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The current status of the molecular surface property approach (MSPA) and its application for analysis and prediction of intermolecular interactions, including chemical reactivity, are reviewed. The MSPA allows for identification and characterization of all potential interaction sites of a molecule or nanoparticle by the computation of one or more molecular properties on an electronic isodensity surface. A wide range of interactions can be analyzed by three properties, which are well-defined within Kohn–Sham density functional theory. These are the electrostatic potential, the average local ionization energy, and the local electron attachment energy. The latter two do not only reflect the electrostatic contribution to a chemical interaction, but also the contributions from polarization and charge transfer. It is demonstrated that the MSPA has a high predictive capacity for non-covalent interactions, for example, hydrogen and halogen bonding, as well as organic substitution and addition reactions. The latter results open up applications within drug design and medicinal chemistry. The application of MSPA has recently been extended to nanoparticles and extended surfaces of metals and metal oxides. In particular, nanostructural effects on the catalytic properties of noble metals are rationalized. The potential for using MSPA in rational design of heterogeneous catalysts is discussed.

1. Introduction

The prediction of sites and strengths of intermolecular interactions, including chemical reactions, is one of the key objectives of computational modeling in chemistry, biology, and material science. The rapid increase in computational power together with the developments within Kohn–Sham density functional theory (KS-DFT) has resulted in that chemical interactions of large systems today can be studied in great detail and with high accuracy. In particular, the computation of transition states of complex chemical reactions has made a major impact on the prediction of chemical reactivity. However, for larger systems with high structural complexity, such detailed modeling of the interactions at each potential interaction site is still impracticable, and in many cases impossible, due to the size of the computational task. Thus, in areas such as drug design, supermolecular chemistry, or heterogeneous catalysis, there is need for alternative methods for the screening of interaction sites and prediction of interaction strengths. The use of KS-DFT-based molecular surface properties has emerged as a viable option for this purpose. This type of approach, has the great advantage that all potential interaction sites of a system, and the interaction strengths at these sites, for different approaching molecules can be estimated by a single KS-DFT computation. While the molecular surface property approach (MSPA) has found its main use in molecular systems, we have recently shown that also larger systems based on nanoparticles, crystals of metals, or metal oxides, can be studied, and thus extensions of the MSPA have the potential to capture an increasingly important role in material science and heterogeneous catalysis. In this progress report, we will summarize the latest advancements within the field of molecular surface properties and discuss future applications.

2. Molecular Surface Properties

2.1. Intermolecular Interactions

In computational quantum chemistry, it is common to partition chemical interactions into different energy components, and
when the partitioning is quantitatively based on quantum chemical analysis, this is commonly referred to as energy decomposition analysis (EDA).\cite{12,13,14,15} Whereas such partitioning can be seen as artificial and lacking theoretical rigor, it can be very useful in the characterization and prediction of chemical interactions. An intermolecular interaction is typically partitioned into the following components:

- Pauli or exchange repulsion, which is the strong short-range repulsion that stems from the overlap of the electron densities of the interacting molecules.
- Electrostatic interaction, which is the Coulombic interaction between the static charge distributions of the interacting molecules.
- Polarization (induction) and charge transfer. Polarization, or induction, is the increase in the Coulombic interaction due to the polarization of each species by the charge distribution of the other. Charge transfer in EDA is considered to be the increase in interaction energy due to the donation of electron density from occupied orbitals of one molecule to virtual orbitals on the other. In many EDA schemes, polarization and charge transfer are considered together, as there is no rigorous method for separating intra and intermolecular redistribution of electron density.
- Dispersion or London interaction, which generally is described as an increased Coulombic interaction due to the instantaneous and mutual polarization of the charge distributions of the interacting molecules, for example, induced dipole–induced dipole interaction. According to the Hellman–Feynman theorem, however, the dispersion interaction is a consequence of an attractive force due to a static polarization of each interacting molecule.\cite{16}

Among these interaction types, it is only the first, the exchange repulsion that is always repulsive in character. In the MASP, this interaction type is accounted for by the use of molecular surfaces characterized by constant electron density, so called isodensity surfaces. As the exchange repulsion is a result of the overlap of the electron densities of the interacting species, it can be assumed that the repulsive potential over an isodensity surface is nearly constant. Therefore, by mapping one or more computed properties that reflect the attractive interactions on such a surface, it is possible to estimate the varying interaction strength over the surface for a probe molecule. In many cases, the MSPA is used to analyze non-covalent interactions and it is therefore common to use isodensity contours, for example, the 0.001 a.u. contour, that give dimensions corresponding to van der Waals radii of atoms. Bader and coworkers have shown that the 0.001 and 0.002 a.u. contours of the electron density give molecular dimensions in agreement with intermolecular equilibrium distances observed in liquids and gases of nonpolar molecules.\cite{17} Polar molecules were found to approach each other more closely, which indicates that favorable interactions, such as electrostatic and polarization interactions, reduce the intermolecular distances. In some cases when the interaction is stronger in character, it can be advantageous to use a contour, for example, 0.004 au, that is closer to the nuclei.\cite{6}

Figure 1, at the top left, shows the bare 0.001 au isodensity surface of nitrobenzene, and at the top right, the same surface mapped by a surface property, the electrostatic potential \( V(\mathbf{r}) \). The variations in the surface \( V(\mathbf{r}) \) \( V_s(\mathbf{r}) \) reflect the varying interaction strength with Lewis bases/nucleophiles and Lewis acids/electrophiles. Generally, nucleophiles are attracted to the most positive regions (red areas) and the electrophiles to the most negative regions (blue areas). However, the quantitative variations in the interaction strength will depend on the type of molecule that interacts with the surface, and the interacting molecule also determines which surface property to use. As we will see later in this report, it is sometimes necessary to use a combination of properties to increase the accuracy of the interaction strength prediction.

2.2. Surface Electrostatic Potential \( (V_s(\mathbf{r})) \)

2.2.1. Theory

The most commonly used property for surface analysis has traditionally been the electrostatic potential \( (V(\mathbf{r})) \), which is rigorously defined at a point \( \mathbf{r} \) in space by

\[
V(\mathbf{r}) = \sum_Z \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \rho(\mathbf{r}') d\mathbf{r}' \frac{1}{|\mathbf{r} - \mathbf{r}'|}.
\]
periodic KS-DFT with plane-wave basis sets, but the absolute $V(r)$ is ill-defined and has to be corrected with respect to the vacuum level.\textsuperscript{10,11}

2.2.2. $V_{S}(r)$ and Intermolecular Interactions

Whereas the $V(r)$ of a neutral atom is spherically symmetric, everywhere positive and asymptotically goes toward zero at large distances, the formation of a molecule from atoms leads to a redistribution of the electron density toward the more electronegative atoms and the appearance of regions of negative $V(r)$. Figure 1 (middle left) shows the surface electrostatic potential ($V_{S}(r)$) of ammonia, and the $V_{S}(r)$ of the more electronegative nitrogen atom is negative with the minimum in $V_{S}(r)$ ($V_{S,min}$) at the lone pair region. In the same manner, there are maxima in $V_{S}(r)$ ($V_{S,max}$) over the less electronegative hydrogen. It is common to find $V_{S,max}$ over the hydrogens in molecules, and the magnitude of the $V_{S,max}$ generally correlates with the hydrogen bond donating capacity of the corresponding hydrogen, for example, it has been shown that empirical hydrogen acidity scales correlate linearly with $V_{S,max}$ for wide ranges of hydrogen bond donors.\textsuperscript{9,19,20} These correlations are in accordance with the accepted picture that hydrogen bonds are primarily electrostatic in character. Correspondingly, there are also good correlations between hydrogen bond basicity and $V_{S,max}$ for oxygen, nitrogen, and sulfur hydrogen bond acceptors.\textsuperscript{2,12,22} However, such correlations are generally of lower quality than the corresponding relationship for hydrogen bond donors, and they improve when families of acceptors of different atom types are taken separately. Figure 1 (bottom left) also shows the $V_{S}(r)$ of PH$_{3}$, which has lower hydrogen $V_{S,max}$ and higher $V_{S,min}$ than NH$_{3}$, in agreement with the weaker hydrogen bond accepting and donating capacities of PH$_{3}$.\textsuperscript{23}

The surface electrostatic potential is generally well-suited for describing the directionality and regioselectivity of non-covalent intermolecular interactions, and this often holds even if the interaction has significant energy contributions from other interaction types than electrostatics, such as dispersion. This is a consequence of the anisotropic character of the $V_{S}(r)$, with regions of both positive and negative surface potentials in a neutral molecule. An extreme example is the $V_{S}(r)$ of halogenated molecules, where individual halogen atoms often feature regions of both negative and positive potential. This was first realized by Brinck et al. in 1992, when they showed that halogens heavier than fluorine, for example, chlorine, bromine, and iodine, typically features a positive region at the end of the halogen, that is, the tip opposite of the bond, even in compounds where the halogen binds to a less electronegative atom, such as carbon.\textsuperscript{24} This phenomenon was rationalized by Clark et al. as the consequence of an electron deficiency at the tip, a $\sigma$–hole, which is formed due to the lower $\sigma$-orbital occupancy in the direction of the bond.\textsuperscript{25} Lewis bases interact with the positive $V_{S}(r)$ of the tip, in an interaction that today is called halogen bonding. It has also been shown that the interaction energy generally correlates with the magnitude of the $V_{S,max}$ at the tip for families of congenic molecules, for example, halogenated methanes or halogenated benzenes.\textsuperscript{26–28} Figure 2 shows the $V_{S}(r)$ of CF$_{3}$Cl and CF$_{3}$I. In both molecules, there is a positive $V_{S,max}$ at the tip of the heavier halogen, but due to the larger polarizability of I compared to Cl,

where $Z_{A}$ is the charge on nucleus $A$ located at $r_{A}$, and $\rho(r)$ is the electron density function. Depending upon whether the contribution from the nuclei or the electrons is dominating at $r$, $V(r)$ will be positive or negative. The term $qV(r)$ gives the interaction energy between a point charge $q$ located at $r$ and the static (unperturbed) charge distribution of the molecule. In contrast to many other properties that reflect the charge distribution of a molecule, such as atomic charges, $V(r)$ is a physical observable and can be determined both experimentally and theoretically.

