Chemical Concepts from Density Functional Theory

Chemistry from the Linear Response Function

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0. Introduction
Interpretive Chemistry: the ongoing need for interpretational concepts and models in quantum chemistry

• Chemistry as an experimental science → accumulation of data of countless number of molecules (CA > 50.000.000 Substances!)

  Need for unifying theories, concepts, models to rationalize, interpret, predict …… in order to avoid an encyclopaedic “science”.

• Nowadays: Computational Chemistry (WATOC …)

  Accumulation of accurate data on countless number of molecules, reactions,…

  Aren’t we generating a new encyclopaedia??

  STILL need for unifying concepts and models to systematize the theoretical data.
Looking back

• many concepts are MO/VB based cf. HOMO/LUMO, frontier MO theory rationalization of the Woodward Hoffmann rules, ...

• Nowadays DFT is the workhorse par excellence for computational studies on medium and large systems

Isn’t there a need for density based concepts?

Part of DFT founded by RG Parr (1978)

CONCEPTUAL DFT

or

CHEMICAL DFT or CHEMICAL REACTIVITY DFT
Today’s talk

1. - A very brief introduction to Conceptual DFT

1. - Concentrating on the linear response function

• Evaluation

• Representation

• Chemistry from the linear response function

  - Concepts: inductive and mesomeric effects, aromaticity,…

  - Substrates: carbon chains, organic rings, inorganic rings,…

  - An excursion into Alchemical Derivatives: exploring Chemical Space

3. – Conclusions
1. Conceptual DFT

Fundamentals of DFT: the Electron Density Function as Carrier of Information

Hohenberg Kohn Theorems

\( \rho(r) \) as basic variable: \( \rho(r) \rightarrow v(r) \rightarrow H_{op} \rightarrow \text{“everything”} \)
Visualisation of the HK Theorem

\[ \rho(r) \] for a given ground state

\[ v(r) \]

- nuclei
- position/charge
• Variational Principle

\[ v(\mathbf{r}) + \frac{\delta F_{HK}}{\delta \rho(\mathbf{r})} = \mu \]

Lagrangian Multiplier

\[ E = \int \rho(\mathbf{r}) v(\mathbf{r}) d\mathbf{r} + F_{HK}[\rho(\mathbf{r})] \]

• Practical implementation: Kohn Sham equations

Computational breakthrough
Starting point for DFT perturbative approach to chemical reactivity

Consider \( E = E[N, v] \)  
Atomic, molecular system, perturbed in number of electrons and/or external potential

\[
dE = \left( \frac{\partial E}{\partial N} \right)_{v(r)} dN + \int \left( \frac{\delta E}{\delta v(r)} \right)_N \delta v(r) dr
\]

identification \( \Rightarrow \) first order perturbation theory

identification \( \mu \)

identification \( \rho(r) \)


\[
\mu = -\chi \quad (Iczkowski - Margrave electronegativity)
\]
Identification of two first derivatives of E with respect to N and v in a DFT context → **response functions** in reactivity theory

\[
\frac{\partial E}{\partial N} = \mu = -\chi \\
\frac{\delta E}{\delta v(r)} = \rho(r)
\]

**Electronic Chemical Potential**

\[
\frac{\partial^2 E}{\partial N^2} = \eta
\]

\[
\frac{\partial^2 E}{\partial N \partial v(r)} \Rightarrow \frac{\delta \mu}{\delta v(r)} = \frac{\partial \rho(r)}{\partial N}
\]

**Chemical hardness**

**Fukui function**

**Linear response Function**

\[
\frac{\delta^2 E}{\delta v(r) \delta v(r')} = \chi(r, r') = f(r)
\]

- P. Geerlings, F. De Proft, PCCP, **10**, 3028 (Third order derivatives)
Hardness and Fukui function have been widely explored but what about the remaining second order derivative?

\[ \chi(r,r') : \text{linear response function} \]

\[ \left( \frac{\delta^2 E}{\delta \nu(r) \delta \nu(r')} \right)_N = \left( \frac{\delta \rho(r)}{\delta \nu(r')} \right)_N \]

Fundamental Importance: Information about propagation in the density throughout the system of an (external potential) perturbation at position \( r' \)
2. The Linear Response Function

