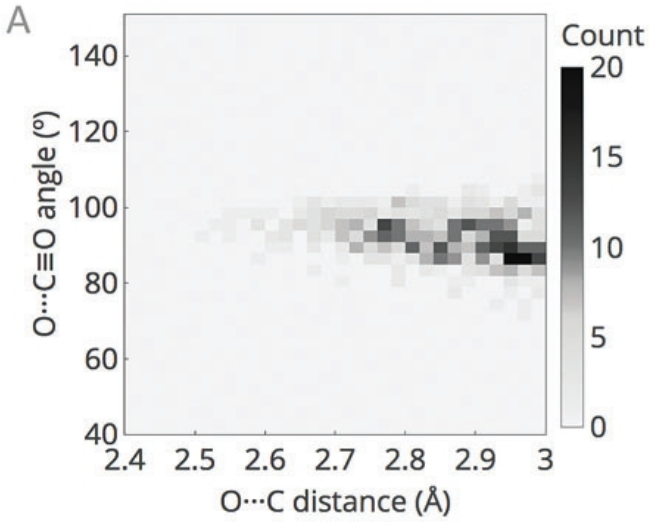
The n→π* interaction in metal complexes

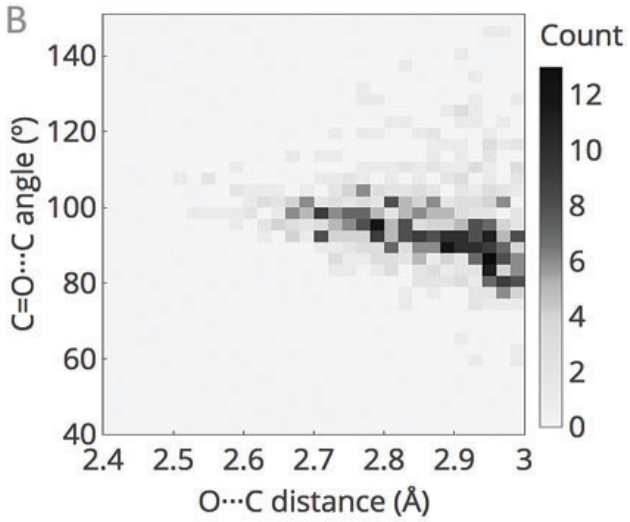


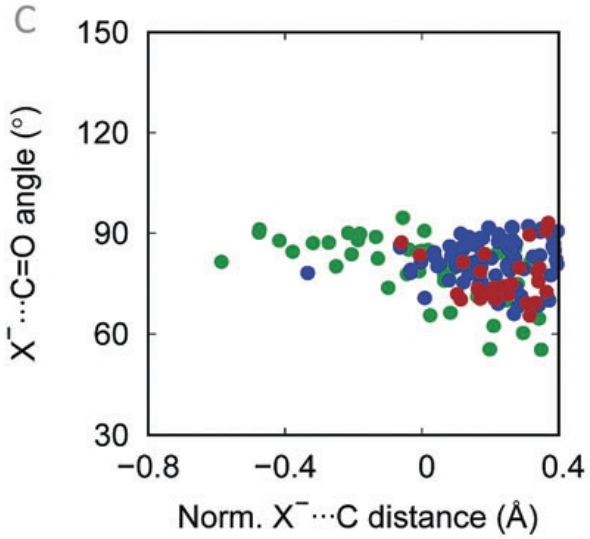
Organic

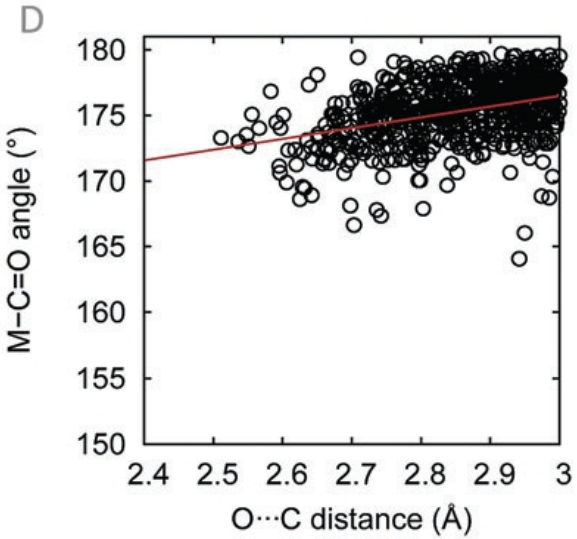


Metallic



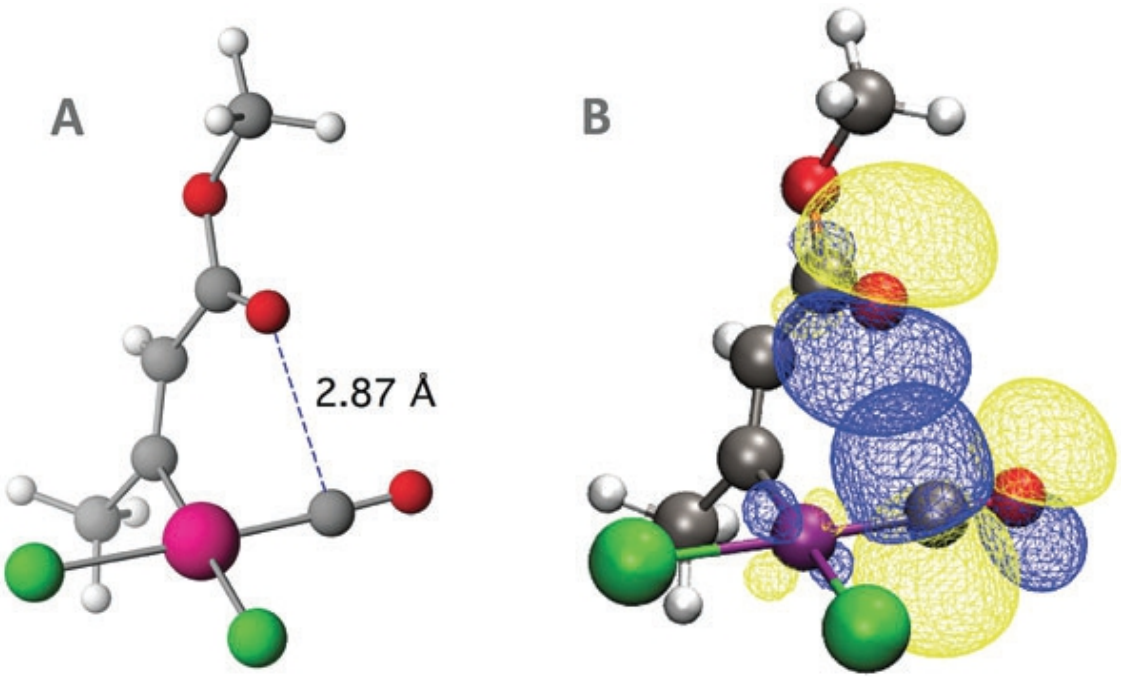






J. Echeverría, *Chem. Commun.* **2018**, *54*, 3061-3064

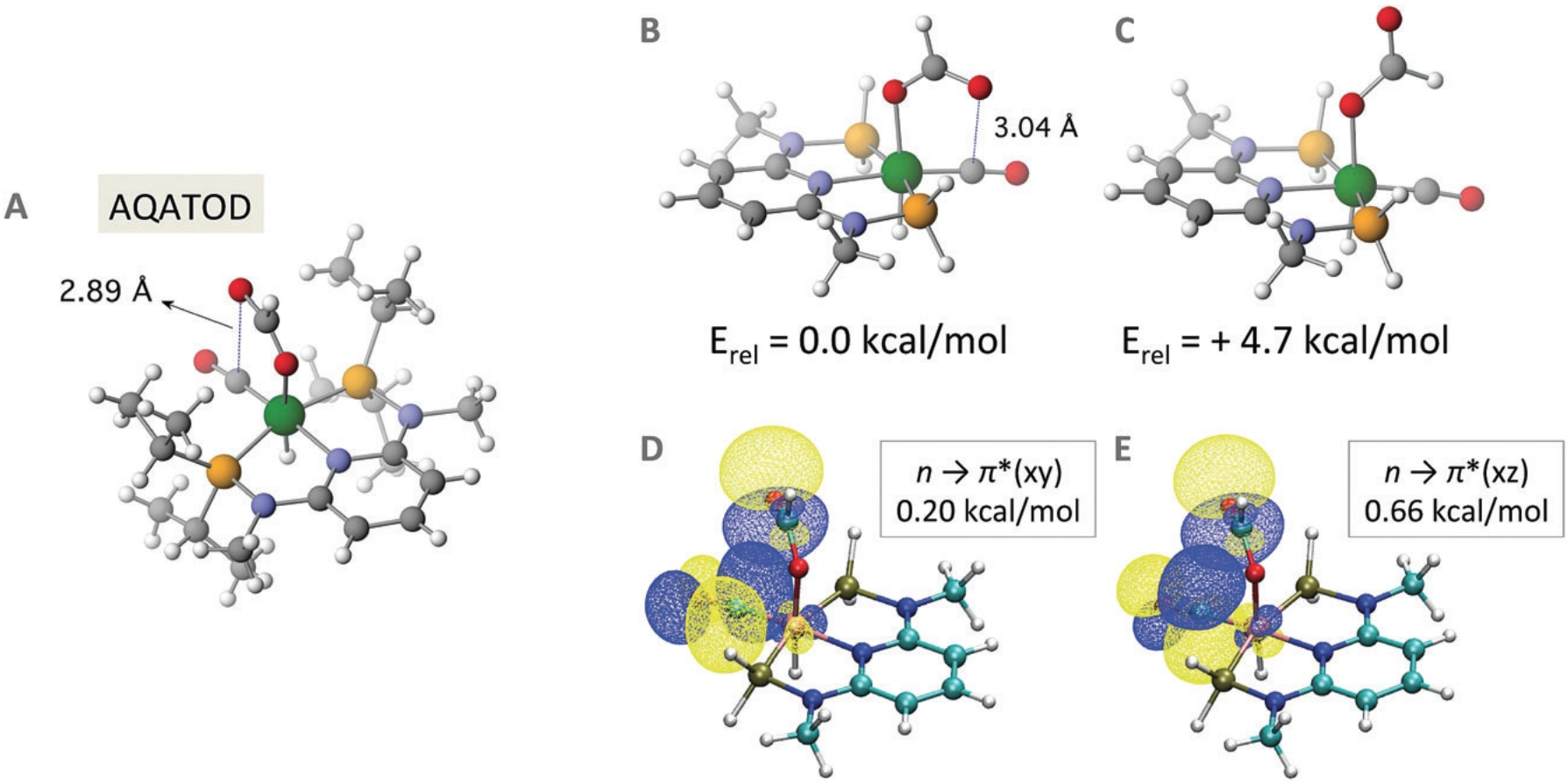
The n→π* interaction in metal complexes



Orbital overlap in a Pt(II) complex

J. Echeverría, *Chem. Commun.* **2018**, *54*, 3061-3064

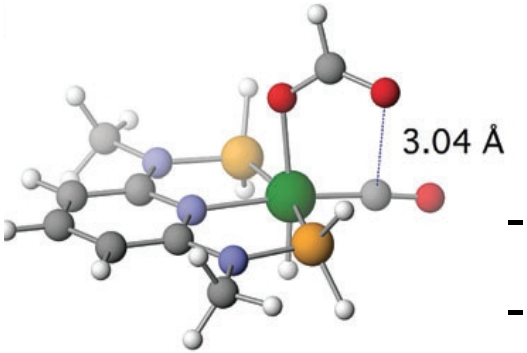
The n→π* interaction in metal complexes



J. Echeverría, *Chem. Commun.* **2018**, *54*, 3061-3064

The n→π* interaction in metal complexes

Int. unit	Non-int. unit	Norm. O···C (Å)	O···CO angle (º)	M-CO Angle (º)	E(2) n→π* (kcal/mol)
=O	-H	-0.23	104.8	175.4	1.08
=S	-H	-0.12	101.7	171.9	1.79
=O	-CF_3	-0.19	104.1	175.2	0.87
=O	-CMe_3	-0.33	103.6	175.0	1.55