The electrostatic potential is a one-electron property, and as such less sensitive to the choice of basis set and computational method than, for example, the calculation of interaction energies. Electrostatic potentials obtained by Hartree–Fock (HF), post HF or KS-DFT generally vary in a similar manner over a molecular isodensity surface, but HF has a tendency to overestimate charge separation and thus the variation is typically greater in magnitude than for the correlated methods.\textsuperscript{18} Basis set effects are often close to converged, already at the size of the double-zeta plus polarization, and the combination of such a basis set and a hybrid KS-DFT functional, for example, B3LYP/6-31G(d,p), is today the standard procedure.\textsuperscript{18} Most modern electronic structure codes that utilize Gaussian basis sets have the option to compute $V(r)$, and the timing for computing a full $V_{S}(r)$ is typically similar in magnitude to determining the full KS-DFT wavefunction. $V(r)$ can also be obtained almost for free when performing pe-

Figure 1. The upper row shows the bare 0.001 isodensity surface of nitrobenzene (left) and the surface mapped with a surface property, that is, the surface electrostatic potential ($V_{S}(r)$) (right). $V_{S}(r)$ and $I_{S}(r)$ are mapped on the 0.001 isodensity surface of NH$_{3}$ and PH$_{3}$ in the middle and bottom rows; the minima in $V_{S}(r)$ ($V_{S,min}$) and $I_{S}(r)$ ($I_{S,min}$) are located at the tip (lone pair) of the N or P. Blue (cyan) indicates nucleophilic sites, red (yellow) electrophilic sites. Color scheme $V_{S}(r)$, kcal mol$^{-1}$: blue $< -10.0 <$ cyan $< -5.0 <$ green $< 10.0 <$ yellow $< 20.0 <$ red; color scheme $I_{S}(r)$, eV: blue $< 8.0 <$ cyan $< 10.5 <$ green. Computational level: B3LYP/6-31+++(g(3df,3pd))/6-31g(d,p).
I have the higher $V_{\text{S, max}}$, the values are 31.4 and 14.4 kcal mol$^{-1}$ for I and Cl, respectively. It can be noted that there is a $V_{\text{S, max}}$ at the tip of each F in CF$_3$Cl and CF$_4$I as well. These $V_{\text{S, max}}$ have much lower values and are even negative, that is, −1.7 and −2.0 kcal mol$^{-1}$ for CF$_3$Cl and CF$_4$I, respectively. However, fluorines bonded to strongly electron-withdrawing groups have more positive $V_{\text{S, max}}$ and have been shown to participate in halogen bonding [29, 30].

Halogen bonding has emerged as a complementary interaction to hydrogen bonding, and is today of increasing importance in areas such as supramolecular chemistry, drug design, and organocatalysis [26, 27, 28]. Computed $V_s(r)$ is the most important tool to rationalize and predict halogen bonding, and today most publications on halogen bonding include some $V_s(r)$ results [26, 28, 29]. The $\sigma$–hole concept has been extended to the IV–VI elements, resulting in the definition of the corresponding classes of intermolecular interactions, which have been named tetrel, pnictogen, and chalcogen bonding, respectively [31, 32]. The $V_{\text{S, max}}$ (yellow spot) of the $\sigma$–hole of PH$_3$ can be seen in Figure 1, and the carbon $\sigma$–holes of CF$_3$Cl and CF$_4$I can be viewed in Figure 2. For all types of $\sigma$–hole bonding, the $V_s(r)$ has been shown to be an excellent tool for identifying interaction sites and for predicting interaction strengths. However, in general, correlations between interaction strengths and $V_{\text{S, max}}$ are limited to groups of congeneric molecules, emphasizing that these interactions often have significant contributions from other energy components than electrostatics. The further extension of the $\sigma$–hole concept to metals, and the use $V_s(r)$ for analyzing interactions of metal or metal oxides with Lewis bases will be discussed later in this report.

#### 2.3. Average Local Ionization Energy ($\bar{I}(r)$)

##### 2.3.1. Theory

The electrostatic potential is well-suited for the analysis and prediction of non-covalent intermolecular interactions, but it is generally less applicable for chemical reactions, which typically involve a higher degree of redistribution of the electron densities of the interacting species. This was recognized by Sjöberg et al. [33] when they introduced the average local ionization energy as a suitable molecular surface property for electrophilic reactions. The $I(r)$ is rigorously defined within Hartree–Fock theory and KS-DFT by \cite{34, 35}

\[
\bar{I}(r) = -\sum_{i=1}^{\text{HOMO}} \frac{e_i \rho_i(r)}{\rho(r)} + V(r) - V_{XC}(r)
\]

where, $e_i$ is the eigenvalue of the $i$th spin orbital, $\rho_i$ is the electron density of the same orbital, and $\rho$ is the total electron density. The summation includes all occupied spin orbitals. Within HF theory, $I(r)$ can be viewed as the average energy needed to ionize an electron at a point $r$ in the space of a molecule, as Koopmans' theorem justifies using the orbital energy as the negative ionization energy of a particular orbital. A similar interpretation can be made in generalized KS-DFT (GKS-DFT) based on Janak’s theorem [36] (vide infra) and the piece-wise linear energy dependence of the number of electrons [37, 38]. The $I(r)$ has also been extended to multiconfigurational wavefunction theory [39]. Furthermore, it has been shown that $I(r)$ is invariant with respect to a unitary transformation of the orbitals, and can be expressed in terms of density functionals, by

\[
\bar{I}(r) = -I_s(r)/\rho(r) + V(r) - V_{XC}(r)
\]

where $I_s(r)$ is the local kinetic energy density, $V(r)$ is the electrostatic potential, and $V_{XC}(r)$ is the exchange-correlation functional (in HF theory $V_{XC} = V_{St}$, the Slater potential). On an isodensity surface, the $V_{XC}(r)$ contribution is expected to be nearly constant and the capacity of $I(r)$ to reflect charge transfer and polarization is due mainly to the kinetic energy density contribution.

Politzer and coworkers have shown that the surface $I(r)$ of a free atom is a chemically meaningful measure of atomic electronegativity [40, 41].

It is our experience that $I(r)$ behaves similarly to the $V(r)$ when it comes to dependence upon method and basis sets. In general, the $I(r)$ values decrease upon increasing amount of Hartree–Fock exchange. However, the variations in $I(r)$ over a molecular surface is relatively insensitive with respect to the DFT functional, and the whole spectrum from HF via hybrid functionals to pure GGA functionals generally works well for quantitative analysis of chemical interactions. Only a few electronic structure codes have so far implemented $I(r)$ as a standard option. It should be noted that computing $I(r)$ is an order of magnitude faster than computing $V(r)$, as the $I(r)$ calculation involves no integrals. $I(r)$ can also be calculated from Kohn–Sham orbitals obtained with periodic plane-wave codes, but the orbital energies have to be shifted with respect to the vacuum level electrostatic potential [40].
2.3.2. \( I_3(r) \) and Chemical Reactivity

Surface minima of \( I_3(r) (I_{3,\text{min}}) \) are, similarly to \( V_{S,\text{min}} \), indicative of sites that interact with Lewis acids or electrophiles. However, comparing \( I_{S,\text{min}} \) and \( V_{S,\text{min}} \) of NH\(_3\) and PH\(_3\) in Figure 1, it is clear that \( I_{3,\text{min}} \) indicates PH\(_3\) to be a stronger Lewis base than NH\(_3\), whereas \( V_{S,\text{min}} \) predicts NH\(_3\) to interact stronger. This is a general trend for \( I_3(r) \), which is opposite to that of \( V_S(r) \), that the minimum value on a Lewis base generally decreases when going down a column of the periodic table for a set of congenic molecules;[23] a behavior which follows Pearson’s concept of hard and soft Lewis bases.[44] According to this concept, hard bases, such as NH\(_3\), interact stronger with hard acids in electrostatically driven interactions, whereas soft bases, such as PH\(_3\), prefer soft acids in interactions dominated by charge transfer and polarization; softness in opposition to hardness increases going down the periodic table. The \( I_{S,\text{min}} \) has also been shown to correlate with the strength of Lewis acid–base interactions, but better and more general correlations are obtained with dual parameter correlations, \( I_{S,\text{min}} \) and \( V_{S,\text{min}} \), where the relative parameter contributions depend on the softness/hardness of the Lewis acid.[3,22]

The real advantage of \( I_{S,\text{min}} \) over \( V_{S,\text{min}} \) is found in the analysis of interactions that lead to covalent bonds, as can be exemplified by electrophilic aromatic substitution (S\(_E\)Ar). Figure 3 shows the \( I_{S,\text{min}} \) of nitrobenzene, benzene, and aniline. In each case, the lowest \( I_{S,\text{min}} \) are found over the positions that are most prone to react with an electrophile, that is, the meta directing versus ortho–para directing tendencies of nitrobenzene and aniline, respectively, are reproduced by the \( I_{S,\text{min}} \) positions.[31] Furthermore, the magnitude of the \( I_{S,\text{min}} \) at the reactive site reflects the relative reactivity at that site, and allows for the ranking of different molecules with respect to their rate constants in, for example, the S\(_{E}\)Ar reaction.[45–47] In the case of aniline, there is also an \( I_{S,\text{min}} \) at the nitrogen that reflects its nucleophilicity and basicity. In contrast, \( V_{S,\text{min}} \) cannot be used to predict regioselectivity and relative reactivity for S\(_E\)Ar in these systems; as an example, there is typically not an \( V_{S,\text{min}} \) associated with the most reactive site.