2.1. Introduction

- Work on formal aspects and mathematical aspects (Parr, Senet, Cohen, Ayers)

- Some numerical work (Coulson, Baekelandt, Cioslowski)

  Hückel MO Theory: mutual atom-atom polarizability \( \pi_{rs} = \frac{\partial q_r}{\partial \alpha_s} \)


- NO direct, practical, generally applicable, nearly exact approach available and/or exploited
2.2. A simple perturbational approach; an independent particle model

2.2.1. Preliminaries

- Numerical evaluation: time consuming → benchmark
  

- Can we calculate \( \chi(r,r') \) in a simpler way?
- Closed shell N-electron system in the KS ansatz; frozen orbital approach
- 1st order Perturbation Theory \( \rightarrow \rho^{(1)}(r) \) → taking functional derivative w.r.t \( v(r) \)

\[
\left(\frac{\delta \rho(r)}{\delta v(r')}\right)_N = \chi(r,r') = 4 \sum_{i=1}^{N/2} \sum_{a=N/2+1}^{\infty} \frac{\varphi_i^*(r) \varphi_a(r) \varphi_a^*(r') \varphi_i(r')}{\varepsilon_i - \varepsilon_a} \]

\( \varphi_i \): occupied orbitals \hspace{1cm} \( \varphi_a \): unoccupied orbitals \hspace{1cm} \( \varepsilon_i, \varepsilon_a \): orbital energies

\[
\left(\frac{\delta \rho(r)}{\delta v_{KS}(r')}\right)_N \hspace{1cm} \rightarrow \hspace{1cm} \text{Zeroth order approximation to the linear response kernel for the interacting system (P.W.Ayers, Faraday Discussions, 135, 161, 2007)}
\]
2.2.2. Atoms revisited

  some light elements

• Light elements (KS ansatz; PBE)
  • Spherical potential perturbation
    • plot $r^2 \chi(r', r') r^2$ : radial distribution of the linear response kernel

• Similar to Savin’s plots

• Positive and negative region, for He, duplicated in Be → shell structure
  → Along diagonal: increasing $v(r)$ → depletion of $\rho(r)$
One dimensional version $r^2 \chi(r, r')$ for a fixed $r' \rightarrow r^2 \chi(r, 0)$

- Positive perturbation $\delta v(r') \rightarrow v(r')$ becomes less negative $\rightarrow$ electron density depletion in the vicinity of the nucleus

- Pointlike perturbation

  \[ \Delta \rho(r) = \int dr' \chi(r, r') \delta v(r') \]

  Pointlike perturbation

  \[ \delta v(r') = A \delta (r' - 0) \quad A > 0 \]

  \[ \Delta \rho(r) = A \chi(r, 0) \]

- Alternating positive and negative regions due to conservation of number of electrons

  also in 2D plot
Extending → the noble gases
$\chi(r,0)$ for Ar in the x,y plane
A direct application → polarizability calculations

\[ \alpha_{ij} = -\int dr \, dr' \, r_i \, \chi(r, r') \, r'_j \]  
\[ i, j = x, y, z \]

- Comparison with high level calculations
- Absolute values deviate, trend is respected

Extension to open shell atoms/ Spin polarized linear Response

Transition to a spin-polarized version of $\chi(r, r')$ in the context of spin polarized conceptual DFT
(F. De Proft, E. Chamorro, P. Perez, M. Duque, F. De Vleeschouwer, P. Geerlings,
Chem. Modell. 6, 63-111 (2009))

\[ E = E[N, N_s, v, v_s] \]

\[ v = \frac{1}{2}(v_\alpha + v_\beta) \]

\[ v_s = \frac{1}{2}(v_\alpha - v_\beta) \]

usual DFT potential

related to $B$ with $v_s = \mu_B B_z (r)$

\[ \chi(r, r') \rightarrow \chi_{NN}(r, r') = \left( \frac{\delta^2 E}{\delta v(r) \delta v(r')} \right)_{N,N_s} \]

\[ = \left( \frac{\delta \rho(r)}{\delta v(r')} \right)_{N,N_s} \]
Introduction of

$$\chi_{NS}(\mathbf{r},\mathbf{r}') = \left( \frac{\delta^2 E}{\delta v(\mathbf{r}) \delta v_s(\mathbf{r}')} \right)_{N,N_s} = \left( \frac{\delta \rho_s}{\delta v(\mathbf{r}')} \right)_{N,N_s}$$

$$\rho_s = \rho_\alpha - \rho_\beta$$

$$\chi_{NS}(\mathbf{r},\mathbf{r}') = \frac{\delta \rho_\alpha(\mathbf{r})}{\delta v(\mathbf{r}')} - \frac{\delta \rho_\beta(\mathbf{r})}{\delta v(\mathbf{r}')}$$

