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GAME: A computer graphics method for calculating and displaying the molecular electrostatic potential

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A new method for calculating and displaying the molecular electrostatic potential on the molecular surface is described. The main advantage of the method, besides some others, is its consistency. This means one only needs one data set for the surface and the MEP: a 3D field of the electron density from any source.

Keywords: ab initio wavefunction, molecular electrostatic potential, automatic color mapping, ab initio molecular surface, pseudopotentials

INTRODUCTION

The molecular electrostatic potential (MEP)[1] is a powerful tool to predict intermolecular interactions, not only for long ranges. Especially in the field of host–guest chemistry the color coding of the MEP on a molecular surface is a stimulating and appropriate method for graphical display.

Numerous methods at different levels of theory and accuracy exist for calculating the MEP at a given point. Nearly all methods can be divided into three groups. In the first group one calculates the MEP exactly from the wavefunction. The application of rigorous bounds to the potential integrals can make the evaluation more effective.[2] In the second group the potential is calculated from the Poisson equation. The analytic solution is slow. Most methods, finally, calculate the MEP from a multipole expansion approximating the molecular electron density. They differ in the truncation and the choice of the centers, for example, monopoles at the nuclei,[3] atomic multipoles at the nuclear positions,[4] multipoles up to quadrupoles at the nuclei and dipoles at the bond center,[5] multipoles up to quadrupoles at the centers of localized molecular orbitals,[6] monopoles at the centers of natural atomic orbitals,[7] and multipoles at the centers of the overlap distribution of Gaussian basis functions.[8] In these methods both steps—multipole expansion of the charge density, MEP calculation from multipoles—to obtain the MEP values at any point can be carried out accurately and quickly. But all algorithms are not especially designed for further usage in computer graphics.

The MEP values are computed for a set of points on a molecular surface. Mostly, a van der Waals or a solvent-accessible surface is chosen as the molecular surface. The van der Waals surface is the surface that cannot be penetrated by another molecule at room temperature.[9]

A great disadvantage of most methods up to now is that they can calculate the potential with any desired accuracy but make relatively crude approximations about the shape of the molecule. The new GAME algorithm (Graphic Adjusted Monopole Expansion) uses one data set for generating a molecular surface and the same data for calculating the MEP.

If one intends to display the MEP on a molecular surface by means of sophisticated computer graphics techniques, one should take the specific requirements into account and take advantage of them. The GAME algorithm will do so in a graphic adjusted approach.

The most popular procedures (see, e.g., Refs. 10–15) to obtain such a colored molecular surface consist of three steps:

1. In the first step, one defines a molecular surface and creates the Cartesian coordinates of evenly distributed points on the surface.
2. In the next step, for every point a MEP value is calculated.
3. Finally, the molecular surface is displayed and the potential color coded on it.

The two basic insufficiencies of the most common methods are the strict separation of the three steps, which makes it impossible to take advantage of inherent links, and the different quality of the approaches in each step. Typically enough, the three steps are often distributed over different data sets, programs, and computers. Our all-in-one approach is described in the following section.

Color plates for this article are on p. 49.

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THE GAME ALGORITHM

The basics

The only necessary input for the whole algorithm is a three-dimensional (3D) scalar field of the electron density ρ. The ρ values, ρ_i at $\mathbf{r}_i$, are evenly spaced in each direction. This regular grid consists of a orthorhombic ($\alpha = \beta = \gamma = 90°$, $a \neq b \neq c$) grid cells. The pictures shown here were generated from a 0.25 (±0.03)-Å grid, which extends 4 Å beyond the dimensions of the molecule. The electron density is calculated from an ab initio wavefunction. The calculations were done with a split valence basis set and with pseudopotentials (effective core potential) replacing the core electrons. The grid contains the complete information bout the shape of the molecule and the electronic charge distribution, which generates the electronic part of the potential.

A van der Waals surface assembled of parametrized atomic subunits is only a crude approximation to the shape of a molecule. Note that the promolecule, the molecule, the anions, and the cations of a compound all have the same shape in this approximation.

Bader et al.[16] showed that the 0.002-a.u. contour of the electron density (1 a.u. = 6.748 333 · 10^{30} e/m^{-3}) provides a reasonable theoretical measure of the molecular size. These theoretical values agree surprisingly well with the experimental values.[17] Therefore an isovalued surface of the electron density is chosen as molecular surface representing the volume and the shape of a molecule.