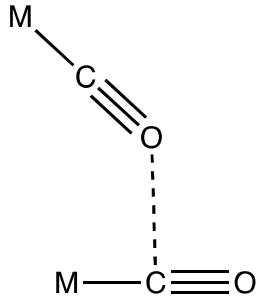


- Sulphur as the donor strengthens the interaction
- All O···CO angles close to the Burgi-Dunitz trajectory
- M-CO angle looses linearity as the interaction makes stronger
- NBO energies larger for good donors (=S, -CMe_3)

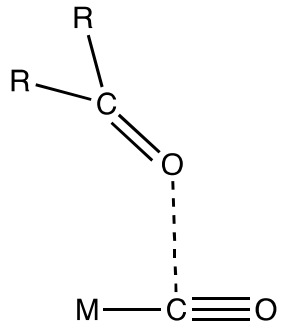
J. Echeverría, *Chem. Commun.* **2018**, *54*, 3061-3064

The n→π* interaction in metal complexes

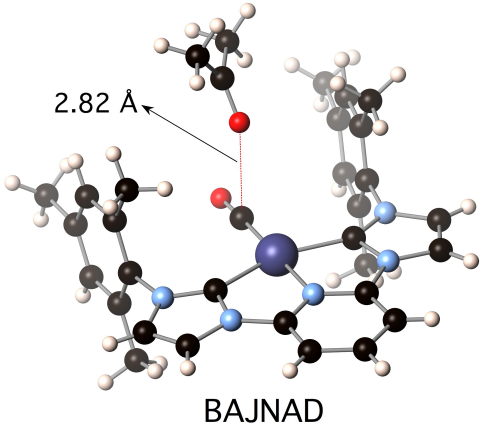
Intermolecular contacts



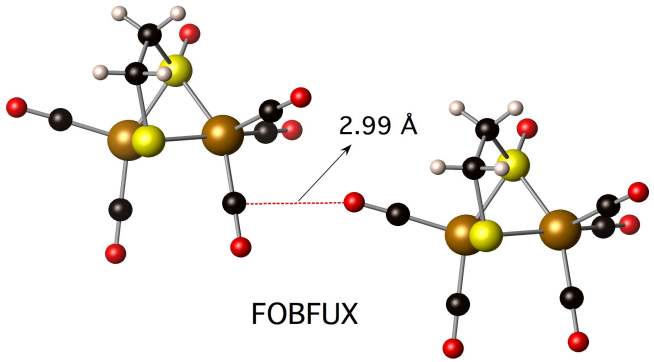
M-CO···CO



R-CO···CO



BAJNAD



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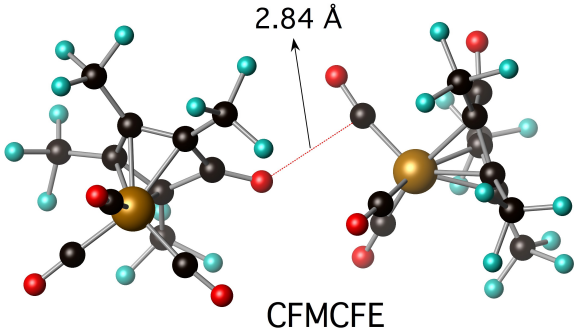


CFMCFE

J. Echeverría, *Inorg. Chem.* **2018**, *57*, 5429-5437

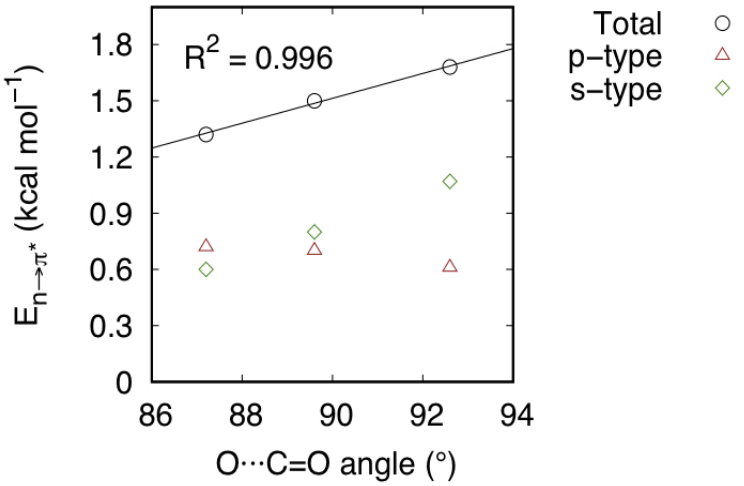
The n→π* interaction in metal complexes

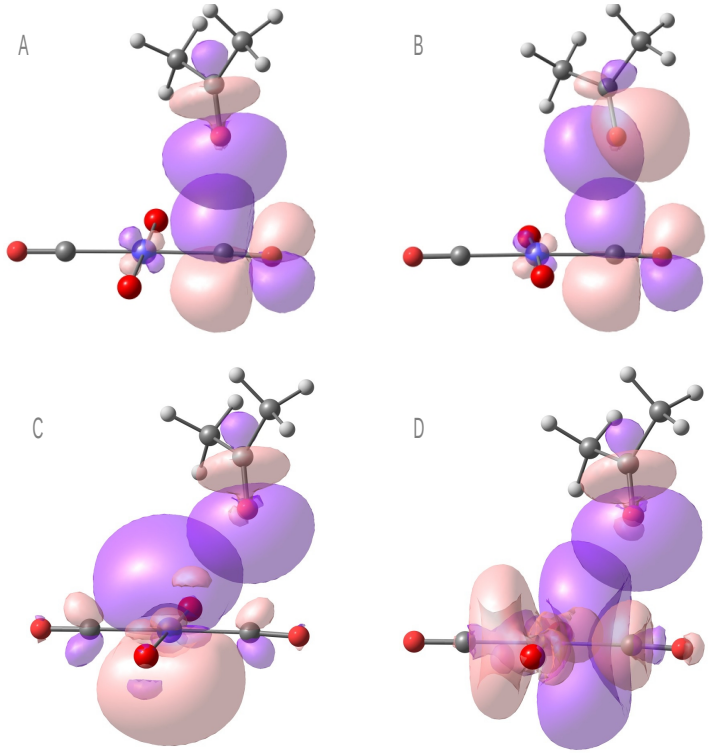
Computational study on the nature of the interaction

