Comparison of Nonlinear Transformation Methods for Electron Density Approximation

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Received: November 29, 2001; In Final Form: February 11, 2002

Ab initio quality electron densities for large molecules can be generated by the combination of precalculated fragment densities stored in a database taking into account all of the short-range interactions within any predetermined envelope surrounding the fragment. For the effective usage of these databases, only a limited number of conformations of each fragment are stored and the electron densities for slightly distorted conformations are calculated by modifying the electron densities of the conformation stored. In this paper, we use two different nonlinear density transformation methods as well as a density matrix transformation method (DMT) to generate the distorted electron densities. The results of the nonlinear density transformations are then compared with direct calculations of the electron densities and with the DMT approximation of the electron densities, which uses a Löwdin transform and an inverse Löwdin transform of the electron density matrix.

1. Introduction

At the present time, conventional quantum chemical calculations are not feasible for large molecules such as proteins and other biochemical macromolecules. To circumvent this problem and to generate ab initio quality electron densities for large molecules, various methods have been investigated to build up macromolecules by combining molecular fragments.[1−11] Two of these methods, the molecular electron density lego approach (MEDLA)[1−7] and the adjustable density matrix assembler (ADMA),[8−11] use fuzzy density fragments or their density matrix representation for a specified basis set, respectively, stored in a database. Direct quantum chemical calculations are required only for those molecular fragments not yet available in the database. One problem of these database approaches is that only a limited number of different conformations for one fragment can be stored because of limited memory size. One possibility to overcome this problem is to approximate the electron density of the actual fragment conformation in the macromolecule by modifying the electron densities of closely related conformations in the database.

To approximate the electron density for a slightly distorted conformation, the complete electron density of the original conformation should be deformed according to the new nuclear positions. Whereas this can be done for four nuclei by a linear homotopy (continuous deformation), there is no such simple linear deformation that can interconvert two arbitrary sets of nuclear coordinates in the general case of five and more nuclei. Nevertheless, a finite number of nonlinear transformations can accomplish this. In this paper, two simple choices for nonlinear transformations, the dimension expansion-reduction method (DER)[9] and the weighted affine transformation method (WAT),[9,11] are used. The results of these transformations are then compared with direct calculations of the electron densities of the distorted nuclear conformations and approximated electron densities, calculated using the density matrix and the overlap matrix of the original conformation as well as the overlap matrix of the distorted conformation, using the density matrix transformation (DMT) method based on a Löwdin transform and an inverse Löwdin transform.[11,12] In the quantum crystallography context, aimed at obtaining quantum chemical information from experimental electron densities, a transformation, similar to the Lowdin−inverse Lowdin transformation used in the present approach, has been employed.[13]

2. Nonlinear Transformation Methods

Both nonlinear transformation methods, the DER and the WAT methods, as well as the DMT method are described elsewhere.[9,11,12] Here only a short description is given. In both density deformation techniques, the main step of the transformation is linear, and nonlinearity is included in a rather transparent way.

2.1. Dimension Expansion−Reduction (DER) Method. In this first nonlinear method, a position vector of the 3D Euclidean space is transformed into a multidimensional vector in a nonlinear manner, and the deformation is carried out by a simple, linear matrix transformation in the multidimensional space, followed by a reduction of dimension to 3D.[9]

For the generation of the multidimensional vector, we consider a molecule or fragment with $n + 1$ nuclei A_i, with the Cartesian coordinates x_i, y_i, and z_i. The components of the vector are then defined as the lexicographically ordered unique products of the powers of the nuclear position vector components. For example, the multidimensional vector $\vec{a}^{(i)}$ for nucleus A_i has the following components:

$$\vec{a}^{(i)} = (x_i,y_i,z_i,x_i \cdot x_i,x_i \cdot y_i,x_i \cdot z_i,y_i \cdot y_i,y_i \cdot z_i,z_i \cdot z_i,x_i \cdot x_i \cdot x_i...)' \tag{1}$$

