Representation of Molecular Electrostatic Potentials by Topological Feature Maps

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Abstract: The self-organizing properties of a Kohonen neural network can be used for the generation of two-dimensional maps of molecular surfaces. Properties of such surfaces such as the molecular electrostatic potential can be visualized in a single map. Such maps allow the comparison of sets of molecules having common three-dimensional features or exhibiting common biological activity.

1. Introduction

Molecular electrostatic potentials (MEPs) give detailed information for studies on chemical reactivity or the biological activity of a compound. The spatial distribution and the values of the electrostatic potential determine the attack of an electrophilic or of a nucleophilic agent as the primary event of a chemical reaction. Furthermore, the three-dimensional distribution of the electrostatic potential is largely responsible for the binding of a substrate at the active site of a receptor.

The electrostatic potential at a certain point around a molecule is the work needed to bring a unit positive charge from infinity to that given point. It can be calculated by quantum mechanical procedures of various degrees of sophistication or by a simple point charge model when the atoms of a molecule have been assigned partial charge values. The electrostatic potential is thus clearly defined for each point in space around a molecule, negative values indicating attraction of a positive charge, positive values standing for repulsive interactions with a positive point charge.

The three-dimensional nature of the electrostatic potential makes it difficult to simultaneously visualize the spatial distribution and the magnitude of the electrostatic potential. Various approaches have been made to indicate parts of the electrostatic potential.

A plane can be cut through a molecule and the surrounding space and the potential at a given position of this space can be indicated by lines of equal electrostatic potential or by coding the different amounts of the electrostatic potential by different colors.

A drawback of this approach is that the electrostatic potential can only be indicated in one plane. A series of such cuts have to be made, particularly in orthogonal planes, to give an impression of the entire three-dimensional distribution of the electrostatic potential.

In another approach, the electrostatic potential is calculated for a certain surface around a molecule, e.g., the surface covering all the atoms of a molecule at the van der Waals radii of the atoms. The electrostatic potential is calculated for points evenly distributed over the van der Waals surface, and the values thus obtained are color-coded at each point. Red points indicate negative potentials and, thus, points of attraction for a positive charge, purple points indicate large positive values of the potential, and intermediate values are shown in yellow, green, and blue. This distribution of colored points on a three-dimensional surface

is viewed from an observation point by displaying it in parallel projection onto a graphics screen (Figure 1).

A disadvantage of this display technique is that a series of different observation points has to be selected to obtain a full picture of the distribution of the electrostatic potential over the entire three-dimensional molecular surface. Or, the molecule has to be interactively rotated in space while simultaneously observing the distribution of the electrostatic potential on the surface. Thus, the conformation of 4-hydroxy-4-methyl-2-pentanone and the point chosen for viewing the molecule shown in Figure 2 hardly give a glimpse of the hydroxy group. Correspondingly, the electrostatic potential at this functional group can not be seen in Figure 1.

These methods make it difficult for the human observer to perceive all essential features of the electrostatic potential around a molecule. This deficiency becomes particularly clear when the electrostatic potentials of two or more molecules have to be compared. This is of special interest when molecules are to be investigated for their biological activity, specifically when molecules having the same kind of activity have to be analyzed to decipher the factors responsible for this activity.

In fact, molecular electrostatic potentials can be used to define molecular similarity. The analysis of molecular similarity based on 3D shape or on electronic properties is of much current interest.[1–3]

It would be quite favorable to have a method that allows one to perceive the essential features of the electrostatic potential around a molecule in one view, in a single picture. Chau and Dean[4] have developed a gnomonic projection method for analyzing a property on a molecular surface, e.g., the electrostatic potential. The gnomonic projection is a central projection whereby a ray from the centroid meets the parameter surface at a pierce point. The value of the parameter at this point is then projected onto a sphere obtained by tessellation of an icosahedron. As pointed out by Blaney et al.[5] such a projection might lead to the loss of information if there are portions of the surface that are reentrant with respect to a line radiating from the center of interest (COI) (Figure 3). Furthermore, the projection is onto the surface of a sphere. Thus, still a series of views have to be taken to obtain the full picture of the entire surface property.

We will show here that the projection of a molecular surface property can be attained by an application of the neural network

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(2) Lipkowitz, K.; Boyd, D. B. Reviews in Computational Chemistry; VCH-Publishers: New York, 1990 and 1991; Vols. 1 and 2.
(3) Warr, W. A. Chemical Structures 2; Springer: Berlin, 1993.
(4) Chau, P. L.; Dean, P. M. J. Mol. Graphics 1987, 5, 97–100.
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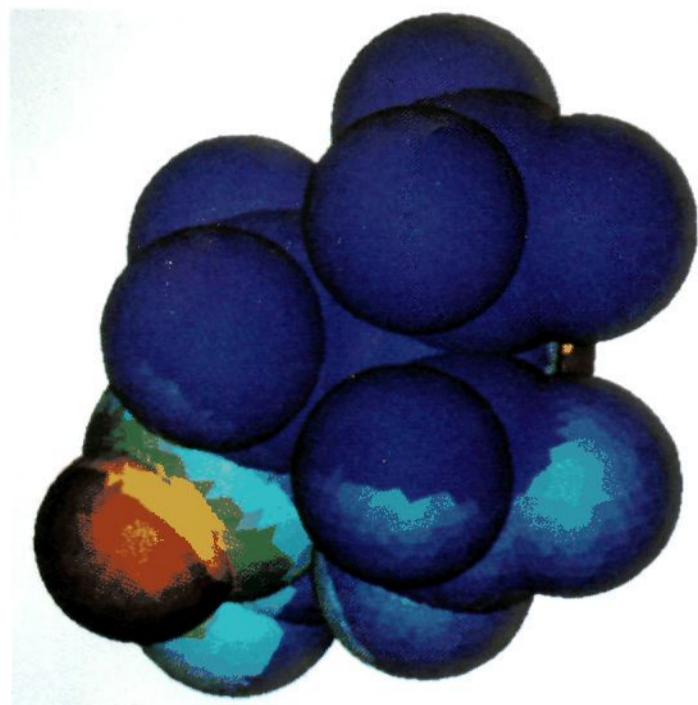
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Figure 1. Parallel projection of the electrostatic potential on the van der Waals surface of 4-hydroxy-4-methyl-2-pentanone in the conformation shown in Figure 2.
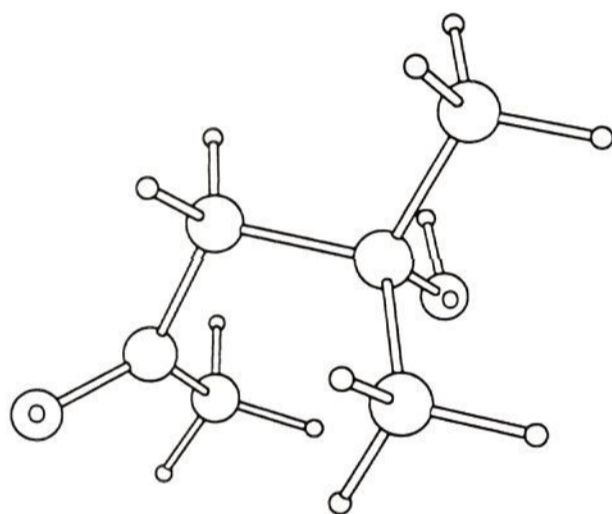

Figure 2. Ball and stick model of 4-hydroxy-4-methyl-2-pentanone.

model of T. Kohonen.[6-8] T. Kohonen has suggested a model for the self-organized formation of topology conserving feature maps. This method can have many applications. In our approach we built on the ability of the Kohonen model to map objects from a multidimensional space into a two-dimensional plane with maximum preservation of the topology of the multidimensional information.

We will first briefly present the Kohonen network as far as necessary for understanding our application and then give a simple example for the mapping of points from a three-dimensional object into a Kohonen network, before discussing the mapping of three-dimensional electrostatic potentials.

2. Kohonen Model

The brain is organized in many places in a way that sensory information is represented in the form of two-dimensional maps. For example, the sensory signals coming from the nerve cells of the various parts of the human body meet in the somatosensory cortex of the brain such that signals coming from the same part of the body excite adjacent sites in the cortex. The more nerve cells a certain part of the body has, the larger is the area reserved for this part in the cortex. Thus, we have a map of our body in the surface of the brain that is known as the somatosensory cortex.

Artificial neural networks, or plainly "neural networks", are models of the information processing in the human brain. A
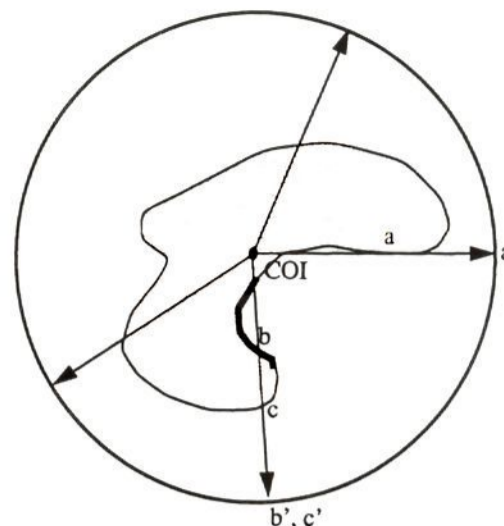
(6) Kohonen, T. *Biol. Cybern.* **1982**, *43*, 59–69.
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Figure 3. Gnomonic projection of a molecular surface that has a series of contacts (a) to a vector radiating from the center of interest and a portion of the surface that is reentrant to such a vector and thus is penetrated twice (b and c) by this vector. The reentrant surface is shown in bold and will not be projected onto the outer sphere.
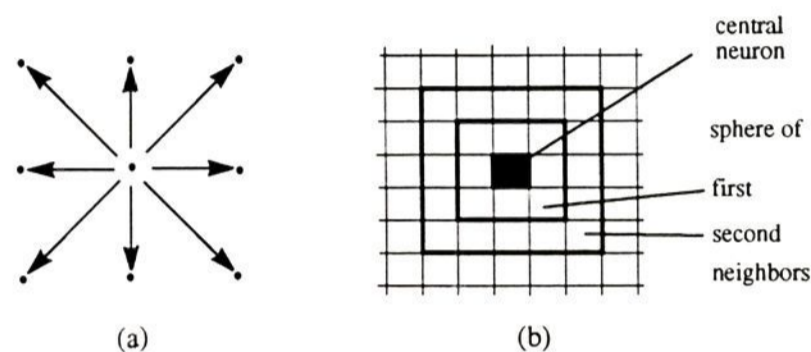

Figure 4. Number of neighbors (a) of a neuron in a Kohonen network and the spheres of neighbors (b).

variety of different models has been developed and applied to a host of problems taken from areas as different as science and the stock market. The application of neural networks to the solution of chemical problems has seen a dramatic increase in recent years.[9-11]

The basic information-processing unit in a neural network is the neuron, a model for the biological neuron or nerve cell. The neuron takes the information sent to it from other neurons or from input units and calculates from these signals a response, an output. An important characteristic of a neural network is how the neurons are connected, how they are arranged in a network. Information passes along these connections and is modified by weights that model the synaptic strengths observed between biological neurons. These weights are initially set at random values and are adjusted in what is called a learning process by presenting the neural network with a series of data. In the Kohonen network the neurons are arranged in a two-dimensional layer.

The neurons in this layer are not connected to each other but are connected to all input units. The number of input units is determined by the number of variables of an object that is used as input to the network. In our examples we have three-dimensional spaces and therefore three units were used to input the Cartesian coordinates x_i ($i = 1-3$) of a point (object) from such a space. Thus, if we select a 15 × 15 Kohonen network, there are 3 × 15 × 15 = 675 connections and thus 675 weights to be determined.

The concept of topology and of topological distance is central to a Kohonen network. Only the topological connectivity (how many neurons are direct neighbors of the neurons considered) and not the Euclidean distance is important (Figure 4a). Thus, in a rectangular network, a neuron has eight neighbors in the first sphere, 16 neurons in the second neighborhood, etc. (Figure 4b).