Studies by Liljenberg et al. and Brown and Cockcroft have shown that \( I_{S,\text{min}} \) is capable of quantitatively predicting regioselectivity and relative reactivity also of more complex molecules, including heteroaromatic systems with multiple rings.[45–47] Whereas the method generally works also in problematic cases where resonance theory or frontier molecular orbital (FMO) theory fail, it does have problems in systems with sterically hindered interaction sites. Such problems are more frequent when the electrophile is large and bulky, as in Friedel–Craft acylations.[57] \( I_{S,\text{min}} \) has been shown to be highly accurate also for predicting the reactivity of kinetically controlled electrophilic reactions other than S\(_E\)Ar, such as electrophilic addition reactions and transmetallation reactions.[46]

2.3.3. \( I_3(r) \) and Basicity

\( I_3(r) \) is a good indicator of the basicity of organic and inorganic compounds.[2,21–23] This has been demonstrated by high linear correlations between experimentally determined aqueous pK\(_a\)s of the conjugate acid and the \( I_{S,\text{min}} \) of the base. Whereas the correlation generally are of higher quality for groups of congenic molecules, for example, nitrogen heteroaromatics,[2] it has also been shown that more general relationships exist; in one of the first studies, a linear correlation with the conjugate base \( I_{S,\text{min}} \) was demonstrated for a variety of neutral carbon, nitrogen, and oxygen acids ranging in pK\(_a\) from –6 to 40.[21] However, in order to reproduce the varying basicity of compounds where the basic atoms are from different rows of the periodic table, it is generally necessary to use a multivariate relationship where \( I_{S,\text{min}} \) is complemented with an electrostatic descriptor, for example, \( V_{S,\text{min}} \).[33]

\( I_3(r) \) has the potential to become an important tool for estimating pK\(_a\) values of systems where experimental characterization is difficult or impossible. This includes systems that are difficult to prepare or systems that have a pK\(_a\) outside the range for which it is directly measurable. As an example, in ref. [21], the pK\(_a\) of the dinitraminic acid, which is a metastable high-energy molecule of interest for space propulsion, was predicted to –6, a value which later was confirmed experimentally. Drug design is another area where the predictive capacity of \( I_3(r) \) can be very useful. The acidity/basicity of a drug and the location of the protonation sites are generally of high importance for the biomedical efficacy. An \( I_3(r) \) map can predict the pK\(_a\) value and rank the different protonation sites in a complex drug molecule based on a calculation that takes less than a minute on a desktop computer. Thus, \( I_3(r) \) can be used

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Figure 3. \( I_3(r) \) mapped on the 0.001 isodensity surface of aniline (activated in S\(_E\)Ar reactions), benzene, and nitrobenzene (deactivated in S\(_E\)Ar). There are minima in \( I_3(r) (I_{S,\text{min}}) \) associated with the most activated sites on each molecule. Blue (cyan) indicates nucleophilic sites. Color scheme \( I_3(r) \), eV: deep blue < 8.5 < blue < 8.95 < cyan < 9.90 < green. Computational level: B3LYP/6-31+g(d,p)///6-31g(d).
for high throughput prediction of basicities in large datasets of pharmaceutical molecules.

2.4. Local Electron Attachment Energy (E(r))

2.4.1. Theory

Until recently, a surface property that complements V_{S}(r) for describing nucleophilic processes, in a similar manner as I_{S}(r) is complementary to V_{S}(r) for electrophilic processes, was missing. In 2003, Clark defined the local electron affinity (E_{S}(r)), which is computed using a similar equation as Equation (2), but where the summation is over the virtual orbitals instead of the occupied.\(^{(4)}\) E_{S}(r) is defined within a minimum basis representation and has exclusively been used with orbitals obtained by semi-empirical calculations of the NDDO-type. E_{S}(r) generally has the problem that it tends to overemphasize the importance of high-energy virtual orbitals, that is, orbitals that have too high energy to play a role in charge-transfer interactions. In order to overcome this problem, and to obtain a surface property that is well-defined within KS-DFT, and has an appropriate behavior at the infinite basis limit, Brinck et al. defined the local electron attachment energy (E(r)) by,\(^{(6)}\)

\[
E(r) = \sum_{\varepsilon_i < 0} \frac{\varepsilon_i \rho_i(r)}{\rho(r)}. \tag{4}
\]

The equation is similar to the \(\bar{I}_S(r)\) expression, but the summation is over virtual orbitals and only includes those with an orbital energy below the free electron limit, that is, \(\varepsilon_i < 0\). As in \(\bar{I}_S(r)\), but different from \(E_S(r)\), the density-weighted sum of orbital energies is divided by the ground state density. \(E_S(r)\) is well-defined within the generalized Kohn–Sham DFT (GKS-DFT) theory and is motivated based on Janak’s theorem and the piece-wise linear energy dependence upon changing the number of electrons. According to Janak’s theorem,\(^{(10)}\) the occupied and virtual orbitals reflect the energy change upon the subtraction or addition, respectively, of a fractional electron to an electronic system, that is,

\[
\frac{\partial E}{\partial n_i} = \varepsilon_i \tag{5}
\]

Since the energy is piece-wise linear upon subtracting or adding electrons,\(^{(10)}\) Janak’s theorem has the implication that within exact GKS-DFT, the vertical ionization energy and electron affinity can be computed directly from the HOMO energy and the LUMO energy, respectively, without consideration of orbital relaxation.\(^{(10)}\) Although, the linear energy dependence upon fractional electron addition to an orbital, that is, \(\Delta E = \Delta n_i \varepsilon_i\), may not hold exactly for other virtual orbitals than the LUMO, it should be a good approximation that justifies the use of \(\rho_i \varepsilon_i\) in Equation (4).

The “cut-off” at \(\varepsilon_i < 0\) is motivated as only orbitals with a negative orbital energy can bind a fractional electron. In addition, the cut-off has the result that the equation is valid also at the infinite basis limit; the use of a large basis set results in the formation of virtual orbitals that represent free unbound electrons, but such orbitals will always have an orbital energy that is \(\varepsilon_i > 0\), and thus they will not contribute to \(E(r)\). It should be noted though that the cut-off is smooth in the sense there is no discontinuous jump in \(E(r)\) when changing the orbital energy of a specific orbital from \(+\varepsilon_i\) to \(-\varepsilon_i\) when \(\varepsilon_i\) approaches zero. This is a consequence of the denominator being independent of the virtual orbital density. The denominator represented by the occupied density further means that denominator is constant over an isodensity surface, and that the surface \(E(r)\) for a system with the LUMO being the only orbital of negative energy will vary over the surface proportionally to the Fukui function for nucleophilic attack \((f^+(r))\).\(^{(14)}\) Thus for simple systems \(E_S(r)\) provides regioselective information that is similar to \(f^+(r)\), but \(E_S(r)\) works also for more complex system with degenerate or near-degenerate LUMO where \(f^+(r)\) fails. In addition, \(E_S(r)\) provides a ranking of the global reactivity between different molecules.

Using the same approach as for \(\bar{I}(r)\) in Equation (3), \(E(r)\) can be divided into different energy components:\(^{(5)}\)

\[
E(r) = \frac{1}{\rho(r)} \sum_{\varepsilon_i < 0, \varepsilon_i > \varepsilon_{HOMO}} \left[ t_i(r) - \rho_i(r) V(r) + \rho_i(r) V_{XC}(r) \right] \tag{6}
\]

where \(t_i(r)\) is the local kinetic energy density of orbital i, which is defined by \(t_i(r) = -1/2 \nabla \psi_i^*(r) \nabla \psi_i(r)\). The \(t_i(r)\) contribution is the only component that has a direct functional dependence of the virtual orbitals. The electrostatic potential \((V(r))\) and the Kohn–Sham potential \((V_{XC}(r))\) are ground state properties and defined by the occupied orbitals, but their local contributions are proportional to the sum of the densities of the contributing virtual orbitals. \(V(r)\) often varies considerably over an isodensity surface, and typically has a large influence on the regioselective information that is provided by \(E_S(r)\). \(V_{XC}(r)\) is expected to be nearly constant at constant density, and thus to show small variation on the isodensity surface. The \(t_i(r)\) component has a larger variation, and will reflect the local charge transfer and polarization contributions to the energy of an interaction.\(^{(6)}\)

Compared to \(V(r)\) or \(\bar{I}(r)\), the computation of \(E(r)\) is much more sensitive to the DFT functional and basis set. On the basis of theoretical considerations, it can be argued that functionals, such as range-separated hybrid-functionals, that give a LUMO energy that is close to the electron affinity should be optimal for \(E(r)\).\(^{(10)}\) However, for practical applications in main row chemistry, we have found that standard hybrid functionals, such as B3LYP and PBE0, which includes 15–25% HF exchange, generally performs better.\(^{(6)}\) In the case of metal compounds, including metal oxides, it can be advantageous to decrease the HF contribution to around 10% or less.\(^{(7,8)}\) For extended metal systems, which are often computationally unattainable by hybrid methods, even pure GGA functionals (e.g., PBE) have been found to perform well. Basis sets that include diffuse functions are generally necessary for obtaining realistic energies of virtual orbitals, and a basis set of the size of 6-31+G(d,p) is minimal for \(E(r)\). Similar to \(\bar{I}(r)\), \(E(r)\) can be computed from plane-wave DFT orbitals, if the orbital energies are shifted with respect to the vacuum level electrostatic potential.\(^{(10)}\) \(E_S(r)\) computations have not yet been implemented in standard electronic structure codes, and is so far only available via research codes, such as the HS95w1r18 of T. Brinck.
E₅(r) is not only able to indicate positional selectivity for S₅Ar, but have also been shown to correlate relative reactivity for a wide range of S₅Ar reactions, including the vicarious nucleophilic substitution (VNS) reaction, which involves hydride substitution. A number of high linear correlations between experimentally determined rate constant and E₅, min values were recently reported for datasets of congeneric molecules. In general, E₅(r) works better for reactions with an early transition state, and, consequently, higher correlations were found for S₅Ar with chlorine and bromine as leaving group compared to fluoride: the former typically proceeds by a concerted mechanism whereas the fluoride substitution follows the step-wise mechanism with a Meisenheimer intermediate.

It is important to realize that E₅(r) cannot always be used as a black-box approach when analyzing S₅Ar reactions, but that the interpretation of the computational results requires chemical knowledge to enable prediction of positional selectivity and reactivity. This can be exemplified by our analysis of a dataset by Berliner and Monack, on S₅Ar reactions in a series of 1-bromo-4-R-2-nitrobenzene compounds. The original experimental study was performed in piperidine and piperidine also functioned as the nucleophile. It is exclusively the bromide that is substituted under the experimental conditions. This is attributed to the good leaving group ability of bromide and the ortho activating effect of the nitro group.