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10.1021/jp014362k CCC: $22.00

where ( )′ denotes transpose. A more general version can also be used with other functions $f_4(x_i,y_i,z_i)$, $f_4(x_i,y_i,z_i)$,..., $f_4(x_i,y_i,z_i)$ as components 4, 5, ..., n, as long as the components of $\vec{a}^{(i)}$ are linearly independent. In the same manner, a multidimensional vector $\vec{b}^{(i)}$ is defined for the distorted nuclei B_i with the coordinates x'_i, y'_i, and z'_i:

$$\vec{a}^{(i)} = (x'_i,y'_i,z'_i,x'_i \cdot x'_i,x'_i \cdot y'_i,x'_i \cdot z'_i,y'_i \cdot y'_i,y'_i \cdot z'_i,z'_i \cdot z'_i,x'_i \cdot x'_i \cdot x'_i,\ldots) \tag{2}$$

On the basis of these vectors, a simple, nonlinear transformation is defined which places all of the n nuclei to the required locations and transforms the electron density so that it follows the nuclear distortion. Accordingly, two matrices **A** and **B** are formed of the column vectors $\vec{a}^{(i)}$ and $\vec{a}^{(i)}$ respectively:

$$A_{ij} = a_j^{(i)} \tag{3}$$

$$B_{ij} = b_j^{(i)} \tag{4}$$

These matrices are then used to calculate a linear transformation matrix **Z** in the multidimensional space (eq 5). Thus, the DER scheme has the advantage of extreme simplicity, requiring a formal linear matrix transformation to obtain a prescribed nonlinear coordinate distortion of a nuclear arrangement and a compatible, continuous deformation of the entire associated electron density cloud:

$$\mathbf{Z} = \mathbf{B} \cdot \mathbf{A}^{-1} \tag{5}$$

2.2. Weighted Affine Transformations (WAT) Method. The second method is based on the family of linear homotopies defined by all possible combinations of four nuclei.[9,11] For each of these combinations, the linear transformation is calculated, which distorts the original Cartesian coordinates $\vec{v}^{(p)}$, $\vec{v}^{(q)}$, $\vec{v}^{(r)}$, and $\vec{v}^{(s)}$ ($\vec{a}^{(i)} = (x_i,y_i,z_i)'$) of the simplex build by the four nuclei p, q, r, and s into the new coordinates $\vec{v}^{(p)}$, $\vec{v}^{(q)}$, $\vec{v}^{(r)}$, and $\vec{v}^{(s)}$ ($\vec{a}^{(i)} = (x_i,y_i,z_i)'$), respectively:

$$\vec{t} = \mathbf{D}^{(p,q,r,s)} \cdot \vec{v} + \vec{u}^{(p,q,r,s)} \tag{6}$$

with

$$\mathbf{D}^{(p,q,r,s)} = \mathbf{S}^{(p,q,r,s,T)} \cdot (\mathbf{S}^{(p,q,r,s,V)})^{-1}$$

$$\vec{u}^{(p,q,r,s)} = \vec{t}^{(s)} - D^{(p,q,r,s)} \cdot \vec{v}^{(s)}$$

and

$$\mathbf{S}^{(p,q,r,s,V)} = \begin{pmatrix} x_p - x_s & y_p - y_s & z_p - z_s \\ x_q - x_s & y_q - y_s & z_q - z_s \\ x_r - x_s & y_r - y_s & z_r - z_s \end{pmatrix}$$

$$\mathbf{S}^{(p,q,r,s,T)} = \begin{pmatrix} x'_p - x'_s & y'_p - y'_s & z'_p - z'_s \\ x'_q - x'_s & y'_q - y'_s & z'_q - z'_s \\ x'_r - x'_s & y'_r - y'_s & z'_r - z'_s \end{pmatrix}$$