: two terms can be expanded (IPM)
\[ \alpha - \beta \]

- Symmetry \( r, r' \)
- Middle region negative: sensitivity of \( \rho_\alpha \) to \( \Delta \) larger than that of \( \rho_\beta \)

\[ \sim (\alpha + \beta) \text{ of Be} \]

\[ \text{cf. ground state configuration} \]

\[ \sim (\alpha + \beta) \text{ of He but contracted} \]

\[ (\text{higher } Z) \]

\( (\text{cf. } N_\alpha > N_\beta) \)
\[ \chi_{NS} \]

\[ \begin{array}{ccc}
\text{Li} & \text{B} & \text{O} \\
\text{Decreasing difference in sensitivity} & & \\
\end{array} \]

Difference in \( n \) \hspace{1cm} \text{Difference in} \ l \hspace{1cm} \text{No (n,l) difference}

Z. Boisdeghien, S. Fias, F. De Proft, P. Geerlings, PCCP, 16, 14614 (2014)
2.2.3. From atoms to molecules

How to extend its use for molecules to look for chemical information

→ condensation at stake in a first approach

An example: \( \text{H}_2\text{CO} \): atom condensed values

<table>
<thead>
<tr>
<th></th>
<th>Present method</th>
<th>Numerical method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td>H</td>
<td>-1.22</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.68</td>
<td>-4.35</td>
</tr>
<tr>
<td>O</td>
<td>0.34</td>
<td>2.99</td>
</tr>
<tr>
<td>H</td>
<td>0.19</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Correlation coefficient between the matrix elements of the two methods:

\[
Y = 0.99x - 0.01 \\
R^2 = 0.96 \\
\text{Slope} \sim 1
\]

For other simple molecules (\( \text{H}_2\text{O}, \text{NH}_3, \text{CO, HCN, NNO} \)) always a high correlation coefficient is obtained with a very small intercept; the slope varies between 1 and 2.

Inductive and mesomeric effects

Transmission of a perturbation through a carbon chain

\[ \chi_{OX} (X = C_0, C_1, C_2 ...) \]

\[ \chi_{NX} \]

Saturated systems

• density response of C atoms on heteroatom perturbation decreases monotonously with distance

• exponential fit: \( r^2 = 0.982 \) (vide infra) → Characterizing and quantifying the inductive effect.
Unsaturated systems

- alternating values
- $C_1, C_3, C_5$ of the chain: minima
  $C_0, C_2, C_4, C_6$ : maxima

$R = \text{OH, NH}_2$: resonance structures

$C_1, C_3, C_5$ : mesomeric passive atoms
  $\rightarrow$ follow same trend as alkane structures (inductive effect)

$C_0, C_2, C_4, C_6$ : mesomeric active atoms
  $\rightarrow$ effect remains consistently large even after 6 bonds (small decrease due to superposition of inductive and mesomeric effect)

N. Sablon, F. De Proft, P. Geerlings, JPClett., 1, 1228, 2010
Substituted benzenes vs cyclohexanes

- cyclohexane:  \( \chi \) decreases exponentially (inductive effect)
  - influence of OH small

- benzene:  
  - maxima at \( C_2, C_4, C_6 \): mesomerically active atoms (mesomeric effect)
  - minima at \( C_3, C_5 \): mesomerically inactive atoms


Aromaticity

Relation with the para delocalization index (PDI) derived from AIM

\[ \delta(A,B) = -2 \int_{A}^{B} \int_{\Gamma} \int_{XC} (r_{1}, r_{2}) \, dr_{1} \, dr_{2} \]

Exchange correlation density; integration over atomic basins

- quantitative idea of the number of electrons delocalized or shared between A and B
  
  (X. Fradera, M.A. Austen, R.F.W Bader, JPCA, 103, 304, 1999.)