M	n(s)→ π_{CO}*	n(p)→ π_{CO}*	n(s)→ σ_{MC}*	n(p)→ σ_{MC}*	n(s)→ n_M*	n(p)→ n_M*
Ni	1.07	0.61	0.20	0.12	0.22	0.63
Pd	0.80	0.70	0.26	0.16	0.39	0.58
Pt	0.60	0.72	0.87	0.20	1.05	0.62

NBO analysis

Model system: $[NiBr_2(CO)_2]$



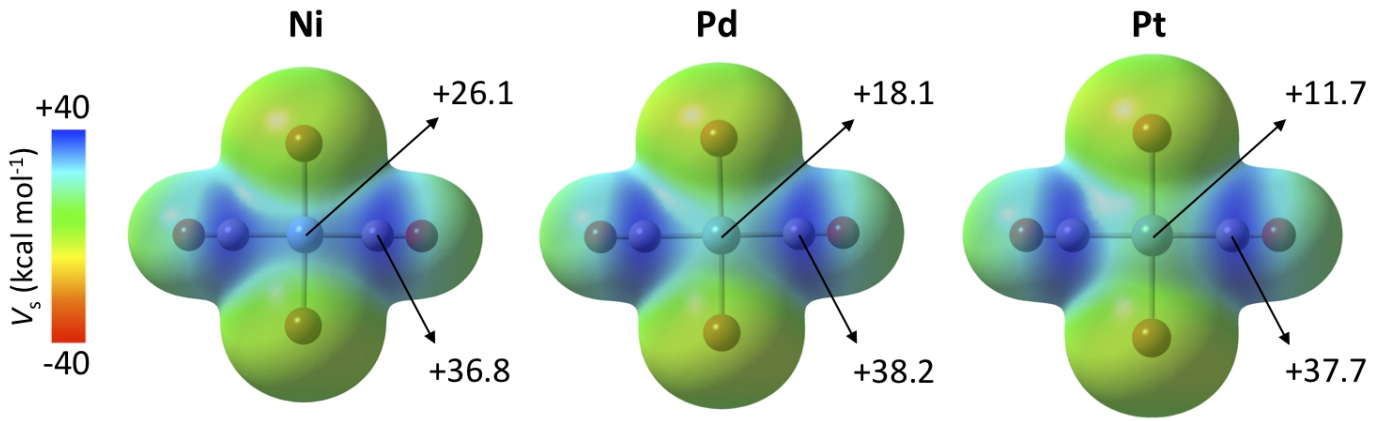


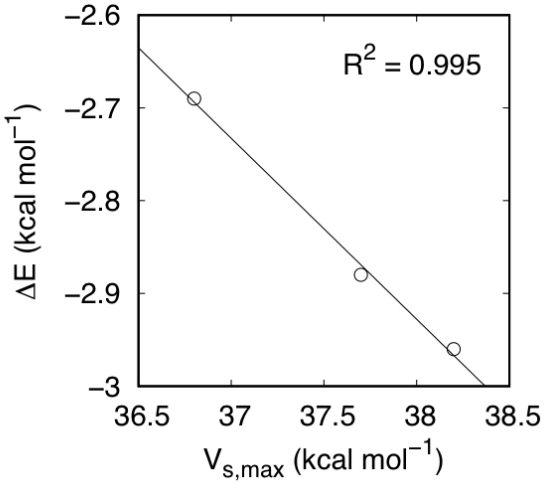
J. Echeverría, *Inorg. Chem.* **2018**, *57*, 5429-5437

The n→π* interaction in metal complexes

Computational study on the nature of the interaction

MEP analysis





J. Echeverría, *Inorg. Chem.* **2018**, *57*, 5429-5437

The n→π* interaction in metal complexes

Computational study on the nature of the interaction

Energy Decomposition Analysis

Metal	ΔE PAULI	ΔE ELECT	ΔE FROZEN	ΔE POLARIZ	ΔE CT	ΔE INT
Ni	4.17	-4.86	-0.70 (26)	-0.90 (33)	-1.10 (41)	-2.69
Pd	4.24	-5.19	-0.95 (32)	-0.91 (31)	-1.09 (37)	-2.96
Pt	4.11	-5.11	-1.00 (35)	-0.87 (30)	-1.02 (35)	-2.88

All energies in Kcal/mol

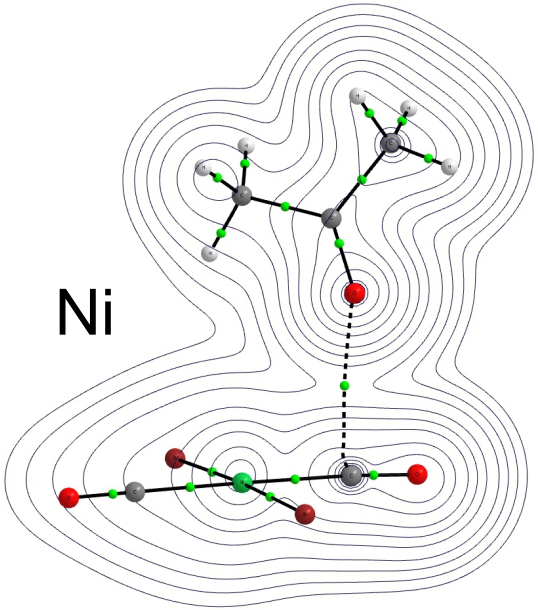
- Electrostatics overcome Pauli repulsion in all cases
- Frozen energy increases when descending the group
- Polarization and Charge Transfer decrease when descending the group

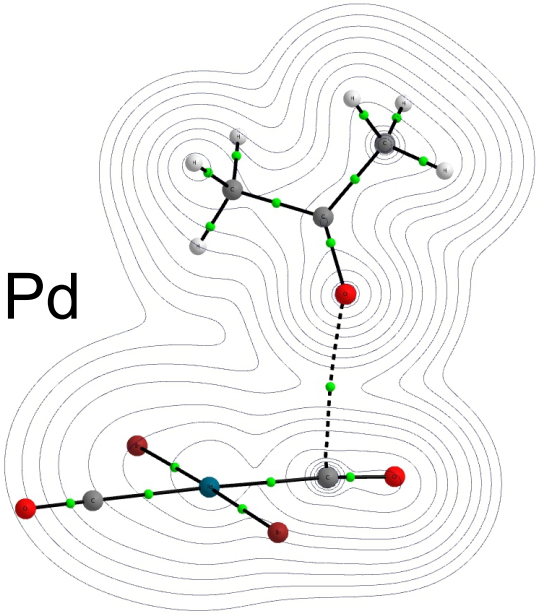
J. Echeverría, *Inorg. Chem.* **2018**, *57*, 5429-5437

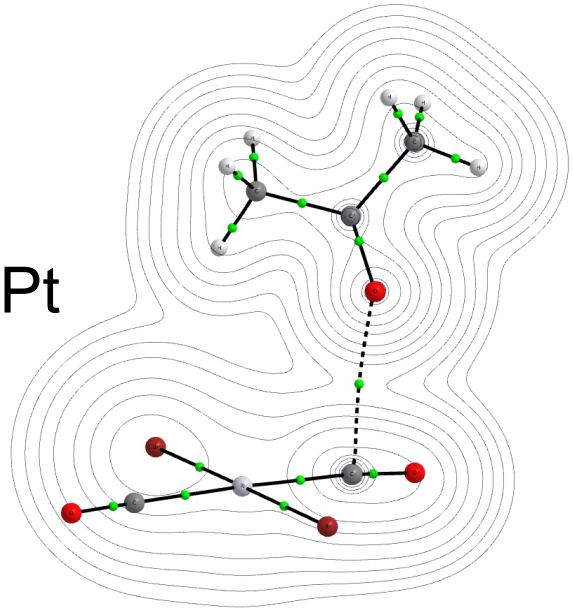
The n→π* interaction in metal complexes

Computational study on the nature of the interaction

Atoms in Molecules (AIM) Theory







metal	ρ	$\nabla^2\rho$	DI(C_{accep},O_{donor})	H	ε
Ni	0.0094	0.0374	0.0422	0.0020	0.7088
Pd	0.0097	0.0382	0.0421	0.0020	0.7710
Pt	0.0094	0.0377	0.0381	0.0020	0.9354

J. Echeverría, *Inorg. Chem.* **2018**, *57*, 5429-5437

The n→π* interaction in metal complexes

Summary & Conclusions

- Carbonyl···carbonyl contacts, both intra and intermolecular are present in metal complexes.

