JCTC Journal of Chemical Theory and Computation

Electrostatic Potentials from Self-Consistent Hirshfeld Atomic Charges

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Abstract: It is shown that molecular electrostatic potentials obtained from iterative or self-consistent Hirshfeld atomic point charges agree remarkably well with the ab initio computed electrostatic potentials. The iterative Hirshfeld scheme performs nearly as well as electrostatic potential derived atomic charges, having the advantage of allowing the definition of the atom in the molecule, rather than just yielding charges. The quality of the iterative Hirshfeld charges for computing electrostatic potentials is examined for a large set of molecules and compared to other commonly used techniques for population analysis.

Introduction

The electrostatic potential (ESP)[1] plays a very important role in the study of chemical reactivity.[2−7] Indeed, when a molecule nears another molecule, the first thing it "notices" from the other molecule is its ESP. Hence, the ESP plays a fundamental role in theories that aim at explaining chemical reactivity, for instance, in so-called conceptual or chemical density functional theory (DFT).[8] The ESP also attracts attention because it has been shown that atomic[9] and molecular energies[10,11] can be expressed in terms of electrostatic potentials at the nuclei and the nuclear charges, such that

$$E = f(\{V_{0,A}, Z_A\}) \tag{1}$$

When used in chemical reactivity, studying where the minima in a molecular ESP occur allows, for example, the prediction of where an electrophile is most likely to attack.[2,3,5,6] Naturally, this is only a first approximation, and one needs to include many more effects when the molecules approach each other more. The interaction energy is then best described in terms of a Taylor expansion of the energy with as variables the number of electrons and the external potential.[12,13] Even if for the latter part the ESP is a good first approximation, it should be taken into account that once two molecules approach each other sufficiently close, the electrostatic potential of the molecules is altered in the electronic polarization process, and as such, one should compute it for every new mutual arrangement of the molecules. In other words, the electrostatic potential of an isolated molecule should only be used as a reactivity index for the very first stages when two distant molecules start approaching each other. Also, if charge transfer happens between the molecules, other reactivity indices need to be studied as well in order to interpret or predict the reactivity. Nevertheless, the ESP remains a very valuable field and is used to understand, e.g., interactions between biomolecules.[4,14−20] A frequently used option in studying the intermolecular interaction is to examine the electrostatic potential at and beyond some minimum distance from the molecule, e.g., on the van der Waals radius.

The ESP of a molecule $V(\mathbf{r})$ can be computed relatively easily given the positions $\mathbf{R}_A$ and charges Z_A of the nuclei in the molecule and the electronic density function $\rho(\mathbf{r})$:

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}') \, d\mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|} \tag{2}$$

As the ESP is of such importance, it is a ubiquitously used field in 3D-QSAR.[19,21] In classical QSAR, often molecular descriptors are used that are related to the ESP.[14,15,22] A good example is atomic charges.

$V(\mathbf{r})$ can also be computed from a sum of contributions from all the multipoles of the charge distribution. One can either take the entire molecular charge distribution or work in terms of certain parts of the molecule, e.g., regions of space associated to certain atoms in the molecule. It follows from Coulomb's law that any distribution of electrical charge creates a potential $V(\mathbf{r})$ at each point in the surrounding space.

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In the elementary example of the discrete charge distribution of a collection of point atomic charges, an approximate electrostatic potential can be computed as

$$V(\mathbf{r}) \approx V'(\mathbf{r}) = \sum_A \frac{q_A}{|\mathbf{r} - \mathbf{R}_A|} \tag{3}$$