The ρ grid not only provides an "ab initio molecular surface" but also the electronic part of the MEP. The MEP, $V^{MEP}(\mathbf{r})$, is defined as the energy that is necessary to bring up a positive point charge from infinity to $\mathbf{r}$ in the presence of the fixed charge distribution of the molecule.

$$V^{MEP}(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int_{Vol} \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|}\, d\mathbf{r}' \qquad (1)$$

nuclei electrons

The atoms A with the nuclear charges Z_A are located at $\mathbf{R}_A$. The integral describes the electrostatic interaction between the electron density and the point charge. Because the electronic charge distribution is already given by the ρ grid, one can advantageously substitute the integral in Eq. (1) by the sum over all the grid points:

$$\int_{Vol} \frac{\rho(\mathbf{r})'}{|\mathbf{r}' - \mathbf{r}|}\, d\mathbf{r}' \quad \text{is replaced by} \quad \sum_i \frac{\rho(\mathbf{r}_i)}{|\mathbf{r}_i - \mathbf{r}|} \Delta V \qquad (2)$$

ΔV denotes the volume of the grid cell. Thus, the continuous electron density is substituted by its granular approximation. The calculation of the nuclear part remains unchanged and is no longer discussed because of its negligible computational effort. As is seen below, it is useful to calculate a grid of MEP values with the same positions of the grid points as in the ρ grid.

The summation of the $1/|\mathbf{r}_i - \mathbf{r}|$ values leads to the problem that in the sum of every grid point $\mathbf{r}$ the denominator becomes zero for $\mathbf{r} = \mathbf{r}_i$. In this special case the corresponding term is replaced by the integral over a sphere with the same volume as the grid cell considered:

$$\frac{\rho(\mathbf{r}_i)}{|\mathbf{r}_i - \mathbf{r}_i|} \quad \text{is replaced by} \quad 2\pi r_{sphere}^2\, \rho(\mathbf{r}_i)$$

$$\text{with } r_{sphere} = \left(\frac{3}{4\pi} \Delta V\right)^{1/3} \qquad (3)$$

Using a spherical cell with radius r_{sphere} instead of the original rectangular one allows integration over $1/r$. This means that one term is replaced by a constant times the corresponding ρ value. Extensive studies showed that the MEP is insensitive against the variation of this particular value and therefore against the small error arising from the spherical cell. This is due to the fundamental property of the MEP: its nonlocality.

Finally, we must introduce the pseudovalence electron density, whose smoothness in the core region supports the GAME algorithm essentially. These densities come from ab initio calculations with pseudopotentials (effective core potentials).[18,19] The use of nodeless pseudovalence orbitals leads to a complete lack of electrons near the nuclei of the elements C, N, and O. But there is practically no difference between the electron density with all electrons and with pseudopotentials in the valence region.[20] An important difference in the numerical processing of the two densities arises from the sharp maxima of the electron density at the nuclei. In the all-electron case one needs many more grid points near the nuclei to attain the right electron number than in the pseudopotential case. The electron number N_e of the grid is given by

$$N_e = \sum_i \rho_i \Delta V \qquad (4)$$

From the computational point of view it is much easier to handle a grid, which is evenly spaced in all regions of the molecule, and much faster, if the grid points need only be as close as in the valence region in every other region. Therefore not only the ab initio calculations benefit from pseudopotentials but also this graphical algorithm. Three figures may illustrate the quality and the advantage of the pseudovalence electron density.

To demonstrate the quality the MEP is calculated exactly [Eq. (1)] from an all-electron wavefunction and from a pseudopotential wavefunction with the same basis set for the valence shell.

Figure 1 shows the difference MEP between the exact MEP and the MEP, calculated by GAME, in the molecular plane of adenine. The use of pseudopotentials definitely does not affect the MEP near the molecular surface.[21] The main deviations lie deep in the molecule far away from the molecular surface.

Figures 2 and 3 serve to illustrate the advantage of the pseudovalence electron density for the GAME algorithm. Figure 2 compares the distribution of positive and negative values of two different MEPs on the molecular surface of adenine. Both MEPs are calculated by GAME, but for the one surface (top) a grid of the pseudovalence electron density was used; for the other (bottom) the all-electron density was used. The dramatic difference comes from the loss of