- These contacts are attractive and follow precise geometrical arrangements.

- The origin of the interaction is the electron delocalization from a lone pair to an antibonding empty orbital.

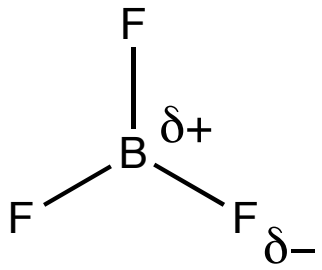
- Electrostatics can also play an important role in the energy stabilization.

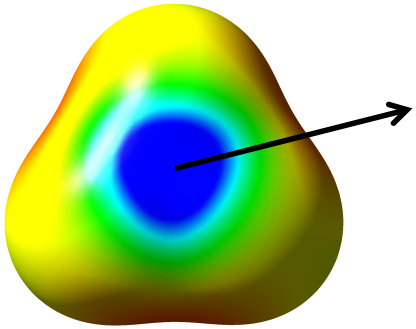
- Opens the way to their use in supramolecular chemistry and crystal design.

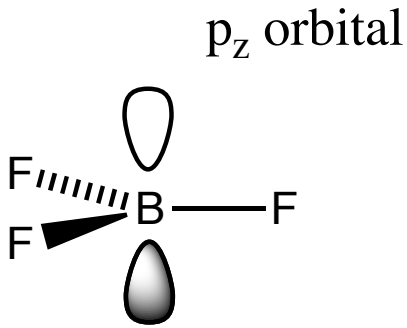
π/σ-hole interactions

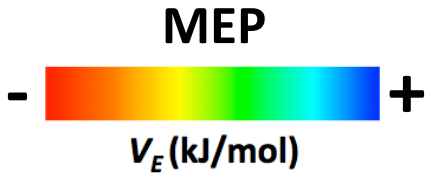
The electron density hole concept

π-hole

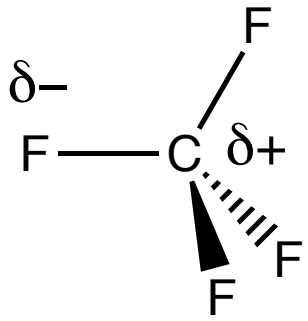


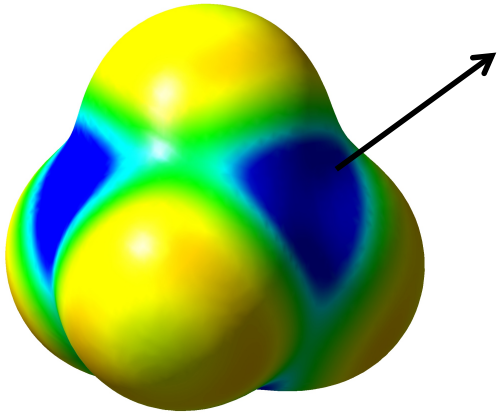


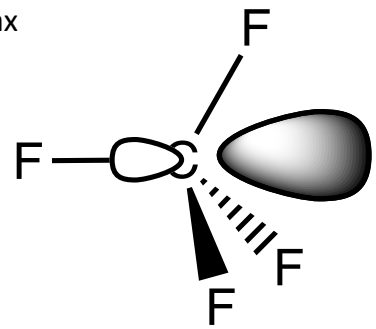




σ-hole

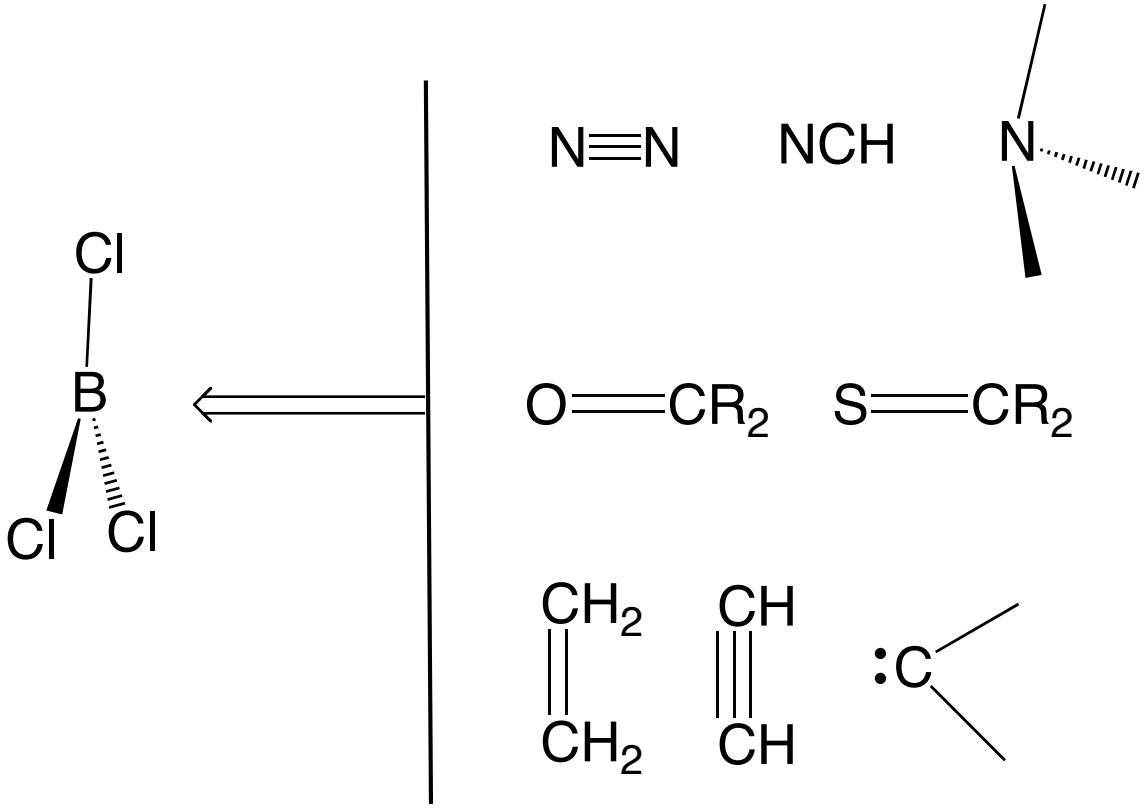






π/σ-hole interactions

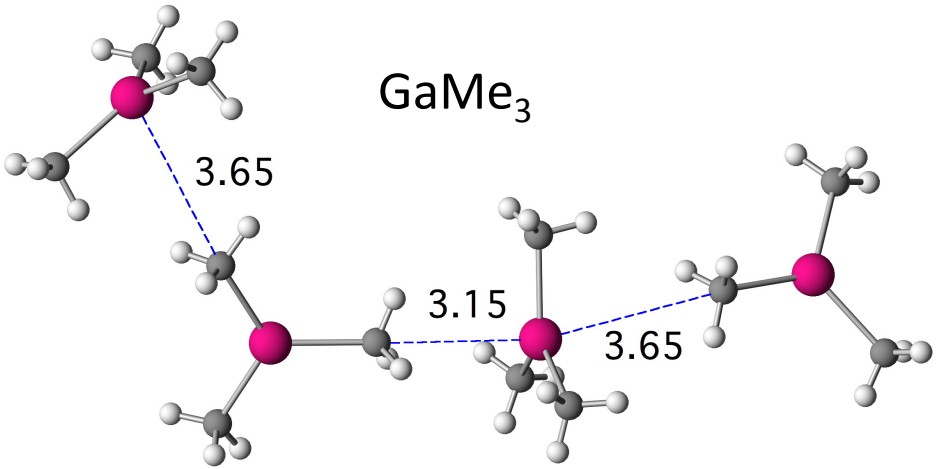
Donors can be: anions, lone pairs, π electron density, carbenes, etc.



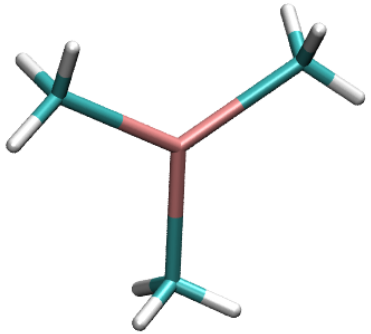
sp^3 carbons?