(9) Zupan, J.; Gasteiger, J. *Anal. Chim. Acta* **1991**, *248*, 1–30.
(10) Gasteiger, J.; Zupan, J. *Angew. Chem.* **1993**, *105*, 510–536; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 503–527.
(11) Zupan, J.; Gasteiger, J. *Neural Networks for Chemists: An Introduction*; VCH Publishers: Weinheim, FRG, 1993.
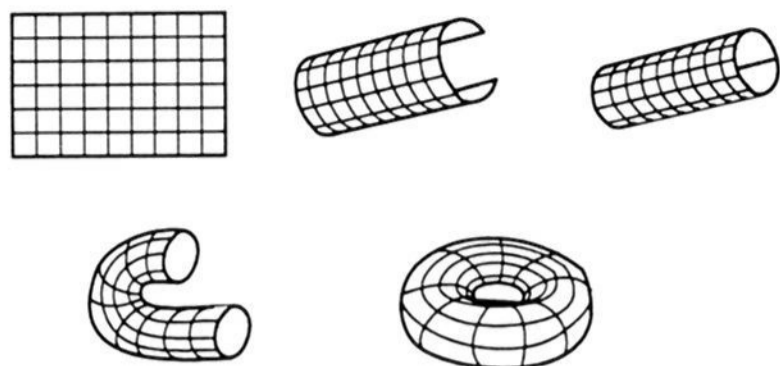
Figure 5. Plane without beginning and without end given by the surface of a torus.
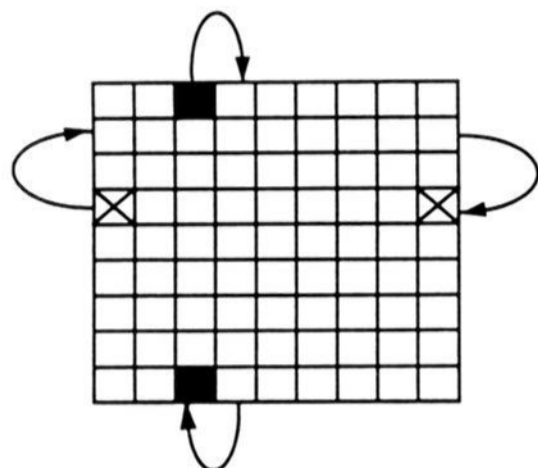

Figure 6. Plane obtained by making two cuts into a torus (see Figure 5) which can be shifted to the left or the right, or up and down. Thus, the two neurons marked by a cross are direct neighbors as are the two neurons marked as black squares.

The simplest way to arrange the neurons of a Kohonen network in two dimensions is by arranging them in a rectangular plane. This arrangement has, however, the drawback that the neurons on the edge of the plane have fewer weights than those in the middle. Thus, a certain kind of dissymmetry among the neurons occurs. Such a drawback can be avoided by connecting the upper border of the "plane" of neurons to the lower lines of neurons and the left end of the plane to the right end. Thus, in effect, the "plane" is modified through a cylinder to a torus, as shown in Figure 5.

The two-dimensional "plane" used for mapping is, indeed, the surface of a torus. In the following discussion and displays, nevertheless, a plane is used for better presentation. However, it should be remembered that this plane does not end at the top row of neurons but is continued in the bottom row. The same is true with the left column of neurons that are direct neighbors of the right-most column of neurons (Figure 6).

In other words, we could take away from such a plane any number of rows of neurons starting from the left row and append them at the right-most row. An analogous procedure can be performed with the lines of neurons. It is essential to understand and remember this when looking at the displays of the Kohonen networks obtained in the examples of the applications.

The adjustment of weights in a Kohonen network is achieved in a competitive learning process. Each neuron competes with every other neuron to become the one that is stimulated by the object k that is input into the network. In the end, only a single neuron is selected for this object. This learning process has therefore been called "the winner takes it all". That neuron is selected as the stimulated one, as a central neuron c, that has weights w_{ci}, that are closest to the input data x_k of object k, i.e.

$$\sum_i^m (x_{k_i} - w_{ci})^2 = \min_j \{ \sum_i^m (x_{k_i} - w_{ji})^2 \} \qquad (1)$$

The weights w_{ci} of this central neuron c are further adjusted to make them even more similar to the input data. Also the
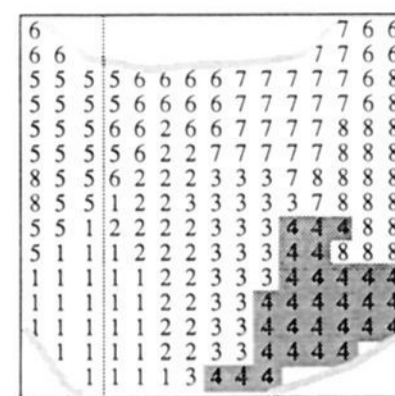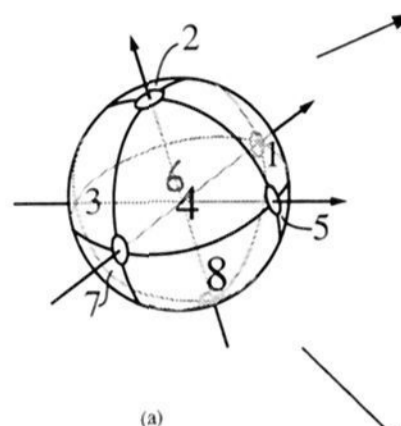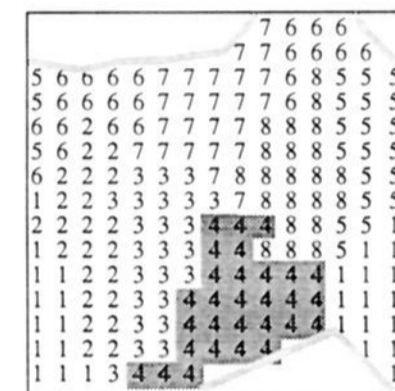
Figure 7. Mapping of the surface of a sphere into a plane by a Kohonen network.

weights of the other neurons are adjusted but to a decreasing amount with increasing (topological) distance to the central neuron.

The formula for the correction of the weights is given by eq 2

$$w_{ji}^{(new)} = w_{ji}^{(old)} + \eta(t)a(d_c - d_j)(x_i - w_{ji}^{(old)}) \qquad (2)$$

In this equation t gives the number of objects already entered into the training process. During training, $\eta(t)$ becomes progressively smaller until, in the end, only the winning neuron is adjusted. The value of the neighborhood function $a(d_c - d_j)$ depends on the distance between the winning neuron c and the neuron j just considered. Quite often, a triangular function is used.

After this adjustment of weights, the next object is taken (a point from a three-dimensional surface in our examples) and again a single neuron (usually a different one) is selected as the winner with a corresponding adjustment of weights.

In the end, each individual object has been assigned to a specific neuron: the objects have been mapped into the plane of neurons.

3. Illustrative Examples: One and Three Spheres

In the representation of molecular electrostatic potentials by a Kohonen network, the points from a three-dimensional surface have to be mapped onto a two-dimensional plane. Therefore, the mapping of a simple three-dimensional surface, of the surface of a sphere, into a Kohonen network is first presented as a simple illustration of the performance of a Kohonen network.

The sphere was dissected into eight spherical triangles that were labeled as shown in Figure 7a. Three input units were needed to send the Cartesian coordinates of a point from such a sphere into the Kohonen network. A 15 × 15 arrangement of neurons was chosen for the Kohonen network. Thus, 3 × 15 × 15 = 675 weights have to be assigned. 2000 points were randomly chosen from the surface of the sphere and used for training the Kohonen network.

For displaying the result of the learning process the neurons of the network were labeled with a number that indicates from which triangle the point came that stimulated a particular neuron. The resulting map is shown in Figure 7b.

It can be seen that points from the same spherical triangle, e.g., the one numbered 4, end up in contiguous parts of the Kohonen

network. A few of the neurons were not stimulated at all; they are left blank in Figure 7b.

In order to indicate that this square map was actually obtained by cutting the surface of a torus (see Figure 5) at two perpendicular but arbitrary lines, two other such cuts were made to give Figure 7c. This is equivalent to shifting the map of Figure 7b three columns to the right.

Further details of the Kohonen maps are worth mentioning. Spherical triangles that directly border each other also have lines in common in the mapping. These lines meet at several points. These points—or sometimes small areas—correspond to points on the sphere where four triangles meet. For example, in the center of the bottom line of Figure 7b the triangles 1–4 meet and thus this area corresponds to the "north pole" of the sphere. In essence, the Kohonen map preserves the essential topological relationship of the spherical triangles (adjacency at lines and points).

Furthermore, the Kohonen projection also preserves geometric features as much as possible. Thus, the spherical triangles 1–8, having equal area size on the sphere, are mapped into areas in the Kohonen network that range between 22 and 29 neurons (1, 28; 2, 23; 3, 24; 4, 29; 5, 22; 6, 23; 7, 24; 8, 22). Thus, although the areas in the Kohonen network are not of completely equal size, they are quite similar.

The Kohonen map in Figure 7 has a number of empty spaces (white area) at the top and at the bottom of the map. These empty spaces indicate neurons that are not activated during the learning process. This is due to the different topology of the sphere compared to that of the torus. Such topological distortions in Kohonen feature maps are quite regular and can provide useful information about the target object.[12] These show up in the map as white areas indicating empty neurons.

In summary, this example shows that the gross features of a three-dimensional surface are preserved in the Kohonen map; this projection method attempts to preserve both topological and geometric information.

It is important to note that each part of a surface will be represented in a Kohonen map and it will be so to an amount that is proportional to its size. Thus, also those parts of a surface that are folded into pockets are shown in its Kohonen map.

Figure 8a shows an assemblage of three spheres of equal size, arranged in a linear sequence and in direct contact with each other. This combination of three spheres can be taken as a prototype of a molecule having a strongly folded surface. The Kohonen map of this arrangement of three spheres is shown in Figure 8b in quadruplicated form by putting four identical maps together like tiles in order to stress the point that the surface of a torus is without boundary. A Kohonen map of the three spheres of Figure 8a can be obtained from Figure 8b by cutting a square of a quarter size at any arbitrary two perpendicular lines. One such Kohonen map showing one complete mapping of the three spheres is indicated by the rectangular frame in Figure 8b.

The important point is that each half sphere of this assembly of three spheres can be seen in the Kohonen map and it is represented by an area of about equal size. In particular, the two half spheres of the two outer spheres pointing inside are clearly represented in the Kohonen maps. In a gnomonic projection the center of interest (COI) would be in the center of the central sphere. The vectors emanating from this COI would project only a minute part of these two half spheres onto a surrounding sphere. Thus, indeed, the Kohonen projection preserves to a large extent geometrical aspects of a complicated three-dimensional surface.

Clearly, because of the different topology of the surface on three spheres and the surface of a torus, the Kohonen projection must lead to distortions.[12] These show up in the map as white areas indicating empty neurons.
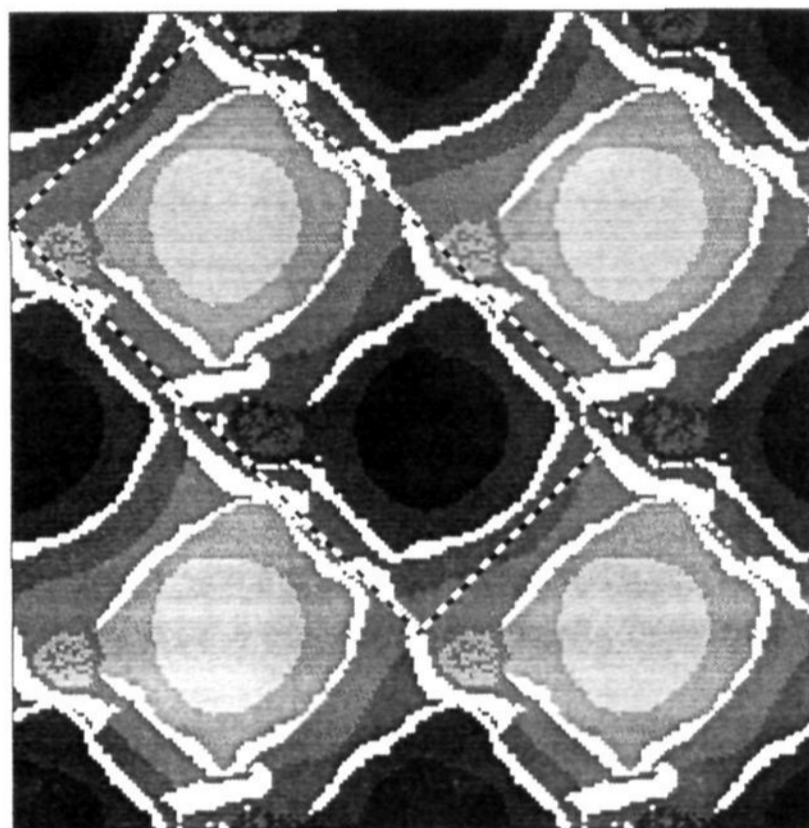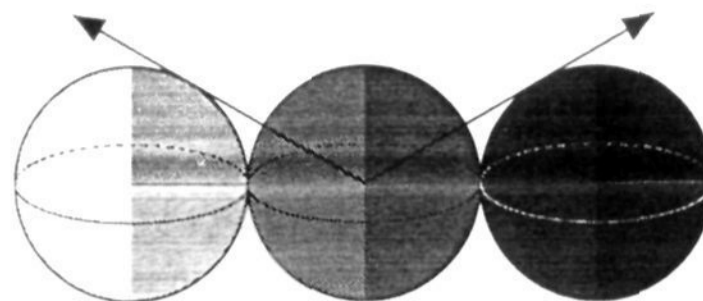
(12) Li, X.; Gasteiger, J.; Zupan, J. *Biol. Cybern.* **1993**, *70*, 189–198.