Such an approximation naturally comes at the cost of a loss of quality of the ESP. Nevertheless, when high throughput of molecules is needed or for very large molecules, such approximate ESP are often used, e.g., in *co*mparative *m*olecular *f*ield *a*nalysis (COMFA).[21] When compared to the ab initio ESP, quite large errors can occur, depending on the technique used for computing the atomic charge. An exception is ESP-derived atomic charges. These naturally reproduce relatively well the ESP as they are obtained via a fit of $V'(\mathbf{r})$ versus $V(\mathbf{r})$ with the atomic charges as variables under some constraints such as that the sum of the atomic charges needs to be equal to the molecular charge and optionally the requirement that the atomic charges reproduce some molecular multipole moments. Different algorithms are commonly used, known under names such as CHELP(G)[23,24] or the Merz−Kollman−Singh[25,26] method. It is important to note that these atomic charges are obtained as a statistical fit to the ab initio potential and as such the charges are not the product of a true "atom in the molecule" (AIM). That is, there is no AIM density function from which the charge is derived as

$$q_A = Z_A - \int \rho_A^{AIM}(\mathbf{r}) \, d\mathbf{r} \tag{4}$$

Moreover, there are quite important statistical problems with ESP-derived charges due to rank problems.[27−29] The wording atom in the molecule (abbreviated AIM) is used in a more general meaning than Bader's technique based on zero flux surface analysis.[30,31] As is clear from the above, the AIM plays an important role in the evaluation of $V'(\mathbf{r})$. The importance of the AIM, however, is far from limited to this use. The AIM forms a cornerstone of chemistry and is quantum chemical object with a density function attached to it. This is also the main distinction between a true AIM method and a population analysis method. The latter methods only yield atomic charges whereas these are only one quantity derivable from the density function. Despite the role of the AIM, its precise nature is still subject of debate[32−34] and many different AIM methods have been described. Recently, one of the authors has described the iterative Hirshfeld method[35,36] (Hirshfeld-I). At that time, it was found that the atomic charges resulting from the Hirshfeld-I AIM density function, correlate well with electrostatic potential derived charges. This raises the question whether this is merely a chance correlation between the two charge sets or whether there is also a good correlation between the Hirshfeld-I based $V'(\mathbf{r})$ and ab initio $V(\mathbf{r})$.

The purpose of the present study is thus to examine how good $V'(\mathbf{r})$ derived from (3) is compared to the ab initio potential. The reason why such a study is highly relevant is that, if the Hirshfeld-I AIM definition derived from solely the molecular density function, gives fairly good $V'(\mathbf{r})$, this suggests that it is a promising source for AIM condensed reactivity indices in general. In other words, even a simple approximate ESP from (3) using Hirshfeld-I charges is able to provide insight in molecular reactivity. Moreover, if the quality of the approximate ESP is roughly similar to the approximate ESP obtained with ESP-derived charges, the Hirshfeld-I method has the important advantage of being an AIM method, rather than merely a technique for population analysis. Moreover, it is a technique that allows defining the atom in the molecule and which does not suffer from numerical instability, as ESP-derived charges do.

Theoretical Background

As stated earlier, the ESP is especially useful for the first stages of an electrostatic interaction, with $V(\mathbf{r})$ being computed on an outer surface of the molecule. A common approach is to use a set of intersecting spheres centered on each atom with some atom specific radius. This may be a number of times the van der Waals radius, or some other appropriate radius. Such a surface can be generated readily for any molecule. Alternatively, one can also use an isodensity surface, as was suggested by Bader et al.[30] The advantage of using such a surface is the fact that it is more molecule specific than using a surface based on intersecting spheres where each atom of a specific element shares the same radius. In the present study, a series of molecular surfaces is generated based on intersecting fixed radius spheres around the different nuclei. This choice is based on the fact that this is also the method used for computing ESP-derived charges and that the Hirshfeld-I based approximate ESP is to be compared to that based on ESP-derived charges. The latter are known to depend to sometimes significant extent on the selection of the surface, hence a fair comparison should be made based on the same appropriate point selection scheme.