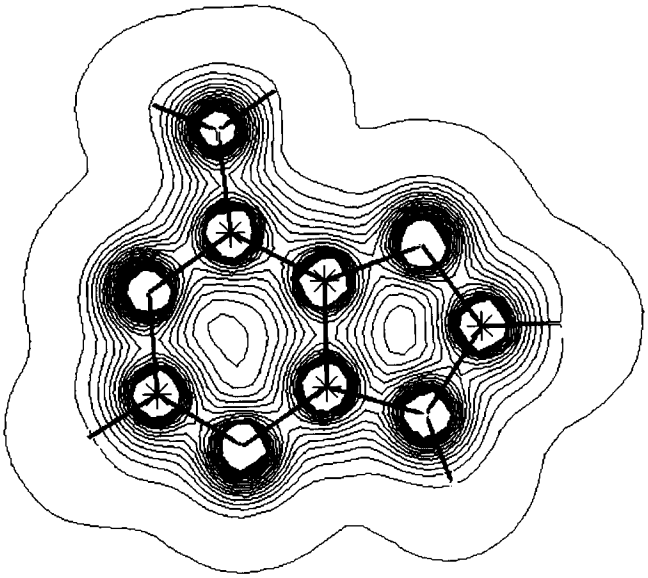

Figure 1. Difference between two MEPs: one calculated exactly from the all-electron wavefunction, the other by the GAME algorithm from the pseudopotential wavefunction. Twenty-two contours are evenly spaced between 0.001 and 0.1 a.u. in the molecular plane. The outermost contour is the 0.002 contour of the electron density.

electron density near the nuclei in the all-electron case owing to the insufficient density of grid points near the nuclei. This loss diminishes the electron part of the MEP and the complete MEP becomes more positive, that is, the negative (black) area on the surface becomes smaller.

Figure 3 makes this difference between the two densities in the molecular plane visible. Note that the five nitrogens exhibit quite different densities, because they are differently located relative to their neighboring grid points.

The color coding

After calculating the MEP grid one has two grids with grid points at the same positions $\mathbf{r}_i$: ρ values in the one grid and MEP values in the other. Now, one can start to generate the colored surface.

The isovalued surface is approximated by a large set of triangles (typically 40 000 for the following examples) generated by an optimized[22] version of the marching cube algorithm.[23] This algorithm processes the grid cells of the ρ grid in scan line order and examines whether a given level surface intersects an edge of the cell. If at least three edges carry the isovalue, that is, the particular cell contributes at least one triangle to the surface, the coordinates of the vertices of the triangle are calculated by a linear interpolation between the adjacent grid points. In the same cycle the MEP values for the vertices are obtained by a second linear interpolation in the MEP grid on the same edges, that is, between the same coordinates as before but in the MEP grid. Finally, the gradients at the vertices are calculated from the ρ grid for rendering the triangulated surface.

If the range of the MEP values on the surface is known, one can map their magnitudes to colors (red–green–blue [RGB] triples, respectively) in a landscape manner, that is,

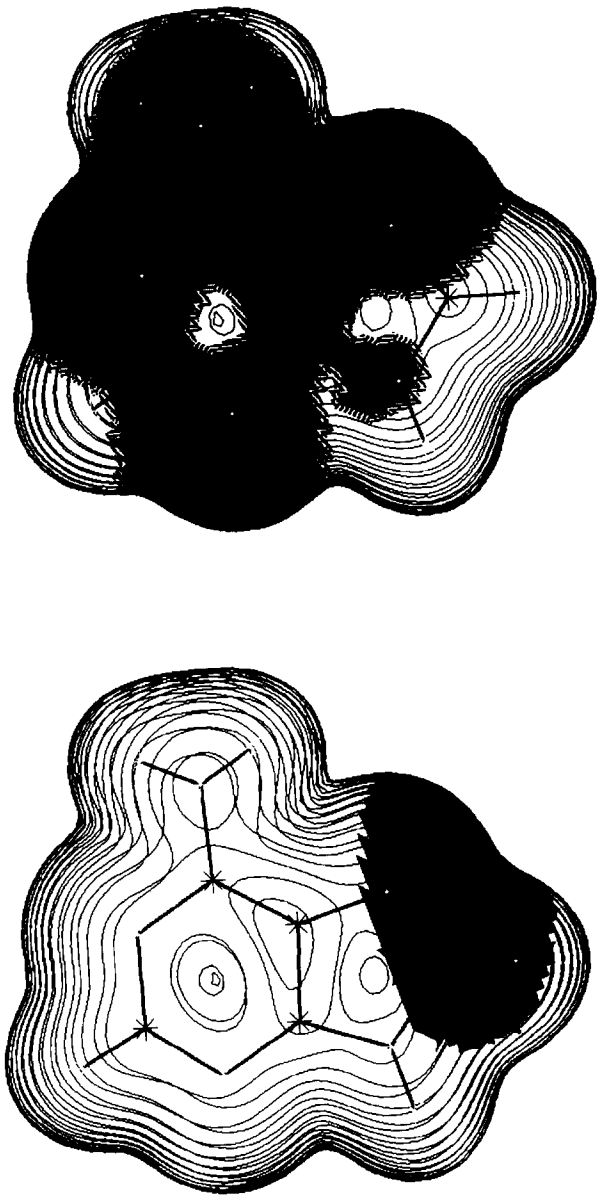

Figure 2. Negative MEP values (solid, black) on the molecular surface of adenine calculated by the GAME algorithm from a pseudovalence electron density (top) and an all-electron density (bottom).