Figure 8. Assemblage of three spheres (a, top) and Kohonen map of their surface in quadruplicate form (b, bottom).

4. Molecular Electrostatic Potentials

Any point in the space around a molecule is characterized by a specific value of its electrostatic potential. The electrostatic potential on a molecular surface is particularly important because it is on the molecular surface that molecules come into intimate contact with chemical reagents or biological receptors. Various types of molecular surfaces[13] have been investigated in studies of the interactions between substrates and receptors: the van der Waals surface, the solvent-accessible surface of Connolly,[14] and the solvent-accessible surface of Lee and Richards.[15]

In this study we have selected to deal with electrostatic potentials on the van der Waals surface of a molecule. However, the basic methodology and the essential results also apply to other types of molecular surfaces and to other surface properties.

Molecular electrostatic potentials can be calculated by quantum mechanical methods of various degrees of sophistication, from semiempirical to *ab initio*—methods employing different basis sets. In our approach, we have chosen a simple, classical point charge model where each atom i of a molecule bears a partial charge, q_i. The partial atomic charges are obtained by partial equalization of orbital electronegativity.[16,17] The electrostatic potential is obtained by moving a unit positive point charge across the van der Waals surface, and at various points j on the surface, the electrostatic potential is calculated from the partial charge on all atoms of a molecule by eq 3 with r_{ji} indicating the distance between point j and atom i.

(13) Bohacek, R. S.; McMartin, C. *J. Med. Chem.* **1992**, *35*, 1671–1684.
(14) Connolly, M. J. *Science* **1983**, *221*, 709–713.
(15) Lee, B.; Richards, F. M. *J. Mol. Biol.* **1971**, *55*, 379–400.
(16) Gasteiger, J.; Marsili, M. *Tetrahedron* **1980**, *36*, 3219–3228.
(17) Gasteiger, J.; Saller, H. *Angew. Chem.* **1985**, *97*, 699–701; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 687–689.

$$V_j = \sum_i^{atoms} \frac{q_i}{r_{ji}} \qquad (3)$$

All three-dimensional models have been obtained from the corresponding connection tables (constitution) by an automatic 3D-model builder, CORINA, developed in our group.[18,19]

Specific small details of the electrostatic potential will certainly depend on the method chosen for its calculation. However, the basic approach of using Kohonen networks for the projection of electrostatic potentials and the principal results are independent of the method selected for the calculation of molecular electrostatic potentials.

5. Projection by Kohonen networks

Learning in Kohonen network is an unsupervised process. Thus, the value of the property to be mapped, in our case the molecular electrostatic potential on the van der Waals surface, is not considered in the learning process. Rather, only the Cartesian coordinates of the points on the van der Waals surface are input into the Kohonen network. In the following pictures we have selected a quadratic arrangement of 100 × 100 neurons. Thus, the architecture of the Kohonen network is as shown in Figure 9, consisting of 100 × 100 neurons, each having three weights.

As alreacy mentioned, the network was chosen such that each neuron has the same number of neighbors in each sphere. This can be achieved by spreading the neurons on the surface of a torus.

The Kohonen network is initialized with randomly generated small connection weights. Then, the Cartesian coordinates of about 20 000 points randomly selected from the van der Waals surface are entered one after the other into the network.

The one neuron having weights most similar to the Cartesian coordinates of the point input is selected as the central neuron, and the weights are adjusted according to eq 1. The entire dataset is sent three times (epochs) through the network to achieve stabilization.

After the network is trained, the way the points were mapped into the plane has to be visualized. To this end, the entire dataset is again sent into the network. For each point, the neuron that is excited by it is marked and obtains the value of the electrostatic potential observed at the selected point.

As the size of the network is much smaller than the size of the dataset, a neuron is normally excited by many points of the dataset. In this case, the neuron obtains the average value of the potential of those points that excite it. Alternatively, we can also assign the minimum or the maximum potential value to that neuron. However, it has turned out by our experiments that there is no significant difference among the Kohonen projections obtained using the three different assignment methods.

6. Representation of Features of the Molecular Electrostatic Potential in Kohonen Maps

6.1. An Example. Before discussing in detail the mapping of MEP by a Kohonen network, an example is given to illustrate its potential. Figure 10 shows the map of the MEP of 4-hydroxy-4-methyl-2-pentanone in the conformation given in Figure 2. In contrast to the linear projection of the MEP of this molecule that is shown in Figure 1, the Kohonen map shows the entire MEP. Both the potential at the hydroxy group, not visible in Figure 1, and the one at the carbonyl group can now clearly be seen as areas of red color.
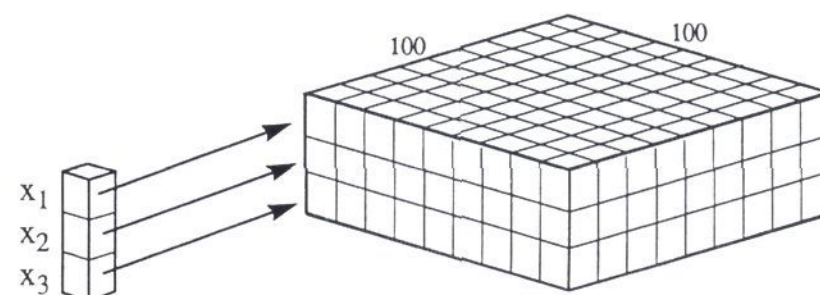
(18) Gasteiger, J.; Rudolph, C.; Sadowski, J. *Tetrahedron Comput. Methododol.* **1992**, *3*, 537–547.

(19) Sadowski, J.; Rudolph, C.; Gasteiger, J. *Anal. Chim. Acta* **1992**, *265*, 233–241.

Figure 9. Architecture of the Kohonen network used for the projection of molecular electrostatic potentials.
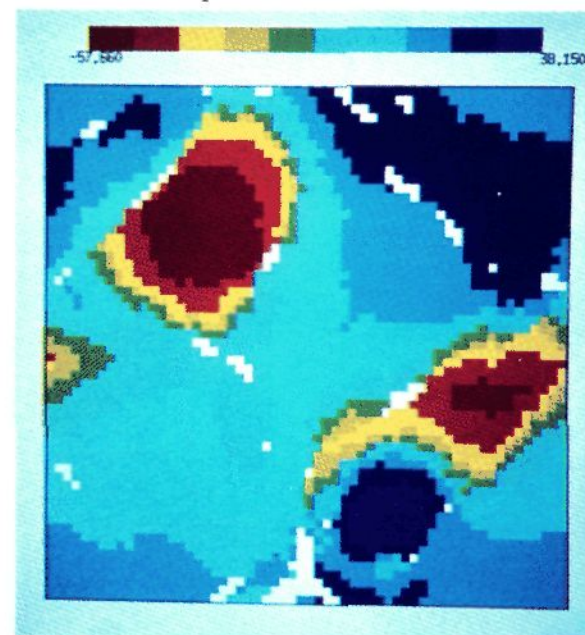

Figure 10. Kohonen map of the electrostatic potential on the van der Waals surface of 4-hydroxy-4-methyl-2-pentanone in the conformation indicated in Figure 2.
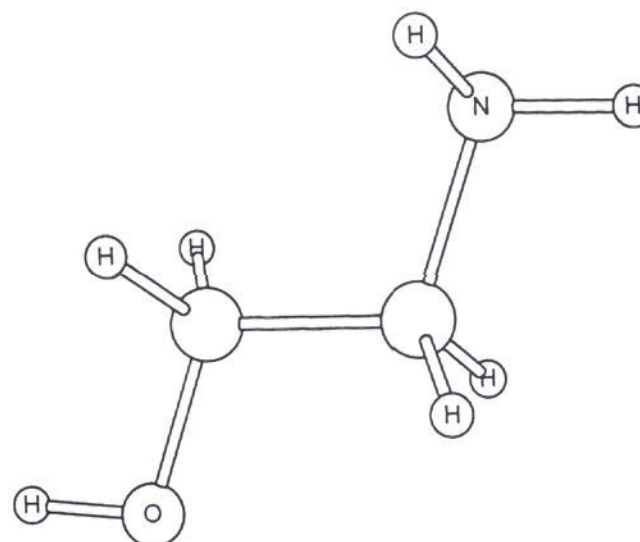

Figure 11. Ball and stick model of 2-amino-ethanol.

In the following we will analyze in more detail how certain structural features in molecules are represented in the Kohonen maps of the MEP.

6.2. Influence of Heteroatoms. In order to indicate how the influence of heteroatoms on the molecular electrostatic potential (MEP) is represented in the Kohonen maps, 2-aminoethanol is investigated in the conformation shown in Figure 11. The MEP is calculated on the van der Waals surface and then projected onto the surface of a torus by the Kohonen learning procedure. The map thus obtained is shown in Figure 12.

2-Aminoethanol has two sites with a negative value of the MEP, one at the oxygen and one at the nitrogen atom. Consistent with this, the Kohonen map (Figure 12a) shows one area with yellow and red color (for the oxygen atom) and one in green color (for the nitrogen atom). The spatial distribution of the MEP at the amino and the hydroxy groups is different, and this is reflected by two different shapes of the projection of the MEP into the Kohonen network. The spatial distribution of large negative values of the MEP on the oxygen atom is essentially preserved in the projection to give a half-moon feature in the map. Furthermore,

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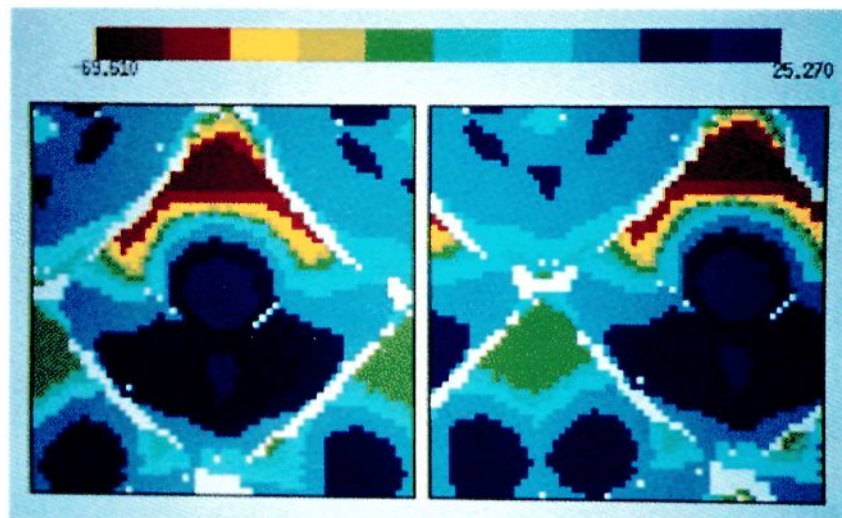
J. Am. Chem. Soc., Vol. 116, No. 11, 1994 4613

Figure 12. Kohonen maps of the molecular electrostatic potential (MEP) of 2-aminoethanol. The map of part b (right) is obtained from the one in part a (left) by shifting it somehow to the right and slightly to the top.
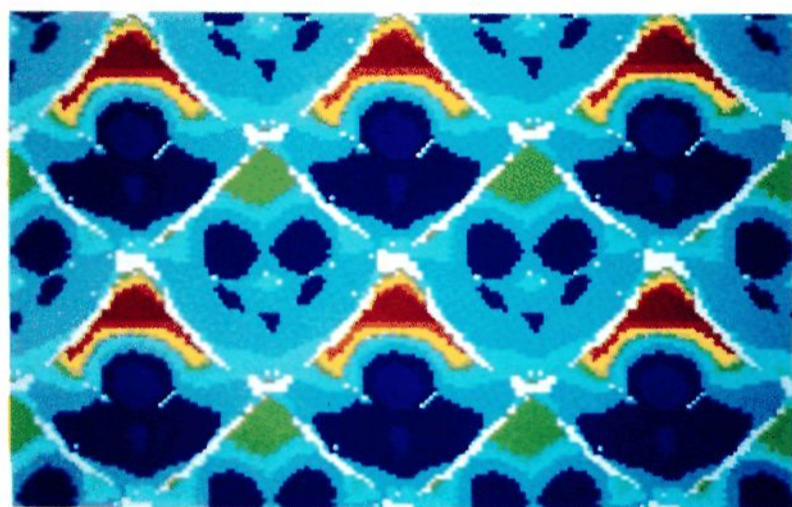

Figure 13. Combination of six identical Kohonen maps (like tiles) of the MEP of 2-aminoethanol (cf. Figure 12a and b).

the hydrogen atom of the hydroxyl group can be located by the circle in purple color embraced by the half-moon feature of the oxygen atom. The MEP at the nitrogen atom is not as pronouncedly negative as that at the oxygen atom and thus only leads to the green color: both hydrogen atoms of the amino group can clearly be located as two purple circles.