In this study it will be examined how well different AIM methods perform for predicting $V'(\mathbf{r})$ compared to ab initio $V(\mathbf{r})$. Most of these methods have already been described in detail in the literature. The exception is the iterative Hirshfeld-I method. In the Hirshfeld-I method, the AIM density function is obtained as follows. First, for a real molecule a promolecule is constructed in exactly the way proposed originally by Hirshfeld.[37] The promolecular density function $\rho_{Mol}^0(\mathbf{r})$ is the union of the density functions $\rho_A^0(\mathbf{r})$ of the isolated atoms A put on exactly the same place in space as in the molecule. At each point in space, the weight $w_A(\mathbf{r})$ of an AIM A is computed as

$$w_A(\mathbf{r}) = \frac{\rho_A^0(\mathbf{r})}{\rho_{Mol}^0(\mathbf{r})} = \frac{\rho_A^0(\mathbf{r})}{\sum_A \rho_A^0(\mathbf{r})} \tag{5}$$

This positive definite weight summed over all atoms equals unity. The density function for an AIM A (denoted) $\rho_A^{AIM}(\mathbf{r})$ is then obtained from the molecular density function $\rho_{Mol}(\mathbf{r})$ via

$$\rho_A^{AIM}(\mathbf{r}) = w_A(\mathbf{r}) \rho_{Mol}(\mathbf{r}) \tag{6}$$

Different authors[32,35,38−40] have shown that there is a fundamental problem with the original Hirshfeld method, as

Table 1. Atomic Charges (in au) in **54** Computed from Different AIM Methods and Methods for Population Analysis

	MKS-VBF	Hirshfeld	Hirshfeld-I	Mulliken	NPA
H	0.1042	0.0273	0.1078	0.1510	0.1797
C	−0.3003	−0.0721	−0.4018	−0.3881	−0.5315
H	0.0699	0.0223	0.0947	0.1242	0.1690
C	0.2782	0.0532	0.2534	−0.1136	0.0673
H	0.0657	0.0277	0.1036	0.1198	0.1765
O	−0.5256	−0.2095	−0.4316	−0.1717	−0.6712
H	0.0320	0.0302	0.0400	0.1473	0.1517
H	−0.0062	0.0193	0.0140	0.1020	0.1257
C	0.3972	0.0516	0.2679	−0.0925	0.0637
C	−0.4205	−0.0681	−0.3897	−0.5204	−0.5134
H	−0.0122	0.0182	0.0116	0.1168	0.1258
H	−0.0072	0.0191	0.0178	0.1104	0.1277
H	0.0872	0.0255	0.0977	0.1218	0.1711
H	0.1231	0.0278	0.1077	0.1454	0.1794
H	0.1181	0.0274	0.1069	0.1475	0.1786

Table 2. Root-Mean-Square Error (rmse, in Units 10^{-3} au), Slope (a) and Intercept (b, in Units 10^{-3} au) of the Regression Line, and R^2 for $V'(\mathbf{r})$ versus $V(\mathbf{r})$ for Molecule **54** and Different AIM Methods and Methods for Population Analysis[a]

	MKS-VBF	Hirshfeld	Hirshfeld-I	Mulliken	NPA
rmse	2.0	5.8	2.8	7.0	10.6
a	0.97	0.49	0.90	0.76	1.81
b	0.0	−0.4	−0.5	−0.6	−0.7
R^2	0.97	0.93	0.94	0.62	0.93

[a] Hirshfeld denotes the original Hirshfeld method and Hirshfeld-I the iterative version.