Figure 4 shows the Eₛ(r), Vₛ(r), and the LUMO of pentachloropyridine. There are local minima in Eₛ(r) (Eₛ,min) on top of the carbon positions, and the relative magnitude of each Eₛ,min reflects the relative reactivity for electrophilic attack at the corresponding position. The carbon Eₛ,min values are −1.57, −1.40, and −1.20 eV in the order para, ortho, and meta, respectively. Experimentally, it has been shown that kinetically controlled nucleophilic aromatic substitution (S₅Ar) of pentachloropyridine with the anion of methanol results in a product distribution of 85% para, 15% ortho and non-detectable amounts of the meta product. Thus, Eₛ(r) does not only predict the expected ortho–para preference for S₅Ar, but also reflects the higher preference for para over ortho. In contrast, Vₛ(r) gives no indication of the regioselectivity for S₅Ar since the most positive potential (ring Vₛ,max) of the aromatic ring is found over the ring center.

The LUMO provides little information about positional selectivity and rather indicates all of the ring atoms, including the nitrogen, to be similarly susceptible for nucleophilic attack. The Fukui function for nucleophilic attack (f⁻) is also insufficient, as f− to a good approximation, is equal to the LUMO orbital density. Clearly, an FMO approach is not applicable in this case, and Eₛ(r) at the B3LYP/6-31+G(d) level has contributions from five virtual orbitals with negative eigenvalues. The energies of these are −2.28, −1.97, −1.63, −0.44, and −0.14 eV. The predicted regioselectivity for nucleophilic attack at the aromatic carbons is mostly defined by the contributions from three lowest virtual orbitals, which are of π*-character. Interestingly, the lowest Eₛ,min is found at the end of the para-chlorine, that is, not on the S₅Ar sites perpendicular to the C-ring sites, and it has negligible contributions from the three lowest π-orbitals. There are also Eₛ,min, but of lower magnitude, at the end (tip) of the ortho and meta chlorines. The halogen Eₛ,min reflects the positional preference and relative susceptibility to halogen bonding, and provides similar predictions as the halogen Vₛ,max. The use of Eₛ(r) for analysis of σ–hole interactions is discussed later in this article. However, at this stage, we like to emphasize that one strength of a multiorbital approach, such as Eₛ,min or Eₛ,max, is the ability to predict interactions with both σ and π regions of a molecule in a single analysis and without having to resort to a manual selection of orbitals.

2.4.2. Eₛ(r) and Nucleophilic Aromatic Substitution

Figure 4. Predicting regioselectivity in S₅Ar from Eₛ(r) at the 0.001 au isosurface of pentachloropyridine. The values of the minima in Eₛ(r) (Eₛ,min) rank the reactivity of the ring positions as para > ortho > meta (with respect to the N position), in good agreement with experiment. Vₛ(r) and the LUMO cannot distinguish between the sites. Color scheme Eₛ(r), eV: red < −1.3 < orange < −1.2 < yellow < −1.0 < green; color scheme Vₛ(r), kcal mol⁻¹: blue < −20.0 < cyan < −10.0 < green < 10 < yellow < 20 < red. Computational level: B3LYP/6-31+G(d,p)/6-31+G(d,p).

In general, Eₛ(r) works better for reactions with an early transition state, and, consequently, higher correlations were found for S₅Ar with chlorine and bromine as leaving group compared to fluoride: the former typically proceeds by a concerted mechanism whereas the fluoride substitution follows the step-wise mechanism with a Meisenheimer intermediate.
correlate as well with \( \ln k \); \( R^2 \) is only 0.79. Similar to the \( E_{S_{\text{min}}} \) results, the correlation improves by explicit coordination of piperidine to H-bonding sites in the TS optimizations; the \( R^2 \) increases to 0.954, which is still lower than for \( E_{S_{\text{min}}} \) with piperidine-coordination.\(^{[47]}\) We find it rewarding that \( E_5(r) \) performs slightly better than the full TS calculations for predicting relative reactivity in this complex system, but also that the improvements in the \( E_5(r) \) results with increasing detail in the solvent representation follow those of the full TS computation. It should be noted that optimizing a TS for a complex reaction of this type is a complex task, which generally requires human intervention by a skilled scientist. In comparison, an \( E_5(r) \) computation can be fully automated and is faster by several orders of magnitude in computational time. Thus, we see that \( E_5(r) \), like \( I_5(r) \) for \( S_{N_{\text{Ar}}} \), has the potential to be used for the screening of large datasets of \( S_{N_{\text{Ar}}} \) reactions in, for example, the pharmaceutical industry.

### 2.4.3. \( E_5(r) \) and Conjugate Addition

The use of \( E_5(r) \) for screening of nucleophilic reactions is not restricted to \( S_{N_{\text{Ar}}} \). Another important reaction type is the conjugate addition, a nucleophilic addition to an activated double bond, which among other reactions includes the Michael reaction. Figure 6 shows the \( E_5(r) \) of \( \alpha \)-nitrostilbene. In line with the discussed \( S_{N_{\text{Ar}}} \) studies, there are \( E_{S_{\text{min}}} \) over the aromatic carbons, which are activated for nucleophilic attack because of the electron-withdrawing nitro group. However, in this type of molecules, it is the \( \beta \)-carbon of the double bond that is most susceptible to nucleophilic attack. This is also the position of the lowest \( E_{S_{\text{min}}} \). Thus, \( E_5(r) \) correctly predicts the site for nucleophilic addition. There is also an almost perfect linear correlation, \( R^2 = 0.986 \), between the \( \ln k \)\(^{[53]} \) for the addition of \( \text{HOCH}_2\text{CH}_2\text{S}^- \) to a group of substituted \( \alpha \)-nitrostilbenes and \( E_{S_{\text{min}}} \) at the \( \beta \)-position.\(^{[56]} \) It can be noted that it is very difficult to analyze this reaction by TS computation, as great care has to be taken to account for the influence of the solvent on the geometry and the energy of the TS; the addition of anionic nucleophiles is barrierless in the gas phase. The \( E_5(r) \) analysis, on the other hand, is capable of reproducing the relative reactivity of the \( \alpha \)-nitrostilbenes based on gas phase KS-DFT computations.

\( E_5(r) \) was further found to reproduce the relative reactivity for conjugate addition of piperidine to substituted benzylidinemalonitriles.\(^{[6]} \) Also in this system, the lowest \( E_{S_{\text{min}}} \) is consistently located at the \( \beta \)-carbon, which is the preferred position for nucleophilic addition. There is a good correlation between the \( \ln k \)\(^{[54]} \) for conjugate addition to the \( \beta \)-carbon and gas phase \( E_{S_{\text{min}}} \) with a linear \( R^2 = 0.92 \).\(^{[56]} \) However, there is a clear need for further investigation.
molecules. The \( E_2(r) \) approach is likely to have a similar predictive capacity, but would only require a fraction of the computational time and could easily be automated.

### 2.4.4. Halogen bonding and the Complementary Nature of \( E_2(r) \) and \( V_3(r) \)

As already discussed, \( E_2(r) \) has a significant component from the electrostatic potential and in some cases variations in \( E_2(r) \) over a molecule or between molecules can parallel variations in \( V_3(r) \). However, in particular, the contributions from the kinetic energy densities of the virtual orbitals to \( E_2(r) \) have the effect that \( E_2(r) \) generally provides a different reactivity pattern from \( V_3(r) \). This becomes obvious from Figure 7A when comparing \( E_2(r) \) and \( V_3(r) \) of methyl bromide; a molecule which has several electrophilic sites.\(^{[66]} \) Methylbromide is known to undergo nucleophilic substitution of the bromide following the S\(_{N}\)2 mechanism, and accordingly there is an \( E_{S,\text{min}} \) (\(-1.14 \) eV) over the methyl group at the location where the nucleophile attacks. The lowest \( E_{S,\text{min}} \) (\(-1.35 \) eV) is located at the tip of bromide, where the molecule can donate a halogen bond. In this sense, the \( E_2(r) \) and \( V_3(r) \) provide similar pictures, and it is well known that the magnitude of \( V_{S,\text{max}} \) (here 25.7 kcal mol\(^{-1} \)) at the halogen tip reflects the halogen bond–donating capacity. However, the most positive areas in \( V_3(r) \), with \( V_{S,\text{max}} \) of 38.2 kcal mol\(^{-1} \), are found over the hydrogens. These \( V_{S,\text{max}} \) reflect the hydrogen bond acidity of the molecule. In contrast, \( E_2(r) \) over the hydrogens is generally close to zero. Thus, the overall electrophilicity pictures that are provided by \( E_2(r) \) and \( V_3(r) \) are very different. \( V_3(r) \) emphasize the sites that are most susceptible to interact with hard Lewis bases, whereas \( E_2(r) \) emphasize the soft interaction sites.

In the classical description, halogen bonding was described as a soft interaction, that is, an interaction dominated by electron transfer from the Lewis base to the unoccupied \( \pi^* \)-orbital of the C–X bond. In recent years, partly as a consequence of the successful utilization of \( V_3(r) \) to rationalize halogen bonding, the electrostatic nature of the halogen bond has been emphasized.\(^{[24,26,28,32,36,36]} \) Electrostatics together with dispersion have been considered to be the main energy components that dictate halogen bond strengths.\(^{[26,28,36]} \) However, the nature of halogen bond has been heavily debated and some scientists argue that charge transfer plays a significant role in many halogen bond interactions.\(^{[13,49,57-59]} \)

In this regard, it is interesting to note that we find a very good linear correlation (\( R^2 = 0.970 \)) between the halogen bonding energy (\( \Delta E_{\text{int}} \))\(^{[56]} \) for binding of formaldehyde and the halogen \( E_{S,\text{min}} \) for a series of substituted methyl halides of the general formula \( \text{CH}_2\text{F}_{3-x}X \), where \( x = 0 \)–3 and \( X = \text{Cl} \) or \( \text{Br} \).\(^{[90]} \) The correlation is actually better than the corresponding correlation between \( \Delta E_{\text{int}} \) and \( V_{S,\text{max}} \), which has \( R^2 = 0.95 \). In this case, the \( E_2(r) \) is dominated by the contribution from the LUMO and there is a good correlation (\( R^2 = 0.968 \)) also between \( \Delta E_{\text{int}} \) and the LUMO energy.

An important indication of \( E_2(r) \)’s capacity to reflect a molecule’s halogen bond–donating ability, is given by an analysis of a set of halogenated benzenes of the type \( \text{C}_6\text{H}_{6-x}\text{F}_x \), where \( x = 0, 2, 5 \) and \( X = \text{Cl}, \text{Br}, \) or \( \text{I} \).\(^{[56]} \) This set of molecules is challenging as the molecules generally have several virtual
Computed the halogen bond in (B): red is of similar quality as the orbitals compared to the gen; this is a consequence of the more localized nature of the \( R \). kcal mol⁻¹. In particular, we find that the C(sp) set of molecules.