It has to be recalled that the projection of the MEP is, in fact, made onto the surface of a torus and that the planar map in Figure 12a is obtained by making two perpendicular cuts through this torus (cf. Figure 5). In Figure 12a the cuts were made in such a way as to place the mapped potential of the hydroxy group into the center of the map. However, any other two perpendicular cuts are equally valid, and thus, the map of Figure 12a can be shifted into any direction. As an example of this, Figure 12b shows the Kohonen map of the MEP of 2-aminoethanol slightly shifted.

To indicate the essential feature of a surface of a torus to be a plane without beginning and without end, we have found it quite helpful to multiply such Kohonen maps and put them together like tiles. Thus, Figure 13 shows Figure 12a being put together six times.

Such figures allow one to perceive the global features of the Kohonen map of the electrostatic potential of a molecule in one view. It can easily be seen that one can extract both parts a and b of Figure 12 from Figure 13.

6.3. Topological Aspects. The example of 2-aminoethanol will be used to further explore the methodology of the Kohonen mapping. It was already said, and indicated in Figure 5, that the projection of the MEP on the van der Waals surface goes onto the surface of a torus. In fact, the torus is not as regular as shown in Figure 5 but is distorted in such a way as to adjust the torus as well as possible to the shape of the molecule and to the topology of the surface information. That is to say that the network provides more neurons to those places where there is a maximum of change
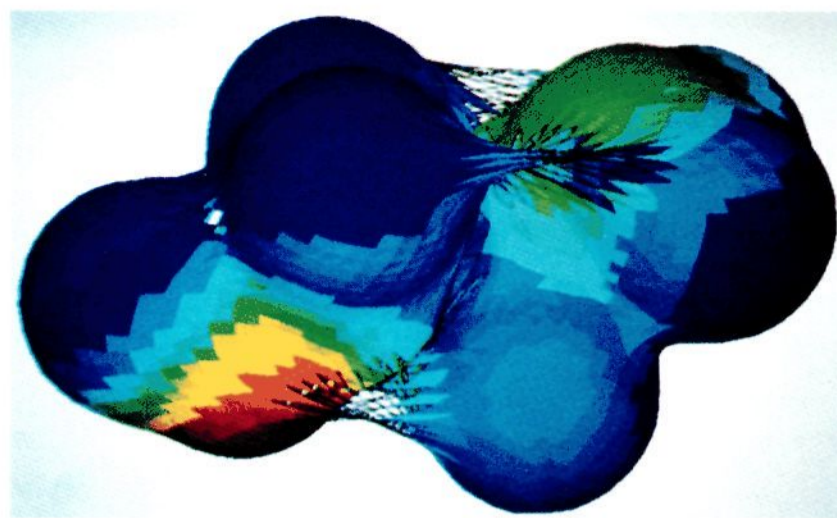

Figure 14. Shape of the torus used for projection as it has adjusted to the shape of the surface of 2-aminoethanol (The MEP is only used for indicating the atoms of the molecule).
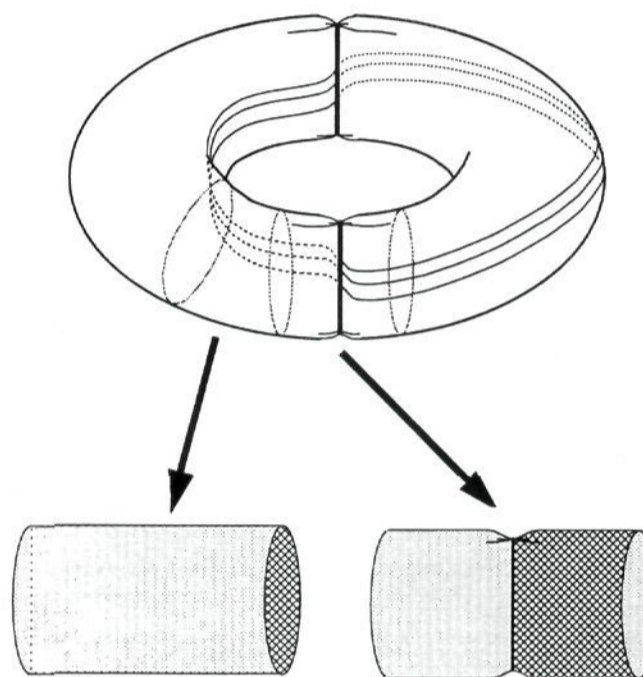

Figure 15. Main characteristics of the topology distortion in the torus used for the Kohonen mapping. The three parallel lines indicate that there exists an inversion at the two sites of discontinuity. Furthermore, the inside of the surface is turned outside at these two places of discontinuity.

in the surface. The shape of the torus as it has adjusted to the surface of 2-aminoethanol in the conformation of Figure 11 is shown in Figure 14.

The central hole of the torus is set into the middle of the molecule; however, it is not a circular hole but a stretched gap, as indicated by the black area in Figure 14. This distortion of the torus into an elongated gap arises from the matching of the electrostatic potential on the surface of a molecule which has essentially a spherical topology to the Kohonen net with the different toroidal topology.[12] This must necessarily lead to some topology distortion, a distortion that is in a simplified manner indicated in Figure 15.

The two points where the two halves of the torus meet are in some way similar to the inversions in a Möbius strip. These two points show up in Figure 14 as those two regions[12] where the surface of the torus is extending like rubber bands. These distortions of the torus result in empty regions in the Kohonen maps indicated by white areas in Figures 12 and 13. In fact, in most molecules that we have studied so far, these empty regions form the pattern of a rhombus, as can be seen in Figures 12 and 13. Thus, the topological distortions of the torus in 2-aminoethanol occur in the area of transition from the oxygen atom to the CH_2 group (Figure 14), and therefore the rhombus of empty neurons directly borders that part of the Kohonen map resulting from the oxygen atom (yellow and red areas in Figure 12a).

However, it should be clear that these topological distortions only reflect geometric aspects of the molecule and are not caused
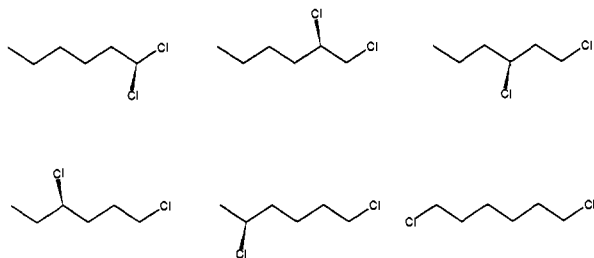
Figure 16. Structure of 1,*n*-dichlorohexanes (*n* = 1–6) used for generating the Kohonen maps of Figure 17.

in any way by the MEP because learning in a Kohonen network is an unsupervised process, the MEP is not considered at all in the learning process, and only the Cartesian coordinates of the points on the molecular surface are used. As we have observed, the points of distortion are determined by cutting a plane through a molecule so as to split it into two halves of about equal size. In an elongated molecule this cut is made through the thinner part of the molecule (see Figure 14). Thus, these topological distortions can give information on geometric aspects of the molecular surface.

A series of projections of the MEPs of various molecules have been made with different random initialization of the Kohonen network. We have observed that the features of the Kohonen map of the MEP characteristic for a given molecule always show up in each separate new map. This attributes to the overall consistency and stability of the Kohonen mapping. However, depending on the different initialization of the Kohonen network with random weights, the maps may be rotated by 90° or 180° or reflected at a line cutting diagonally through the center of the plane of the map.

6.4. Influence of the Distance between Heteroatoms. In order to investigate the effect of distance between two heteroatoms on the Kohonen maps of a MEP, a series of hexanes substituted by two chlorine atoms was studied. One chlorine atom was always kept at position 1 of the hexane system, whereas the second chlorine atom was incrementally positioned at carbon atoms 1–6 (see Figure 16).

The series of Kohonen mapping of the MEP of these different dichlorohexanes is shown in Figure 17.

In all of the six Kohonen maps of the 1,*n*-dichlorohexanes (*n* = 1–6) the two chlorine atoms are clearly distinguished by the yellow and red color indicating a large negative electrostatic potential. The two spots corresponding to these two chlorine atoms increasingly move apart in progressing from 1,1-dichlorohexane to the 1,6-dichloro compound. The chlorine atoms induce a positive potential on the hydrogen atoms of the carbon atom bearing the chlorine atom. This is indicated by the blue and purple color in the Kohonen maps. Clearly, when the two chlorine atoms are close together (in the 1,1- and 1,2-dichlorohexane), they have a synergetic effect in this polarization of the C–H bonds, and a large positive potential is observed. The more the two chlorine atoms are separated from each other, the less pronounced is this polarization to give a positive potential at CH groups and the less intense are these blue spots in the Kohonen maps.

In 1,1- and 1,2-dichlorohexane, a large part of the molecule is electronically unaffected by the two chlorine substituents, and this is expressed in the Kohonen maps of the MEP by large areas of green color signifying basically zero electrostatic potential. (Again, it should be recalled that the maps in Figure 17 have been obtained by making two perpendicular cuts through the surface of a torus. Thus, the green areas in the four corners of Figure 17a actually form a continuous (green) area of zero electrostatic potential, indicating the long hydrocarbon-like part of 1,1-dichlorohexane.

At the other end of the scale is the map of the MEP of 1,6-dichlorohexane that, in effect, consists of two rhombi, one that

is clearly visible in Figure 17f and an identical one that is cut into four parts in Figure 17f. Thus, the molecular symmetry in 1,6-dichlorohexane (see Figure 16) is expressed in these two identical parts of the Kohonen maps.

The patterns of white spots and lines in Figure 17a–f, indicating empty neurons, are nearly identical in all six pictures. This underlines our previously made conclusion (section 6.4) that the topological distortions in the torus that is adjusted to the shape of the molecule give information on the geometry of the molecule. As all six 1,*n*-dichlorohexanes have, overall, nearly the same molecular shape, the topological distortions are very similar and occur at analogous positions in the 1,*n*-dichlorohexanes and are thus given nearly the same patterns of empty neurons.

6.5. Conformation. With a change in conformation, the electrostatic potential on the van der Waals surface might change and this should be reflected in the corresponding Kohonen maps. Figure 18 shows four conformations of 1,2-ethanediol obtained by a rotation of 180° around a C–O or the C–C bond.

The Kohonen maps of the MEP of these four conformations are also shown in Figure 18. As can be seen, the geometry of the left-hand half of the molecule in all four conformations is kept constant; only the right-hand half is changed. Therefore, intentionally, the map of the MEP around the OH group on the right-hand side of the molecule was put into the center of the maps to clearly indicate the changes in the MEP implicated by the conformational changes.

The *all-trans*-conformation of 1,2-ethanediol (Figure 18a) consists of two identical halves, and this is reflected in the Kohonen map of the MEP by two identical halves (Figure 18e) (Recall that the maps in the four corners have to be put together as parts of the surface of a torus and then given a rhomboid identical to the one in the center of Figure 18e). The two OH groups in the *trans,trans,cis*-conformation of 1,2-ethanediol (Figure 18b) have different molecular environments, and this is reflected by two different shapes of the negative MEP at the two OH-groups (Figure 18f). The *trans,cis,trans*-conformation of 1,2-ethanediol (Figure 18c) has of all conformations the largest negative potential, as a positive charge between the two oxygen atoms will be attracted by both oxygen atoms. This is reflected in the Kohonen map of Figure 18g by a large section of red color. The topology distortion of the map[12] cuts between these two oxygen atoms, and therefore the red and yellow colors extend along the white lines indicating empty neurons. Figure 18h shows the map of the MEP of the *trans,cis,cis*-conformation of 1,2-ethanediol (Figure 18d). Again, the topology distortion cuts the molecule into two halfs and thus cuts across the OH group in the *trans*-conformation. This is indicated by the yellow color extending along the lines of empty neurons (in white). The oxygen of the OH group in the *cis*-conformation is rather freely accessible. This is indicated by the large yellow (and red) ellipsoid spot in the Kohonen map of the MEP.

