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## Local molecular properties and their use in predicting reactivity

Received: 5 May 2003 / Accepted: 8 July 2003 / Published online: 2 September 2003  
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**Abstract** Expressions for the local electron affinity, electronegativity and hardness are derived in analogy to the local ionization energy introduced by Sjöberg, Murray and Politzer. The local polarizability is also defined based on an additive atomic orbital polarizability model that uses Rivail's variational technique. The characteristics of these local properties at molecular surfaces and their relevance to electrophilic aromatic substitution, to  $S_N2$  reactivity and to the nucleophilicity of enolate ions are discussed.

**Keywords** Surface properties · AM1 · Local ionization energy · Local electron affinity · Local hardness

### Introduction

The use of molecular surfaces, based either on the molecular electron density or on simple geometric criteria, onto which local properties such as the molecular electrostatic potential (MEP) have been projected [1] has a long tradition in the qualitative interpretation of chemical reactivity. The molecular electrostatic potential gives a powerful description of molecular properties, such as strong non-covalent interactions, that are predominantly electrostatic in nature. However, much classical chemical reactivity depends on two-electron donor–acceptor interactions that are not encoded in the MEP. Local properties such as the various types of superdelocalizability [2, 3] and Fukui function [4, 5] have been formulated in order to describe such interactions and are still often used. These properties are fundamentally different to the MEP because they are not physically observable, but nevertheless provide information about regio- or stereoselectivity of reactions, the relative reactivity of different substrates etc. Murray and Politzer

[6, 7, 8, 9, 10] have used the MEP projected onto the isodensity molecular surface to derive descriptors for predicting the physical properties of molecules and we [11, 12, 13, 14, 15, 16, 17, 18] have used such descriptors calculated with semiempirical molecular orbital (MO) theory extensively in quantitative structure–property relationships (QSPRs). These descriptors, however, only treat electrostatic, not donor–acceptor interactions and therefore do not provide a complete description of the surface properties of molecules. Sjöberg et al. [19] recognized this deficiency and introduced the local ionization energy,  $IE_L$ , defined as

$$IE_L = \frac{\sum_{i=1}^{HOMO} -\rho_i \varepsilon_i}{\sum_{i=1}^{HOMO} \rho_i} \quad (1)$$

where *HOMO* is the highest occupied molecular orbital (MO),  $p_i$  the electron density attributable to the *i*th MO at the point being considered, and  $\varepsilon_i$  the Eigenvalue (i.e.  $-\varepsilon_i$  is the Koopmans' theorem ionization potential associated with the *i*th MO).

Murray and Politzer [19, 21, 22, 23] have discussed the properties of the local ionization energy in detail, but it is clear that it only describes the donor properties of the molecule directly. We now report extensions of this idea to describe acceptor and other electronic properties at molecular surfaces or in the vicinity of molecules.

### Local properties

The normal extension of Koopmans' theorem to electron affinities can be used to define the local electron affinity,  $EA_L$ , exactly analogously to the local ionization energy as

$$EA_L = \frac{\sum_{i=LUMO}^{norbs} -\rho_i \varepsilon_i}{\sum_{i=LUMO}^{norbs} \rho_i} \quad (2)$$

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where *LUMO* is the lowest unoccupied MO and *norbs* is the number of MOs.

The local electron affinity should describe the acceptor properties of the molecule, but can also be used in combination with the local ionization energy to give two further local properties, the local Mulliken electronegativity, [24]  $\chi_L$  and the local hardness, [25]  $\eta_L$