- investigated as a potential index of aromaticity
  

- six membered rings of planar PAH’s
  
  - successful correlation of the (1,4) (para) delocalization index with NICS, HOMA, ...

- Does Linear response function \( \chi_{1,4} \) contain similar information?
16 non equivalent sixrings studied by Sola et al.
typical benzene-type pattern encountered before
→ Linear response function as an “electronic” descriptor of aromaticity
Digging further in aromaticity → $\sigma,\pi$ aromaticity (applying $\sigma,\pi$ separation)

**Benzene**

- Decreasing $\sigma$ contribution (cfr. Cyclohexane)
- Zig/zag for $\pi$ and total
- Anti-aromatic molecules: Cyclobutadiene, COT
  
  "*inverted zig zag*"

\[\begin{array}{cccccc}
\chi_{11} & \chi_{12} & \chi_{13} & \chi_{14} & \chi_{15} & \chi_{16} \\
\chi_{\sigma\pi}^{\text{AB}} & -2.668 & 0.537 & 0.281 & 0.503 & 0.281 & 0.537 \\
\chi_{\sigma}^{\text{AB}} & -1.128 & 0.226 & 0.074 & 0.020 & 0.074 & 0.226 \\
\chi_{\pi}^{\text{AB}} & -1.540 & 0.311 & 0.206 & 0.483 & 0.206 & 0.311 \\
\end{array}\]

**S. Fias, P. Geerlings, P. Ayers, F. De Proft, PCCP, 15, 2882 (2013)**
Inorganic rings

Borazine

Boroxine

s-triphosphatriborin
Valence Bond Structures

X = NH, O, PH

\[
\begin{align*}
\text{(I)} & \quad \text{(II)} & \quad \text{(III)} & \quad \text{(IV)} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Molecule</th>
<th>$E_{\text{res}}$</th>
<th>$W$(I)</th>
<th>$W$(II)</th>
<th>$W$(III)</th>
<th>$W$(IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B$_3$N$_3$H$_6$</td>
<td>61.6</td>
<td>0.05</td>
<td>0.05</td>
<td>0.90</td>
<td>0.00</td>
</tr>
<tr>
<td>B$_3$O$_3$H$_3$</td>
<td>27.6</td>
<td>0.02</td>
<td>0.02</td>
<td>0.96</td>
<td>0.00</td>
</tr>
<tr>
<td>B$_3$P$_3$H$_6$</td>
<td>132.6</td>
<td>0.21</td>
<td>0.21</td>
<td>0.58</td>
<td>0.00</td>
</tr>
<tr>
<td>C$_6$H$_6$</td>
<td>161.4</td>
<td>0.47</td>
<td>0.47</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Resonance Energy (kJ mol$^{-1}$) and weights W of the four Valence Bond Structures.


13/04/2015  Pag.33
Borazine

- Typical **resonance** pattern observed in aromatic systems is recovered if one of the N-atoms is chosen as the reference atom.

- Purely **inductive** behaviour (exponential decay of electron delocalization with internuclear distance) is recovered if one of the B-atoms is chosen as the reference atom.

  Dual picture of aromatic character of borazine (cfr. ongoing debate in the literature)

*N. Sablon, F. De Proft, M. Sola, P. Geerlings, PCCP, 14, 3960 (2012)*
2.3. Beyond the independent Particle Model

- Using a CPKS approach

\[ \chi(r, r') = -2 \sum_{i,a, \sigma} \sum_{j,b, \tau} (M^{-1})_{ia\sigma, jb\tau} \phi_{ia\sigma}^*(r) \phi_{ia\sigma}^*(r') \phi_{jb\tau}(r') \phi_{jb\tau}(r') \]

- Independent particle: \[ M_{ia\sigma, jb\tau} = (\varepsilon_b - \varepsilon_j) \delta_{ij} \delta_{ab} \delta_{\sigma\tau} \]

- Random Phase: \[ M_{ia\sigma, jb\tau} = (\varepsilon_b - \varepsilon_j) \delta_{ij} \delta_{ab} \delta_{\sigma\tau} + 2 (ia\sigma \mid jb\tau) \]