the color code runs from black through magenta, blue, cyan, green, yellow, red, to white. The most attractive part of a molecule for a proton becomes black, the most repulsive white. The mapping is done automatically and for each value individually by a new algorithm. The range of values is divided into five intervals of equal size. Each interval is mapped on an RGB triple, which consists of a maximal component, a minimal component, and one proportional to the MEP value. The roles of the components are reversed from interval to interval. The maximal value of a component is fixed to 0.8 and not to 1.0 in order to leave some clearance for the rendering algorithm. Figure 4 shows the RGB values as a function of the MEP values ranging from 1.0 to 5.0.

After having calculated the RGB values at the vertices in this way, the colors between the vertices are interpolated by

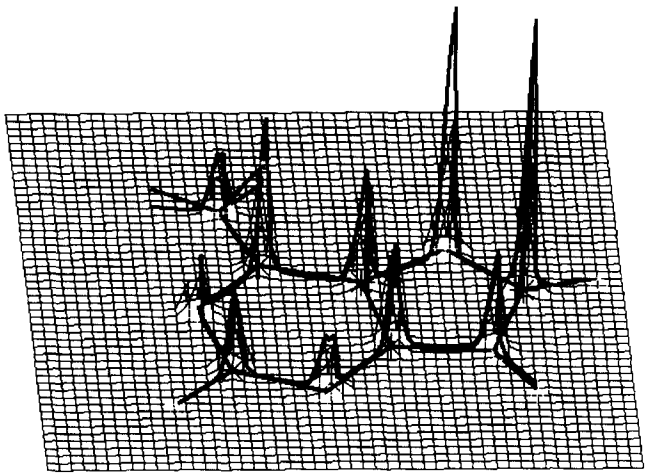

Figure 3. Difference between the all-electron density and the pseudovalence electron density in the molecular plane of adenine. The values are between 0.0 and −36.6 a.u.

Gouraud shading to color the triangles of the surface completely. Note that the color at every vertex is determined by the successive application of two algorithms: one for color coding and one for shading according to the given light sources, shading model, and depth cueing parameters. Nevertheless, the user can grasp the whole information of the picture at least qualitatively because the algorithms use basic visual experiences.

The acceleration

The algorithm described up to this point is of limited utility. One needs to improve the performance greatly. The two most important improvements to speed up the algorithm and the program, respectively, are described here.

First, one must avoid calculating the whole MEP grid. At the moment one has to calculate an MEP value, the information about the ρ value of this particular point is available. If the ρ value is too far away from 0.002 and therefore from the molecular surface, one simply omits the calculation and goes to the next point.

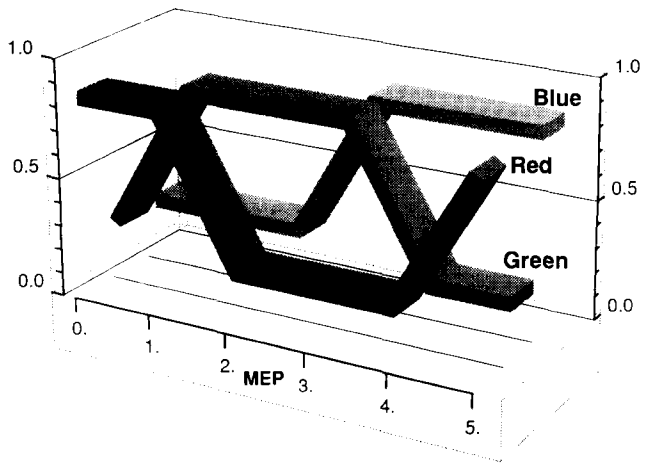

Figure 4. Color coding of the MEP: RGB triples as a function of the MEP values ranging from 1.0 to 5.0.

Because finding the square root is the most time-consuming step in the calculation of $|\mathbf{r}_i - \mathbf{r}|$ in Eq. (2), one should avoid this arithmetic operation. The set of distances one calculates once for any point $\mathbf{r}$ is the same at every other point. The members of this set can be labeled for further usage by the differences of the three indices of the array in which the MEP values are stored.

The distances are now determined as follows. One calculates the distances from the first grid point to all others. In this special case the indices are equal to the differences and can be used without further conversion to label the distances. A distance is stored at the element of a three-dimensional, temporary array that is assigned by the three index differences. In the MEP calculation it is not the real distances that are determined but the differences of the indices between two points. These index differences are used to fetch the distances from the distance array. Because the calculation is done in three nested loops, in most cases only the difference of the index in the deepest loop changes in every iteration. This improvement of the distance calculation makes the program run six times faster.