A transformation that is defined in terms of simplices not including a given point pair ($\vec{v}^{(p)}$, $\vec{t}^{(p)}$) may transform point $\vec{v}^{(p)}$ into a point different from $\vec{t}^{(p)}$. Consequently, a simple average of the results for all of these linear transformations is not suitable in general for transforming the set of original nuclear positions to the set of distorted positions and to deform the electron density accordingly. However, by introducing a nonlinear, individual weighting for each transformation, which depends on the distance of the arbitrary position vector $\vec{v}$ from the various vertexes of the simplexes, one can construct an exact transformation that assigns each original point to the corresponding distorted point. First, a $\vec{v}$-dependent function $f^{(i)}(\vec{v})$ is assigned to each nuclear position vector $\vec{v}^{(i)}$:

$$f^{(i)}(\vec{v}) = \Pi_{j(j \neq i)} d(\vec{v},\vec{v}^{(j)}) \tag{7}$$

with

$d(\vec{v},\vec{v}^{(j)})$:
distance between point $\vec{v}$ and nuclear position $\vec{v}^{(i)}$

For each simplex, (p,q,r,s), a continuous function (eq 8) is used based on the $\vec{v}$-dependent function for each vertex of the simplex. To satisfy the condition that the sum of the weighting factors for each point must be equal to 1, the weighting function $w^{(p,q,r,s)}(\vec{v})$ is defined according to eq 9

$$g^{(p,q,r,s)} = f^{(p)}(\vec{v}) + f^{(q)}(\vec{v}) + f^{(r)}(\vec{v}) + f^{(s)}(\vec{v}) \tag{8}$$

$$w^{(p,q,r,s)}(\vec{v}) = \frac{g^{(p,q,r,s)}}{\sum_{(p,q,r,s)} g^{(p,q,r,s)}} \tag{9}$$

The distorted coordinates for the position vector is then calculated by the weighted average using these weighting factors, and a continuous transformation of the electron density is achieved:

$$\vec{t} = \sum_{(p,q,r,s)} g^{(p,q,r,s)} \cdot (\mathbf{D}^{(p,q,r,s)} \cdot \vec{v} + \vec{u}^{(p,q,r,s)}) \tag{10}$$

3. Electron Density Approximation Using Overlap Matrices

The transformation methods mentioned so far use the total electron density calculated on a rectangular grid and the nuclear position of the original and distorted conformation only. Using the density matrix in a technique, based on the Löwdin transforms and referred to as the density matrix transformation (DMT) method, another approximation of the electron density can be achieved.[12]

The set of atomic orbital basis functions with centers at the nuclear locations corresponding to the original conformation $\vec{v}^{(i)}$ is denoted by the formal vector $\vec{\varphi}(\vec{v}^{(i)})$, with the components $\varphi(\vec{r},\vec{v}^{(i)})$ of the individual AO basis functions. The overlap matrix for this set of AOs is denoted by $\mathbf{S}(\vec{v}^{(i)})$. The Löwdin transform of a density matrix $\mathbf{P}(\vec{v}^{(i)})$ expressed in terms of the AO basis set $\vec{\varphi}(\vec{a}^{(i)})$ involves pre- and postmultiplication by the matrix $\mathbf{S}(\vec{v}^{(i)})^{1/2}$:

$$\mathbf{S}(\vec{v}^{(i)})^{1/2} \cdot \mathbf{P}(\vec{v}^{(i)}) \cdot \mathbf{S}(\vec{v}^{(i)})^{1/2} \tag{11}$$

For the distorted conformation, the set of new AO basis functions $\vec{\varphi}(\vec{t}^{(i)})$ is the set $\vec{\varphi}(\vec{v}^{(i)})$ placed in the new nuclear locations $\vec{t}^{(i)}$. In terms of this new basis set, the overlap matrix $\mathbf{S}(\vec{t}^{(i)})$ is determined. An inverse Löwdin transform of the matrix $\mathbf{S}(\vec{v}^{(i)})^{1/2} \cdot \mathbf{P}(\vec{v}^{(i)}) \cdot \mathbf{S}(\vec{v}^{(i)})^{1/2}$, generated by the new overlap matrix $\mathbf{S}(\vec{t}^{(i)})$, gives the approximation of the density matrix $\mathbf{P}(\vec{t}^{(i)})$ at the distorted nuclear geometry $\vec{t}^{(i)}$:

$$\mathbf{P}(\vec{t}^{(i)},[\vec{v}^{(i)}]) = \mathbf{S}(\vec{t}^{(i)})^{-1/2} \cdot \mathbf{S}(\vec{v}^{(i)})^{1/2} \cdot \mathbf{P}(\vec{v}^{(i)}) \cdot \mathbf{S}(\vec{v}^{(i)})^{1/2} \cdot \mathbf{S}(\vec{t}^{(i)})^{-1/2} \tag{12}$$