- General CPKS: \[ M_{ia\sigma, jb\tau} = (\varepsilon_b - \varepsilon_j) \delta_{ij} \delta_{ab} \delta_{\sigma\tau} + 2 (ia\sigma \mid jb\tau) + 2 (ia\sigma \mid f_{xc}(r, r') \mid jb\tau) \]

\[ f_{xc}(r, r') = \frac{\delta^2 E_{xc}}{\delta \rho(r) \delta \rho(r')} \]

Planar Metallic Systems: Unintegrated plots

Aromaticity order

\[
\frac{1}{2}(\chi_{13}^{13} + \chi_{24}^{24}) \rightarrow \text{Expected order (Feixas et al)}
\]

Mainly $\sigma$ aromatic ($\sim 65\%$)

Insertion of C: decreasing aromaticity, sequence unaltered; but increasing $\sigma$ component

• The use of unintegrated plots

\[
\begin{align*}
\text{Benzene} & \quad \text{Al}_{4}^{2+} \\
\sigma & \quad \text{in plane} \\
\pi & \quad \text{perturbation at top nucleus}
\end{align*}
\]

\[
\begin{align*}
\text{Al}_{4}^{2+} & \quad \text{0.5 au above plane} \\
\sigma & \quad \text{perturbation in that plane at top nucleus}
\end{align*}
\]

Delocalized Nature of the linear Response more pronounced in the $\sigma$ electron density

$\sigma$ Aromatic character

2.4 An extension to Alchemical Derivatives: exploring Chemical Space

  O.A. Von Lilienfeld, IJQC, 13, 1676 (2013)

\[
\left( \frac{\partial E}{\partial Z_\alpha} \right)_{N,Z_\beta,R^M} \quad : \text{change in molecular energy upon changing atomic nuclear charge}
\]

alchemical potential

\[
\text{cf} \quad \left( \frac{\partial E}{\partial N} \right)_{Z^M,R^M} = \left( \frac{\partial E}{\partial N} \right)_v = \mu \quad \text{electronic chemical potential}
\]

\[
\left( \frac{\partial^2 E}{\partial Z^2_\alpha \partial Z^2_\beta} \right)_{N,Z_\gamma,R} \quad \text{cf} \quad \left( \frac{\partial^2 E}{\partial N^2} \right)_v = \eta \quad \text{electronic chemical hardness}
\]

alchemical hardness
Chemical Significance: navigation through the huge Chemical Compound Space for tracing interesting compounds by “Transmutation Reactions”

Chemical Compound Space: set of all possible combinations of chemical elements prone to form stable compounds

\[ \delta_{N_2} \quad CN^- \leftrightarrow N_2 \leftrightarrow ON^+ \]
\[ \delta_{N_1} \quad C_2^{2-} \quad NC^{-1} \quad OC \]

\[ N = \text{cte} \]
\[ \Delta Z = \pm 1 \]

Instead of calculating the energy of each of the “transmutants”, concentrate on the central compound and its alchemical derivatives


\[ Z^M = (Z_1, Z_2, ..., Z_M) \]  nuclear charge vector

\[ R^M = (R_1, R_2, ..., R_M) \]  nuclear position vector

\[ = \sum_{\alpha} \left( \frac{\partial E}{\partial Z_\alpha} \right)_{N,Z_\beta,R} dZ_\alpha + \sum_{\alpha} \sum_{\beta} \left( \frac{\partial^2 E}{\partial Z_\alpha \partial Z_\beta} \right)_{N,Z_\gamma,R} dZ_\alpha dZ_\beta + ... \]

- alchemical potential
- electronic part

- alchemical hardness (diagonal and off-diagonal)
- electronic part
Connection with linear response function

\[
\left( \frac{\partial^2 E}{\partial Z_\alpha \partial Z_\beta} \right)_N = \int \int \left( \frac{\delta^2 E}{\delta v(r) \delta v(r')} \right)_N \frac{\partial v(r)}{\partial Z_\alpha} \frac{\partial v(r')}{\partial Z_\beta} \, dr \, dr'
\]

\[
= \int \chi(r, r') \frac{1}{|r - R_\alpha|} \frac{1}{|r - R_\beta|} \, dr \, dr'
\]
Evaluation of the alchemical potential and hardness