The advantages

The most important advantages of the GAME algorithm are as follows:

- The main advantage of GAME is the consistency of the data. This means that the molecular surface and the potential on it have the same source; a change of source affects both and they arise from the same level of theory. Some authors[24] prefer another contour for the molecular surface. There arises no problem from turning to another surface, because every surface has its own MEP values.
- Electron densities from ab initio calculations with pseudopotentials can be used.
- The GAME algorithm can be vectorized and parallelized efficiently because it has no interdependence among the grid points and no decisions (IFs) but a large number of equal operations.
- The algorithm uses only the simple operations Load, Store, Add, Multiply, and Calculate Absolute Value, which can all be done within one clock cycle. This is important on modern RISC-CPUs. They handle more complex arithmetic instructions beginning from the division by a slow, iterative procedure. The time-consuming calculation of r is already eliminated from the loops over all the grid points.
- The algorithm is of great numerical stability, because every MEP value is a large sum of reals that do not differ too greatly in magnitude; there is no difference of two large numbers, no arithmetic between small numbers or dominance of a single summand. No difference can be seen between two pictures, whether the calculation of the underlying MEP values is carried out in single or in double precision.
- There is no doubt about the choice of the grid points. The choice that is good for the electron density, is also good for the MEP.
- The MEP data build up a regular grid that is convenient for further processing by numerical methods. It is easy, for example, to calculate the gradient of the MEP, a valuable quantity for further interpretation.

- The quality of the MEP can be checked easily and rapidly. The Poisson equation ($\nabla^2 V^{MEP} = -4\pi\rho$) connects the electron density with its potential. Whereas it is difficult to calculate the potential from the electron density, the reverse calculation can be done efficiently by a numerical differentiation. A comparison of the original value of the electron density and the recalculated one from the Poisson equation is a quantitative test for the quality of the MEP.
- The MEP does not depend directly on the basis set of the ab initio calculation. The basic grid of the electron density does, but it is easier to calculate the density than the MEP.
- The regular grid of the electron density, especially of extended molecules, contains a large number of points of negligible magnitude. But, below which threshold can one neglect density values without loss of accuracy? The GAME algorithm offers an a priori criterion for this decision. Obviously the loss of electrons owing to neglect below the threshold diminishes the electronic part of the MEP. Using Eq. (4) one can determine how the electron number depends on the threshold. Using the Poisson equation one can determine how the MEP values depend on the loss. Figure 5 illustrates these two dependencies for adenine.

  The point is that both quantities are correlated and therefore the loss of electrons can predict the corresponding error in the MEP. The calculation of the electron number by Eq. (4) takes less than 1 s. A loss of less than 0.1% results from a threshold of 0.000 1 a.u. for all the molecules treated so far. The corresponding mean error in the MEP values was always less than the acceptable 0.000 23 a.u. (1 a.u. = $3.027676 \cdot 10^{-9}$ C/m).

The disadvantages

The advantages are opposed by two disadvantages.

- It is essential for the quality of the numerical integration [Eq. (2)] to avoid the sharp maximums in the core region. Therefore the method is limited to valence electron densities from nodeless pseudovalence orbitals. This limitation is not a serious problem for organic molecules.
- GAME is not suitable for calculating only a few MEP values—an unusual application—because of the overhead for calculating a complete ρ grid.

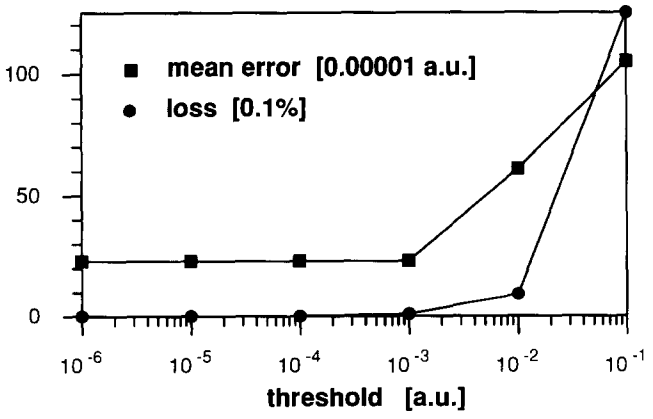

Figure 5. Loss of electrons and mean error of the MEP values as a function of the threshold for neglecting of ρ values. Only MEP values near the molecular surface (the corresponding ρ values are in the range from 0.000 1 to 0.01 a.u.) are taken into account.