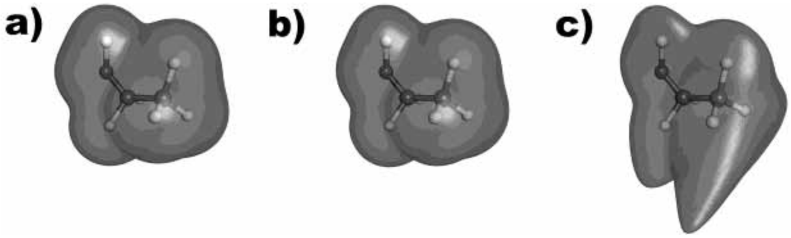

Figure 1. MIDCO surfaces of the electron densities of the original conformation of ethanol (a) and distorted conformations resulting from a rotation of the methyl-group by 1 (b) and 10° (c), respectively. The electron densities for the distorted conformations are calculated using the DER method. The threshold value for all isodensity surfaces is set to 0.002 au.

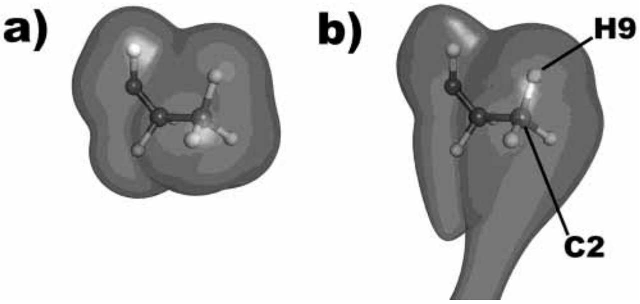

Figure 2. MIDCO surfaces of the electron densities of the original conformation of ethanol (a) and a distorted conformation resulting from a stretching of the bond between H9 and C2 by 0.01 Å (b). The electron densities for the distorted conformations are calculated using the DER method. The threshold value for all isodensity surfaces is set to 0.002 au.

The overall transformation of $\mathbf{P}(\vec{v}^{(i)})$ into the new density matrix $\mathbf{P}(\vec{t}^{(i)},[\vec{v}^{(i)}])$ is analogous to an orthonormalization−deorthonormalization process that is using the original and displaced basis sets at the two nuclear geometries $\vec{v}^{(i)}$ and $\vec{t}^{(i)}$, respectively.

4. Test Calculations on Ethanol

To find the scope as well as the shortcomings of the various transformation methods, multiple calculations of the electron density of ethanol were performed. These calculations are designed to reflect differences in the conformation stored in the database and the conformation under investigation. Frequently appearing deformations are bond stretching and changes of dihedral angles. Thus, the effects on the electron density of the rotation of the whole methyl group as well as the stretching of one H−C-bond are described in this paper. As a starting point, these calculations use the electron density calculated at the 6-31G** level of basis[14−18] with Gaussian 98[19] using the conformation of ethanol shown in Figure 1a. For comparison purposes, the electron densities of the distorted conformations are also calculated directly at the same level of basis. The molecular isodensity contour (MIDCO) surfaces used for the visual inspection are calculated and visualized using MOLCAD II module[20−22] of the SYBYL molecular modeling package.[23]

The easiest and fastest transformation method described here is the DER method. One transformation matrix has to be calculated only, and the transformation of all points is performed using this matrix. For this reason, this method will easily be preferred for an effective use of databases. Unfortunately, for all but the smallest distortions, the nonlinear transformation results in an unexpectedly poor approximation of the electron densities (Figures 1 and 2) although the nuclei are transformed to the correct positions. In Figure 1, the original electron density of ethanol (a) and the electron density of two distorted conformations calculated with the DER method are shown. The two distorted conformations result from rotations of the methyl group with an increment of 1° (b) and of 10° (c), respectively. Even through the smallest deformation, noticeable deviations of the electron density can be recognized. For larger deformations, electron densities calculated with the DER method can no longer be regarded as acceptable approximations of the real electron densities.