$$\chi_L = \frac{IP_L + EA_L}{2} \quad (3)$$

$$\eta_L = \frac{IP_L - EA_L}{2} \quad (4)$$

Peter Politzer has pointed out that the concept of a local electronegativity is not consistent with the principle of electronegativity equalization. This objection is valid if, as is usually assumed, the electronegativity can be equated to minus the chemical potential and if, as suggested by our naming convention, the local electron affinity actually corresponds to the energy gained by attaching an electron. This is not the place to discuss the relationship between electronegativity and chemical potential, which has been treated more completely by Parr et al. [26] and by Politzer and Weinstein, [27] but we can justify the use of Eq. (3) pragmatically.  $EA_L$  does not actually represent an electron affinity, even within the definition of Koopmans' theorem. It is perhaps better described as a local index of the acceptor properties of the molecule and is more closely related to attack by a nucleophile than to one-electron reduction. We retain the misnomer "local electron affinity", however, in order to emphasize the analogy to the definition of the local ionization energy. Our local electronegativity does not show much variation over the surface of molecules (see discussion below) but it is also not constant. Its variation over the molecular surface therefore probably reflects the deficiencies of our definitions of local properties, rather than providing any fundamental description of the molecule. This view is supported by further work on descriptors derived from the local properties. [28]

The above properties should describe most intermolecular interactions adequately, but we also have the opportunity to define the local polarizability directly, rather than indirectly via the hardness. This is particularly interesting in view of a recent paper by Ping, Murray and Politzer [29] in which the relationship between the local ionization energy and the local polarizability is discussed in detail. We now have the opportunity to define a local polarizability as a density-weighted property.

Within the NDDO approximation used in most modern semiempirical techniques, the molecular electronic polarizability is easily accessible using the parameterized version [30] of the variational technique introduced by Rivail. [31] Moreover, we have defined [32] an additive atomic polarizability model on the basis of this technique. The partitioning scheme described for atomic polarizabilities can equally well be used to define "atomic orbital polarizabilities". [33] This allows us to define the local polarizability,  $\alpha_L$ , at a point near the molecule as

$$\alpha_L = \frac{\sum_{j=1}^{norbs} \rho_j^1 q_j \bar{a}_j}{\sum_{j=1}^{norbs} \rho_j^1 q_j} \quad (5)$$

where  $q_j$  is the Coulson occupation and  $\bar{a}_j$  the isotropic polarizability attributed to atomic orbital  $j$ . The density  $\rho_j^1$  is defined as the electron density at the point in question due to an exactly singly occupied atomic orbital  $j$ . Note that the sum is now over atomic orbitals, rather than MOs as for the other local properties. Thus, the local polarizability is a simple occupation-weighted sum of the orbital polarizabilities in which the contribution of each AO is determined by the density of the individual AO at the point being considered.

The local ionization energy, electron affinity, electronegativity and hardness can be calculated from the output of any molecular orbital program. We have made a simple graphical user interface, GEISHA [34] that uses a standard .sdf file written by VAMP 8.1. [35] The local polarizability requires a version 8.2 of VAMP (not yet released), which can calculate the atomic orbital polarizabilities. GEISHA calculates the values of the local properties at the centers of the tesserae of a triangulated solvent-excluded surface (SES) [36] and color codes the surface accordingly.

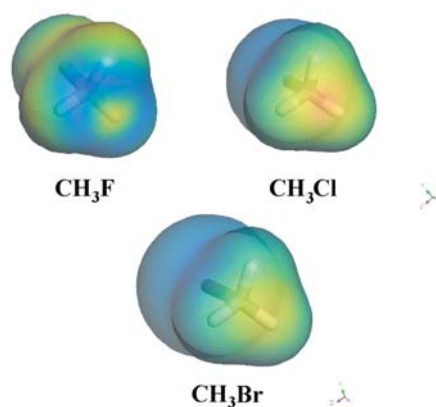
In the following, we give some examples of the characteristics of the local properties and their relevance for chemical reactivity.