The lowest \( \Delta E_{\text{int}} \) is, the larger polarizability of Br as acceptor compared to Br⁻ as acceptor. Thus, this indicates that the relative importance of electrostatics versus charge transfer and polarization is much higher for the NH₁ interaction. This is in line with NH₁ being a harder Lewis base than Br⁻, that is, the larger polarizability of Br⁻ and its negative charge result in a larger contribution from polarization to the overall interaction energy compared to NH₁.

We like to conclude that two descriptor correlations of the type given above are not only advantageous because they quantitatively improve the predictive capacity compared to one descriptor correlations, but also because they can improve the understanding of the physicochemical character of the interaction. In this respect, we advise caution in interpreting the results of a single descriptor; a good linear correlation between \( \Delta E_{\text{int}} \) and a particular descriptor, for example, \( V_{\text{S,max}} \) for a set of congenic molecules does not necessarily imply that the interaction is dominated by the interaction type that is represented by the descriptor. As an example, the high correlation between \( \Delta E_{\text{int}} \) and \( V_{\text{S,max}} \) for many halogen bonding datasets is no proof that electrostatics is the dominating interaction type for halogen bonding, but only shows that the variations in \( V_{\text{S,max}} \) follow those of \( \Delta E_{\text{int}} \) within the datasets. In the following text, we will discuss how the use of surface properties and dual descriptor relationships can facilitate orbitals of negative energy, and for half of the molecules, the LUMO is an aromatic \( \pi^* \)-orbital rather than a halogen \( \sigma^* \)-orbital. Still, the lowest \( E_{\text{S,min}} \) is in all cases found over the heavy halogen; this is a consequence of the more localized nature of the \( \sigma^* \)-orbitals compared to the \( \pi^* \)-orbitals. Riley et al. originally computed the halogen bond \( \Delta E_{\text{int}} \) for the binding of acetone to this set of molecules.\(^{[26]}\)

We found a very good linear correlation (\( R^2 = 0.979 \)) between \( \Delta E_{\text{int}} \) and \( V_{\text{S,min}} \) (Figure 7C).\(^{[6]}\) This correlation is of similar quality as the \( \Delta E_{\text{int}} \) versus \( V_{\text{S,max}} \) correlation, with \( R^2 = 0.975 \). A statistically significant improvement of the \( E_{\text{S,min}} \) correlation is obtained by a two-variable linear relationship with \( E_{\text{S,min}} \) and \( V_{\text{S,max}} \) as independent descriptors, with a \( R^2 \) of 0.993 (Figure 7D); the standard deviation of the predicted \( \Delta E_{\text{int}} \) is only 0.10 kcal mol⁻¹ relative to the reference data. We have found this as a general trend that improved and more general correlations for halogen bonding are obtained when incorporating both \( E_{\text{S,min}} \) and \( V_{\text{S,max}} \) in the statistical analysis. This is particularly obvious from a recent, but yet unpublished study, where we have investigated the binding of ammonia (NH₃) and bromide anion (Br⁻) to a diverse set of bromine bond donors; the dataset includes donor sites where the bromine is bonded to either sp or sp² carbon. In this case, for both halogen bond acceptors, we find relatively poor overall correlations for \( \Delta E_{\text{int}} \) when \( E_{\text{S,min}} \) and \( V_{\text{S,max}} \) are used separately as descriptors. In particular, we find that the C(sp³)–Br and the C(sp)–Br halogen bond acceptors form separate correlation lines that are nearly parallel to each other. Much improved general correlations are obtained based on relationships of the type

\[
\Delta E_{\text{int}} = aE_{\text{S,min}} - bV_{\text{S,max}} + c.
\]

It is noteworthy that the relative importance of \( E_{\text{S,min}} \) versus \( V_{\text{S,max}} \), that is, the value of the \( b/a \) ratio depends on the character of the acceptor. In this particular study, we found \( b/a \) to be a factor 2.8 higher in the correlation for NH₁ as acceptor compared to Br⁻ as acceptor. Thus, this indicates that the relative importance of electrostatics versus charge transfer and polarization is much higher for the NH₁ interaction.

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the understanding of other types of interactions, in particular the interactions of metals and metal oxides with Lewis bases.

3. Applications of MSPA to Metals and Metal Oxides

3.1. Background

Transition metals and transition metal oxides are commonly used catalyst materials for heterogeneous catalysis. KS-DFT has played an important role in providing a computational framework for estimating the catalytic activity of different materials and has been used as an in silico tool for catalyst design.\cite{60,61} Traditionally, the catalyst surface has been represented by a perfect crystalline surface simulated by a periodic KS-DFT computation using a plane-wave representation. However, commercially important heterogeneous catalysts typically comprise catalytically active nanoparticles dispersed on an oxide support material. The local structure has been found to play a key role in determining the catalytical activity,\cite{62} and this has been difficult to address by conventional KS-DFT methods due to the large size and structural complexity of the catalytic nanoparticles. In this sense, the MSPA has a great potential as it, in principle, can be used to identify the local interaction sites and their interaction energies with different substrate molecules from a single DFT computation of the nanoparticle. In several recent studies, we have demonstrated that the MSPA indeed is applicable to this type of systems, and can become a very important complement to the traditional DFT approach for design of new catalysts.\cite{55-11}

3.2. Nanostructural Effects and Gold Catalysis

We will begin by discussing how the MSPA can be used to explain and predict the nanostructural dependence on the catalytic activity of gold; an element that traditionally has been considered the noblest of all elements because of its chemical inertness. In the late 1980s, it was rather surprisingly discovered that nanoparticles of gold are efficient catalysts.\cite{63} Today, it is well established that the catalytic properties of gold are linked to the stronger bonding of Lewis bases to low-coordinated Au-atoms.\cite{54-66} On gold nanoparticles it is mainly the corners, but also the edges that form the catalytic sites, and the lower activity of larger particles is a consequence of the dilution of active sites with increasing particle size.\cite{64} The high activity of nanoporous gold has a similar explanation, as the active sites appear at kinks on surface steps on the inside of the pores.\cite{65} Recently, it has also been found that Au adatoms on crystalline surfaces have much enhanced binding of Lewis bases.\cite{67} Whereas the connection between catalytic activity and coordination number is well established, the physico-chemical rationale for this relationship has until recently been unknown.

Figure 8A shows \(V_\sigma(r)\) on the surface of the gold dimer, Au\(_{12}\); there is a negative \(V_\sigma(r)\) region in the bonding region in the middle of the molecule, and similar to the \(\sigma\)-hole on halogens, there is a positive \(V_{S,max}\) at the end (tip) of each Au atom.\cite{11} The \(V_\sigma(r)\) pattern is a consequence of the valence electron configuration of Au; when the unpaired \(\sigma\)-orbitals combine to form the bonding \(\sigma\)-orbital, this results in a polarization of the electron density toward the bonding region and a deficiency in the electron density, a \(\sigma\)-hole, at the end of each Au. The redistribution of electron density in Au\(_{12}\) is similar to the textbook example of H\(_2\), where the \(1s\) orbitals combine to a bonding \(\sigma\)-orbital, and consequently the \(V_\sigma(r)\) of H\(_2\) is similar to that of Au\(_{12}\) (see Figure 8A). The \(\sigma\)-holes of H\(_2\) and Au\(_{12}\) stem from the overlap of \(\sigma\)-orbitals and are different from those of halogen compounds, which are the result of p-orbital overlap. We refer to the former as \(\sigma\)-holes and the latter as \(\sigma\)-holes, respectively. The \(\sigma\)-holes are more directional in character than the \(\sigma\)-holes, as a result of the elongated shape of the \(\sigma\)-orbital; for both types, the positive \(V_\sigma(r)\) of the \(\sigma\)-hole results in an increased binding affinity for Lewis bases. The appearance of \(\sigma\)-holes is not restricted to Au\(_{12}\), and positive \(V_{S,max}\) are also found at low-coordinated Au atoms of bigger Au clusters. Figure 8A also shows the \(V_\sigma(r)\) of a low-energy Au\(_{13}\) cluster of \(C_2\)-symmetry, and there is a \(V_{S,max}\) associated with each unique Au atom. As shown in Figure 8A, there is a linear correlation between the \(\Delta E_{\text{int}}\) for the binding of both CO and H\(_2\)O and the \(V_{S,max}\). The two correlation lines are nearly parallel and H\(_2\)O is consistently the weaker binder of the two molecules. Considering that H\(_2\)O has the higher polarity of the molecules, and a lower \(V_{S,min}\) this indicates that not only electrostatics but also other interaction types contribute to the binding. However, the high correlation between \(\Delta E_{\text{int}}\) and \(V_{S,max}\) for both substrates shows that the surface electrostatic potential is of major importance for the positional selectivity.