PROGRAMS

The ab initio calculations were carried out with the program POLYZENT.[25] All illustrations in this article were generated with the program package Ψscope,[26] which is written in Fortran and uses the graphic library of PHIGS+.[27] The use of standards lets Ψscope run on different graphic workstations: Alliant GX4340, SUN SPARCstation 1+ and SPARCstation 2 GT, and Evans & Sutherland ESV3+. The programs calculating the grids (Topos and EEP) are also written in Fortran and run on any UNIX-Host.

APPLICATIONS

This section begins with the presentation of a few typical numbers for adenine (listed in Table 1).

Some applications of the GAME algorithm should illustrate its capacity and the quality of its results. ICoMS, an application that extends the basic considerations of GAME, is described in detail elsewhere.[28]

Besides color plates, another technique is used to show a region of certain values on a molecular surface. A wireframe depicts the whole surface and the region of interest is marked by a black part of the corresponding solid surface.

Test of the basis set

Is a (21) valence basis set (3*s*, 3*p* on C, N, O; 3*s* on H) sufficient for calculating reasonable MEP values? To answer this question the difference between a MEP grid from a (21) basis and one from a (211) basis, strictly speaking from the corresponding ρ grids, is computed and used for coloring the molecular surface from the (21) electron density. The differences due to the augmentation of the basis set are one order of magnitude less than the real changes in

Table 1. Typical numbers of the GAME algorithm calculating the MEP grid of adenine

Parameter	Value
Number of grid points	180 000 (75*80*30)
Number of calculated MEP values	12 005
Electron number calculated according to Eq. (4)	49.990
Threshold for neglecting ρ_i	0.000 1 a.u.
Loss of electrons owing to the neglect	0.003
Neglected ρ_i	47%
Time for calculating the distance array[a]	2.6 s
Time for calculating the MEP values[a]	5 505 s
Time for testing the quality[a]	17.0 s

[a]On a SUN SPARCstation 2.

the potential. This means that the systematic errors are substantially below the physical effects. Therefore the (21) valence basis set is used in all the following examples. The greatest negative difference is found at the center of the heterocyclic system (Figure 6, top), the positive near N-1 and N-3 (Figure 6, bottom). The extended and therefore more flexible basis makes the nitrogens more basic by shifting electronic charge toward them.

Changes of the MEP during docking

The second example (Color Plates 1 and 2) shows the changes in the MEP of a drug (1*H*-2,3,8-trimethylimidazo[1,2-*a*]pyridine$^+$)[28] when it approaches two formiates. The color code is the same for both pictures. The formiates are a simple model for a receptor. The two pictures come from a video clip[29] that visualizes the complete docking procedure as calculated by semiempirical methods. With the first and the last geometry from the semiempirical simulation the molecules were calculated ab initio in a supermolecule approach; this means that charge transfer and mutual polarization are taken into account. If the interaction between a drug and a receptor is discussed on the basis of the MEP, in most cases only the MEP of the isolated drug is taken into account. Although the heavy changes of the MEP caused by the drug–receptor interaction that are illustrated in this example are ignored the deduced criteria are often of surprising reliability.[30] For example, the white spot on the surface of the drug will attempt to come as near as possible to the black spot on the formiate (Color Plate 1). This approach has happened in Color Plate 2.