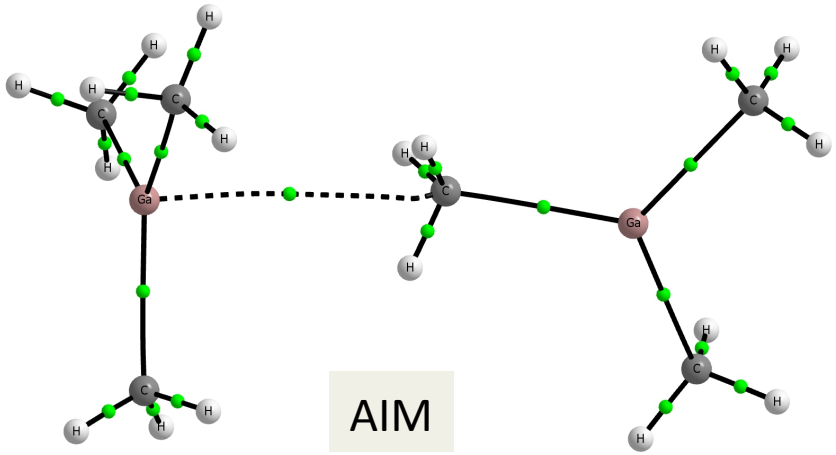
Alkyl groups as electron density donors

Structural evidence

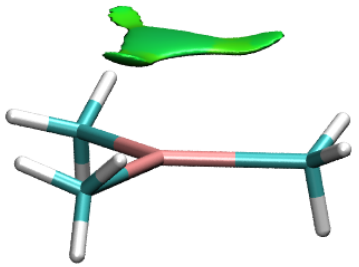


NCIPlot



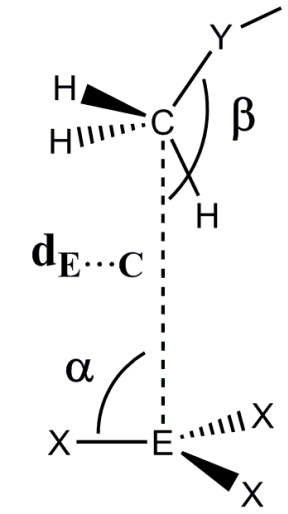


AIM

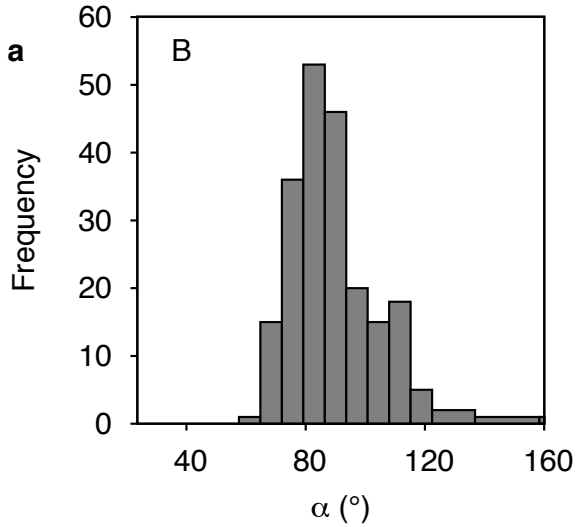


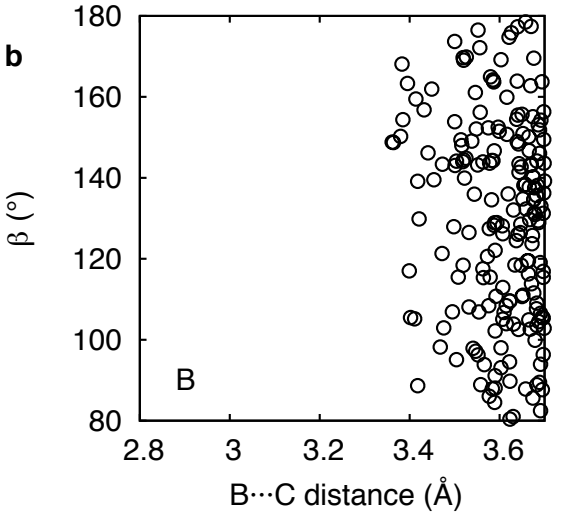
Green areas indicate
weak non-covalent interaction

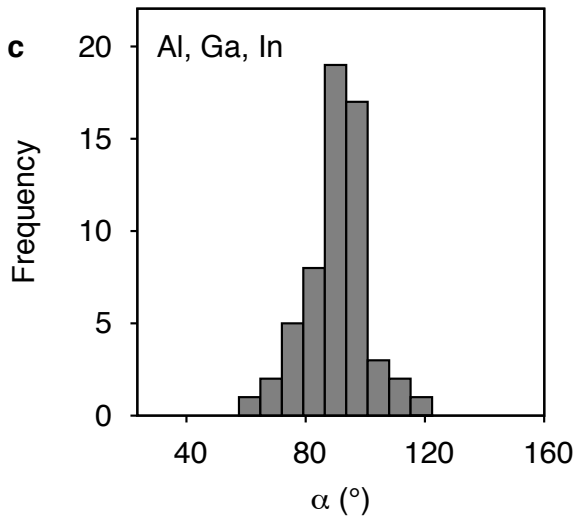
Alkyl groups as electron density donors

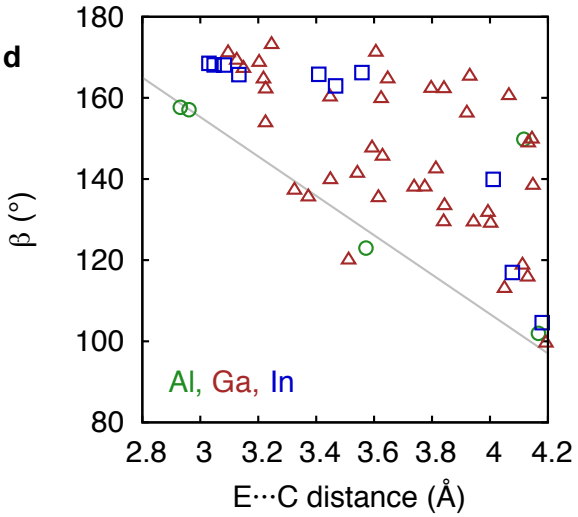


E = B, Al, Ga, In



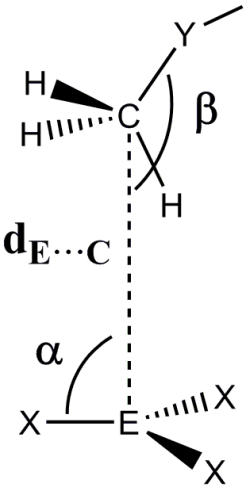




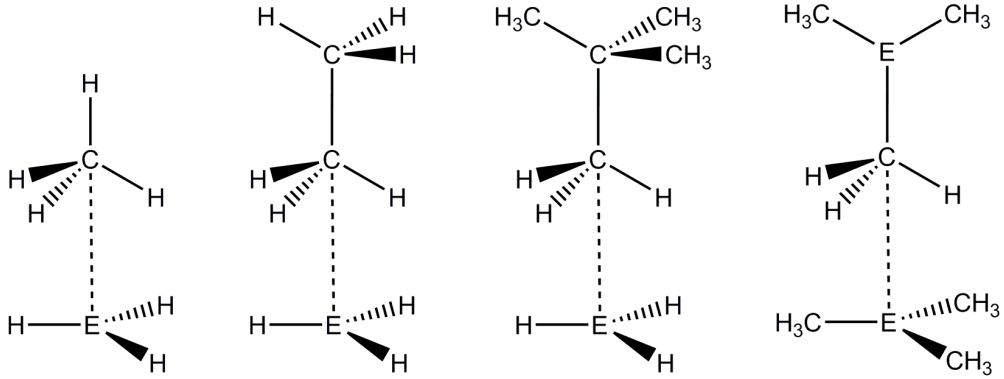


Alkyl groups as electron density donors

Computational analysis (MP2/aug-cc-pVTZ)