the AIM density function depends quite strongly on the isolated atom densities used. For instance, in a molecule like N_2, Davidson et al.[32] have shown that different atomic charges are found for the nitrogen atoms depending on whether the promolecule was constructed of two neutral nitrogen atoms or a positive and a negative one. Bader et al.[40] criticized the method because it, indeed, also gives very small atomic charges on highly ionic compounds. These problems were addressed by Bultinck et al.[35,36] by iteratively changing the isolated atoms used for computing the AIM density function. Starting from some chosen set of isolated atom fragments (neutral or charged), $w_A(\mathbf{r})$ is computed according to (5). Using this weight function, AIM densities for all A are computed via (6). From this density function, the AIM electronic population is computed. For this precise electronic population, a new $\rho_A^0(\mathbf{r})$ is computed for all A. Then, a new $w_A(\mathbf{r})$ can be computed, yielding new AIM density functions. The procedure is repeated until convergence, meaning that the atomic electronic populations used for computing $w_A(\mathbf{r})$ no longer differ from those obtained by integrating $\rho_A^{AIM}(\mathbf{r})$. For the exact details of the method, called Hirshfeld-I, including the method of how to deal with noninteger electronic populations, the reader is referred to Bultinck et al.[35,36] Hirshfeld-I AIM density functions no longer depend on the starting set of atomic densities and always produce the same unique solution and are fairly independent of the basis set used.[36]

Computational Methods

In order to assess the quality of $V'(\mathbf{r})$ from (3) by comparison to the exact $V(\mathbf{r})$, the molecular ESP is computed ab initio at the RHF/6-311++G** level. As explained above, the ESP is a reactivity descriptor for the first stages of approach between two molecules. Hence, the ESP is computed on a grid of points on an outer surface of the molecule. A self-written program allows computing points on a single layer or on different layers around the molecule in a similar way as in the Merz−Singh−Kollman scheme introduced by U. C. Singh and P. A. Kollman.[25] In the present study, the grid points are located on four layers around the molecule. The first layer is constructed from atom-centered spherical surfaces with all Merz−Kollman radii of the spheres scaled by a factor of 1.4. The grid density on these surfaces is chosen at 5 points per unit surface. For the more distant layers, the radii of the atom centered spheres are increased as prescribed in ref 26. On the resulting total set of points, the ab initio ESP is computed and stored as reference.

From the molecular density function, the AIM are computed in each molecule using different techniques: the Mulliken[33] method, the original Hirshfeld method, and Hirshfeld-I and natural population analysis[41] (NPA). $V'(\mathbf{r})$ are computed from (3) with atomic charges obtained from (4). $V'(\mathbf{r})$ are also computed from atomic charges derived from electrostatic potential fitting. For the latter, a least-squares regression fit is performed between $V'(\mathbf{r})$ and $V(\mathbf{r})$ with the atomic charges as variables. Considering the grid used in the present study, the resulting atomic charges should be quite close to results obtained with the Merz−Kollman−Singh algorithm, as the grid points are sampled according to the Merz−Kollman−Singh scheme. Our calculations revealed this to be the case. Results of this fit with our own grid will be denoted as MKS-VBF.

In order to be able to properly assess the quality of $V'(\mathbf{r})$, a set of 158 molecules is used. These molecular structures for the test set are available in the Supporting Information. For each molecule individually, the root-mean-square error between $V'(\mathbf{r})$ and RHF/6-311++G** $V(\mathbf{r})$ is computed as well as the squared correlation coefficient R^2 between both. The average R^2 considering all molecules is also computed, together with its standard deviation. Finally, also the R^2 over all grid points in all molecules is computed.

All molecular density functions in the present work were computed at the RHF/6-311++G** level of theory using Gaussian-03.[42] AIM density functions and atomic charges were computed with self-developed programs, except for the NPA atomic charges that were taken from Gaussian-03 directly.

Results and Discussion

In order to make the presentation of the results as clear as possible, each step is illustrated by just one molecule, namely ethoxyethane (molecule **54**), after which the results over the entire molecular set are presented. Table 1 gives the atomic charges on all atoms of molecule **54** for the different types of AIM methods or population analysis.