In the case of bond stretching, the results are even less satisfactory. The small stretching of only 0.01 Å results in an extreme deformation of the electron density (Figure 2b). This result of the DER method cannot be regarded as an acceptable approximation of the real electron density.

The main reason for the poor behavior of the method is the actual type of nonlinearity introduced. Small distortions have a large, nonlinear effect on points lying far away from the actual site of nuclear geometry distortion. To get a good approximation, the transformation method should only deform a small part of the electron density around the distortion. A possible improvement to achieve this could be the introduction of a distance dependent scaling function in the DER method.

Examples for approximations of electron densities using the WAT and DMT methods are shown in Figures 3 and 4. The electron densities are calculated for distorted conformations resulting from a bond stretching of 0.1 Å and a rotation by 10° (Figures 3 and 4, respectively). Additionally, the electron densities calculated directly for the distorted conformation at the 6-31G** level are shown. These examples demonstrate that the approximated electron densities are nearly indistinguishable from the direct calculations.

To quantify the differences, the relative error between the approximations and the real electron density is shade-coded on the MIDCO surfaces. It can be seen clearly, that the error of the DMT method is almost negligible. For the WAT method, the relative error reaches up to 100% in some regions. Because these errors are lying in regions of large gradients of the density, the differences in the MIDCO surfaces are very small. Thus, the WAT method gives also good approximations of the electron density. In contrast to the DMT method, the errors of the WAT method do not appear at the location of the distortion only but extend over the whole molecule.

Because of the smaller errors of the DMT method, larger distortions can be approximated. Even a rotation of the methyl group by 60° can be treated by this method with an acceptable error (Figure 5). Thus, considering the symmetry of the methyl group, the whole rotation space of the methyl group is reasonably well described with a single quantum chemical calculation of the electron density.

In addition, only the DMT method can handle deformations including bond breaking (Figure 6). Although the WAT method predicts an accumulation of electron density between the atoms for each distance between the hydrogen and carbon atom, the DMT method describes the decrease in electron density at larger distances according to bond breaking. The failure of the WAT method to describe bond breaking can be explained by the

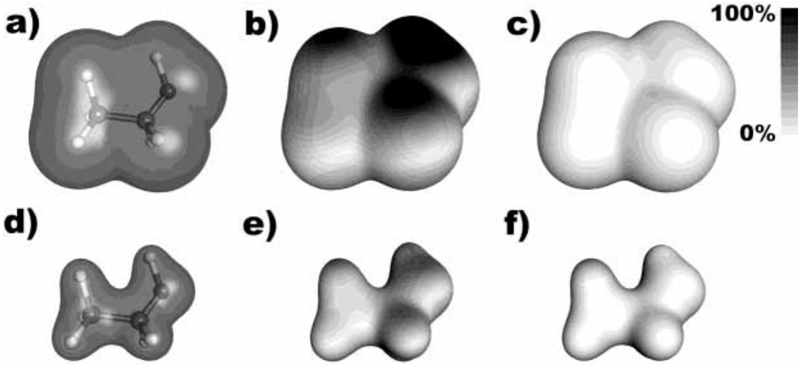

Figure 3. MIDCO surfaces of the electron densities of the distorted conformation resulting from a stretching of the bond between H9 and C2 by 0.1 Å (see Figure 2). The threshold value for the upper and lower row of isodensity surfaces is set to 0.002 and 0.05 au, respectively. The MIDCO surfaces of the approximated electron densities are shade-coded according to the relative error to the real electron density. (a and d) Direct calculation using the 6-31G** basis set; (b and e) WAT method; (c and f) DMT method.

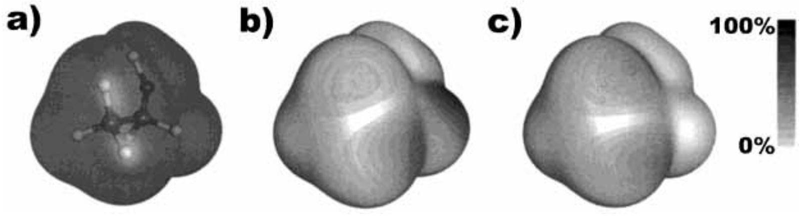

Figure 4. MIDCO surfaces of the electron densities of the distorted conformation resulting from a rotation of the methyl group by 10°. The threshold value for all isodensity surfaces is set to 0.002 au. The MIDCO surfaces of the approximated electron densities are shade-coded according to the relative error to the real electron density. (a) Direct calculation using the 6-31G** basis set; (b) WAT method; (c) DMT method.