## Nucleophilic substitution

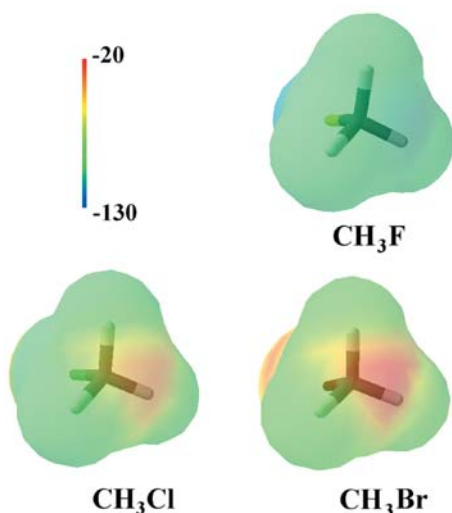
Figure 1 shows the nucleophilic Fukui function (calculated with Dmol<sup>3</sup> [37] within Materials Studio 2.2 [38] using a double numerical plus  $d$  (DND) basis set [37] and the Perdew–Wang 91 density functional [39]) for CH<sub>3</sub>F, CH<sub>3</sub>Cl and CH<sub>3</sub>Br. The increased reactivity of the chloride and bromide is clear, but not necessarily that the bromide is more reactive than the chloride. These pictures are shown for comparison with our new local properties.

Figure 2 shows the local electron affinity at the backside of CH<sub>3</sub>F, CH<sub>3</sub>Cl and CH<sub>3</sub>Br with the same color scale for all three molecules.

The reactivity order for S<sub>N</sub>2 substitution (and the position of attack) can be seen clearly from the areas of most positive local electron affinity (i.e. those areas where accepting an electron is most favorable) at the backside of the molecules. More extensive investigations with other S<sub>N</sub>2 substrates suggest that there is at least a qualitative correlation between  $IE_L$  on the molecular surface at the position of attack and the reactivity of the molecule. Figure 3 shows the local hardness for the three molecules. This property is in this case less informative than the local electron affinity, but agrees qualitatively with expectations.



**Fig. 1** The nucleophilic Fukui function (PW91/DND) for fluoro-, chloro- and bromomethane. The color code ranges from 0.0014 a.u. (blue) to 0.033 a.u. (red) for all three molecules

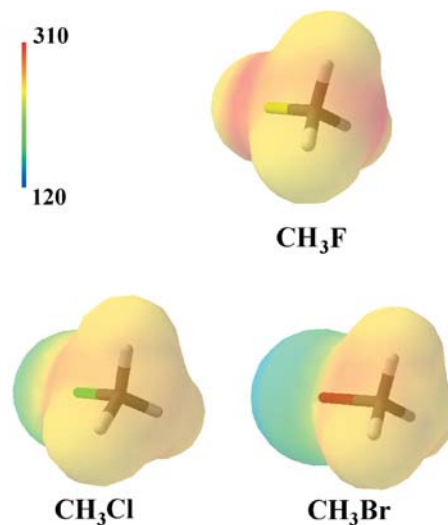


**Fig. 2** The local electron affinity for fluoro-, chloro- and bromomethane (AM1) shown from the direction of attack by a nucleophile. The color scale ranges from  $-130$  (blue) to  $-20$  kcal mol<sup>-1</sup> (red) and is the same for all three molecules. Red areas are those for which the interaction with a donor is most favorable

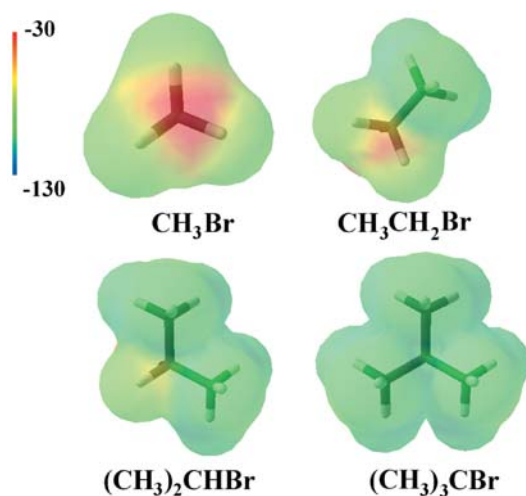
Perhaps a little surprisingly, the local electron affinity can also visualize the effects of increased branching on S<sub>N</sub>2 reactivity, as shown in Fig. 4. The red area indicating favorable attack by a nucleophile decreases both in size and in the magnitude of the most positive local electron affinity with increasing substitution at the central carbon atom.

