

Visualization of Regional Properties of Hardness and Softness in Molecules

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The local atomic quantities of hardness and softness are generated from semiempirical and *ab initio* MO calculations and can be displayed in different rendering modes such as Connolly surfaces, ball-and-stick models of CPK models.

1. INTRODUCTION

Visualization of the extent of molecular properties in different areas of the molecule is an important technique to support structural concepts by computer graphics.

The electronic structure of chemical compounds is the fundamental quantity of that what we call "STRUCTURE"; it is responsible for the strength of the chemical bonds, for the spatial structure, for the chemical behavior, and for all of the physico-chemical properties. In the language of quantum mechanics, the properties (observables) are expectation values of the corresponding operators applied to the molecular wave functions. This should be kept in mind for all Structure–Property Relations we want to derive in our investigations or exploit in predicting new properties or activities for new structures.

What is the relation between the calculated electronic structure of a molecule by quantum mechanical approaches and the well-known empirical schema of Hard and Soft Acids and Bases,¹ which was derived 30 years ago by Pearson?

2. CONCEPT OF HARD AND SOFT ACIDS AND BASES

The development of structural thinking in chemistry was often based on empirical relations between those properties, which can be measured or can be found in literature and those which one wants to investigate. This is thoroughly useful because both quantities result from the same electronic structure of the molecule under consideration. Those concepts which do not originate from a "strong" theory but clearly and vividly describe a series of relations among chemical data are important, and because of their simplicity they accompany our structural thinking and the technical terms in our scientific language in chemistry. Sometimes they can be improved on the bases of theoretical methods. This was the case for the well-known HARD and SOFT ACIDS and BASES concept and related terms, like the following:

- electronegativity
- donor and acceptor numbers
- electrophilic and nucleophilic scales
- polarity and polarizability (empirical scales)
- incremental scheme (group contributions) for electronic, magnetic, thermodynamic, and other properties

Hardness and softness in the sense of the HSAB concept¹ were developed on the basis of empirical data. The historical

development shows this progress for the HSAB concept by the following steps:

- 1963 PEARSON¹ qualitative HSAB-concept with examples of molecules, ligands, and fragments grouping roughly together
- 1968 KLOPMAN² quantum-mechanically derived concept of Charge and Frontier-Orbital Controlled Chemical Reactions (based on perturbation theoretical treatment) in terms of hard and soft donors and acceptors.
- 1983 PARR, PEARSON³ first theoretical definition of electronegativity (χ) and hardness (η) as global molecular quantities within the quantum mechanical Density Functional Theory (DFT). Global softness⁴ has been formulated in a similar way.
- 1985 PEARSON⁵ empirical scheme of numerical values for "Absolute Hardness" (e.g., ref 6) calculated from experimental data of molecular ionization potentials and electron affinities.
- 1993 NALEWAJSKI⁷ "Charge Sensitive Analysis" (CSA) for a new rationalization of the HSAB principle, in order to get local values of hardness and softness.

Here we will demonstrate how local atomic quantities of hardness and softness, generated from semiempirical and *ab initio* MO calculations followed by CSA, can be visualized and used to understand chemical properties, intermolecular interactions, and chemical reactivity.

Molecular structures can be taken into account by spatial, electronic, and energetic features as listed in Table 1.

In the interpretation of intermolecular interactions and chemical reactivity, we have to take into account that the reactivity of the molecule as a whole may be divided into regions of different behavior (regioselectivity). So we have to replace some global characteristics by local ones. Visualization of the extent of molecular properties in different areas of the molecule is a helpful and important technique to support structural concepts by computer graphics, to relate the expected or observed physico-chemical properties and the chemical behavior of molecules to the calculated electronic structure.