As was reported previously by Bultinck et al., Hirshfeld-I charges correlate relatively well with the ESP-derived
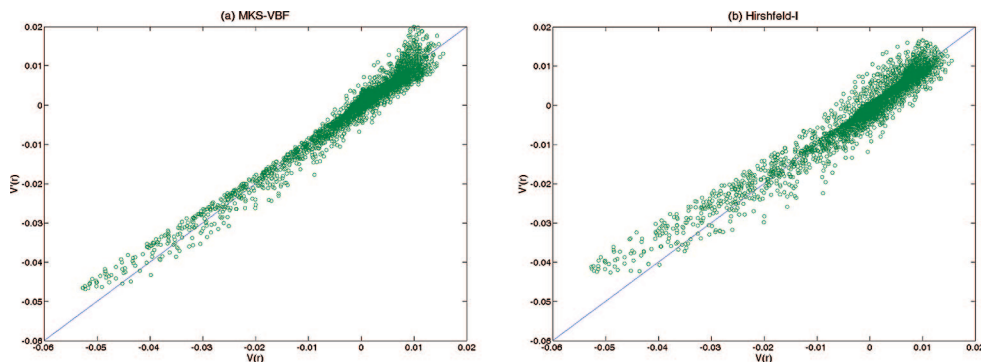
Figure 1. Correlation between $V'(\mathbf{r})$ and $V(\mathbf{r})$ (in au) for molecule **54** for (a) MKS-VBF and (b) Hirshfeld-I.

charges. The R^2 between MKS-VBF and Hirshfeld-I is 0.81. Having computed the atomic charges and the exact ab initio molecular ESP $V(\mathbf{r})$, $V'(\mathbf{r})$ is computed from (3). Table 2 gives for each method the root-mean-square error (rmse) between both potentials for molecule **54**, as well as the slope and intercept of the regression line $V(\mathbf{r}) = aV'(\mathbf{r}) + b$ and R^2 between the ab initio and approximate ESP.

As expected, Table 2 reveals that the rmse is quite low for the MKS-VBF method and that the R^2 is quite high. Interestingly, the rmse is quite low for the Hirshfeld-I technique as well. Also, the R^2 is quite good. The correlation between $V(\mathbf{r})$ and $V'(\mathbf{r})$ is shown in Figure 1 for both MKS-VBF and Hirshfeld-I.

Figure 1 shows that the regression line is even relatively close to the bisector. The other sets of atomic charges perform less good. At least for molecule **54**, Hirshfeld-I is nearly as good as the MKS-VBF method. There is also a clear improvement for Hirshfeld-I compared to Hirshfeld, despite the fact that the squared correlation coefficient and intercept are very similar. The slope is completely different, which may have important consequences when making comparisons among different molecules (see below). This shows that it is important to include the iterative procedure in the Hirshfeld method.

Naturally, a single molecule does not suffice to draw general conclusions and so the entire molecular set must be considered. The table giving the statistical characteristics for each molecule in the molecular set can be found in the Supporting Information. When considering the entire set, it is found that for some molecules, e.g., NPA charges give very good R^2 but relatively high rmse. This means that the regression line differs quite strongly from the bisector. Even with individual high R^2 for every molecule separately, one can have poor performance for the comparison of different molecules. In order to establish to what extent the different methods perform over the entire test set, Table 3 gives the average rmse with the associated standard deviation, the average R^2 with the standard deviation and R^2. The latter value is the squared correlation coefficient over the union of all grid points in all molecules. This value indicates whether there is a common correlation beneath a set of individually good correlations per molecule. Also included are the average slope and intercept for the regression equation $V(\mathbf{r}) = aV'(\mathbf{r}) + b$ and the standard deviations on these values.

**Table 3.** Average Root Mean Square Error (rmse, in Units 10^{-3} au), Slope (*a*) and Intercept (*b*, in Units 10^{-3} au), R^2 over All Molecules with Standard Deviation, and R^2 over all Grid Points in All Molecules[a]

	MKS-VBF	Hirshfeld	Hirshfeld-I	Mulliken	NPA
rmse	2.2	8.11	*4.4*	14.4	7.6
	0.7	0.9	*1.0*	10.9	2.0
a	0.97	0.52	*0.83*	0.81	1.22
	0.02	0.14	*0.12*	0.48	0.23
b	0.0	−0.2	−0.4	−1.1	−1.1
	0.0	*0.2*	*0.2*	1.1	0.5
R^2	0.97	0.87	*0.93*	0.61	0.89
	0.02	0.09	*0.05*	0.32	0.08
R^2_{all}	0.98	0.86	*0.93*	0.36	0.89

[a] The first number denotes the average, the second the standard deviation. For each parameter, the best value is italicized (excluding MKS-VBF).