The connection between the coordination number of an Au atom and the magnitude of the \(V_{S,max}\) becomes further apparent when larger symmetrical clusters are studied. Figure 8B shows the \(V_\sigma(r)\) of the icosahedral and cuboctahedral Au\(_{13}\), Au\(_{55}\), and Au\(_{147}\) clusters. There are \(V_{S,max}\) above the Au atoms and their magnitudes vary consistently with the reactivity ordering, that is, corners > edges > facets. The corner \(V_{S,max}\) are in the range 8.0 to 11.4 kcal mol\(^{-1}\), and there is no correlation between the magnitude of the \(V_{S,max}\) and the particle size.\cite{11} Larger symmetric systems of the size up to Au\(_{561}\) were studied by means of periodic KS-DFT using a plane-wave basis set. The \(V_\sigma(r)\) results, as shown in Figure 8C, are fully consistent with those for the smaller clusters. Even the biggest cluster, Au\(_{561}\), for which the facet adsorption energies are similar to crystalline gold, has a corner \(V_{S,max}\) of similar magnitude as the smaller clusters.\cite{11}

Recently, we have also analyzed the effects of Au adatoms on crystalline gold surfaces (unpublished results). As shown in Figure 8D, there is a \(V_{S,max}\) also on top of the Au atoms at the crystalline Au(111) surface. However, it is only slightly positive and similar in magnitude to the facet \(V_{S,max}\) of the symmetrical clusters. The adatom \(V_{S,max}\), on the other hand, is much higher, 14.0 kcal mol\(^{-1}\) for the Au(111) surface with one adatom per (4 x 4) cell (i.e., 1 adatom per 16 surface Au), and thus it is even more positive than the corner \(V_{S,max}\) of the symmetrical clusters. This is in line with the strong adsorption of Lewis bases to Au adatoms that have been found by experiments.\cite{67} Interestingly, the \(V_{S,max}\) at the “normal” Au atoms decreases upon addition of the adatom, indicating that electron density is transferred from the adatom toward the surface. As shown in Figure 8D, there are also \(E_{S,min}\) at the same positions as the \(V_{S,max}\). The significance of \(E_{S,min}\) in describing the strength of \(\sigma\)-hole bonding to metal nanoparticles and metal surfaces will be discussed later in this report.
Figure 8. $V_S(r)$ for A–C) various gold nanoparticles and D) surfaces. For all structures, the undercoordinated sites have the most positive $V_{S,max}$. In (A), the local $V_{S,max}$ are plotted versus $H_2O$ and $CO$ adsorption energies for an Au$_{13}$ cluster. The $V_S(r)$ for the nanoparticles in (A) and (B) are evaluated using atomic-centered basis sets at the PBE/def2-SV(P) level of theory. In (C) and (D), periodic PBE calculations were employed with a plane wave basis set of 300/400 eV (in (C),(D)). An arbitrary scale is used for the $V_S(r)$ color scale in (C). (D) shows the Au(111) surface with and without Au adatoms (colored in orange). Here both $V_S(r)$ and $E_S(r)$ are included. Color scheme in (D) for $E_S(r)$ range from red ($–1.1$ eV) to blue ($–0.4$ eV to $–9.2$ kcal mol$^{-1}$). The $0.001$ au isosurface is used throughout. Panels (A)–(C) are adapted with permission.[11] Copyright 2017, American Chemical Society.

3.3. $\sigma$–Hole Bonding of Transition Metal Clusters

The formation of $\sigma$–holes at low-coordinated metal atoms due to the overlap of valence $s$-orbitals is not restricted to gold. Copper and silver also have a valence configuration with a singly occupied $s$-orbital, and form $\sigma$–holes that can be characterized by their associated $V_{S,max}$.[8] The three metals have comparable catalytic properties, and interact similarly with Lewis bases. In addition, the dependence of adsorption energy upon coordination number is similar. This led us to introduce the term regium bonding to categorize the bonding of the three metals to Lewis bases.[9] We will discuss regium bonding later in this report, and introduce the combination of $V_S(r)$ and $E_S(r)$ to differentiate Lewis base interactions both depending upon the metal and the Lewis base.

Positive $V_{S,max}$ at low coordinated atoms are also found for other transition metals, and can often explain the nanostructural effects in heterogeneous catalysis; such $V_{S,max}$ are generally signatures of $\sigma$–holes.[8] We have introduced three unique types of $\sigma$–holes to categorize the varying character of the $\sigma$–hole with respect to the electron density distribution. This classification
also provides a link between the \(\sigma\)-hole bonding of main row compounds and transition metal compounds. The three types of \(\sigma\)-holes are exemplified by the \(V_S(r)\) of HF, \(I_2\), and square planar Pt in Figure 9.\(^{[6]}\) In HF, the \(\sigma_{\text{g}}\)-hole is the result of the addition of the 1s orbital of H to an \(sp^3\) hybridized orbital of F to form the bonding \(\sigma\)-orbital. The \(\sigma\)-orbital is strongly polarized toward F, which results in a significant \(\sigma_{\text{p}}\)-hole at H and a strongly positive \(V_S\) at the end of each \(\sigma\). Since the \(\sigma\)-hole originates from the spherically symmetric 1s orbital, the \(\sigma_{\text{g}}\)-hole is diffuse and non-directional. The \(I_2\) molecule has a \(\sigma_{\text{p}}\)-hole at the end of each I, with an associated \(V_S\) that is formed because of the overlap of the two \(5p\) orbitals. The \(\sigma_{\text{p}}\)-hole is a result of the depletion of electron density at the end region. Because of the shape of the \(p\) orbitals, the \(\sigma_{\text{p}}\)-holes are more localized and directed along the extension of the \(\sigma\)-bond. The difference in character between the \(\sigma_{\text{g}}\)-hole and the \(\sigma_{\text{p}}\)-hole can be exemplified by the well-known tendency of hydrogen bonds to have angles (e.g., O–H···O) significantly smaller than 180°, whereas halogen-bond angles typically are close to 180°.

There are also \(\sigma_{\text{d}}\)-holes originating from orbitals of d-character. The square planar Pt, complex features eight equivalent \(\sigma_{\text{d}}\)-holes, which are formed as consequence of the Pt valence occupation of \(5d^96s^1\).\(^{[8]}\) The partially occupied d-orbitals and the symmetric structure results in a \(\sigma_{\text{d}}\)-hole, reflected by a \(V_S\) along the extension of each Pt–Pt bond. In this structure the bonding \(\sigma_{\text{d}}\)-orbitals are formed from the overlap of (s-mixed) 5d\(_{x^2}\) and 5d\(_{x^2-y^2}\) orbitals (i.e., the \(e_y\) orbitals). Thus the \(V_S\) at the ends of the Pt–Pt bonds can be characterized as \(\sigma_{\text{d}}\)-holes. The \(\sigma_{\text{d}}\)-holes are similar to the \(\sigma_{\text{d}}\)-holes in their localized and directional character.

Similar \(\sigma_{\text{d}}\)-holes are also found on the cubic Pt\(_8\) nanoclusters (NBO valence occupation: \(5d^{10}6s^16p^2\)) of Figure 9.\(^{[8]}\) Again it is the overlap of the 5d\(_{x^2}\) and 5d\(_{x^2-y^2}\) orbitals that give rise to the \(\sigma_{\text{d}}\)-hole. As expected, the cubic Au\(_8\) (5d\(^{10}\)6s\(^{0.86}\)6p\(^{0.22}\)) has \(\sigma_{\text{d}}\)-holes at the corners of the Au\(_8\) cube. The Ir\(_8\) cube (5d\(^{5.77}\)6s\(^{0.73}\)6p\(^{0.25}\)) features a different \(V_S(r)\) pattern with a triangular shaped area of high \(V_S(r)\) around the \(V_S\) around the \(\sigma_{\text{d}}\)-hole, which appears to be the result of a combined \(\sigma_{\text{d}}\)-hole. Compared to Pt\(_8\), Ir\(_8\) has a lower d-occupation and d-orbitals of all angular momenta are partially occupied. Thus the \(V_S\) results from the overlap of \(\sigma_{\text{d}}\)-holes of different origins.\(^{[8]}\)

The differentiation between \(\sigma_{\text{g}}\)-hole and \(\sigma_{\text{d}}\)-holes in the analysis above is facilitated by the high symmetry of the structures. In more complex structures, such discrimination becomes increasingly difficult. However, it should be remembered that it is the \(V_S\) in itself and its magnitude rather than the somewhat fictitious \(\sigma\)-hole that characterize a potential interaction site. This has been emphasized by Politzer et al. in regard to the analysis of main row \(\sigma\)-hole binding, and it is equally applicable to the interactions of transition metal clusters.\(^{[16]}\)

In ref. \(^{[8]}\), we further investigate a series of low-energy TM\(_{13}\) nanoclusters (TM = Au, Cu, Pt, Pd, Co, Rh, Ir, Ru including the Cu\(_{18}\)) and computed both \(V_S(r)\) and \(E_S(r)\). Out of these, we will discuss the Au, Pt, and Ir clusters, which are shown in Figure 10. Au\(_{13}\) is the same cluster as discussed above. The Ir\(_{13}\) (\(S = 1\frac{1}{2}\)) and Pt\(_{11}\) (\(S = 1\)) clusters have open structures, whereas Au\(_{13}\) (\(S = 1\)) has a more compact structure that is similar to a closed-packed arrangement. As already discussed, Au\(_{13}\) has a \(V_S\), at each corner, as a consequence of a \(\sigma_{\text{g}}\)-hole. Pt\(_{11}\) and also Ir\(_{13}\) show \(V_S(r)\) profiles dominated by \(\sigma_{\text{d}}\)-holes. Pt\(_{13}\) has one \(\sigma_{\text{g}}\)-hole at its weakest

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**Figure 9.** \(V_S(r)\) of cubic TM\(_4\) nanoparticles of Au, Pt, and Ir at the 0.001 au isosurface in the top row. The bottom row shows examples of different types of \(\sigma\)-holes as indicated by their associated \(V_S\). Adapted under the terms of the CC BY 4.0 license. (https://creativecommons.org/licenses/by/4.0/).\(^{[6]}\)
adsorption site, and the $V_{S_{\text{max}}}$ of the capping atom of Ir$_{13}$ can be described as a $\sigma_d$–hole or mixed $\sigma_d$–hole. The remaining $V_{S_{\text{max}}}$ (14 for Pt and 16 for Ir) are the results of $\sigma_s$–holes. Moreover, it is found that the $V_S(t)$ and $E_S(t)$ profiles agree well, with $V_{S_{\text{max}}}$ and $E_{S_{\text{min}}}$ located at almost identical positions. This holds for Au, Pt, and Ir, whereas there are some deviations for the other TM$_{13}$ clusters as discussed in ref. [8].