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Table 1. Some Characteristics of the General Term “STRUCTURE”

spatial	electronic	energetic
position of the nuclei	electron distribution	interactions
atomic coordinates	electron densities	force constants
bond length, bond angle	atomic charges	molecular orbitals
molecular volume	molecular electrostatic potential	total energy
CPK- or ball-stick model		heat of formation

Table 2. Structure and Dynamics in Relation to the HSAB Concept

	structure	dynamics
geometrical structure	spatial arrangement of atoms	flexibility
exp. observation	X-ray scattering	NMR relaxation
electronic structure	electron density	electron move ability
exp. observation	polarity, dipole moment μ (vector)	polarizability α (tensor)
HSAB concept	hardness	softness

Table 3. Convenient Terms To Describe the Electronic Structure

	local	global	HSAB
static	atomic charge	polarity	hardness
dynamic	move ability	polarizability	softness

In Table 2 we summarize some conventional terms of the electronic structure compared with those used in the HSAB concept. Similar to structure and dynamics (Table 2) we have to take into account both of these aspects of an electronic structure (Table 3).

3. CHARGE SENSITIVE ANALYSIS

Within the quantum mechanical Charge Sensitive Analysis (CSA),⁶ we are able to derive local atomic quantities for electronegativity, hardness and softness besides the global quantities from calculated geometrical and electronic structure data. These data can be converted from any quantum mechanical calculation. We use it for semiempirical MO programs (MOPAC, ZINDO) and some ab initio programs (GAUSSIAN94, TURBOMOLE, GAMESS, ADF, DGauss, deMon) successfully.

At the moment we can calculate the following CSA-values:⁸

•molecular and atomic electronegativity

$$\chi_M = -\left(\frac{\partial E}{\partial N}\right) = \frac{I + A}{2} = -\mu$$

•atomic hardness

$$\eta = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right) = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right) = \frac{I - A}{2}$$

•molecular softness

$$\sigma = \frac{1}{\eta}$$

•atomic Fukui index: the relation of local to global softness

$$f_i = \frac{\sigma_i}{\sigma_g}$$

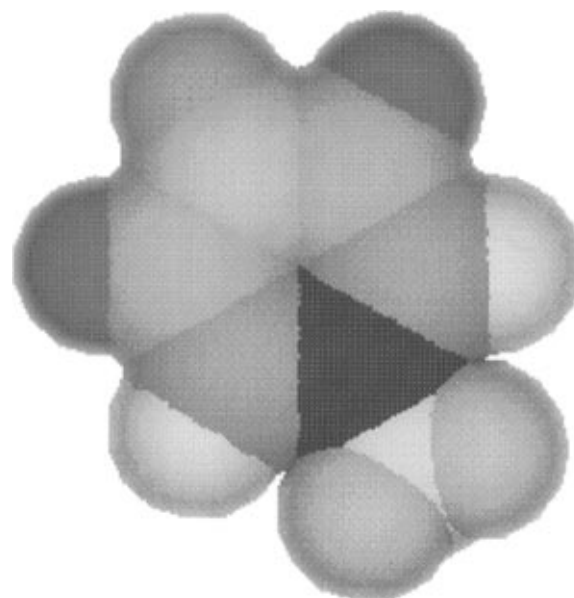
We summarize some of the calculated atomic quantities of the aromatic heterocyclic compounds pyrrole (Table 4) and pyridine (Table 5). The numbering of the atoms in these

Table 4. Atomic Values for the Pyrrole Molecule

atom	charge	hardness	Fukui index	electronegativity
N1	−0.224	0.413	0.000	0.216
C2	−0.028	0.359	0.071	0.204
C3	−0.130	0.326	0.118	0.193
H1	0.199	0.586	0.135	0.278
H2	0.093	0.554	0.134	0.272
H3	0.077	0.550	0.110	0.254

Table 5. Atomic Values for the Pyridine Molecule

atom	charge	hardness	Fukui index	electronegativity
N1	−0.230	0.410	0.141	0.196
C2	0.054	0.374	−0.005	0.211
C3	−0.124	0.328	0.151	0.213
C4	−0.008	0.365	−0.022	0.219
H2	0.084	0.552	0.138	0.273
H3	0.072	0.548	0.092	0.269
H4	0.066	0.547	0.131	0.274

**Figure 1.** Aniline atomic hardness colored with the “rainbow” model.

structures starts from the heteroatom, and symmetric positions are counted only once.