E = B, Al, Ga, In



1 2 3 4

· Interaction strength: 1 < 2 < 3 < 4 and B << Ga < Al

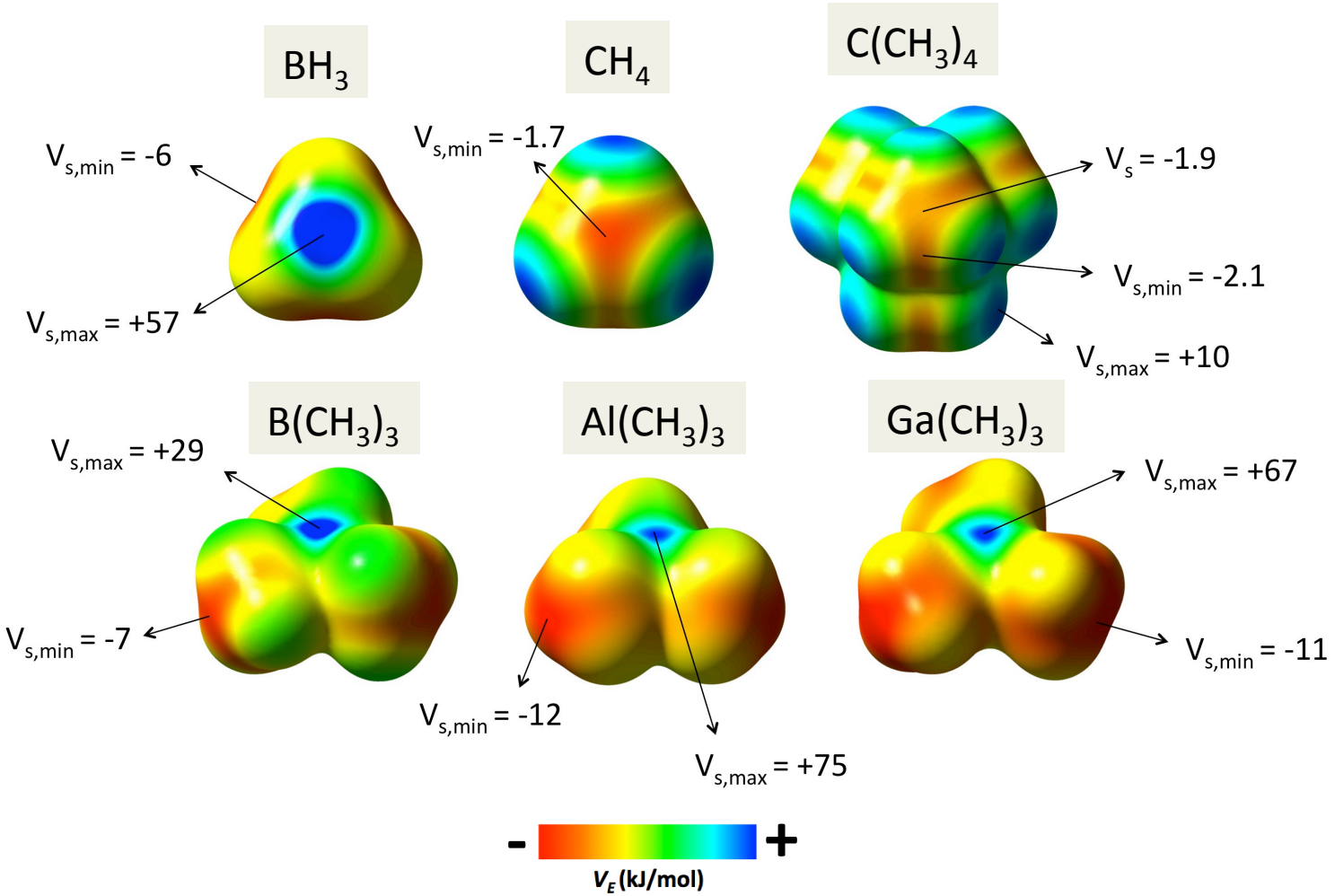
· Angle α = 90 ± 5°

· Angle β: for Al and Ga ≈ 140 – 180°

· Good match with experimental structures

Alkyl groups as electron density donors

Nature of the interaction



· Good agreement with Interaction strength: B << Ga < Al

Alkyl groups as electron density donors

Nature of the interaction

ENERGY DECOMPOSITION ANALYSIS (kcal/mol) [B3LYP-D3]

Dimer	ΔE_{Pauli}	ΔE_{Elec}	ΔE_{Disp}	ΔE_{Pol}	ΔE_{CT}	ΔE_{int}
$[B(CH_3)_3]_2$	6.53	−4.18	−3.63	−0.14	−0.51	−1.94
$[Al(CH_3)_3]_2$	25.44	−16.46	−5.14	−6.44	−3.83	−6.45
$[Ga(CH_3)_3]_2$	27.75	−16.71	−5.58	−5.45	−3.49	−3.32

· Electrostatic: The largest term in all cases (≈ 50%)

· Dispersion: For B is 43%, for Al and Ga only 16 - 17%

· Orbital: Significant for Al and Ga; negligible for B

The silane-methane dimer

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Chemical Physics Letters 397 (2004) 314–318
CHEMICAL PHYSICS LETTERS
www.elsevier.com/locate/cplett

A theoretical study of the dispersion-bound silane–methane dimer

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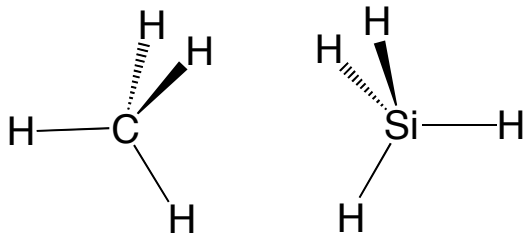
Received 29 July 2004; in final form 26 August 2004
Available online 16 September 2004

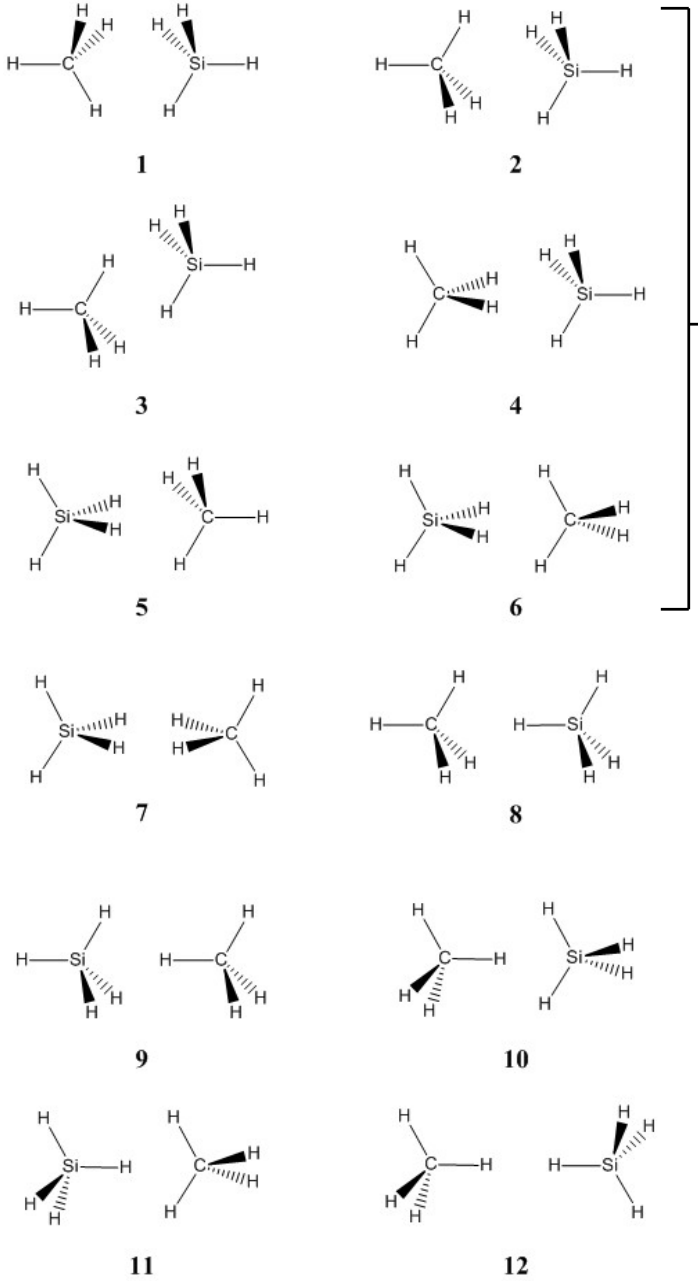
Abstract

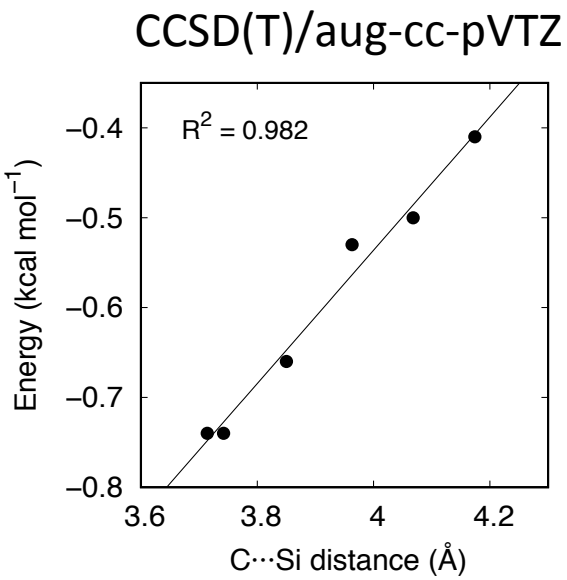
We studied six conformers of the silane–methane dimer using CCSD(T) with basis sets up to aug-cc-pVQZ. The binding energies of the conformers increase with the number of hydrogen contacts between the monomers. The most stable conformer has an eclipsed, C_{3v} arrangement and is bound by 0.81 kcal/mol. The use of counterpoise corrections and basis set extrapolation schemes separately give unsatisfactory binding energies. However, extrapolation of the counterpoise corrected energies provided binding energies in excellent agreement with counterpoise-corrected CCSD(T)/aug-cc-pVQZ results.