Coupled Perturbed Kohn Sham Theory (cf linear response function)


Prediction of energies of molecules with charge of the central nuclei changed by ± 1

\[ E(Z \pm 1) = E(Z) + \sum_{i=1}^{N} \frac{1}{i!} \left( \frac{\partial^i E}{\partial Z^i} \right) (\pm 1)^i \]

Cf \( \text{CH}_4 \) (HF)

\[ E_0 = -40.214 \text{ au} \quad \frac{\partial E}{\partial Z} = -14.752 \text{ au} \quad \frac{\partial^2 E}{\partial Z^2} = -3.023 \text{ au} \quad \left( \frac{\partial^3 E}{\partial Z^3} \right) = -0.135 \text{ au} \]

\[ E_0(Z + 1) = E_0(\text{NH}_4^+) = -56.500 \quad \text{cf “exact”} \quad -56.565 \]

\[ E_0(Z - 1) = E_0(\text{BH}_4^-) = -26.950 \quad -26.987 \]
For the complete series of six $\text{N}_2$ transmutation reactions (B3LYP/cc-pVTZ) an error between “vertical” and alchemical transmutation energies of 0.03 a.u. was obtained

\[ \text{N}_2 \rightarrow \text{CO} \text{ case: } 0.004 \text{ au } \sim 2.5 \text{ kcal mol}^{-1} \]

Not “chemical accuracy” yet but the ordering of the energy of the compounds comes out correctly

Straightforward procedure for looking at neighbouring structures when exploring chemical space

Recent quantum chemical interest in Molecular Design

A more involved application: transmutation of benzene

\[
(C-H)_n \rightarrow N_n \rightarrow \text{azines} \quad \text{iso-electronic transmutations}
\]

\[
(C-C)_n \rightarrow (B-N)_n \rightarrow \text{azoborines}
\]

Azoborines
- n-sequence correctly reproduced
- sequence of isomers
  - n=1 (3)
  - n=2 (11)
  - n=3 (3)

Transmutation energies and alchemical derivates effective tools for stability prediction and exploring CCS

Present work: CC \rightarrow BN substitution in fullerenes, graphene, ...

3. Conclusions

• Conceptual DFT offers a broad spectrum of reactivity descriptors in line with the need for unifying concepts.

• The “missing” second order derivative, the “linear response function”, comes within reach with various techniques of increasing complexity. It is a tool to see how $\Delta v$ perturbations are propagated through an atom or molecule. Its physical relevance becomes apparent, thanks to various representations of the kernel for atoms revealing atomic shell structure, and extensions in the context of spin polarized Conceptual DFT.

• The computational results on molecules reveal that important chemical information can be retrieved from the linear response function: from inductive and mesomeric effects to the aromatic character of organic and inorganic rings. In the context of alchemical derivatives it opens the gate for exploring chemical compound space in an efficient way.
• The role of the linear response function in conduction of molecular electronic devices.

  First results: $\chi \rightarrow$ atom – atom polarizabilities  
  (Hückel-\(\pi\)-type approach)


• The role of DFT based reactivity descriptors in molecular design

  Inverse design of stable radicals with highly electrophilic or nucleophilic character: role of the electrophilicity ($\omega = \mu^2 / 2\eta$)

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Featuring work from the ALGC research group, focusing on Conceptual Density Functional Theory for more than 20 years, with applications to various subfields of chemistry: inorganic, organic, bio- and materials-chemistry. Prof. Paul Geerlings, Algemene Chemie, Vrije Universiteit Brussel, Pleinlaan 2, 1050 Brussels, Belgium.

Conceptual DFT: chemistry from the linear response function

Within the context of reactivity descriptors known in Conceptual DFT, the linear response function ($\chi(r,r')$) remained nearly unexploited. Its evaluation and visualization are highlighted in the present review, revealing its chemical and physical significance, retrieving atomic shell structure, inductive and mesomeric effects, electron delocalisation, aromaticity...