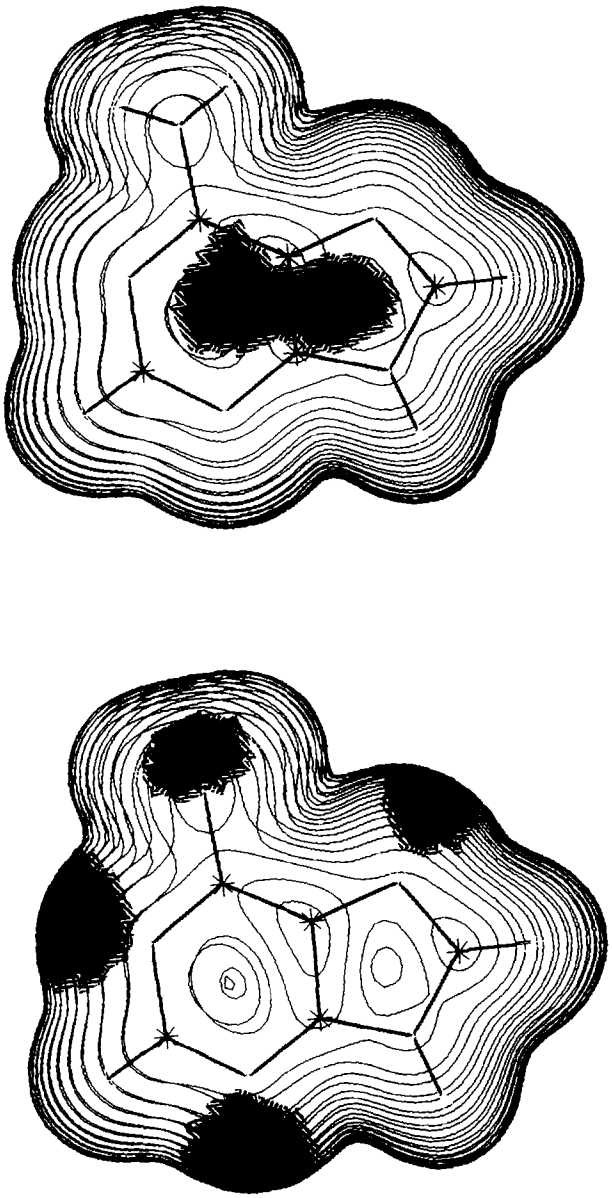

Figure 6. On the molecular surface of adenine the differences between an MEP from a (21) basis set and an MEP from a (211) basis set are shown. The regions of the greatest negative differences (from −0.013 to −0.01 a.u., top) and the positive differences (from 0.0 to 0.006 a.u., bottom) are marked in black.

Changes of the MEP by a proton

Color Plate 3 shows how the MEP of adenine is affected by protonation in position 1. The difference between the MEP before and after the protonation is color coded on the molecular surface of adenine. The change of the MEP is only a function of the distance from the position of protonation. The electronic structure of the heterocyclic system exerts no visible influence on the structure of the change.

The quality of a monopole expansion

The fourth example examines the quality of an MEP obtained from a monopole expansion in comparison with one from GAME. The monopoles are the net atomic charges of a Mulliken population analysis.[31] The atomic charges and the ρ grid were obtained from the same wavefunction. These charges were used to compute a second MEP grid in the same way as the nuclear part in Eq. (1). The procedure from GAME for mapping the MEP on the surface is applied in both cases but one MEP grid comes from the monopoles, the other from the ρ grid. This means that the surfaces are the same in both pictures, only the MEP values on them are different. The criterion for the comparison is the zero potential line on the surface. Figure 7 presents this line as the border between the black solid surface (negative) and the wireframe.

The most obvious differences are in the region of the five-membered ring and over the center of the six-membered ring. The other features are so less responsive that even such a rough approximation is able to reproduce them. The result will certainly not be improved by the usage of a more primitive surface.

The extrema of the MEP

The last application should demonstrate that the GAME algorithm can calculate MEP values on, but also within, a molecular surface if the grid points are still not too close to the nuclei. Figure 8 also shows that the minimums on the isodensity surface give a good impression where the minimums of the MEP are situated. For adenine a complete MEP grid was computed in order to visualize the MEP by some isopotential surfaces. Figure 8 (top) presents the lo-