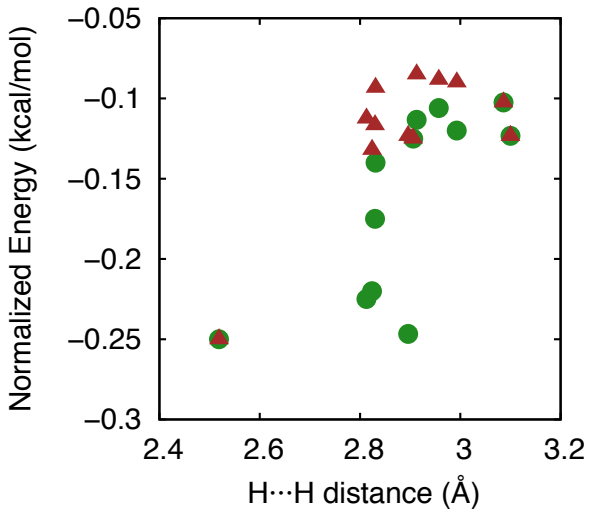


Johnson & DiLabio, *Chem. Phys. Lett.* **2004**, *397*, 314-318

The silane-methane dimer revisited

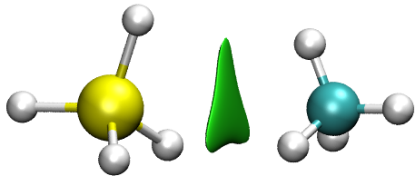




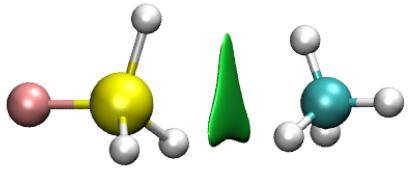


The silane-methane dimer revisited

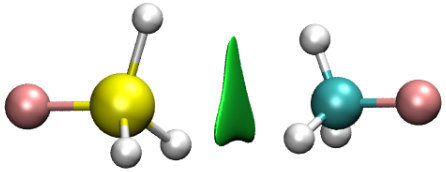
NCIPlot surfaces



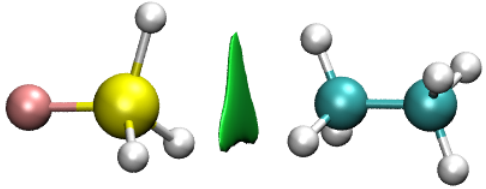
-0.74 kcal/mol



-1.00 kcal/mol



-0.12 kcal/mol



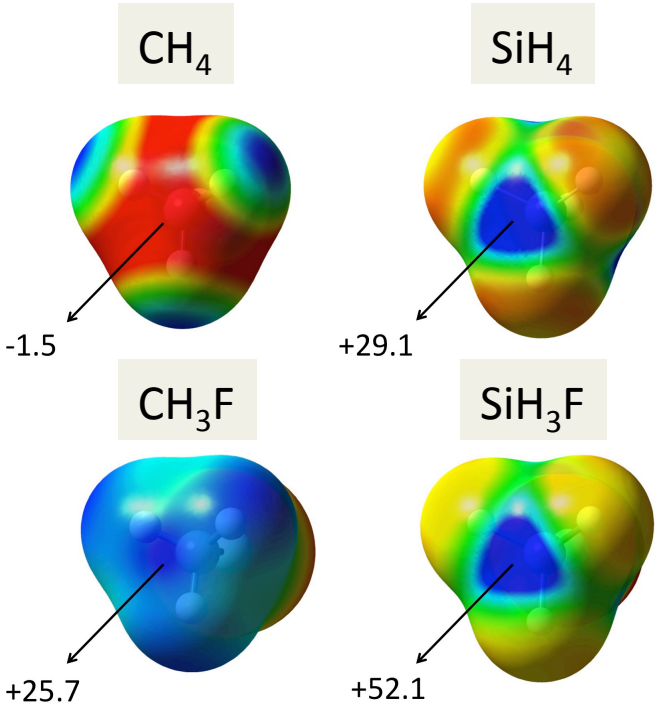
-1.16 kcal/mol

σ-donors in C / σ-attractors in Si

Strengthen the interaction

Electrostatic interaction?

The silane-methane dimer revisited



ALMO-EDA (B3LYP-D3) kcal/mol

Dimer	Topol.	ΔE_{Pauli}	ΔE_{Elec}	ΔE_{Disp}	ΔE_{Pol}	ΔE_{CT}	ΔE_{int}
$CH_4\cdots SiH_4$	**1**	2.381	-1.51 (48)	-1.37 (44)	-0.04 (1)	-0.20 (7)	-0.74
$FCH_3\cdots SiH_4$	**1**	2.034	-1.02 (38)	-1.36 (51)	-0.09 (3)	-0.18 (7)	-0.61
$FCH_3\cdots SiH_3F$	**1**	2.096	-0.58 (25)	-1.43 (61)	-0.14 (6)	-0.18 (8)	-0.23
$H_3C\text{-}CH_3\cdots SiH_3F$	**1**	3.558	-2.39 (51)	-1.80 (38)	-0.16 (3)	-0.37 (8)	-1.18
$CH_4\cdots SiH_4$	**12**	0.953	-0.58 (47)	-0.49 (40)	-0.01 (1)	-0.14 (12)	-0.27

Summary

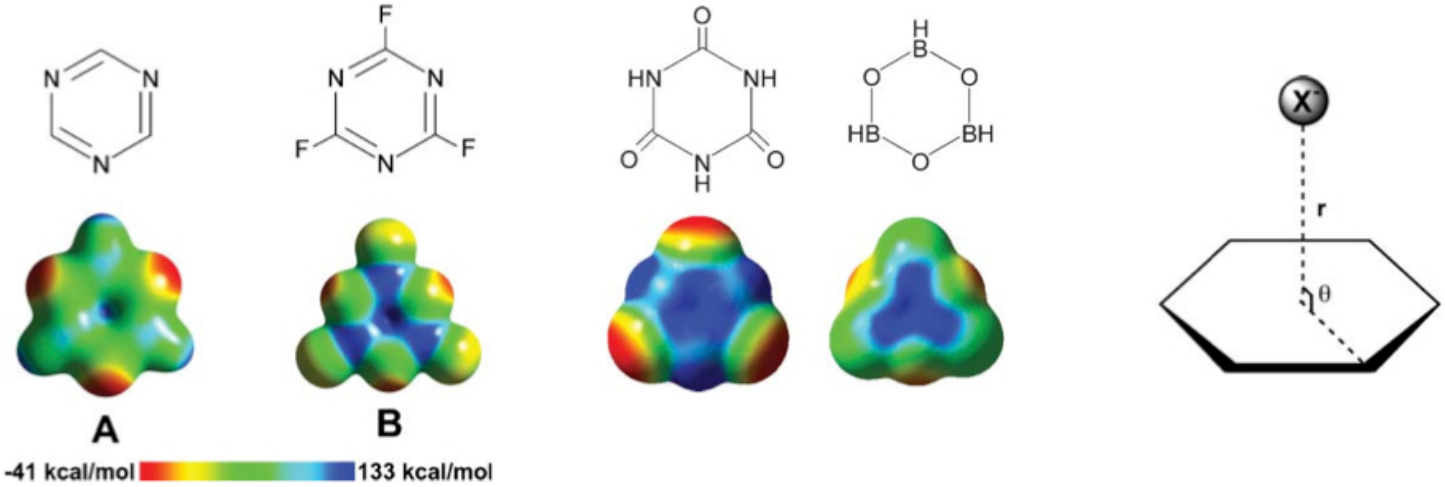
- Alkyl groups can act as donors in π- and σ-hole bonding
- Structural evidence of interaction with triel Lewis acids
- Directional and relatively strong interaction (1 − 8 kcal/mol)
- Electrostatic nature with significant orbital contribution for Al and Ga
- Electrostatics / dispersion interplay dominates methane-silane
- Interaction strength can be modulated by substitution

J. Echeverría, *CrystEngComm* **2017**, *19*, 6289 - 6296

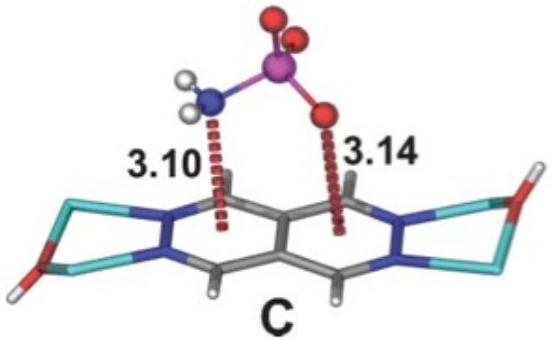
J. Echeverría, *Phys. Chem. Chem. Phys.* **2017**, *19*, 32662 - 32669