We found that H$_2$O adsorbs O-down to all identified $\sigma$–holes, and for all three clusters, the site with the strongest interaction consistently corresponds to the position of the highest $V_{S_{\text{max}}}$ (and lowest $E_{S_{\text{min}}}$). For the Pt$_{13}$ and Ir$_{13}$ clusters, the average deviation in distance between the position of the $V_{S_{\text{max}}}$ and H$_2$O adsorption site is small (~0.45 Å) whereas the deviation is larger (0.83 Å) for Au$_{13}$.[9] This is a reflection of the stronger directionality of the $\sigma_d$–holes of Pt$_{13}$ and Ir$_{13}$ compared to the $\sigma_s$–holes of Au$_{13}$. Regions of negative $V_S(t)$ are located in between atoms; H$_2$O was found to adsorb H-down to these regions except for the case of Ir$_{13}$. The computed interaction energy correlations with $V_{S_{\text{max}}}$ and $E_{S_{\text{min}}}$ are high for many of the TM$_{13}$ clusters, especially for the $d^9$ and $d^{10}$ TM and the strongest adsorption sites of Ir$_{13}$.[9]

3.4. Regium Bonding and Lewis Acid–Base Interactions of Au, Ag, and Cu

As already mentioned, we have introduced the term regium bonding to categorize the $\sigma$–hole bonding of d$^{10}$s$^1$ elements, Cu, Ag and Au, with Lewis bases, but compounds comprising these elements can potentially also interact with Lewis acids.[9] In order to investigate the predictive capacity of the MASP for both types of interactions, we analyzed the $V_S(t)$, $E_S(t)$, and $I_S(t)$ of the Au$_{11}$, Ag$_{11}$, and Cu$_{11}$ nanoclusters and the larger Ag$_{17}$, Ag$_{18}$, and Ag$_{19}$ clusters.[9] As reference data, we used computed interaction energies for interactions of the cluster with the Lewis bases H$_2$O, H$_3$S, NH$_3$, and CO, as well as with the Lewis acids, BF$_3$, BH$_3$, Na$^+$, and HCl (H-down).

The $V(t)$, $I(t)$, and $E(t)$ properties evaluated at 0.001 isodensity surfaces are shown in Figure 11 for the Au$_{11}$, Ag$_{11}$, and Cu$_{11}$ clusters ($S = \frac{1}{2}$ spin state).[9] The figure also shows the LUMO/SOMO; spatially the LUMO and SOMO (singly occupied molecular orbital) are almost identical for these compounds, and consequently FMO theory predicts the same interaction sites for Lewis acids and bases. In reality, the interaction sites differ considerably with the Lewis bases attaching on top of the metal atoms, and the Lewis acids preferentially binding to hollow and bridge sites in between atoms. Without much further analysis, it can be concluded that the FMO theory fails utterly in identifying and ranking the bindings sites of both Lewis bases and acids. In contrast, the multiorbital approaches, $E_S(t)$ and $I_S(t)$, which considers the almost band-like electronic structure of the clusters, perform considerably better. Taking $E_S(t)$ as an example, there are 22–40 virtual orbitals of negative energy per cluster that contribute to $E_S(t)$; and the combined contributions of these orbitals generally allows for the identification and ranking of all binding sites for Lewis bases.

We will begin by focusing on the Lewis acidities of the Au$_{11}$, Ag$_{11}$, and Cu$_{11}$ clusters in other words, the propensities for the three clusters to participate in regium bonding with Lewis bases.
The adsorption of H$_2$O and H$_2$S was analyzed by interaction energy calculations for all potential interaction sites.\textsuperscript{[9]} First we note that there is a $V_{S,max}$ on top of each metal atom, and their locations coincide with the binding sites for the Lewis bases. In a similar manner, there is an $E_{S,min}$ on top of each atom, but the position is in some cases slightly shifted relative to the $V_{S,max}$. For each cluster, the highest $V_{S,max}$ and lowest $E_{S,min}$ are located at position 4, which is the site with highest Lewis base affinity according to the computed $\Delta E_{int}$ (Figure 11).\textsuperscript{[9]} However, according to the magnitude of the $V_{S,max}$, Cu$_{8}$ is predicted to have the strongest binding affinity followed by Ag$_{9}$ and Au$_{10}$. $E_{S,min}$ instead predicts the order Au$_{10} >$ Cu$_{8} >$ Ag$_{9}$. The $\Delta E_{int}$ values show that H$_2$O binds most strongly to Cu$_{8}$, and that H$_2$S, not surprisingly, has a preference for Au$_{10}$; Ag$_{9}$ is the weakest binder of both H$_2$O and H$_2$S. Thus, although both properties predict the right positional selectivity, they convey different information regarding the relative reactivity of the metals. This observation prevails also after analyzing the data for all binding sites, as shown in Figure 12. There are high linear correlations, with $R^2$ ranging from 0.946 to 0.971, between $\Delta E_{int}$ and $V_{S,max}$, when each metal cluster is taken separately.\textsuperscript{[9]} However, whereas the correlation lines for Cu and Au almost coincide, the Ag correlation forms a separate line with a different slope; it can be interpreted as $V_{S}(r)$ overpredicting the binding affinities of Ag relative Au and Cu. When it comes to $\Delta E_{int}$ versus $E_{S,min}$, we find even better correlations, with $R^2$ close to 0.99, for each metal cluster taken separately. For $E_{S,min}$, the correlation lines for Ag and Cu overlap, although they have different slopes, and the Au line is parallel with Cu. Here $E_{S,min}$ can be seen as overestimating the binding affinities of Au relative Ag and Cu for the hard Lewis base H$_2$O. Similar to the previously discussed case with halogen bonding of NH$_3$ and Br$^-to C(sp^3)$-Br and C(sp$^3$)-Br compounds, we find that the binding affinities of all three metals can be correlated by a dual descriptor correlation of the type $\Delta E_{int}(\text{pred}) = -0.134 V_{S,max} + 0.495 E_{S,min} - 1.174$. The $R^2$ is 0.85, which is a significant improvement compared to the all-metal correlations using $V_{S,max}$ or $E_{S,min}$ separately with $R^2 = 0.79$ and 0.82, respectively.\textsuperscript{[9]}

Turning to the adsorption of the softer Lewis base H$_2$S, we find three well-separated and nearly parallel correlation lines for $\Delta E_{int}$ versus $V_{S,max}$ (Figure 12).\textsuperscript{[9]} The $R^2$ values are lower than for H$_2$O adsorption, and particularly so for the Au correlation, which only has $R^2 = 0.86$; this is likely to be a consequence of the strong binding of H$_2$S to Au, which generally involves a significant structure relaxation of the Au cluster. The separation of
the correlation lines, show that the $V_{S,\text{max}}$ severely underestimate the binding affinities of Au relative to Cu and Ag. The $E_{S,\text{min}}$ correlations are similar to the $V_{S,\text{max}}$ correlations, with three separated correlation lines of almost the same slope. However, the $\Delta E_{\text{int}}$ versus $E_{S,\text{min}}$ for Au is significantly better with $R^2 = 0.92$ ($R^2 = 0.86$ for $V_{S,\text{max}}$). Also $E_{S,\text{min}}$ underestimates the binding affinities of Au relative to Cu and Ag, but the deviation is less than with $V_{S,\text{max}}$. The binding of H$_2$S to all three clusters is well described by a single two-descriptor correlation of the same type as for H$_2$O, but the correlation coefficient ($R^2 = 0.89$) is significantly higher than for the H$_2$O correlation.\[9\] Compared to the H$_2$O correlation, the coefficient for $V_{S,\text{max}}$ changes sign from negative to positive. At first it may seem counterintuitive that the binding should become weaker with increasing magnitude of $V_{S,\text{max}}$. However, it should be noted that $E_{S}(r)$ (see Equation (5)) has a significant contribution from $V_{S}(r)$ and the change of sign simply means that a fraction of the $V_{S}(r)$ contribution is subtracted from the $E_{S,\text{min}}$ to give a stronger emphasis to the kinetic energy density contribution. This latter contribution, which we interpret as reflecting charge transfer and polarization, seems to be highly significant for the high binding affinity of Au to H$_2$S. We do find it rewarding that the same type of two-descriptor relationship that can describe the $\sigma$–hole bonding of halogen bond donors (see Section 2.3.2) also works for the $\sigma$–hole bonding of regium bond donors. This provides support for the physical significance and generality of the surface properties $V_{S}(r)$ and $E_{S}(r)$.

The interactions of the Ag$_9$ with the additional Lewis bases, NH$_3$ and CO, were also investigated.\[9\] The correlation with $\Delta E_{\text{int}}$ for NH$_3$ is high with both $V_{S,\text{max}}$ and $E_{S,\text{min}}$ as descriptors. CO gives a slightly lower correlation than the other Lewis bases,
which can be explained by the intricate bonding of CO, which has been indicated to comprise back donation. The correlation lines for the four Lewis bases are nearly parallel with binding affinities in the order, NH$_3$ > H$_2$S ≈ CO > H$_2$O. Whereas the ordering of NH$_3$, H$_2$S, and H$_2$O can be rationalized from the $V_S$ and $\bar{I}_S$ of the bases, the CO binding is stronger than anticipated, and back bonding may provide a partial rationale. The binding of CO to the bigger clusters, Ag$_{11}$, Ag$_{17}$, and Ag$_{87}$a, was also studied and similar correlations as for Ag$_{5b}$ was obtained. Relatively high $\Delta E_{\text{int}}$ versus $V_{S,\text{max}}$ and $\Delta E_{\text{int}}$ versus $E_{S,\text{min}}$ correlations were found encompassing all clusters taken together. This indicates that a correlation equation (calibration curve) can be determined for one or more smaller clusters, and thereby be used to predict binding affinities of larger and more complex systems.

We also investigated the capacity of $V_S(r)$ and $\bar{I}_S(r)$ to predict binding sites and binding affinities for Lewis acids. As can be seen in Figure 11, the locations of $V_{S,\text{min}}$ and $\bar{I}_{S,\text{min}}$ are typically in the bonding regions between the atoms, and they generally coincide with binding sites of Lewis acids. The quantitative correlations for the binding of Lewis acids are generally not as good as those for the Lewis bases. This can, at least partly, be rationalized by the more complex interactions with the Lewis acids, including structural relaxation of the Lewis acid, and multiple site interactions, for example, BH$_3$ interacts via both the H and B sites.

3.5. Interactions of Lewis Bases with Metal Oxide Clusters

Metal oxides are of great interest for applications in electronics, renewable energy systems, and heterogeneous catalysis. The advantages of using metal oxides as materials for catalysts, and other applications, are connected to a greater chemical design space compared to metallic systems, since the chemical properties of oxides can be varied by combinatorial design, both by changing the chemical composition globally and locally (doping). This can enable the design of less expensive catalysts, as the traditionally used rare metals, for example, Pt, Pd, and Au, can be substituted for more common and cheaper metals, for example, Ni, Cu, and Fe. However, the transferability in properties between different systems is not as prevalent for oxides as for metals, and depends more strongly on structural factors; consequently, commonly used DFT approaches for designing metal catalysts, such as the d-band model, is less applicable to oxides.