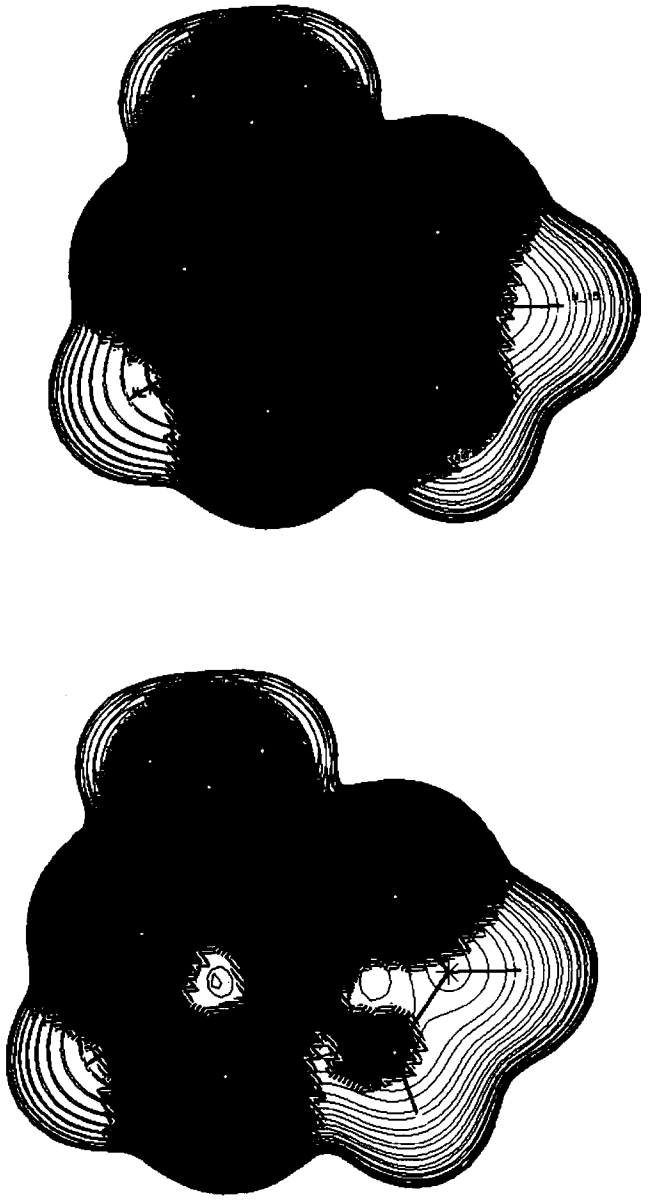

Figure 7. Comparison of two methods for calculating the MEP by comparing the zero potential lines [black solid surface, $V^{MEP}(\mathbf{r}) < 0$; wireframe, $0 < V^{MEP}(\mathbf{r})$] on the surface of adenine. The MEP is calculated from a monopole expansion (top) and by GAME (bottom).

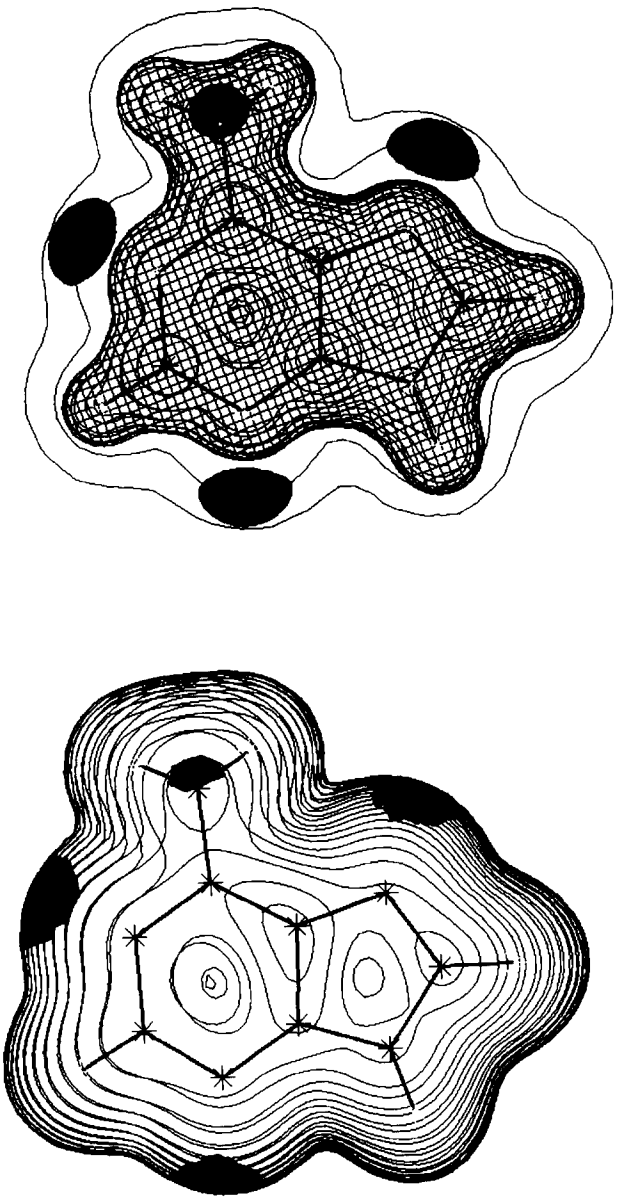

Figure 8. The two contour lines (0.002, 0.02 a.u. from inside to outside) of the electron density give an impression of the size of the molecule and the location of the minimums (solid, −0.08 a.u.) and the maximum (wireframe, 0.2 a.u.) of the MEP (top). The second picture (bottom) shows the appearance of the minimums on the molecular surface.

cation of the minimums of the MEP in relation to the size of the molecule depicted by different contour lines of the electron density. The minimums are inside the molecular surface near the 0.02-a.u. contour. There is a proof[32] that the MEP cannot have local maxima. Therefore one cannot find more than one positive isopotential surface but four negative ones.

CONCLUSIONS

The GAME algorithm approximates the MEP in any quality on an ab initio molecular surface from an all-in-one approach. The quality of the approximation can be easily predicted and checked. The MEP and the surface come from the same wavefunction. The guideline for the design of the complete algorithm was the intention to make use of requirements and possibilities of modern computer graphics. The quality of the MEP depends only on the quality of the 3D field of the electron density.

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