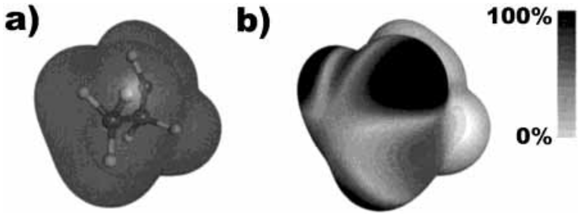

Figure 5. MIDCO surfaces of the electron densities of the distorted conformation resulting from a rotation of the methyl group by 60°.The threshold value for both isodensity surfaces is set to 0.002 au. The MIDCO surface of the approximated electron densities is shade-coded according to the relative error to the real electron density. (a) Direct calculation using the 6-31G** basis set; (b) DMT method.

continuous transformation of the electron density. In contrast, the DMT method uses the correct overlap matrix for the distorted conformation. The reduced overlap of the basis functions located at the two nuclei results in the decrease of the electron density.

5. Verification of the Results

Another method, beside the visual inspection of isodensity surfaces shown so far, to compare electron densities and, thus, to verify the results of the different approximations is the calculation of quantum molecular similarity measures (see Besalú et al.[24] and Solà et al.[25] and references therein). In this paper, we use two well-known similarity measures: the Carbó index r_{AB}[26−28] and the Hodgkin index s_{AB}.[29,30] The definitions of these indices are shown in eqs 13 and 14, respectively:

$$r_{AB} = \frac{\int \rho_A \rho_B \, d\tau}{(\int \rho_A \rho_A \, d\tau)^{1/2} \cdot (\int \rho_B \rho_B \, d\tau)^{1/2}} \tag{13}$$

$$s_{AB} = \frac{2 \int \rho_A \rho_B \, d\tau}{(\int \rho_A \rho_A \, d\tau) + (\int \rho_B \rho_B \, d\tau)} \tag{14}$$

According to these equations, the similarity indices are in the

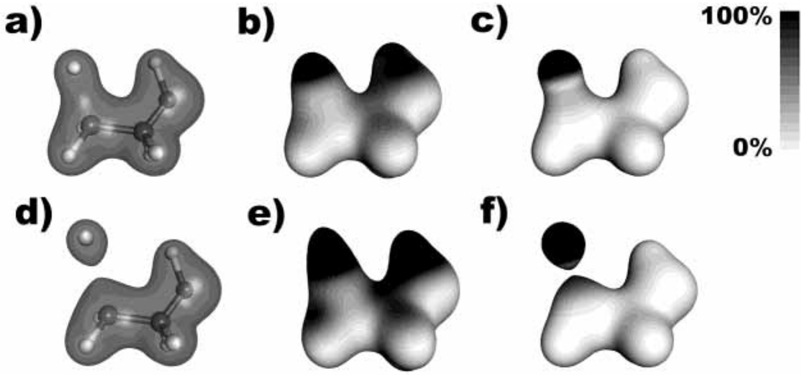

Figure 6. MIDCO surfaces of the electron densities of the distorted conformations resulting from a stretching of the bond between H9 and C2 by 0.5 (a−c) and 1.0 Å (d−f). The threshold value for all isodensity surfaces is set to 0.05 au. The MIDCO surfaces of the approximated electron densities are shade-coded according to the relative error to the real electron density. (a and d) Direct calculation using the 6-31G** basis set; (b and e) WAT method; (c and f) DMT method.