Table 3 clearly shows that the average rmse is quite low for MKS-VBF, as expected. Also, the standard deviation is relatively low, meaning that for all molecules the rmse is roughly equally good. As MKS-VBF is a least-squares fit between the ab initio and approximate ESP, all statistical parameters describing their mutual relationship are the best over all methods. The original Hirshfeld method performs acceptably for both rmse and its standard deviation. The Mulliken method performs poorly, with NPA in between. Hirshfeld-I performs very well, as will be discussed below in more detail. Roughly the same picture is found based on the R^2. The average R^2 is best for MKS-VBF and Hirshfeld-I. Occasionally, Mulliken or NPA can also give high R^2 for individual molecules, but not in a consistent fashion. This is clearly revealed by the large standard deviation in R^2 for these methods. As a graphical representation of the performance of the different methods, Figure 2 shows the values for the rmse, R^2, slope, and intercept for every molecule individually for all methods used.

As Figure 2 clearly shows, the ranges in all statistical parameters are relatively small for MKS-VBF and Hirshfeld-I. This is clearly not the case for Mulliken and NPA. A further interesting comparison lies in the slope and intercept of the regression lines between $V(\mathbf{r})$ and $V'(\mathbf{r})$. As Table 3 shows, the average slope is relatively close to 1 for MKS-VBF, Hirshfeld-I, NPA, and surprisingly also Mulliken. For the Mulliken method, however, this high slope comes with a very large standard deviation, which is not the case for MKS-VBF and Hirshfeld-I. The average slope for the Hirshfeld method deviates quite a lot from 1.0. The average
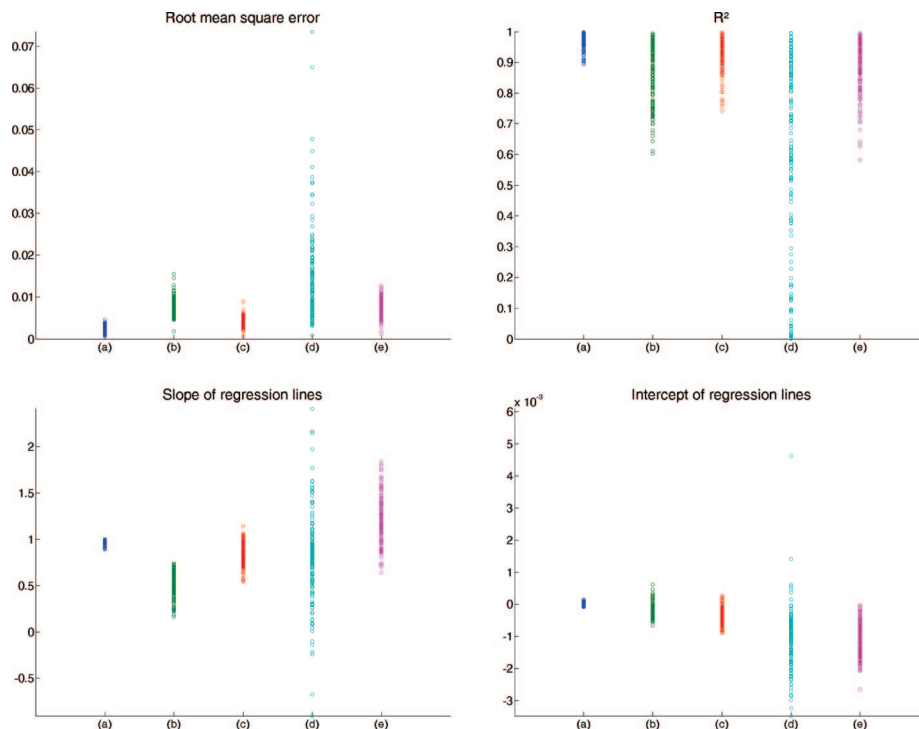
Figure 2. Rmse (au), R^2, slope, and intercept (au) for each molecule for MKS-VBF (a), Hirshfeld (b), Hirshfeld-I (c), Mulliken (d), and NPA (e).