6.6. Chirality. It was already mentioned in section 6.3 that the repetition of the projection of the MEP of one and the same molecule in a fixed geometry may nevertheless lead to Kohonen maps that are rotated by 90° or 180° or are reflected across the diagonal of the square used for showing the map. Thus, it seems that chirality information is lost in a Kohonen projection, as the map can be an image or its mirror image. Indeed, it was found that the *R*- and the *S*-forms of a chiral molecule can give the *same* Kohonen map if the training was started with arbitrary randomly initialized Kohonen nets. However, if a Kohonen net is trained with the *R*- and the *S*-forms of a chiral molecule starting in both cases with the *same* randomly initialized Kohonen net, the maps of the *R*- and the *S*-forms are always mirror images of each other. Thus, in such an application, chirality information is preserved in the Kohonen projection.
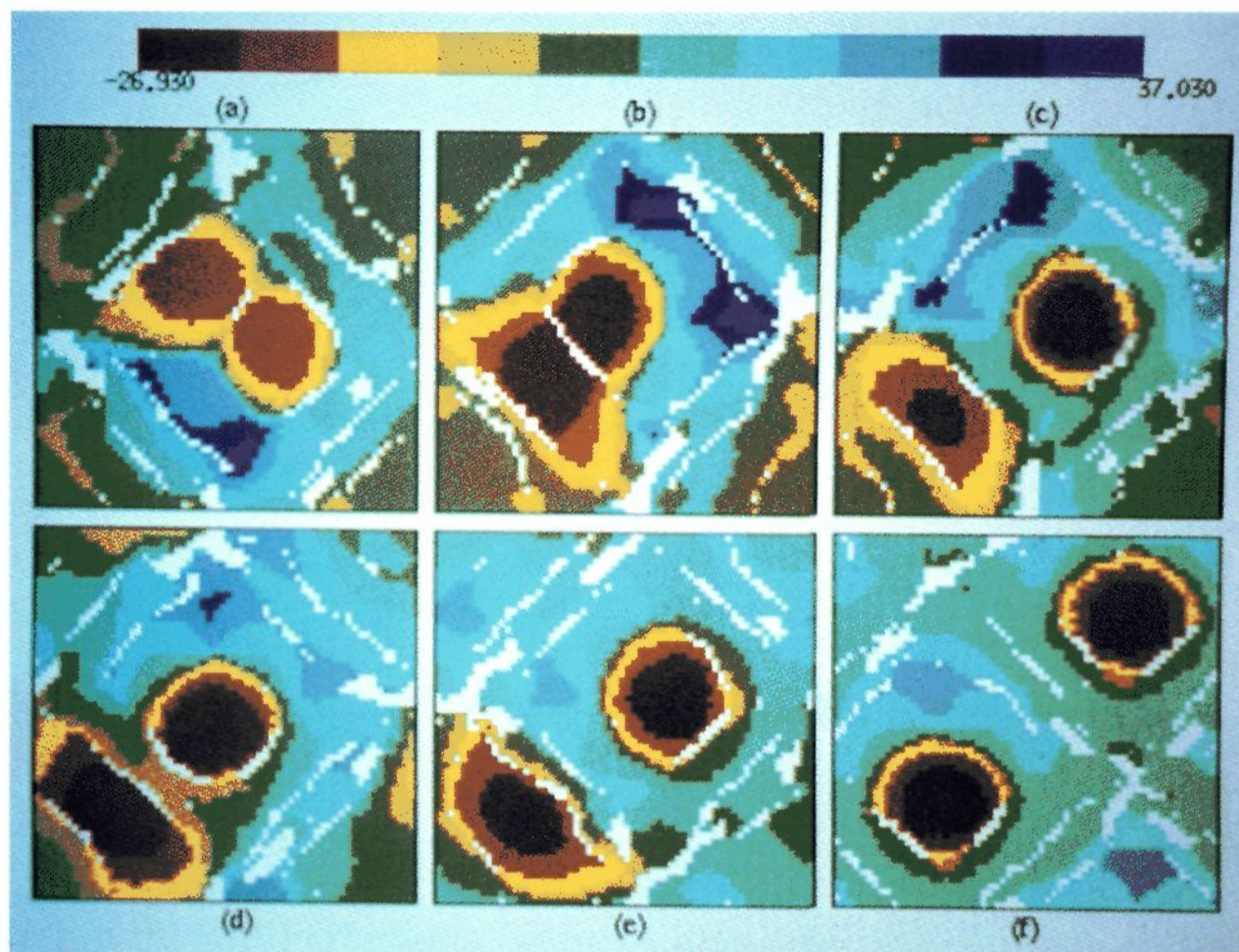
Representation of Molecular Electrostatic Potentials

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Figure 17. Kohonen maps of the MEP of (a) 1,1-, (b) 1,2-, (c) 1,3-, (d) 1,4-, (e) 1,5-, and (f) 1,6-dichlorohexane in the conformations shown in Figure 16.
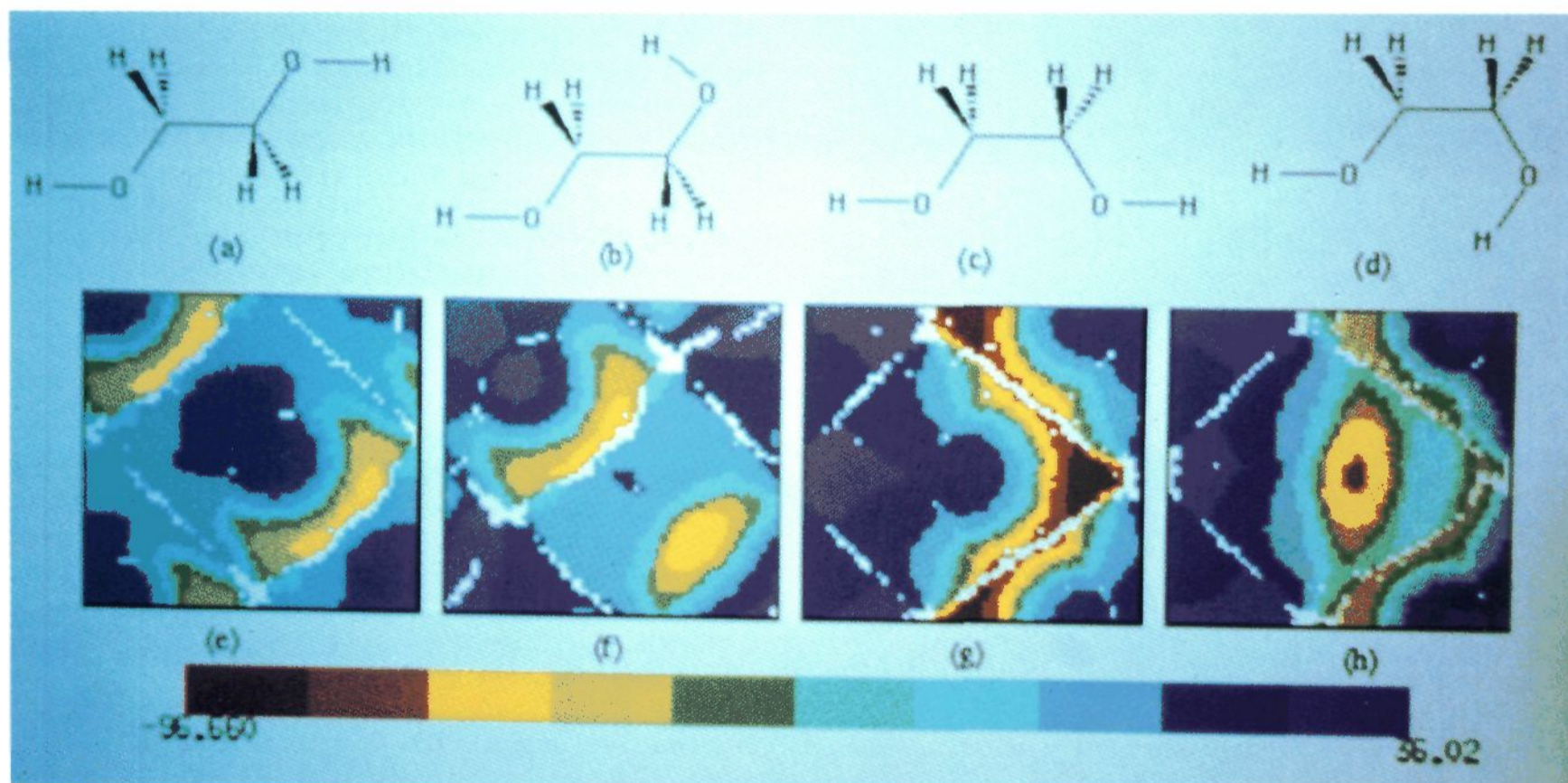

Figure 18. Four conformations of 1,2-ethanediol and the associated Kohonen maps of their MEPs: (a) *all-trans*; (b) *trans,trans,cis*; (c) *trans,cis,trans*; (d) *trans,cis,cis*.

7. Examples of Applications

7.1. Glucose and Saccharose. In Figure 19 the three-dimensional structures of glucose and saccharose and their Kohonen maps are presented. One purpose of this investigation was to find out how the glucose subunit of saccharose can be identified on the basis of the Kohonen maps of the MEP. In order to facilitate this comparison, an adjustment in the size of the Kohonen nets was made. Saccharose has twice as many carbon atoms as glucose has, and therefore a Kohonen net was selected for saccharose that has approximately twice as many neurons than the one chosen for mapping glucose. This was achieved by using a 70 × 70 (4900 neurons) network in the case of glucose and a 100 × 100 (10 000 neurons) network in the case of saccharose.

Glucose contains six oxygen atoms that are clearly distinguished in the MEP of this molecule. However, in the usually employed linear projection of the MEP, whatever observation point is chosen, at most only five of these oxygen atoms can be distinguished, one of them only barely so. The Kohonen mapping of the MEP of glucose, however, shows all six oxygen atoms; two of them are close together, and the maps of their MEPs nearly merge to one spot that has the largest negative potential (red spot) (Figure 19a).

In addition, a prominent feature is the large spot in dark blue and purple color in the Kohonen map of the MEP of glucose (Figure 19a). This shows that there is a sizable region on the surface of glucose exhibiting hydrophobic character. An unfortunately chosen observation point in the normally used
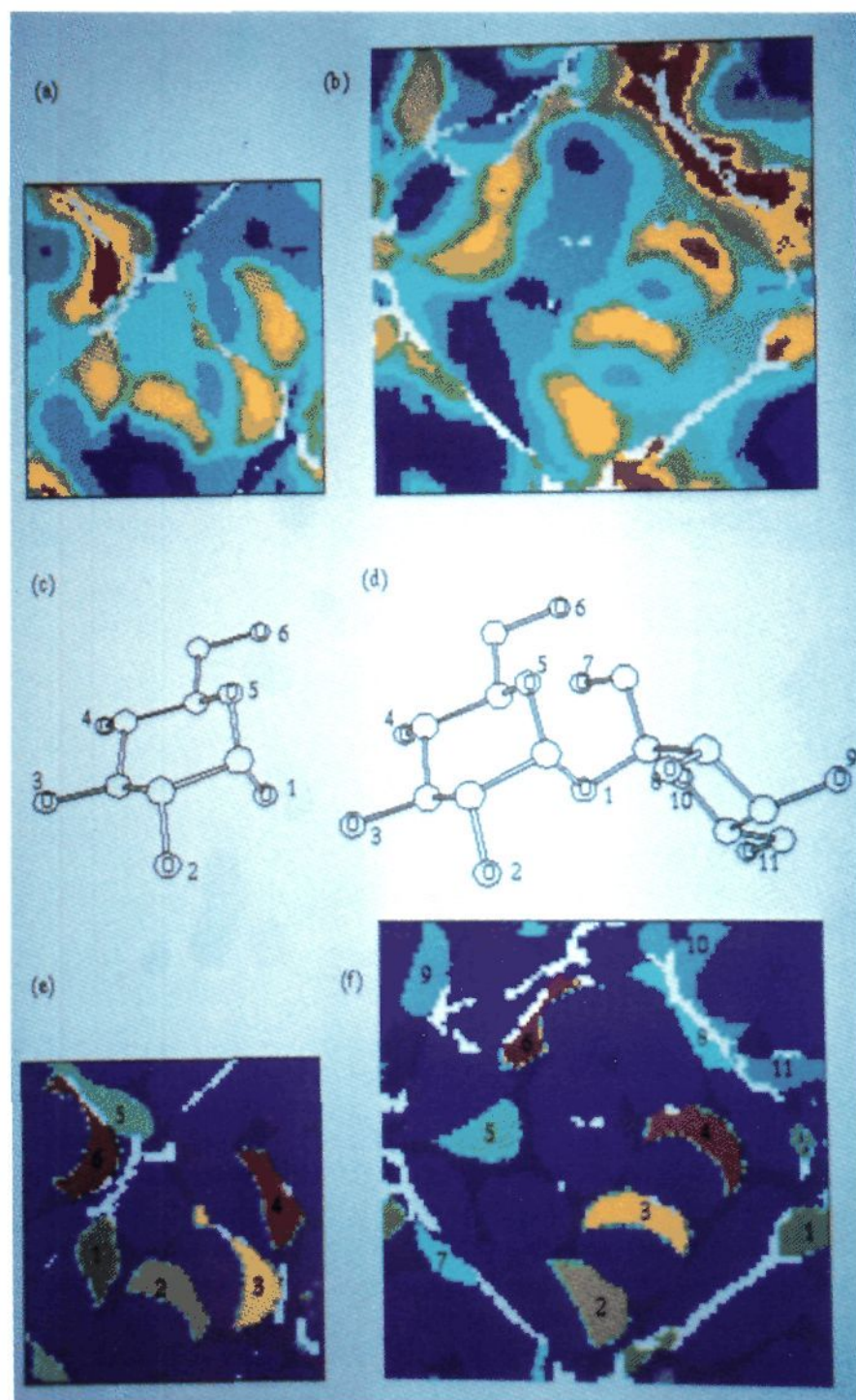
Figure 19. Kohonen maps of the MEPs (a and b) and of atomic surface assignments (e and f) of glucose and saccharose, together with their ball and stick models (c and d).

