Three-Dimensional Molecular Illustrations I: Isoelectron Density Contours and Isoelectrostatic Energy Contours

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Abstract □ A method of depicting dimensional illustrations of molecules *in vacuo* that are sensitive to small electronic perturbations was attempted. This method would be useful in determining the effects of either perturbing groups from other molecules or changes produced by the addition or modification of an existing atom or chemical group on the same molecule. Isoelectron density contours for small molecules such as benzene, ammonia, and formaldehyde were first considered using the CNDO/2 molecular approximation method and then extended to the use of deorthogonalized CNDO/2 eigenvectors. These methods were similar in molecular projections but insensitive to electronic alterations. Therefore, the electrostatic potential energy was considered in developing contour surfaces of several of the molecules studied. In this case, acute and visually discernible changes were evidenced by electron exchange in the three-dimensional illustration of formaldehyde. The effect on the two-dimensional contour map of ammonia was strikingly altered by the addition of a proton, further substantiating the sensitivity of electrostatic contours to perturbing influences. These methods are considered and amplified in this report.

Keyphrases □ Molecular structure—method of depicting three-dimensional illustrations sensitive to small electronic perturbations developed, electrostatic potential energy contours considered □ Electrostatic potential energy contours—considered in depicting three-dimensional illustrations of molecular structure sensitive to small electronic perturbations

The concept that a three-dimensional picture of a molecule can be drawn and visualized is attractive. Additional importance can be attached to this configurational viewing of molecules when one attempts to relate the physical shape with the pharmacological response of the therapeutic agent. On occasion, molecules possessing unrelated configurations produce similar pharmacological responses. In many instances, these dissimilar molecules may be spatially manipulated to assume similar configurations.

The utility of three-dimensional molecular illustrations becomes apparent from the vast number of investigations and publications dealing with stereochemistry and structure-activity relationships of medicinal agents (1–8).

BACKGROUND

Many series of biologically active compounds have been investigated with respect to the effects caused by the addition, deletion, or alteration of a functional group on a parent moiety. Generally, these investigations have dealt with the chemical group as a whole rather than the more detailed electronic configuration of the individual atoms. In some advanced studies, a more comprehensive analysis of the compounds has been used, taking into consideration more detailed parameters such as the charge distribution and the position of lone-pair electrons.

Atoms and functional groups do not exist as single entities that can be considered independently of each other but rather as a complex arrangement of electrons surrounding the nuclei. Therefore, the spatial configuration of a molecule should not be considered simply as a collection of atoms but rather as a summation of the complex interactions among all of the nuclei and electrons of the entire molecule.

Therefore, this work involved the development of illustrating simple molecules, initially in terms of their isoelectron density contour surfaces. This technique, however, was insensitive to electronic changes in these molecules and led to the consideration of isoelectrostatic energy contours.

Both the isoelectron density and the isoelectrostatic energy contours will be discussed.

Schnaare and Martin (9) reviewed the application of quantum theory to the study of drug systems. Theoretical calculations on the π-electron systems of several drugs were correlated with physical–chemical parameters. The orientation of the molecules involved in the benzocaine–caffeine complex was proposed. Also, the preferred site of hydroxylation on indole derivatives and the pKa values of a series of sulfonamides were correlated with electronic charge.

A detailed examination of this subject explained the many types of molecular interactions involved when a drug is introduced into a biological system (10). Various methods used to calculate molecular orbital indexes were discussed, as well as the shortcomings of each. Extensive consideration was given to the application of quantum mechanical calculations to drug systems. Many types of physical–chemical interactions and pharmacological classes of drugs were examined by this approach.

Graphical illustrations were produced showing how the value of the wavefunction varies with increasing distance on a radius from the nucleus (11–13). Bordass and Linnett (14), using isometric projections, illustrated how the magnitude of the wavefunction varies concurrently with two spatial coordinates. A computer line printer was utilized to produce a two-dimensional matrix of data representing the electron density probability on a plane through the atom (15). Isodensity contour lines may then be drawn through equal values of electron density probability. Other isodensity contours of atomic orbitals also were reported (12, 13).