In order to investigate the potential of the MSPA approach for oxides we analyzed the binding of Lewis bases to a set of (TiO$_2$)$_n$ clusters of the sizes $n = 7$–10 (see Figure 13). These nanoparticles are ionic in character, with fully coordinated Ti and O bearing formal charges of $+4$ and $-2$, respectively. Even though it is well recognized that the formal charges overestimate the charge separation in these type of systems, the clusters indeed show much larger variations in $V_S(r)$ than the previously discussed metallic systems. As an example, the highest $V_{S,\text{max}}$ of (TiO$_2$)$_7$ is almost 155 kcal mol$^{-1}$, whereas for an Au cluster, a $V_{S,\text{max}}$ with a value one tenth that size (15 kcal mol$^{-1}$) is considered very high. The large charge separation of the oxide clusters has the consequence that the interactions of these nanoparticles with Lewis bases are dominated by electrostatics, and it is not surprising that we have found $V_S(r)$ to be an excellent tool for describing the regioselectivity and strength of Lewis base adsorption. However, the ionic character of the internal bonding, does not per se mean that active sites can easily be identified from any representation of the charge distribution. The most positively charged Ti atoms are typically highly coordinated and shielded by negative oxygens, and thus less accessible for an approaching Lewis base. Therefore, partial charges, independent of method for determination, are poor descriptors for characterizing binding sites.

The $V_S(r)$ of (TiO$_2$)$_7$ is shown in Figure 13, and the most positive areas are found over the Ti with relatively high but distorted coordination, which leaves the Ti atom partly exposed. We identified in total 27 unique binding sites for the four

![Figure 13](https://example.com/figure13.png)

**Figure 13.** A) (TiO$_2$)$_n$ nanoparticles and B) adsorption structures for the most favorable interaction of the particles with H$_2$O, H$_2$S, NH$_3$, and CO. C) The 0.001 au isosurface $V_S(r)$, $E_S(r)$, and the LUMO shown for the (TiO$_2$)$_7$. Color code $E_S(r)$, eV: red $<-25.0$, yellow $<-10.0$, green; color code $V_S(r)$, kcal mol$^{-1}$: blue $<-30$, cyan $<-15$, green $<-25$, yellow $<-90$, red. Computational level: PBE0/LANL2-TZ[Ti]:6-311+G(2d,2p)[O]. Adapted with permission.[7] Copyright 2017, American Chemical Society.
There are high linear correlations between $\Delta E_{\text{int}}$ and $V_{S,max}$ for all four Lewis bases, with generally $R^2 \geq 0.95$; NH$_3$, which is the strongest binder, is the exception with a lower $R^2$ of 0.92 (see Figure 14). The four Lewis bases form separate but nearly parallel correlation lines.\cite{7} The separation of the lines shows a relative difference in binding affinity in the order NH$_3 >$ H$_2$O $> H_2S \approx$ CO. It can be noted that this ordering is very different from the binding order for the adsorption to the noble atom clusters, where a mix of interaction energy contributions determines the binding strength. Here, not surprisingly, the order follows the magnitude of negative $V(\tau)$ associated with the lone pair of the Lewis base. Indeed by including the spatial minimum of $V(\tau)$ ($V_{\text{min}}$) as a descriptor for the base strength, we are able to gather all Lewis bases on the same correlation line; there is a good dual descriptor ($V_{S,max}$, $V_{\text{min}}$) linear correlation with an $R^2 = 0.963$ that encompasses all the unique (108) interactions (see Figure 14).\cite{7} This result is very encouraging and indicates that the strength of interactions between additional TiO$_2$ particles and Lewis bases can be predicted, using this relationship, solely from the $V_{S,max}$ of the particle and the $V_{\text{min}}$ of the base. It seems clear that electrostatics is the dominating, but not the sole, contribution to the interaction energy in this type of systems. Dispersion, polarization, and charge transfer are likely to contribute as well, but do not determine the difference in interaction energy between the different sites. In this context, it is interesting that $E_r(\tau)$ gives a very similar interaction map as $V_S(\tau)$, as is clear from Figure 13. There are also correlations between $\Delta E_{\text{int}}$ and $E_{S,min}$ for the different Lewis bases that are very similar to the $\Delta E_{\text{int}}$ Versus $V_{S,max}$ correlations, but the $R^2$ values of the $E_{S,min}$ correlations are in general slightly lower. These observations should not be seen as an indication that polarization/charge transfer plays a highly important role for the interaction, but rather that the variations in $E_r(\tau)$ mainly follows the $V_S(\tau)$ component according to Equation (6), and that the other components vary less.

4. Summary and Perspectives

In this report, we have summarized the MSPA and discussed a number of applications. We have shown that a large variety of molecular interactions of importance in organic chemistry, medicinal chemistry, supramolecular chemistry, and heterogeneous catalysis can be analyzed and rationalized in terms of three properties, which are computed on electronic isodensity surfaces. The three properties are well-defined in Kohn–Sham DFT, and are straightforward to determine from Kohn–Sham orbitals obtained from an electronic structure calculation with a Gaussian or plane-wave basis set.

The first of these properties, the electrostatic potential ($V(\tau)$), is best suited for studies of non-covalent interactions. In particular, the surface $V_S(\tau)$ is widely used for the analysis of interactions that can be categorized as $\sigma$–hole bonding, such as hydrogen and halogen bonding; $\sigma$–hole bond donors and acceptors are characterized by their associated $V_S(\tau)$ maxima ($V_{S,max}$) and minima ($V_{S,min}$), respectively. Furthermore, we have also shown, based on $V_S(\tau)$ analysis of nanoparticles, that the interactions of Lewis bases with metals and metal oxides generally can be viewed as $\sigma$–hole interactions. As an example, the noble metals, Cu, Ag, and...
Au, all interact preferentially with Lewis bases at low-coordinated sites, which have associated $V_{S,max}$ because of $\sigma$-holes. This type of interactions has been named regium bonding in analogy with the term halogen bonding. The $V_S(r)$ of nanoclusters and the $\sigma$–hole concept have provided a physicochemical rationale for the nanostructural effects of gold.

The second property is the average local ionization energy ($I(r)$), which was introduced as a complement to $V(r)$ for analyzing interactions that lead to covalent bonds. Surface minima in $I_S(r)$ are indicative of sites susceptible to electrophilic attack. In contrast to $V_S(r)$, $I(r)$ not only reflects the electrostatic component of an intermolecular interaction but also the contributions from charge transfer and polarization. We have discussed some of the application of $I_S(r)$, which include determining positional selectivity and product distributions in electrophilic aromatic substitution, as well as determining basicities and protonation sites of organic and inorganic bases.

The recent introduction of the third property, the local electron attachment energy ($E(r)$), has greatly extended the applicability of the MSPA. The $E_S(r)$ is similar in character to $I_S(r)$, but reflects the chemical reactivity toward nucleophiles rather than electrophiles. Nucleophilic aromatic substitution and conjugate addition are among the important reactions that have been analyzed with $E_S(r)$, and for which $E_S(r)$ have shown a high predictive capacity with respect to positional selectivity and global reactivity. However, we have also shown that $E_S(r)$ is complementary to $V_S(r)$ for the analysis of $\sigma$–hole interactions. The balance between electrostatics and polarization/charge transfer in $\sigma$–hole bonding varies depending on the characters of the $\sigma$–hole bond and acceptors, and can be estimated based on their surface properties. We have shown that dual descriptor relationships with $V_{S,\text{max}}$ and $E_{S,\text{min}}$ can be used to analyze the strengths of both halogen bonding and regium bonding with respect to changes in chemical composition of the donors and acceptors.

The appeal of the MSPA is partly connected to its simplicity; by the means of a molecular surface property graph, the individual interaction sites on a molecule, or particle, and their relative strengths are easily identified by visual inspection. However, the real potential of the approach goes beyond “pretty pictures.” The computation of surface properties for large datasets of molecules, together with the identification of minima and maxima in the properties, which characterize interaction sites, is computationally inexpensive and easily automated. As an example, a large database of drug molecules can easily be scanned and the protonation sites and basicities of all molecules can be determined. Similarly, the MSPA could be utilized in an automated tool for synthetic chemists to estimate regioselectivity of organic reactions, such as aromatic substitutions. We have also touched upon the prospect upon using the MSPA and particularly the $E_{S,\text{min}}$ descriptor as a mean for developing an in silico Ames test. Such a test could be used to analyze drug candidates for potential carcinogenicity without having to synthesize the molecules.

There are numerous potential applications of MSPA within solid-state chemistry and material science. The $V_S(r)$ is already widely used in supramolecular chemistry to characterize hydrogen and halogen bond donors and acceptors. Another promising application of the MSPA is for the design of catalysts for heterogeneous catalysis. An MSPA analysis can identify all the catalytic sites, and provide an estimate of their relative binding affinities to different Lewis bases by means of a single KS-DFT computation; a similar analysis is virtually impossible by the traditional “supermolecule” approach, where all the potential interactions have to be analyzed by a separate DFT structure optimization. The important savings in computational time can allow for investigating the role of the support material, or for the screening of materials with different chemical composition or geometrical structure. Although, we like to emphasize the simplicity of the MSPA approach, which allows for a range of intermolecular interactions to be predicted based on a few computed surface properties, it is important to realize that the analysis of the computational results generally benefits from experience and chemical knowledge. However, we do see a great potential in combining the MSPA with additional descriptors and to use artificial intelligence (AI) to develop more general and predictive models.

5. Computational Methods Section

See the original articles for computational details. Additional molecular structures were optimized and followed by single point calculations to obtain Kohn–Sham orbitals and electron densities using the B3LYP functional and the Gaussian09 code.[88] The surface properties $V_S(r)$, $I(r)$, and $E_S(r)$ were computed and analyzed using the H95ver18 code of T. Brinck. Periodic plane-wave computations with the PBE functional and the projected augmented wave method were performed using VASP.[69,70] The surface properties $V_S(r)$ and $E_S(r)$ were evaluated from the VASP computations using a code developed by J. H. Stenlid. The UCSF Chimera[71] and VESTA[72] software were used for graphical visualization of surface properties.

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Conflict of Interest
The authors declare no conflict of interest.

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