Table 1. Assignment of Colors to the Atoms (Numbered As Shown in Figure 19) in Glucose and Saccharose

color	glucose	saccharose
green	O-1	O-1
light green	O-2	O-2
yellow	O-3	O-3
orange	O-4	O-4
blue green	O-5	O-5
red	O-6	O-6
light blue		O-7, O-8
blue		O-9, O-10, O-11
dark blue	all carbon atoms	
purple	all hydrogen atoms	

from that part of the surface associated with an individual atom obtains a color that has been chosen for this atom. Thus, in effect, we use the *very same* Kohonen net as for the mapping of the MEP but color it differently according to atom surface assignment (ASA). Table 1 shows the assignment of colors to the various atoms in glucose and saccharose. In this way, instead of Figure 19a and b, the corresponding maps of Figure 19e and f are obtained.

The ASA of Figure 19e allows one to unambiguously assign the area of negative MEP to the various oxygen atoms of glucose, and they provide a deeper understanding of the nonlinear mapping of the Kohonen network. A large part of the map of Figure 19e is colored in purple, indicating surface areas assigned to hydrogen atoms. This is not too surprising, as the hydrogen atoms dominate the surface of glucose and, indeed, of most organic molecules. The carbon atoms, indicated in dark blue are barely visible, as they are buried deeper in an organic molecule and thus do not contribute much to the molecular surface. The oxygen atoms O-1 to O-6 are clearly visible in a counterclockwise arrangement of the spots colored in green, light green, yellow, orange, blue green, and red. The areas of oxygen atoms O-5 (blue green) and O-6 (red) are very close together, making the MEP resulting from them merge into a single spot. The close spatial proximity of these two oxygen atoms in the molecular model gives an explanation for this observation. The topological distortions occurring in the projection by a Kohonen network are indicated by patterns of empty neurons (white areas) (cf. Figure 15 and section 6.3). These topological distortions occur between O-6 and O-5, O-6 and O-1, and O-3 and O-4. Thus, the plane cutting through glucose (cf. Figure 15) can be located and is indicated in Figure 20a by a line cutting through the molecular model.

The atom surface assignment (ASA) of saccharose is shown in Figure 19f. The global features are the same as in the map of glucose: a large part of the map is in purple, as the molecular surface is dominated by hydrogen atoms, and the carbon atoms (in dark blue) are barely visible. The coloring of the oxygen atoms in saccharose was chosen so as to identify the glucose subunit of saccharose in the Kohonen map.

Clearly, the map of glucose (Figure 19e) cannot simply be identified in the map of saccharose as a part that can be cut out from Figure 19f. This would only be possible in a linear projection; the Kohonen projection, however, has two important features that prevent one from overlaying the map of glucose onto the map of saccharose: (1) the nonlinearity in the projection and (2) the topological distortion (cf. section 6.3).

The counterclockwise arrangement of spots for the oxygen atoms O-2 (light green), O-3 (yellow), O-4 (orange), O-6 (red), and O-5 (blue green) in Figure 19f is substantiated by the sequence of these atoms in the molecular model of Figure 19d. However, the spot resulting from O-1 (green) has been moved completely and is now split into two parts. Furthermore, the pattern of white spots, indicating empty neurons and thus the topological distortion, now passes through these two spots of green color. This indicates that the topological distortion exactly occurs at this oxygen atom, O-1. Furthermore, the topological distortion
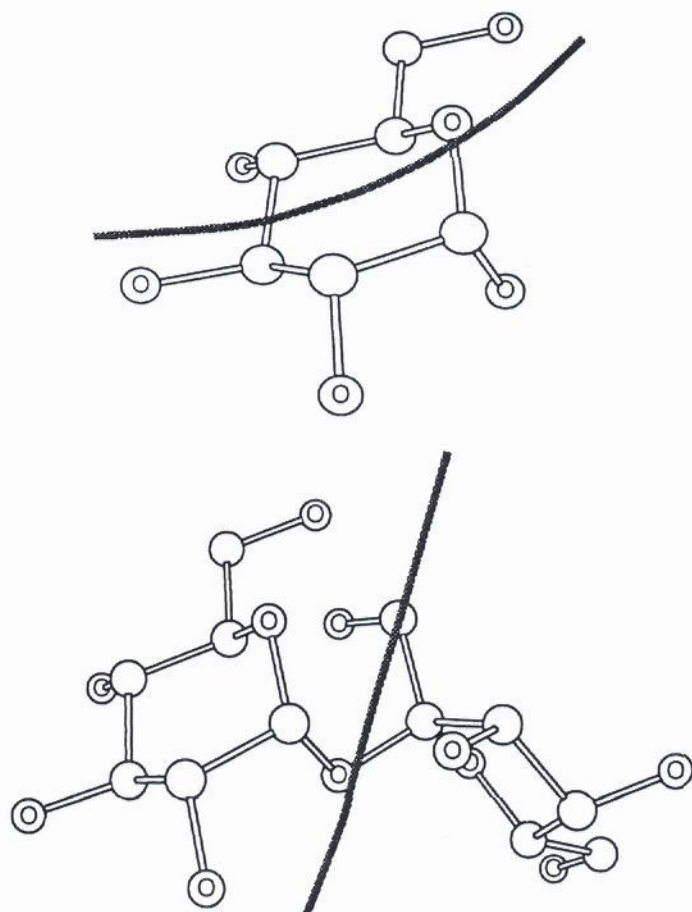
presentation of MEPs on a graphics screen (linear projection) might not reveal this fact. A Kohonen map of the MEP of glucose will always indicate this hydrophobic part of glucose, as all essential features of the MEP are shown in *one* picture.

Figure 19b shows the Kohonen map of the MEP of saccharose. Saccharose has eleven oxygen atoms, each one having a negative MEP. Clearly, some of the oxygen atoms are quite close together and thus their regions of negative MEP might merge. Consistent with this, nine areas of yellow (and red) color, indicating a negative MEP, can be distinguished in the Kohonen map for saccharose; one of these areas is quite large indeed and has a pronounced negative MEP.

The question is now which yellow spot in the MEP map of glucose and saccharose belongs to which oxygen atom? In order to make this assignment it has to be recalled that the training of the Kohonen network is only made with the three Cartesian coordinates of points on the van der Waals surface of the molecule. The neurons thus are associated with such points of the molecular surface, and it is up to the user to "color" them with any desired property. Thus, whereas until now we had decided to color them according to the electrostatic potential observed at this particular point, we now color them according to the atom this particular point belongs to. In other words, the molecular surface is cut into parts that are assigned to the individual atoms that contribute this specific part to the entire molecular surface. Any point coming

Figure 20. Molecular models of glucose and saccharose with lines indicating where the topological distortion (cf. Figure 15) occurs.

separates one of the oxygen atoms represented in light blue from the other oxygen atom in light blue and those in blue (the other oxygen atoms O-7 to O-11). This allows one to pinpoint the plane where the topological distortion cuts through saccharose (see Figure 20b). Whereas in the Kohonen map of glucose the topological distortion cuts directly through the molecule, in saccharose this topological distortion leaves the α-D-glucose subunit basically untouched. Thus, that part of the map of saccharose representing glucose is an undistorted representation of glucose and should be identifiable as such in Kohonen maps of other oligosaccharides containing α-D-glucose units.

7.2. Morphine and Methadone. The purpose of the next example is to investigate to what extent two molecules having common biological activity show similarity in the Kohonen maps of their MEPs. Morphine and methadone are both strong analgesics.

The three-dimensional structures of morphine and methadone chosen for this investigation are shown in Figure 21c and d. For methadone a conformation was selected that brings maximum coincidence between its nitrogen atom and that of morphine, between the ether oxygen of morphine and the oxygen atom in methadone, as well as between the carbon atoms of the "left-hand" phenyl group of methadone and the benzene ring in morphine.

The Kohonen maps of the MEP of morphine and of methadone are shown in Figure 21a and b, respectively. At first sight, not much similarity might be discernible in these two Kohonen maps. To further clarify the situation, several domains of atoms were defined in these two molecules. These assignments were made in such a way as to create sets of atoms deemed to correspond to each other. Figure 21c and d and Table 2 show these corresponding assignments of groups of atoms.

Several different assignments of the atoms in methadone were made. The one shown in Figure 21d gave the best correspondence between the Kohonen maps of morphine and methadone. In Figure 21d (and Table 2), the methyl part of the ethyl group attached to the carbonyl group of methadone is assigned to the group of atoms on the "right-hand" phenyl group with atomic surfaces shown in dark blue.