Pictorial descriptions of molecular orbitals produced by methods similar to those for atomic orbitals include the line printer (15–17) and isometric projections (18, 19). A series of three-membered ring molecules was investigated with respect to the shape of two-dimensional isodensity contours (20, 21). In one attempt to examine the three-dimensional character of these contours, a series of charge density contour maps, each on a successive plane through the gallium arsenide crystal, were combined into a movie (22). Furthermore, the electrostatic potential was investigated with respect to its ability to predict the most stable conformation in a bimolecular system (23).

COMPUTATION

Electron Density Calculations—The proposed methods of illustrating molecules required a large number of repetitious numerical evaluations of algebraic functions, which were performed by a computer[1] using Fortran IV language. The molecular illustrations were produced on an incremental plotter[2], which was operated off-line from the computer.

The method developed to produce three-dimensional electron density illustrations of molecules involves the following sequence: determining the atomic coordinates, calculating the orthogonalized and deorthogonalized orbital populations, producing a matrix of data representing the electron density probability at numerous points surrounding the molecule, determining the points in this matrix that represent the boundary corresponding to the desired level of probability, and plotting these points by a method that produces a three-dimensional illustration.

The atomic coordinates of the system being investigated may be obtained from various sources. For purely qualitative interpretation of the resulting illustrations, the atomic positions may be derived from tables of standard bond lengths and bond angles (24). More accurate data concerning specific compounds may be derived from X-ray crystallographic techniques.

The orbital electron populations were determined by the CNDO/2

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[1] IBM 370/155.
[2] Broomall Industries M-2000 drum-type.

molecular orbital approximation (25)[3] using computer program CNINDO (26). This method considers only the outer shell or valence orbitals. Since the electrons contained in the inner or nonvalence shells participate only to a very limited extent in any type of sharing or transfer with other atoms, these orbitals were assumed to contain 2.0 electrons each unless otherwise noted.

In theory, a box representing a three-dimensional array is placed over the molecule. With formaldehyde as a model, it was found that when the boundaries were restricted to a distance no less than 0.9 Å from the nearest hydrogen atom and 1.5 Å from the nearest second row atom, approximately 99.5% of all electrons were included. These restrictions were adhered to for all electron cloud illustrations.

The illustrations produced from these data are contour plots where points of equal density probability are connected with a line.

The nuclear coordinates, Slater atomic orbitals, ϕ, and the corresponding orbital population coefficients, $P\mu\mu$, are utilized to calculate the electron density probability, D, at all points, r, according to:

$$D(r) = \sum_{\mu} P\mu\mu\phi(r)^2 \qquad \text{(Eq. 1)}$$

Simultaneously, a total is accumulated representing the total density probability in the matrix.

Deorthogonalized CNDO/2 Eigenvectors—The orbital populations, $P\mu\mu$, obtained by the CNDO/2 method are considered to be compatible with the Slater-type orbitals in spite of the zero differential overlap approximation of the method. However, the CNDO/2 eigenvectors may be considered as orthogonalized orbitals derived from Slater orbitals by the Lowdin transformation (27). Since the Slater orbitals are nonorthogonal, a more exact interpretation of the electron density probability will be provided if the eigenvectors are deorthogonalized by the matrix product:

$$C^x = S^{-1/2}C^\lambda \qquad \text{(Eq. 2)}$$

where S is the overlap matrix and C^λ and C^x are the CNDO/2 and deorthogonalized eigenvectors, respectively. This procedure was used previously (28, 29) in conjunction with Slater-type orbitals.

With the deorthogonalized CNDO/2 eigenvectors, C, the density probability at point r may be determined by the double summation:

$$D(r) = 2 \sum_{i} \left[\sum_{\mu} c_{\mu i}\phi\mu(r) \right]^2 \qquad \text{(Eq. 3)}$$

The summation over i includes only the occupied molecular orbitals. The summation over μ represents the combination of atomic orbitals, $\phi\mu$, composing the ith molecular orbital.