Anion-π interactions

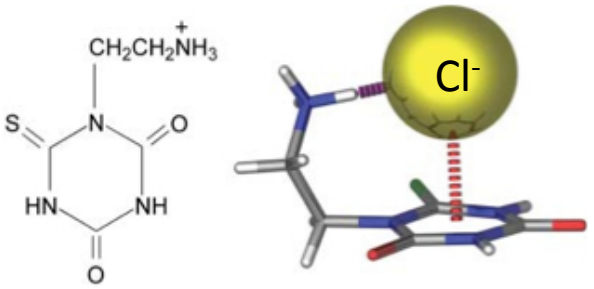
Electron depleted rings



Anion-π



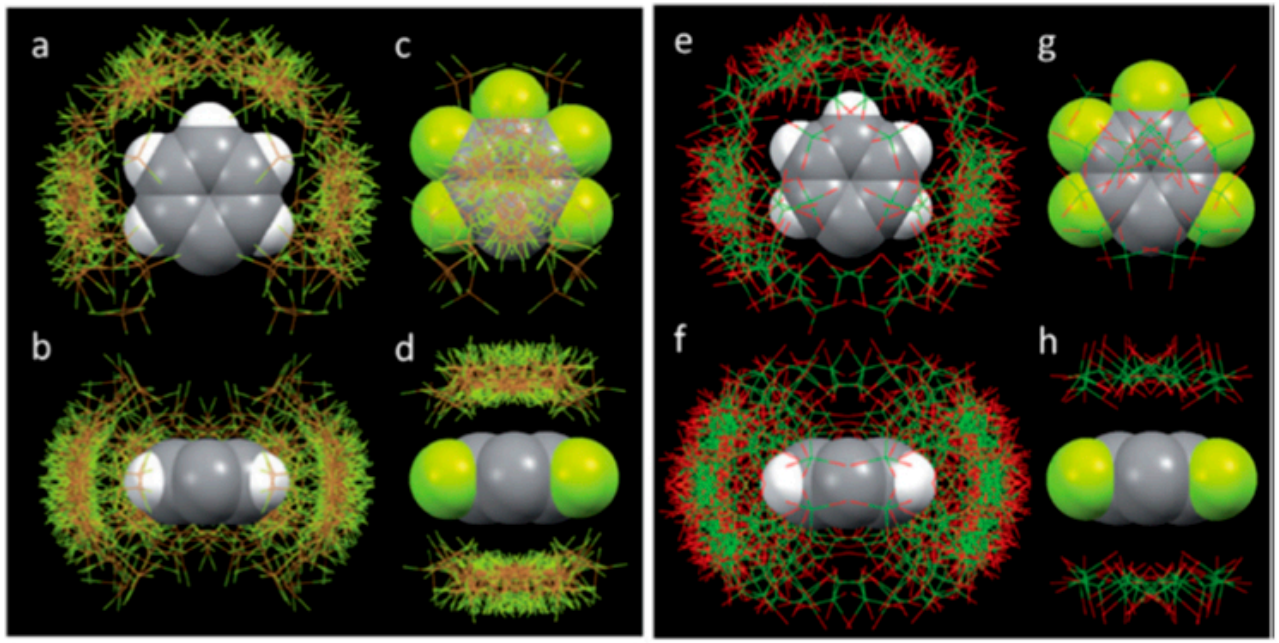
Anion-π + H-bond



Dumbar et al., *Chem. Soc. Rev.* **2008**, *37*, 68-83

Anion-π interactions

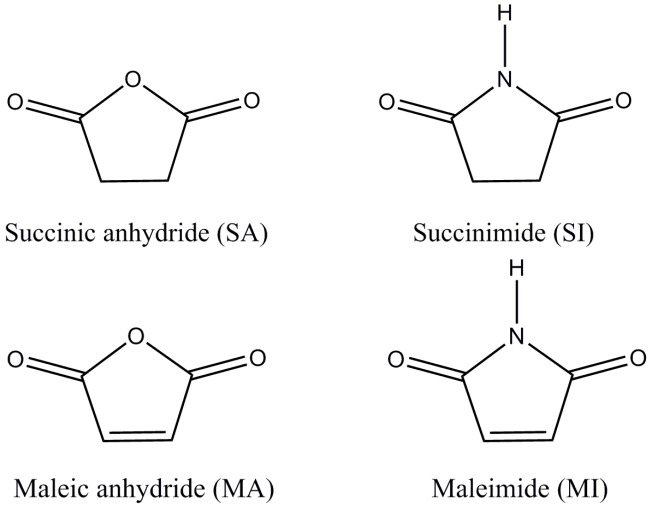
IsoStar plots of contacts between C_6H_6 / C_6F_6 and BF_4^- and ClO_4^-

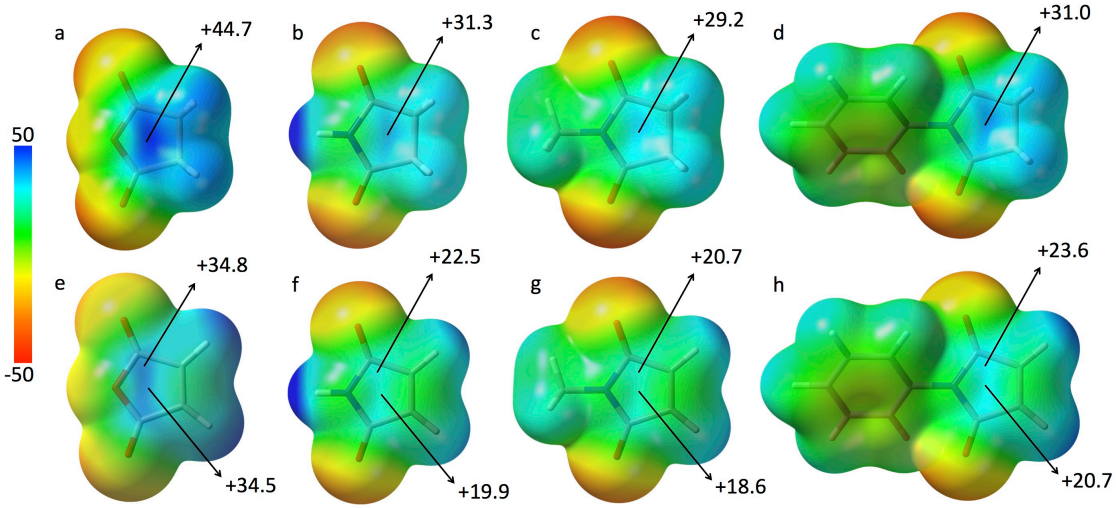


Rissanen et al., *Chem. Rev.* **2015**, *115*, 8867-8895

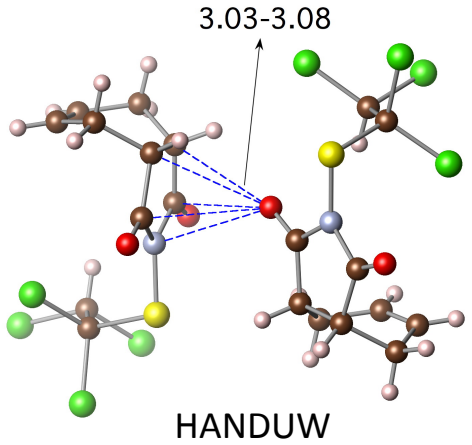
Lone pair-π interactions

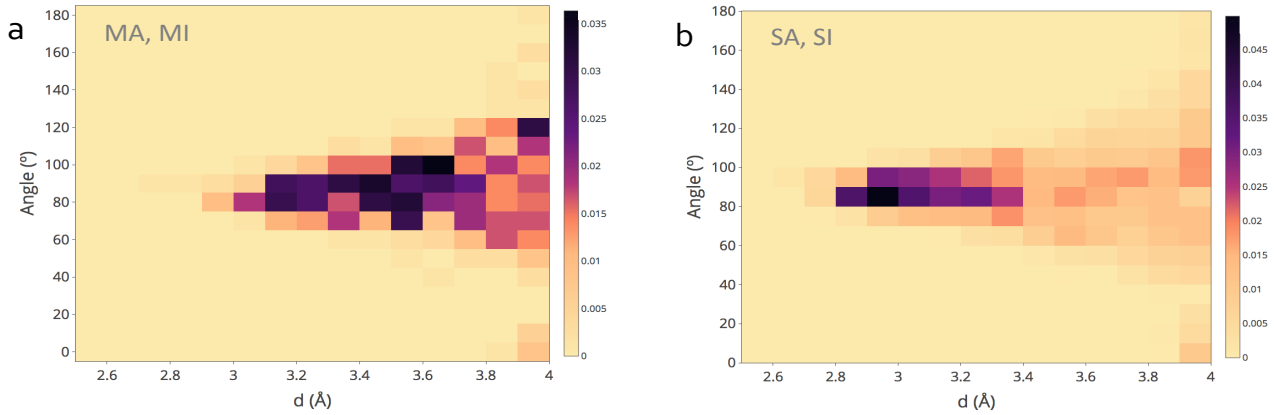
Noncovalent interactions in succinic and maleic anhydride derivatives





CSD Structural Analysis





Echeverría, *Cryst. Growth Des.* **2018**, *18*, 506-512

Take Home Message

- NCIs are everywhere, they are subtle but not faint

- Important when working additively or cooperatively

- They can affect properties of materials, crystal packing, surface adsorption, etc.

- Structural databases are key to see trends

- In calculations, look for trends to rationalize

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