The neurons in the Kohonen maps of morphine and methadone are then colored according to the atom surface assignments (ASA).
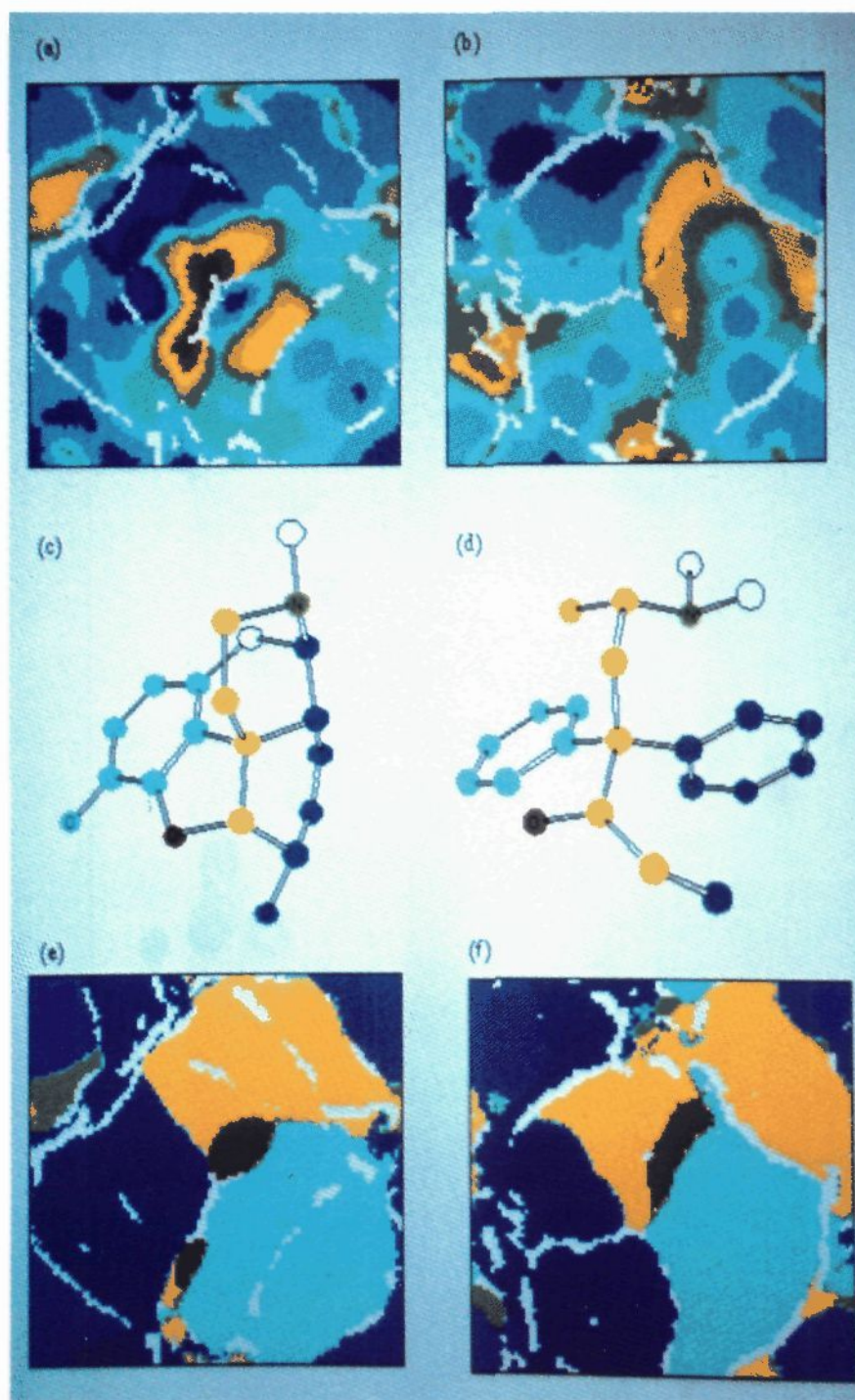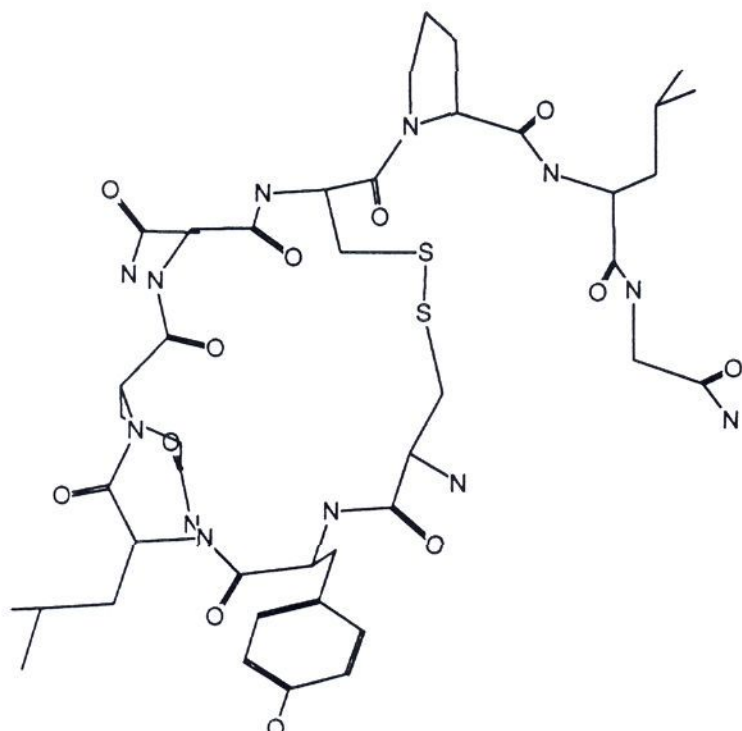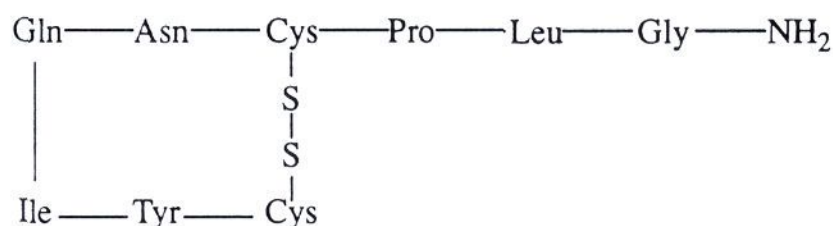

Figure 21. Kohonen maps of the MEP of morphine (a) and of methadone (b), assignment of groups of atoms and their identification through coloring in morphine (c) and methadone (d), and the corresponding Kohonen maps of the ASA (e and f).

This leads to Figure 21e and f. It should be stressed again that parts a and e of Figure 21 have been obtained from the same original Kohonen map of morphine; in one case (Figure 21a) the neurons were colored according to the electrostatic potential observed at the points mapped into the respective neuron, and in the other case (Figure 21e) the colors were determined by the atom group assignment. The same applies to Figure 21b and f, respectively.

This definition of groups of atoms allows one to much better understand the mapping of the molecular surface in the Kohonen network. The oxygen atom (red) is located at a similar place in the two maps. The nitrogen atom (shown in green) is located directly where the topological distortion occurs, and therefore its surface is torn apart and projected into several places in the maps. The stronger negative potential at the oxygen atom in the case of morphine results from the close proximity of a second oxygen atom (from the phenol group) and a third oxygen atom from the alcohol group. In the ASA map of morphine, the one oxygen atom is colored in the same manner as the entire benzene ring (in light blue) and the other oxygen atom is colored like the chain of five carbon atoms extending from the nitrogen atom (dark blue) and can therefore not be located any more. The molecular backbone, colored in yellow, covers similar sites of the map extending into the space between the maps of the nitrogen and the oxygen atom. The light-blue and dark-blue areas are well
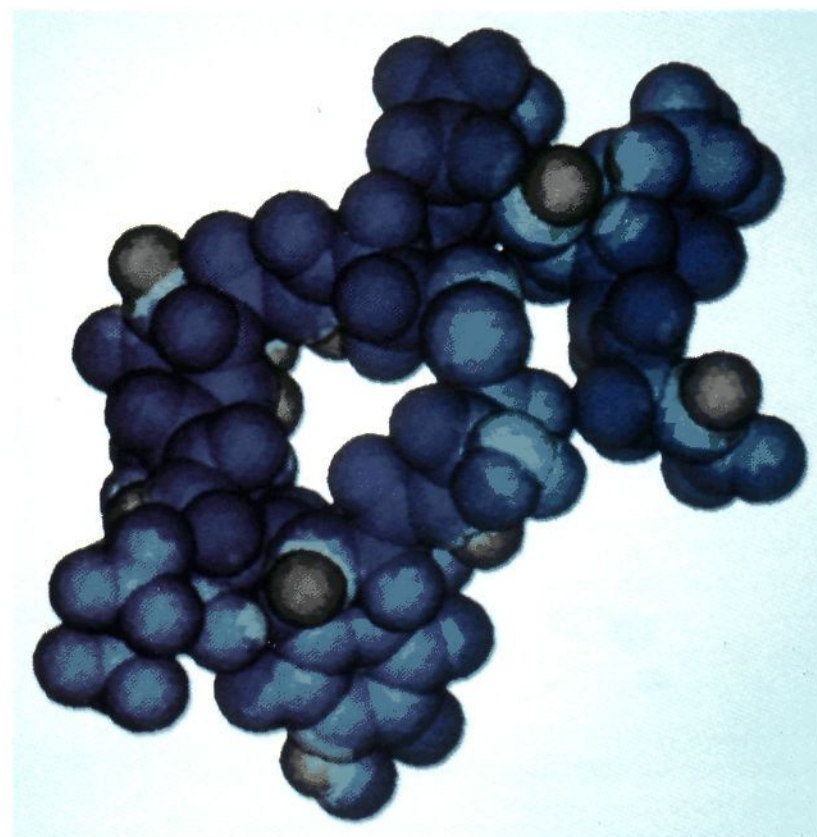
Table 2. Assignment of Groups of Atoms Corresponding to Each Other in Morphine and in Methadone (Two Different Assignments)

color	groups of atoms in	
	morphine	methadone
green	nitrogen	nitrogen
red	ring oxygen	carbonyl oxygen
yellow	shortest path of four carbon atoms (and their hydrogen atoms) leading from the nitrogen to the oxygen atom and an extra methylene and methyl group	
light blue	carbon and hydrogen atoms of the benzene ring and phenolic oxygen	carbon and hydrogen atoms of the "left-hand" phenyl group
dark blue	chain of five carbon and one oxygen atoms (and associated hydrogen atoms) starting at the nitrogen atom	carbon and hydrogen atoms of the "right-hand" phenyl group and an additional methyl group
purple	N-methyl and CH_2 group at the benzene ring	two N-methyl groups

Gln——Asn——Cys——Pro——Leu——Gly——NH₂

(peptide sequence diagram with disulfide bridge: Cys—S—S—Cys, connecting to Ile——Tyr——Cys)

Figure 23. MEP of oxytocin as seen in a linear projection.

Figure 22. Nonapeptide oxytocin and a three-dimensional model of this compound.

separated and cover similar sites in both Kohonen maps (Figure 21e and f). The methyl groups on the nitrogen atom and the CH_2 group bonded to the phenyl group in morphine are colored in purple. These ASA maps of morphine and methadone show a *high degree of similarity. This indicates that the assignment of atoms in methadone in Figure 21d, in particular the assignment of the methyl part of the ethyl group at the carbonyl group together with the "right-hand" phenyl group, to the chain of six atoms extending from the nitrogen atom in morphine is a good model. This indicates that on the molecular level of activity these groups of atoms in morphine and in methadone correspond to each other.*

The distributions of empty neurons in the maps of both molecules show a series of similarities. In particular, they separate the light-blue and dark-blue areas and cut from the nitrogen (green) to the oxygen (red) atom. Thus, the topological distortions in the mapping of morphine and methadone occur at similar sites of the two molecules. This attributes to the similarity in the geometry of these two molecules. Again, it is realized that the topological distortions in the Kohonen mapping can give valuable additional information.

The Kohonen maps of the MEP and, in particular, of the ASA show that morphine and methadone have indeed a lot of similarities that might be responsible for their similar analgetic activity.

Clearly these similarities were found when a specific conformation was chosen for methadone and when certain parts of morphine and methadone were assigned to corresponding groups of atoms. Both assignments incorporate certain assumptions; they constitute a *model* for the similarity between morphine and methadone. In this sense we have used the Kohonen network for testing various conformations of methadone and various hypotheses underlying the different models of assignment of atoms that we have investigated. The detection of common features in the Kohonen maps of morphine and methadone attributes to the validity of these model assumptions.

In this way, one can establish a series of models for the similarity of molecules having common biological activities. Kohonen networks can then be used to explain these models and extract the one having largest similarity in the corresponding Kohonen maps of the molecular electrostatic potential and of the atomic surface assignment.

7.3. Oxytocin. In the next example a peptide was investigated because of the overwhelming importance of peptides and proteins as substrates or receptors controlling many biological functions. Figure 22 shows the three-dimensional model obtained with CORINA for oxytocin, a hormone of the hypophysis that contains nine amino acids. Clearly, this 3D model is only one of many possibilities, as oxytocin has conformational flexibility.