To produce a three-dimensional isodensity contour illustration, it is necessary to choose the appropriate level of density probability. An arbitrary value of $D(r)$ is chosen, and the data are scanned for all values equal to or greater than this cutoff value. Several more values are chosen, and the procedure is repeated. A plot of these percentages versus the cutoff values allows selection of an appropriate limiting value of $D(r)$ corresponding to the desired probability.

The data needed to produce the actual electron density illustration (i.e., for the plotting program) include only the three cartesian coordinates for each grid point located on the contour surface.

To plot these data, a program was developed to generate instructions subsequently used to drive the plotting instrument. The resulting illustration is a three-dimensional plot consisting of a series of contour lines in either the xy or yz plane. Each contour represents the data found in one slice or plane of the coordinate matrix. Plotting begins with the plane closest to the viewer, and subsequent planes are plotted until the back of the object is reached.

A total of 36 possible views is provided by this program. The data matrix, or object, may be viewed from any one of the four sides. Thus, the molecule may be rotated about the y axis 360° in 90° increments. For each side of the object, there are nine possible viewing angles.

An integral part of this routine is its ability to eliminate lines that are hidden from the viewer. The plotting surface is divided into many columns. The area plotted in each column is stored, and these data are referred to each time subsequent lines are to be drawn.

The resulting illustrations are only pseudo three dimensional because no consideration is given to perspective. The scale is identical in the front and rear portions of the illustration, allowing measurement of actual molecular distances on any plane parallel to the page. Because perspective
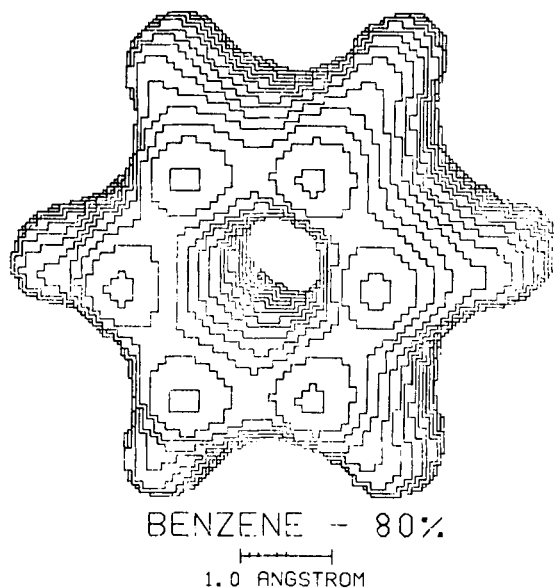

BENZENE – 80%

1.0 ANGSTROM

Figure 1—*Electron density probability contour surface of benzene using a minimal basis set and CNDO/2 orbital population coefficients.*

is neglected, the hidden-line problem is simplified and the computer processing time is minimized.

The program also has the additional ability to plot several colors on one illustration. This feature is not necessary for the electron density models where only one variable is plotted (e.g., isodensity contours) but enhances illustrations where several variables are plotted simultaneously (e.g., electrostatic potential energy contours).

RESULTS

Electron Density for Small Molecules—Three fairly simple molecules, benzene, ammonia, and formaldehyde, were chosen to test the programs that produce three-dimensional electron density illustrations. In each case, standard bond lengths and bond angles (24) were used to determine the nuclear coordinates.

Figure 1 represents the electron cloud of the benzene molecule at an isodensity value of 80%. If the 100% isodensity contour were chosen, the contours would simply be slightly larger; the 80% contours retained all features required for these illustrations. The data for this figure were generated from a minimal basis set (i.e., all atomic orbitals up to and including the valence shell of each atom). As might be expected, this il-
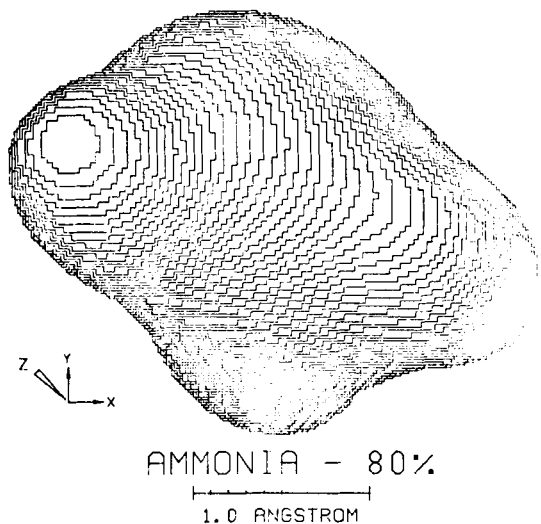