## Nucleophiles

The local properties are also useful for visualizing the strengths and characters of nucleophiles. Figure 5 shows the local ionization energy for two neutral nucleophiles, water and H<sub>2</sub>S and their anionic equivalents, OH<sup>-</sup> and



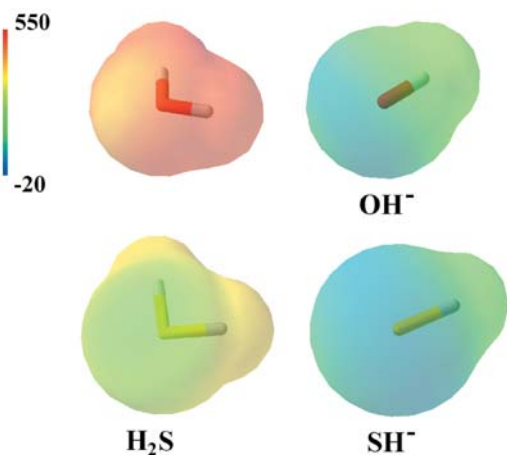
**Fig. 3** The local hardness for fluoro-, chloro- and bromomethane (AM1). The color scale ranges from 120 (blue) to 310 kcal mol<sup>-1</sup> (red) and is the same for all three molecules. Red areas are those for which the interaction with a donor is most favorable



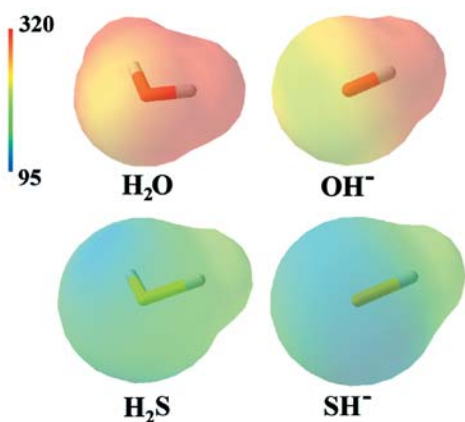
**Fig. 4** The local electron affinity shown from the position of S<sub>N</sub>2-attack for bromomethane, bromoethane, 2-bromopropane and 2-bromo-2-methylpropane (AM1). The color scale ranges from  $-130$  (blue) to  $-30$  kcal mol<sup>-1</sup> (red) and is the same for all four molecules. Red areas are those for which the interaction with a donor is most favorable

SH<sup>-</sup>. Both the facts that the sulfur nucleophiles are stronger than their oxygen equivalents and that the anions are better nucleophiles than the neutral compounds are clearly visible.

The local hardness, shown for the four nucleophiles in Fig. 6, encodes different information and emphasizes the difference between the oxygen and sulfur nucleophiles. The local electronegativity, on the other hand, differentiates the nucleophiles on the basis both of the central element and the charge. This is shown in Fig. 7. Note also that the local electronegativity is relatively constant on the surface of each species, as discussed above.