TABLE 1: Quantum Molecular Similarity Measures of the Approximation Methods for the Different Deformations of Ethanol Compared to Direct Quantum Chemical Calculations[a]

deformation	DER method	WAT method	DMT method
bond stretching	0.987071	0.999974	0.999996
0.01 Å	0.985909	0.999974	0.999996
bond stretching		0.994094	0.999992
0.1 Å		0.993928	0.999992
bond stretching		0.981164	0.999961
0.5 Å		0.979878	0.999961
bond stretching		0.952376	0.999912
1.0 Å		0.948195	0.999912
rotation	0.999833	0.999887	0.999993
1°	0.999730	0.999885	0.999993
rotation	0.980379	0.997638	0.999988
10°	0.969218	0.997564	0.999988
rotation			0.999944
60°			0.999944

[a] First values correspond to the Carbó index,[26−28] and second ones correspond to the Hodgkin index.[29,30]

range from 0 to 1, where higher values imply greater similarity. The values of these similarity measures of all deformations of the ethanol molecule are summarized in Table 1. It can be seen that values near 1 result even from the bad approximations of the DER method. Both indices are dominated by regions with high values of the electron densities. On one hand, the approximation methods are designed to reproduce the exact coordinates of the nuclei in the deformed molecule and thus, the electron density in the regions around the nuclei are also transformed accordingly resulting in a very good approximation. On the other hand, larger errors of the electron density methods appear further away from the nuclei, where the electron density is low. These errors have only a very small influence on the value of the similarity measures but can nevertheless be used to divide the results into good and bad approximations. Approximations with values of the similarity measures over 0.995 have also been qualified as reasonable by the visual inspection of MIDCO surfaces. These approximations are well suited to be used in similarity studies based on the electron density like quantitative shape activity relationships (QShAR).

In addition to similarity analysis, the approximated electron densities can also be used to calculate molecular properties. To demonstrate that, dipole moments of the distorted conformations are calculated using the approximations as well as quantum chemical calculations with the Gaussian 98 program.[19] The results are shown in Table 2 and demonstrate that the dipole moments are more sensitive to errors in low value regions of the electron density than the similarity indices. This can be seen by the large differences between the values of the real dipole moments and the ones obtained by the poor DER approximations as well as by the other two methods with large bond deformations. Small bond deformations and rotations of functional groups can be handled with reasonable errors with the DER method and to some extent with the WAT method.

TABLE 2: Dipole Moments by the Approximation Methods and of Direct Quantum Chemical Calculations for the Different Deformations of Ethanol[a]

deformation	Gaussian 98	DER method	WAT method	DMT method
bond stretching	1.948	24.868	1.847	1.964
0.1 Å		1176.3%	5.2%	0.8%
		84.3°	1.9°	0.5°
bond stretching	1.850		2.036	2.061
0.1 Å			10.1%	11.4%
			16.0°	4.1°
bond stretching	1.292		3.161	2.376
0.5 Å			144.6%	83.9%
			107.5°	26.6°
bond stretching	1.105		8.091	2.670
1.0 Å			632.4%	141.7%
			70.7°	91.0°
rotation	1.957	3.819	1.929	1.949
1°		95.1%	1.4%	0.411%
		48.9°	1.9°	0.4%
rotation	1.961	23.736	1.901	1.948
10°		1110.5%	3.6%	0.7%
		70.2°	11.6°	1.5%
rotation	1.999			2.297
60°				14.9%
				5.5°

[a] The absolute values (debye) as well as the relative errors and the angles between the approximations and the quantum chemical calculations are given.

6. Electron Density Approximations of Two Alanine Conformations

The amino acid alanine is treated as a last test example. Therefore, crystallographic structures of two alaninium salts are taken from the Cambridge Structural Database:[31] L-alaninium