AMMONIA – 80%

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Figure 2—*Electron density probability contour surface of ammonia using a minimal basis set and CNDO/2 orbital population coefficients.*
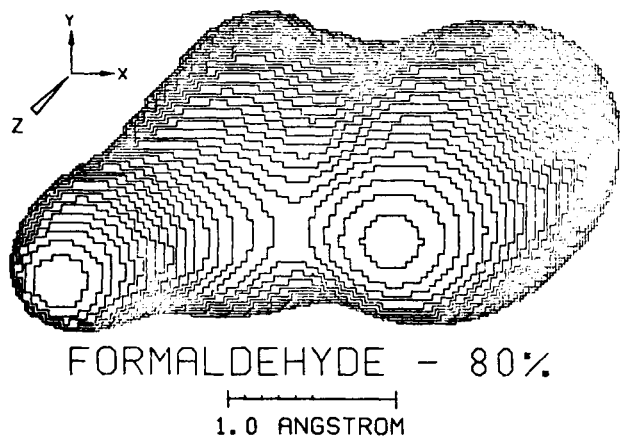
FORMALDEHYDE — 80%

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Figure 3—*Electron density contour surface of formaldehyde at 80% probability using a minimal basis set and CNDO/2 orbital population coefficients.*

lustration clearly shows the hole through this aromatic system. Another distinctive feature is the relative size of the carbon and hydrogen atoms. The density is more pronounced in the region between bonded atoms, but the areas separating nonbonded atoms are deficient in this respect.

The mechanism of the plotting routine may be better understood from this figure. Close examination reveals the contours for each of the many slices through the molecule. These individual contours, each on a plane parallel to the page, are superimposed upon each other to form the three-dimensional structure. The viewing angle is controlled by displacing each plane in the vertical and/or horizontal direction. The contours are drawn in stepwise fashion; each step represents one of the many points at which the electron density probability functions were evaluated. Although the curves are not smooth, the illustration possesses visual clarity.

From orbital populations, an illustration of ammonia at an isodensity value of 80% is given in Fig. 2. The atoms of the molecule are located at the corners of a tetrahedron, with the nitrogen atom positioned at its center. Again, the drawing shows the relative sizes of the atoms and allows the heteroatom to be distinguished from the hydrogen atoms. The lone pair of electrons associated with the nitrogen atom extends the contour surface in the vertical direction, parallel to the y axis.

A similar illustration of formaldehyde, obtained from a minimal basis set and the atomic orbital populations, is given in Fig. 3. An oxygen atom would be expected to be slightly smaller in size than a carbon atom. In this case, the slightly greater electronegativity of the oxygen atom withdraws electrons from the carbon atom, thus increasing the electron population of the atomic orbitals associated with the oxygen atom. As a consequence of these excess electrons, the oxygen atom is enlarged in comparison to the carbon atom. Most of these electrons are in the $2px$ and $2pz$ orbitals; the oxygen atom is elongated in the xz plane, which is perpendicular to the page.