**Fig. 5** The local ionization energy shown for water, OH<sup>-</sup>, H<sub>2</sub>S and SH<sup>-</sup> (AM1). The color scale ranges from -20 (blue) to 550 kcal mol<sup>-1</sup> (red) and is the same for all four nucleophiles. The blue areas are those for which interaction with an acceptor is most favorable

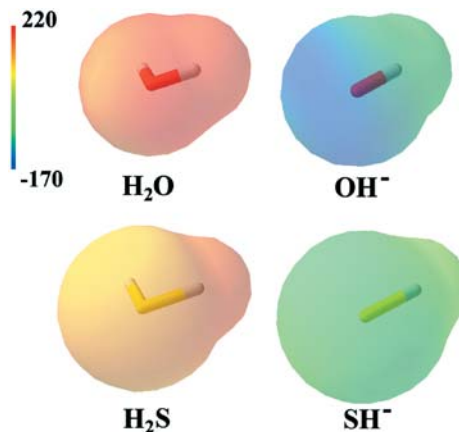


**Fig. 6** The local hardness shown for water, OH<sup>-</sup>, H<sub>2</sub>S and SH<sup>-</sup> (AM1). The color scale ranges from 95 (blue) to 320 kcal mol<sup>-1</sup> (red) and is the same for all four nucleophiles

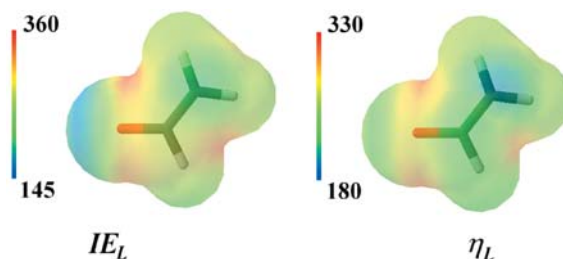
The local ionization potential and hardness can also visualize reactivity differences within a single nucleophile, as shown in Fig. 8. The lowest local ionization energy occurs at the surface around the oxygen atom, whereas the local hardness clearly identifies the methylene carbon as the softest nucleophile. This figure suggests that the local ionization energy and hardness may be combined to give a more complete description of nucleophilicity index that can be matched to electrophiles.

### Electrophilic aromatic substitution

Electrophilic aromatic substitution offers a fascinating example for the visualization of reactivity properties because both the overall reactivity of the aromatic substrate and the regioselectivity of the substitution should be visible. The local ionization energy can



**Fig. 7** The local electronegativity shown for water, OH<sup>-</sup>, H<sub>2</sub>S and SH<sup>-</sup> (AM1). The color scale ranges from -170 (blue) to 220 kcal mol<sup>-1</sup> (red) and is the same for all four nucleophiles



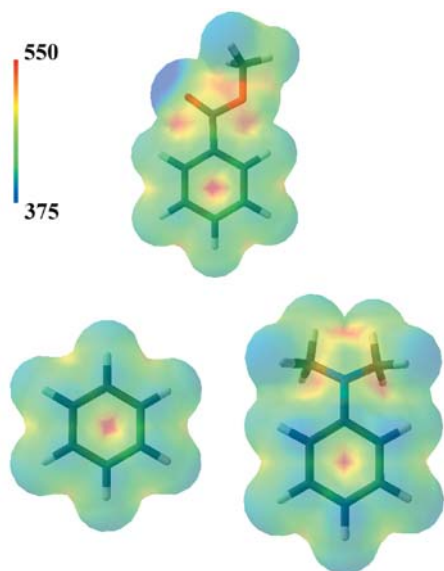
**Fig. 8** The local ionization energy and local hardness for the acetaldehyde enolate anion. The color scales (kcal mol<sup>-1</sup>) are shown next to the surfaces

represent both aspects. The absolute reactivity can be judged from the values of the local ionization energy at the  $\pi$ -surface of the aromatic compound, as shown in Fig. 9.