intercept for the different methods points out that both Hirshfeld and Hirshfeld-I perform very well. R^2 confirms the conclusions from the other statistical parameters, namely that MKS-VBF and Hirshfeld-I perform consistently well and Mulliken performs very badly.

The Hirshfeld-I method, although not fitted to the ESP, performs nearly as well as MKS-VBF. This is a very interesting observation as the Hirshfeld-I method is an AIM method and not merely a method for atomic charges. This is very important as, given an AIM density function, one can compute all the expectation values that can be computed from a density function in the usual quantum mechanical way. Atomic dipole moments can, e.g., be computed. This is not the case with ESP-derived charges as one has no density function.

When comparing to the original Hirshfeld method it is seen that the inclusion of the iterative procedure in Hirshfeld-I improves the quality of the fit between $V(\mathbf{r})$ and $V'(\mathbf{r})$. All parameters describing the quality of the fit are significantly better for Hirshfeld-I than for the original method except for a slightly better average intercept. The difference, however, is very small. Bultinck et al.[35] previously pointed out that there are significant differences in atomic charges between Hirshfeld-I and the original Hirshfeld method. These results are opposite to those of Nalewajski et al.,[43] who report only a weak dependence of resulting AIM charges on the promolecule chosen. According to them, using an ionic promolecule leads to only a slightly larger charge separation for NaCl. Our calculations reveal that this effect is quite large. For NaCl the difference in charge separation amounts roughly 0.5 between the Hirshfeld and Hirshfeld-I schemes. The present results show that the inclusion of the self-

consistently obtained promolecule in the Hirshfeld-I procedure also has a marked effect on the agreement between $V'(\mathbf{r})$ and $V(\mathbf{r})$.

Finally, the question arises to what extent the good performance of the Hirshfeld-I scheme allows one to conclude it as the best or final AIM method. We believe that such a far-reaching conclusion cannot be drawn from this study. The present study only shows that, among the methods tested, it is the best performing AIM method when it comes to yielding approximate ESP's that are most similar to the ab initio ones. Good performance in an approximate scheme cannot be used as an argument for more general conclusions. We do, however, stress that the present study is a clear indication that for atom condensed reactivity indices, which are almost always computed in some approximate way,[44] the very good performance of Hirshfeld-I shows that they may be the best choice for computing such indices. Other AIM techniques that already do not perform well for a simple field like electrostatic potential can hardly be expected to perform well for more subtle fields. The main advantage of the Hirshfeld-I approach to ESP as opposed to the electrostatic potential derived charges based ESP is that no statistical rank problems exist with the Hirshfeld-I method and that it gives a true AIM density function instead of merely a set of atomic charges.

Conclusions

It has been shown that the quality of electrostatic potentials derived from a simple monopole approximation compared to the true ab initio electrostatic potentials on a surface surrounding the molecule depends strongly on the atoms in molecules method or population analysis technique. ESP-

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derived atomic charges perform well, as expected, but have the drawback that they do not define the atom in the molecule. The Hirshfeld-I method does give an atom in the molecule with its own density function and the atomic charges derived from it give a statistical fit to the true electrostatic potential that is nearly as good as that for the ESP-derived charges. This suggests that the Hirshfeld-I method could be a very good candidate for use in other atom condensed reactivity indices.

Supporting Information Available: Structures of the molecules used in the study and the statistical characteristics for each molecule individually are listed. This information is available free of charge via the Internet at http://pubs.acs.org.

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CT800394Q