The charge distribution in molecules is very common for the interpretation of chemical behavior and chemical reactivity. But we cannot compare directly the calculated charges between different kinds of atoms. For example we have a different electronegativity (capability for withdrawing electrons from neighbor atoms) for carbon and nitrogen atoms. Compounds with negatively charged nitrogen atoms are very usual, but this does not mean that the electrophilic attack goes to that atom.

Atomic hardness, e.g., is one of those atomic quantities which can be compared. In both molecules above we see that the carbon atoms have the lowest values of hardness that means they represent the softest region in the structures for electrophilic attack (softness is just the reciprocal value of the hardness).

In the pyridine the electrophilic substitution takes place preferentially at the carbon atom C3; this is supported by the smallest value of the hardness. The ratio of ortho, meta, and para substitution is well reflected by the hardness and the Fukui-index.

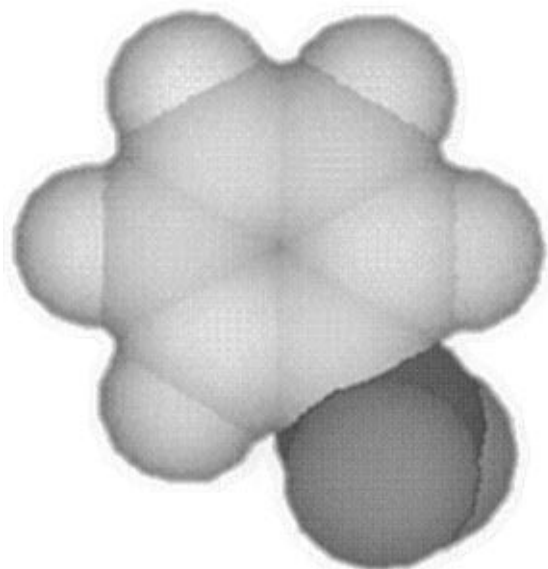


Figure 2. Atomic hardness in nitrobenzene.

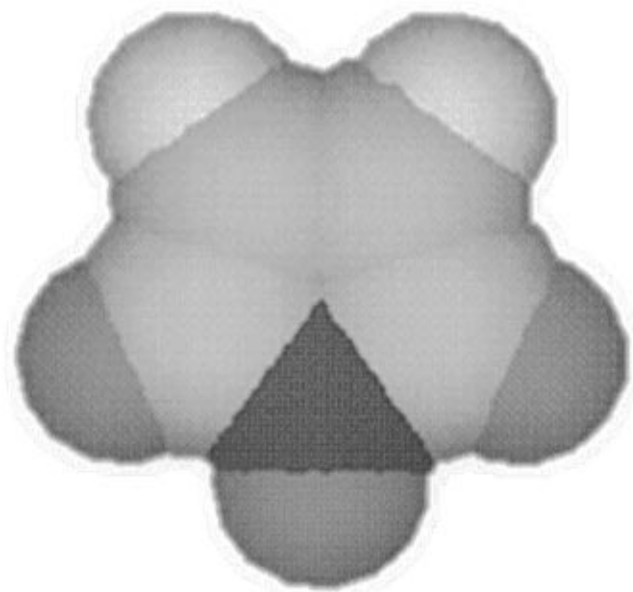


Figure 3. Atomic hardness of pyrrole.

For the visualization of these local atomic quantities on a molecular surface we developed a program, written in C running under AIX operating system in a X-Windows environment on a IBM-RS/6000-Graphics-Workstation. The generated molecular surface (Connolly Surface) is colored with the actual atomic quantities in two kinds:

- “rainbow”: the calculated values are normalized and colored linearly to the different colors of the rainbow.
- “intensity”: the normalized atomic quantities are used to scale the intensity of the surface color. The kind of color is only dependent on the type of the chemical element.

We prefer the rainbow coloring model, because it shows slight differences in better representations. The figures in this article are shown in black and white. (See Supporting Information for color figures.)