Figure 4 illustrates the 60% probability contour surface of formaldehyde. A discontinuity of electron density appears between the carbon and
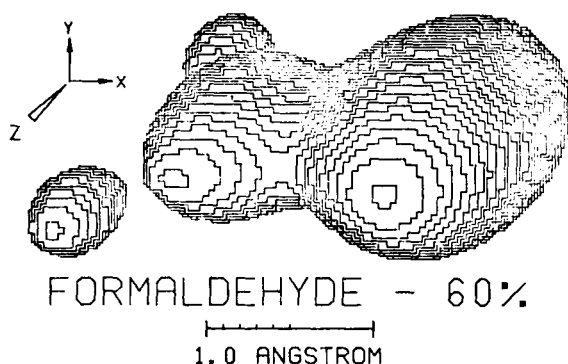

FORMALDEHYDE — 80%

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Figure 5—*Electron density probability contour surface of formaldehyde using only a valence basis set and CNDO/2 orbital population coefficients.*

hydrogen atoms but not between the nonhydrogen atoms. This phenomenon is fully expected when the relative number of electrons participating in the various bonds is considered. Further reductions of the probability will, in sequence, produce a gap in the carbon–oxygen bond, eliminate the hydrogens, and, finally, eliminate the carbon atom. Such a series of illustrations, produced by successively reducing the probability, allows one to distinguish the most densely populated area in the molecule.

By eliminating the calculations involving the $1s$ orbitals of all second-row atoms, such as carbon and oxygen, isodensity contours may be produced in terms of the valence orbitals only. The resulting illustration of formaldehyde, at 80% probability, is shown in Fig. 5. A comparison may be made with Fig. 6, where all atomic orbitals were utilized. It can be visually discerned from Fig. 6 that the molecule is slightly enlarged. These larger contours are a result of the nuclear cores of the nonhydrogen atoms being very sparsely populated. To enclose the same percentage of electrons, the contour surface has to extend outward. A similar comparison of the ammonia molecule, with and without the nonvalence orbitals, also shows this enlarging effect. In that case, the effect is less pronounced because of the smaller number of nonvalence electrons.

In the method that conforms strictly to the CNDO/2 approximation, the eigenvectors must first be deorthogonalized. The illustrations are then produced by summing the molecular orbital contributions to the density probability, as opposed to those of the atomic orbitals. Figure 6 is a result of these computations performed on formaldehyde.

A comparison between Figs. 5, where atomic orbital approximation was used, and 6 reveals only very slight differences in the overall shape

FORMALDEHYDE — 60%

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Figure 4—*Electron density contour surface of formaldehyde at 60% probability using a minimal basis set and CNDO/2 orbital population coefficients.*
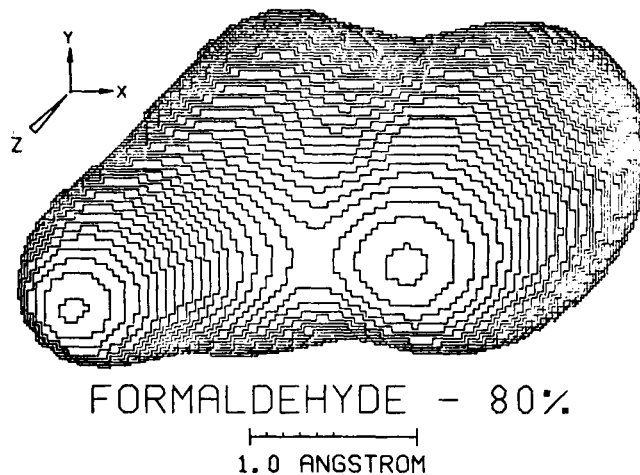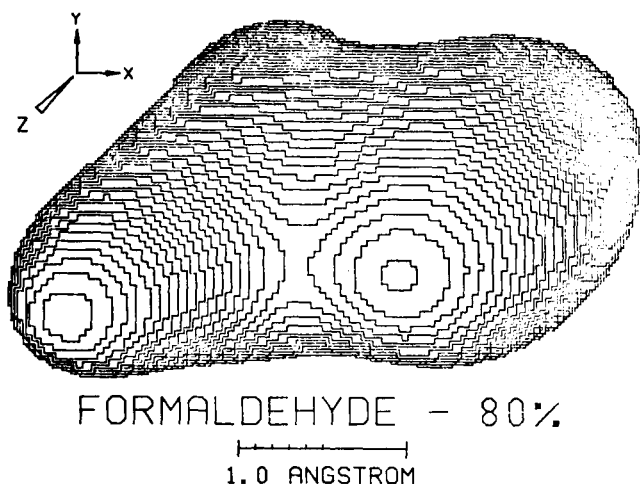