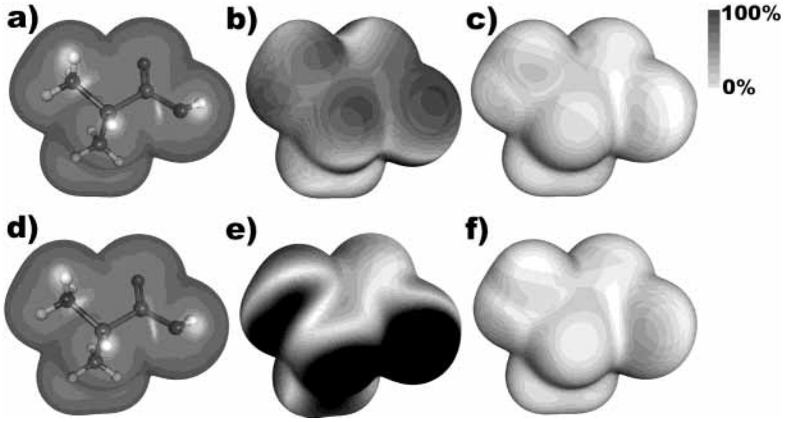

Figure 7. MIDCO surfaces of the electron densities of two conformations of the alanine cation. Parts a−c correspond to the crystallographic structure of L-alaninium nitrate, and parts d−f correspond to the one of bis-(L-alanine)-tetrachloro-palladium(II). The threshold value for all isodensity surfaces is set to 0.002 au. The MIDCO surfaces of the approximated electron densities are shade-coded according to the relative error to the real electron density. (a and d) Direct calculation using the 6-31G** basis set; (b and e) WAT method; (c and f) DMT method.

TABLE 3: Quantum Molecular Similarity Measures of the Approximation Methods for Two Different Conformations of the Alanine Cation[a]

	WAT method	DMT method
L-alaninium nitrate	0.838395	0.999961
	0.808553	0.999960
bis-(L-alanine)-tetrachloro-palladium(II)	0.799748	0.999935
	0.798943	0.999934

[a] First values correspond to the Carbó index,[26−28] and the second ones correspond to the Hodgkin index.[29,30]

nitrate (entry LOKFIA[32]) and bis-(L-alanine)-tetrachloro-palladium(II) (entry YODTOA[33]). The two conformations of the alanine cation have an atomic root-mean-square deviation of 0.122 Å, and the maximum distance of two corresponding atoms is 0.241 Å. To test the approximation methods the electron density of one conformation is used as input to approximate the electron density of the other conformation. The results are shown in Figure 7, and the values of the quantum similarity measures are summarized in Table 3. On one hand, reasonable results can be obtained with the DMT method, which shows that this method can be used effectively to approximate similar conformations of amino acids as they appear in different proteins. On the other hand, the quality of the approximations of the WAT method decreases with the size of the molecule. However, this method should mainly be used with the MEDLA method for a fast generation of electron densities used in QShAR studies. This MEDLA approach uses the combination of small molecular fragments to generate the electron density for a larger molecule. In this way, the WAT method is only applied to the small fragments in which case reasonable results can be achieved.

7. Conclusion

In the first part of this paper, results of two nonlinear transformation methods (DER and WAT methods), which interconvert two arbitrary sets of nuclear coordinates and deform the complete electron density accordingly, are presented. The approximations obtained by these methods are then compared firstly with the electron densities, calculated directly from the distorted nuclear positions, and secondly with approximated electron densities, calculated using the density matrix and the overlap matrix of the original conformation as well as the overlap matrix of the distorted conformation using a Löwdin transform and an inverse Löwdin transform (DMT method).

On the basis of these results, we conclude that, although the DER method in its present form should not be used to approximate the electron density of a slightly distorted conformation, the electron densities resulting from both WAT and DMT methods give good approximations of the real electron density, where the results of the DMT method are better throughout. Because of these better results, the DMT method should be used whenever possible. In combination with the ADMA method, in which fuzzy fragment density matrices are stored in a database, a very effective approximation of electron densities of large biochemical macromolecules can be achieved. In combination with the earlier MEDLA method, it is not possible to use the DMT method directly, because only the electron density calculated on a grid is stored in the database. In those cases when the density matrix is not known, the electron density of slightly distorted conformation can be calculated in good approximation using the WAT method.

Acknowledgment. We sincerely thank Prof. J. Brickmann for the supply of the MOLCAD II module and the Natural Sciences and Engineering Research Council of Canada for the financial support of this work. T.E. gratefully acknowledges the Alexander von Humboldt Foundation for a Feodor Lynen research fellowship.

Note Added after ASAP Posting. This article was released ASAP on 5/7/2002 before author corrections were included. The corrected article was posted 5/8/2002.

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