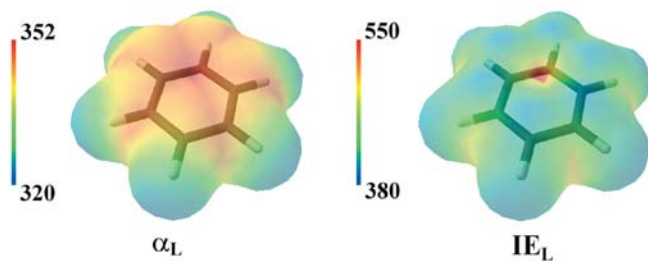
The gradation of the local ionization energy in the relevant areas of the molecular surfaces from the deactivated benzoic acid ester through benzene itself to the activated dimethylaniline are clearly seen. The low (blue) values of the local ionization energy indicate high reactivity to electrophilic substitution. However, the regioselectivity can also be seen. The lowest  $IE_L$  values are found above the *ortho* and *para* positions for dimethylaniline and above the *meta* positions for methyl benzoate. Larger reactivity differences, such as those between pyridine, benzene and pyrrole, are even more evident. Similarly, the positions of electrophilic attack in substituted olefins are also clearly seen on the molecular surfaces color coded with  $IE_L$ .

### The local polarizability

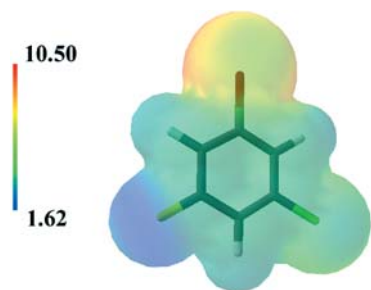
Figure 10 shows the local polarizability (the units are  $\text{\AA}^3 \times 10^3$ ) calculated at the SES surface of benzene with AM1. The local polarizability reflects the properties of



**Fig. 9** The local ionization energy at the SES surfaces of methyl benzoate, benzene and dimethylaniline. The color scale ranges from 375 (blue) to 550 kcal mol<sup>-1</sup> (red) and is the same for all three molecules. The blue areas are those for which interaction with an acceptor is most favorable



**Fig. 10** The local polarizability (Å<sup>3</sup> × 10<sup>3</sup>) and ionization energy (kcal mol<sup>-1</sup>) at the solvent-excluded surface of benzene (AM1)



**Fig. 11** The local polarizability (Å<sup>3</sup>) at the solvent-excluded surface of 1-bromo-3-chloro-5-fluorobenzene (AM1)

the molecule well. The most polarizable electron density is found at the  $\pi$ -face around the centers of the C–C bonds. The hydrogen atoms are the least polarizable components of the molecule. The local ionization energy is also shown. As suggested by Murray and Politzer, [19, 20, 21, 22, 23] there is considerable similarity between

the two properties, but the local polarizability shows up the polarizable nature of the  $\pi$ -cloud between the carbon atoms, whereas the local ionization energy is lowest above the rung at the positions of the carbon atoms themselves.

Figure 11 shows a more chemically varied molecule, 1-bromo-3-chloro-5-fluorobenzene. In this case, the local polarizability of the benzene ring is very similar to that of the parent compound, whereas those of the three halogens reflect their character. The local polarizability is thus less of an instrument for visualizing the reactivity of molecules than for showing their potential for weak interactions. It is thus expected to be important for describing intermolecular interactions. [28]

## Conclusions

The local properties presented here can be calculated quickly and easily at any point in space around a molecule and serve to visualize electrophilic/nucleophilic aspects of the chemical reactivity. We have concentrated here on their use for visualization but are also investigating whether they can be used in quantitative predictions of reaction rates and products. As pointed out by Politzer and Murray in their original work on  $IE_L$ , [19, 20, 21, 22, 23] local properties that can describe the donor/acceptor character of regions of molecules are complementary to the MEP and help to provide a more complete description of the intermolecular interactions. We have not treated radical reactivity here because it is generally not susceptible to simple donor/acceptor arguments, but rather to a resonance-like treatment. [40] We have also not considered complex formation and van der Waals' complexes. However, the local properties described here are very effective in describing partitioning and binding phenomena. [28]

**Acknowledgments** We especially thank Peter Politzer for stimulating discussions. We thank Pfizer Ltd and the Fonds der Chemischen Industrie for financial support.

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