FORMALDEHYDE — 80%

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Figure 6—*Electron density probability contour surface of formaldehyde using only a valence basis set and deorthogonalized CNDO/2 eigenvectors.*
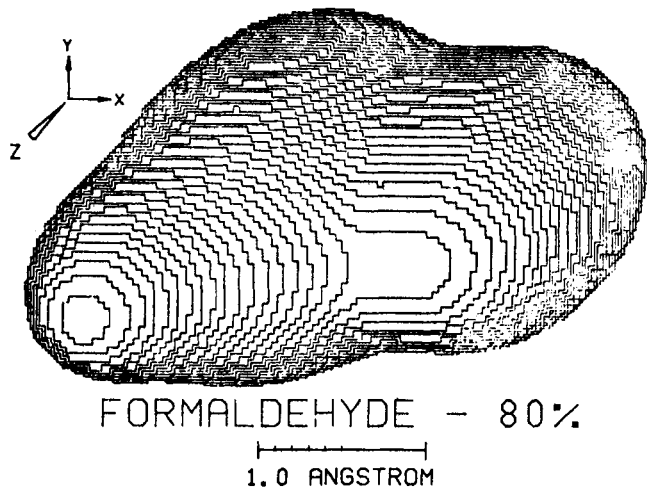
Figure 7—*Electron density probability contour surface of formaldehyde using only a valence basis set and CNDO/2 orbital population coefficients. The coefficients for the carbon and oxygen atoms are reversed.*

and size of the portrayed molecule. A similar comparison using ammonia also reveals only very slight differences in size and shape.

It may be inferred from these comparisons that the approximation utilizing the CNDO/2 atomic orbital populations is probably a valid and accurate method that can lead to electron density illustrations of molecules. The importance of this approximation is the substantial reduction in the total number of calculations necessary and the corresponding reduction in the computer processing time compared with the method utilizing the deorthogonalized CNDO/2 eigenvector matrix. It is more efficient to utilize this method for illustrations of larger molecules such as drug entities.

To test the sensitivity of the electron density illustrations, another set of data was generated for formaldehyde using only the valence orbitals. The orbital populations corresponding to the oxygen and carbon atoms were reversed. In the resulting illustration (Fig. 7), the shift of electrons caused a corresponding change in the relative sizes of the constituent atoms. When this surface contour is compared with Fig. 5, it is seen that the carbon atom is now slightly larger than the oxygen atom. However, the differences between these two illustrations are not as pronounced as might be expected. As a result of the exchange, the total valence population of carbon has increased by 63% and that of oxygen has decreased by 39% compared to those populations used to generate Fig. 5. The magnitude of even this gross and unrealistic shift of electrons does not radically change the appearance of the molecule. The exponential portion of the Slater orbitals has such a large influence that, although the number of electrons associated with the atoms is significantly altered, they are still confined to approximately the same volume in space.

The ability of the electron density illustrations to show much smaller and more realistic electron shifts would, therefore, leave much to be desired. Comparisons among a series of similar compounds would illustrate little, if any, differences in the electron clouds of the common portions of the molecules. As a result of this insensitivity, the electrostatic potential energy was investigated for its capacity to portray visually small changes in the electron distribution of a molecule.

The isoelectron density contours that had been computed and the illustrations derived from these molecular elements were insensitive to electronic perturbations of significant magnitude.

The major intent of this work was to develop a method that would produce a molecular projection with sensitivity to small electronic differences of similar molecules. This molecular parameter would have to discern visually the changes caused by these shifts or various chemical groupings. It would be desirable to illustrate various molecules in a three-dimensional fashion when only relatively minor chemical changes were made. For this purpose, the electrostatic potential was chosen as the molecular parameter.