For the visualization one can choose from three different molecular representations:

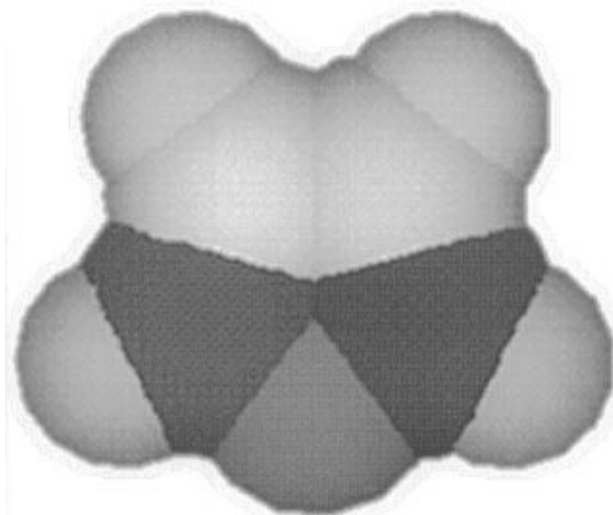


Figure 4. Atomic hardness of furane.

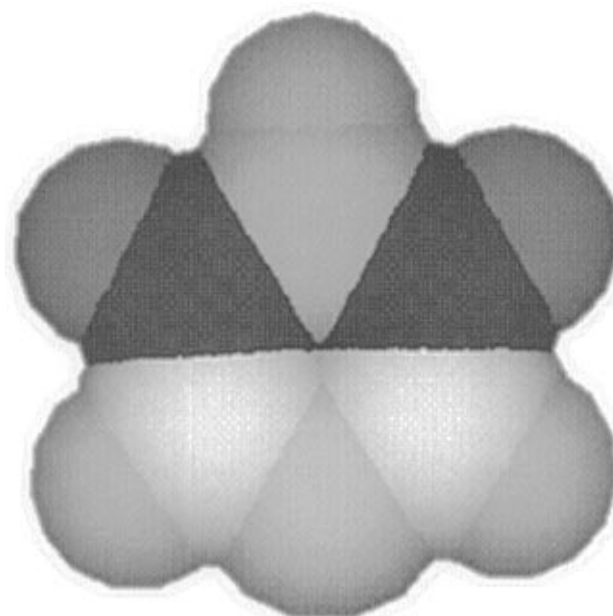


Figure 5. Atomic hardness of pyridine molecule.

- Ball and Stick model
- CPK volume model
- Connolly surface model

The next figures show some examples of applications of the CSA_VIEW program. The calculated CSA atomic hardness of the aniline molecule are calculated from atomic MNDO-charges (MOPAC program).

Figure 1 gives a good impression of the equivalent atomic positions and shows the electronic substituent effect in the ortho, meta, and para positions to the amino group in the benzene ring.

The next example (Figure 2) is the nitrobenzene molecule showing the withdrawing substituent effect of the nitro group.

The following three examples want to show the electronic effect of heteroatoms in aromatic rings. These pictures show the CSA values of the electron distribution of the valence electrons, but there is no possibility for a separate representation of electrons belonging to the σ - or to the π -symmetry (those may have quite different effects, $-I$ and $+M$).

Further development of the visualization of the two important properties of an electronic structure, the hardness and softness, will be the interpretation of the calculated Fukui function and a distance dependent contribution from neighboring atoms to the value of an atomic surface area.

4. SUMMARY

With the 30 years of history, the HSAB concept has made enormous progress. It has been developed from an empirical qualitative to a quantitative concept, whose terms can be derived on the basis of modern quantum mechanics. The global molecular quantities like electronegativity, hardness, and softness can be calculated. Within the Charge Sensitive Analysis, it is possible to go to the essential regional values to characterize the chemical behavior and chemical reactivity of the alternative centers of a molecule.

We have programmed recently a pictorial representation, to visualize hardness and softness as a local property on the molecular surface of molecules. The derived numerical values can be visualized with the CSA_VIEW program⁹ running with X-Windows on UNIX graphic workstations. The coloring of the atomic spheres is similar to those well-known pictures of the Molecular Electrostatic Potential (MEP) or the Molecular Lipophilic Potential (MLP) which were successfully used in molecular modeling.

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Supporting Information Available: The figures in this paper are available in color on the World Wide Web. See any current masthead page for Internet access instructions.

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