The electrostatic potential on the van der Waals surface is shown in the traditional way, as a linear projection, in Figure 23. Clearly, only a certain part of the molecule can be seen. This
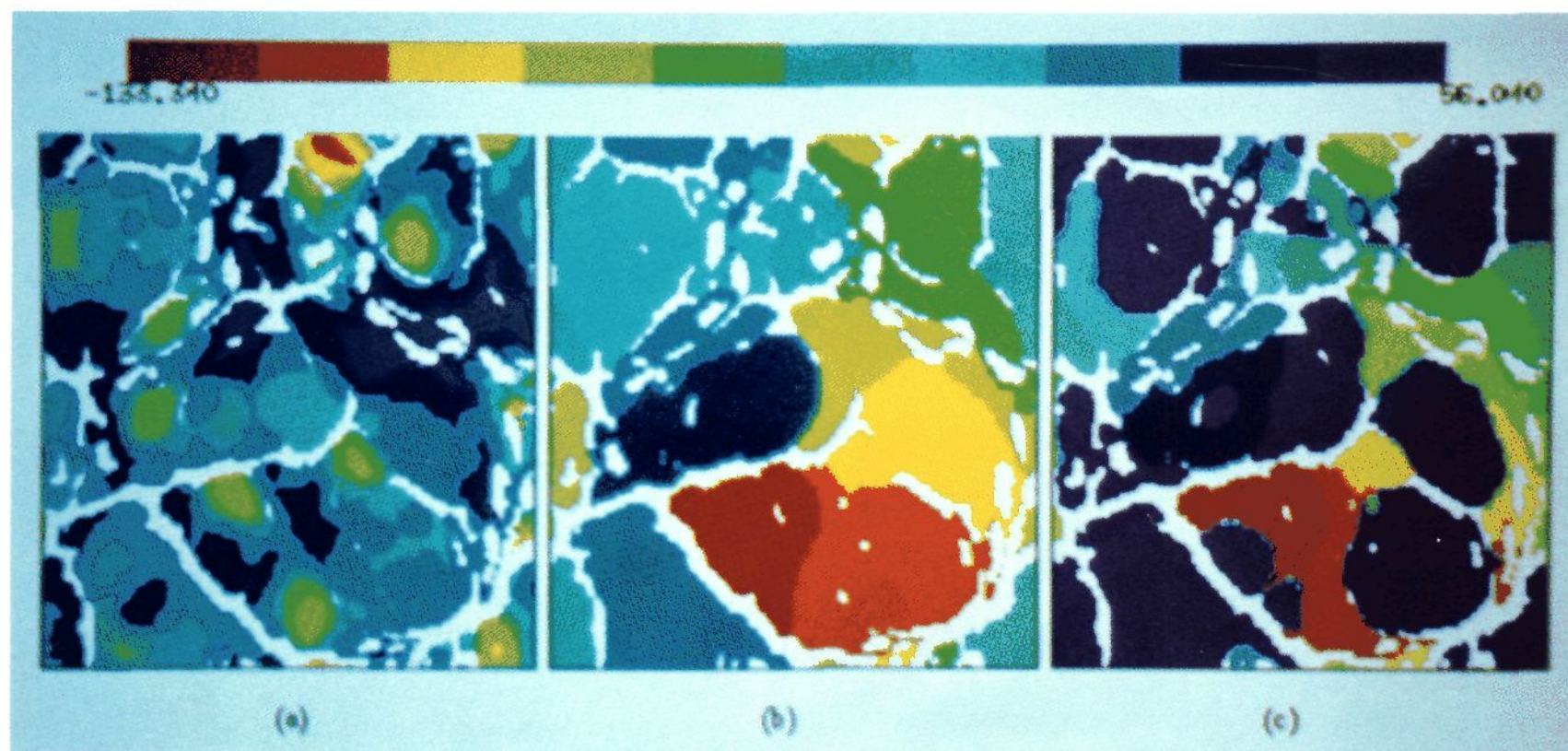
Figure 24. Kohonen maps of the van der Waals surface of oxytocin: (a) MEP; (b) ASA of the entire amino acids; (c) ASA of the backbone of peptide bonds.

Table 3. Assignment of Colors to the Amino Acids of Oxytocin

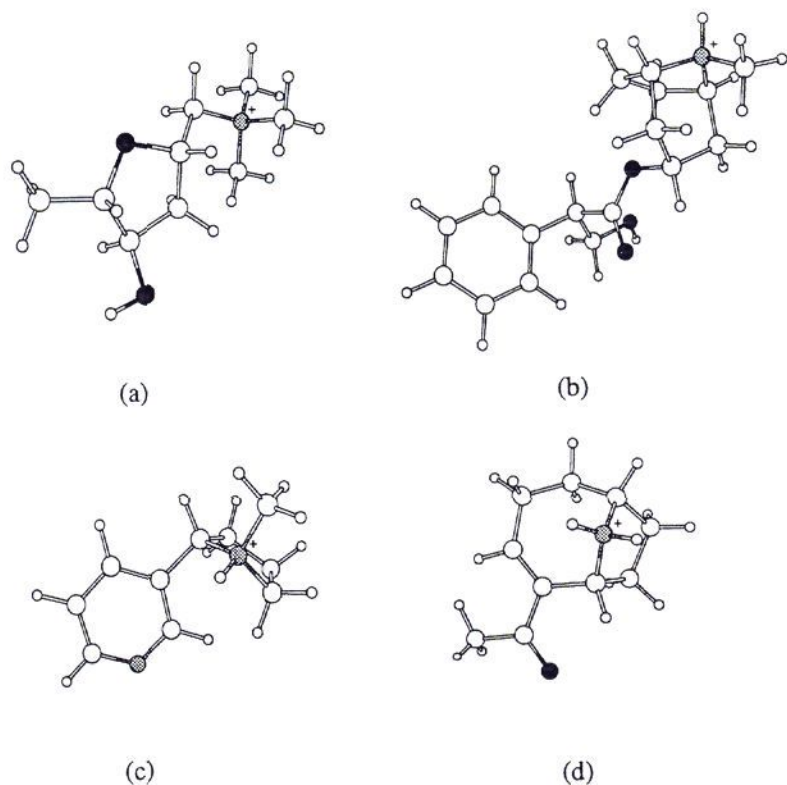| amino acid	color	amino acid	color
Gly-NH$_2$	red	Gln	blue green
Len	orange	Ile	light blue
Pro	yellow	Tyr	blue
Cys	light green	Cys	dark blue
Asn	green		

Figure 25. Ball and stick models of (a) muscarine and the protonated form of (b) atropine, (c) nicotine, and (d) anatoxin-a.

Figure 26. Kohonen maps of the MEP of the structures of Figure 25: (a) muscarine and protonated (b) atropine, (c) nicotine, and (d) anatoxin-a.

view indicates a sizable portion with a positive MEP by the area in purple color.

Figure 24a shows the Kohonen map of the entire electrostatic potential of oxytocin on the van der Waals surface. Several sites with negative MEPs can be identified as spots with light-green, yellow, or red color. One site with a very pronounced negative potential is indicated by a red and orange spot, a site not visible in Figure 23. The sizeable area in purple, indicating a positive MEP, on the other hand, is also visible in Figure 23. This is perhaps a good example of how the *entire* MEP of a molecule is shown in a *single* Kohonen map.
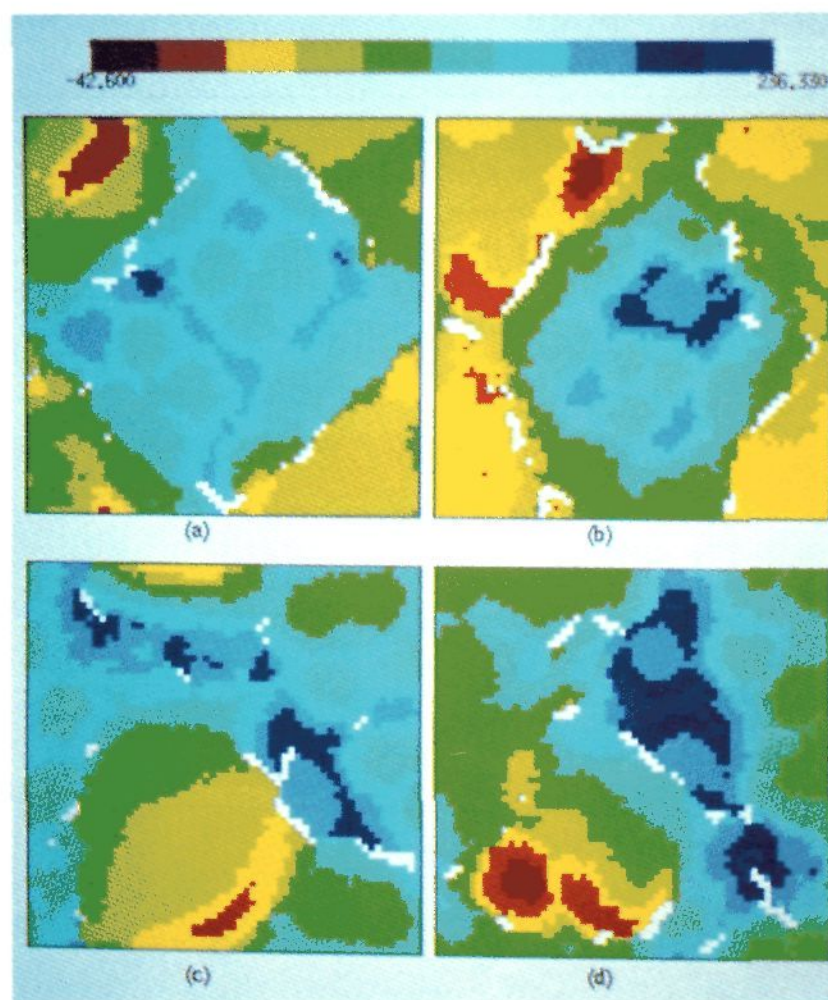
In order to identify solely on the basis of the Kohonen map which part of oxytocin has the strongly negative MEP, the molecular surfaces of the various amino acids were put into different colors. This assignment is given in Table 3; the atomic surface assignment (ASA) Kohonen map is shown in Figure 24b. This figure allows one to identify the site with the strongly negative MEP at a point where Cys, Asn, and Gln meet. Figure 22 shows that two nitrogen and two oxygen atoms are in close vicinity and are thus giving a point of high attraction for a proton. Figure 24b shows in addition how the amino acid sequence, the primary structure of the peptide, is mapped into the plane of the Kohonen map. The sequence Gly-Leu-Pro-Cys-Asn-Gln-Ile-Tyr-Cys-S-S-Cys can clearly be seen in the sequence of colors red-orange-

yellow-light green-green-blue green-light blue-blue-dark blue (Remember again that we look onto the surface of a torus, i.e., that the top of Figure 24b has its continuation at the bottom (cf. Figure 6)). On the other hand, the mapping of the *entire* surface of such a complicated molecule as oxytocin onto the surface of a torus must lead to distortions. To further analyze the mapping of the molecular surface of oxytocin, a different coloring scheme was used. The molecular surfaces of the atoms of the amide bonds and of the CH groups of the α-carbon atoms of the various amino acids were colored as given in Table 3. The surfaces of the organic residues on the α-carbon atoms, on the other hand, were all colored in purple. Figure 24c shows the Kohonen map thus obtained. This Figure 24c allows one to identify how the molecular backbone of the peptide bonds is mapped and where the organic residues are located. It is clear that the molecular surface of a peptide is largely covered by the organic residues of the amino acids indicated by the large areas in purple in Figure 24c. However, the entire sequence of amino acids can also be seen.

7.4. Neurotransmitters. The last application investigates Kohonen maps of compounds that bind to different receptors. The neurotransmitter acetylcholine binds to at least two different receptors, the muscarinic and the nicotinic receptor. On the other hand, the conformationally less flexible molecules muscarine and atropine only bind to the muscarinic receptor, whereas nicotine and anatoxin-a only bind to the nicotinic receptor. Muscarine has a unit positive charge and the other three compounds bind in their protonated form to the respective receptors.[20] Thus, the binding of these substrates to their receptors is to a large extent determined by electrostatic effects. Kohonen maps of the MEP of muscarine and the protonated forms of atropine, nicotine, and anatoxin-a were generated to investigate whether they allow one to perceive similarity within compounds that bind to the same receptor and differences between compounds binding to different receptors.

Figure 25 shows the 3D models of the structures investigated as obtained from the 3D-model builder CORINA.[18,19]

Figure 26 shows the Kohonen maps of the MEP on the van der Waals surface of the four structures of Figure 25.

Without going into details, distinct similarities in the Kohonen maps of the MEPs of the two muscarinic compounds and differences to those of the nicotinic compounds can be discerned. This allows the conclusions (i) that the interactions between these substrates and their receptors are strongly influenced by the molecular electrostatic potential and (ii) that the characteristics of the MEP responsible for the binding to the two different receptors are conserved to a certain extent in the Kohonen mapping. A more extensive investigation of a series of these compounds has appeared.[11,21]

8. Conclusions

Kohonen networks allow one to view molecular surface properties such as the molecular electrostatic potential in a single map. These maps clearly reflect important features of molecular surface properties resulting from heteroatoms, conformation, and chirality. Furthermore, they give an indication of the general three-dimensional shape of a molecule. These maps can be used to find similarities in a series of molecules and thus locate essential features necessary for a certain biological activity. It could be shown that there are distinct hydrophobic parts in glucose and saccharose. Furthermore, the group of atoms that correspond to each other in morphine and methadone were identified. The maps of the MEP show distinct similarities for compounds that bind to the same receptor and differences for those binding to different ones, as indicated by a set of muscarinic and nicotinic compounds. A study on oxytocin points to the use of this method in analyzing features of peptides and proteins.

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