As featured in:


www.rsc.org/chemsocrev
Inverse Molecular Design

Introduction

- Previous part: application of concepts and indices to understand electronic structure and its relation to reactivity for atoms and indices

- Alchemical Derivatives: a first step towards exploring chemical space

- Exploring the properties of molecules encountered upon navigating through molecular space: molecule $\rightarrow$ property

- Now: design of new compounds with optimized reactivity indices: property $\rightarrow$ molecule $\rightarrow$ Inverse Molecular Design

- Case study: design of stable organic radicals
Intrinsic Radical Stability Scale

- Homolytic bond cleavage of the molecule A-B into the radicals A and B

\[ A - B \rightarrow A^* + B^* \]

- Characterized by the bond dissociation enthalpy (BDE)

- Use BDE to quantify radical stability through a model

\[
BDE(A - B) = \begin{cases} 
(stab_A + stab_B) + \alpha \Delta \omega_A \Delta \omega_B & \text{if } \Delta \chi_A < 0 \text{ and } \Delta \chi_B < 0 \\
(stab_A + stab_B) + \alpha \Delta \omega_A \Delta \omega_B + b \Delta \chi_A \Delta \chi_A & \text{otherwise}
\end{cases}
\]

\textit{stab: intrinsic stability of the radical}
\[
BDE(A - B) = \begin{cases} 
(\text{stab}_A + \text{stab}_B) + a\Delta\omega_A\Delta\omega_B \\
(\text{stab}_A + \text{stab}_B) + a\Delta\omega_A\Delta\omega_B + b\Delta\chi_A\Delta\chi_A 
\end{cases}
\]

if \( \Delta\chi_A < 0 \) and \( \Delta\chi_B < 0 \), otherwise

Computed BDE (B3P86/6-311+G**)

\((\omega = \mu^2/2\eta; \omega_{\text{ref}} = 2\) : borderline between electrophilic and nucleophilic radicals

Intrinsic stabilities

enhanced electrophilicities

\(\chi_{\text{ref}} = 3\) (\(~\text{medium value between highest and lowest Pauling, Electronegativity in database}\) enhanced electronegativities

Performance of the model:

\[
y = 1.057x - 26.123 \\
R^2 = 0.958 
\]
<table>
<thead>
<tr>
<th>Group</th>
<th>Stability in kJ mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂CN</td>
<td>70.7</td>
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**unstable radicals**

**stable radicals**

Inverse design approach

- Use of this model (against H in A-B) to design stable organic radicals
  → Start from BDE (A-H)

- Inverse molecular design: find an optimal external potential of the system, generating a molecular system with the associated target properties (cfr W.Yang, X.Hu, D.N.Beratan, W.Yang, J.Am.Chem.Soc., 128, 3228 (2006))

- Challenge ! large number of possible structures accessible through the systematic variation of the composition of the molecular system
  
  e.g. for a given framework : 5 sites and 21 substituents yield $21^5$ combinations
  $\sim 4 \times 10^6$
Approach:

1. Choice of a molecular framework of interest
   - determine number of sites that can be modified
   - determine number of substituents per site

2. Define property of interest to be optimized (here: \textit{stab} values)

3. Choice of property optimizing method

Molecular framework: thiadiazeynil structure

Stable radical: \( \text{stab} = 70 \text{ kJ mol}^{-1} \)

5 sites and 21 substituents per site:

size of chemical space $= 21^5 \approx 4 \times 10^6$ molecules
• Choice of property optimizing method: Best-First-Search Methodology

• Algorithm:

  • optimizes the property of a molecule by making chemical changes and evaluating the influence of those changes on the property of interest

  • chemical changes brought in through the independent site approximation, so the various sites are optimized individually
Results: most stable radicals

- **Thiadiazinyl_opt**
  - $\text{stab} = 13 \text{ kJ mol}^{-1}$

- **Thiadiazinyl_opt_OH**
  - $\text{stab} = 19 \text{ kJ mol}^{-1}$

- **Thiadiazinyl_opt_Ph**
  - $\text{stab} = 32 \text{ kJ mol}^{-1}$
Comparison with other stable organic radicals

(a) Triphenylmethyl

(b) Phenalenyl

(c) N,N-diphenyl-N′-picrylhydrazyl

(d) 1,5-diphenylverdazyl

(e) 1,3,5-triphenylverdazyl