In a molecular system, the nuclear charges are fixed quantities at relatively stationary positions. However, the electrons are distributed in molecular orbitals. As a result, the charge distribution varies throughout the molecular environment. Electrostatic potential energy is derived from the magnitudes of the electronic and nuclear charges and their relative

positions. A great deal of information about a molecule may be obtained from this parameter.

Electrostatic Potential Energy: Calculations—Three-dimensional illustrations of molecules represented by isoelectrostatic potential energy contour surfaces are generated by the following sequence: determining the atomic coordinates, calculating the atomic populations, producing a matrix of potential energy data at points in the molecular environment, determining which points are isoenergy values, and plotting these points. The procedures followed in this method are similar to those required for the electron density illustrations.

The electrostatic potential energy, V, at a point, r, is determined by summing the electrostatic interactions of the protons and electrons in a molecule with a unit positive charge placed at point r (5):

$$V(r) = \sum_a \frac{Za}{R} - \sum_{\mu s \nu} P\mu\nu \int \frac{X_\mu X_\nu}{R} d\tau \qquad \text{(Eq. 4)}$$

where Za is the nuclear charge of atom a and R is the distance between atom a and point r. The second summation represents the nuclear attraction integrals of the distribution $X_\mu X_\nu$ with the proton. The molecular charge distribution is considered unperturbed by the proton.

The orbital populations, $P\mu\nu$, obtained from CNINDO must be deorthogonalized to be strictly compatible with Slater-type orbitals. This step results in the evaluation of a large number of integrals. The computer time necessary to perform these calculations prohibits the consideration of even moderate size molecules.

An approximation to the true electrostatic potential is given by (28):

$$V(r) = \sum_a \left(\frac{Za}{r} - PaVah\right) \qquad \text{(Eq. 5)}$$

where Pa is the total electron population of atom a and Za is its effective nuclear charge. This quantity is made equal to the number of valence electrons of a neutral atom, in keeping with the all-valence orbital CNDO/2 method. The term Vah is the nuclear attraction integral of atom a with the point charge at r. This integral extends over s atomic orbitals to retain spherical symmetry. As a result of this approximation, only one calculation per atom per point is necessary. Algebraic evaluation of this integral was published previously (30).

The program performs a function in that a three-dimensional grid of data is calculated. In this instance, the electrostatic potential energy function replaces the atomic orbital basis functions. The size of the matrix and the required computer processing time to fill the matrix with data are greatly reduced in comparison to the electron density calculations.

Several reasons account for this increased efficiency. The size of the box enclosing the molecule is usually much smaller. The restriction of enclosing essentially 100% of the electrons does not apply. Consequently, the boundaries need not extend as far from the molecule. In the electrostatic potential illustrations, the curvature of the contours is much more gradual than that produced by the isodensity contours. As a result, less points per unit area are needed to describe the contours.

Another feature is that the calculations are performed on the atoms as a whole rather than on the individual atomic orbitals, resulting in an overall reduction in the number of calculations necessary for each grid point.

The large matrix containing the potential energy data is searched for the desired isoenergy value(s). The y coordinate of each point is calculated and placed in a second smaller matrix. With this type of molecular illustration, it is often desirable to draw contours at several specific values of electrostatic potential. The resulting triply subscripted array contains the y coordinates, and the x and z coordinates are generated from two of the array subscripts.

The third subscript not only identifies the point as being located on an upper or lower surface but also identifies to which isoenergy contour it corresponds. This information is necessary if the illustration contains more than one isoenergy contour surface and is plotted in two or more colors.

The type of plot produced by this program is similar to the electron density plot. However, it can distinguish between the various levels of the coordinate matrix and associates the desired colors with these levels. Thus, a multicolored plot may be drawn, each color representing a particular isoenergy contour surface.

Positioning the molecule in the box in preparation for running the program is sometimes difficult. Unless the user has some idea as to the position and magnitude of the negative energy lobes, these may be omitted or truncated by improper positioning. The program used produces a two-dimensional illustration of the isoenergy contours on a plane representing a slice through the molecule.
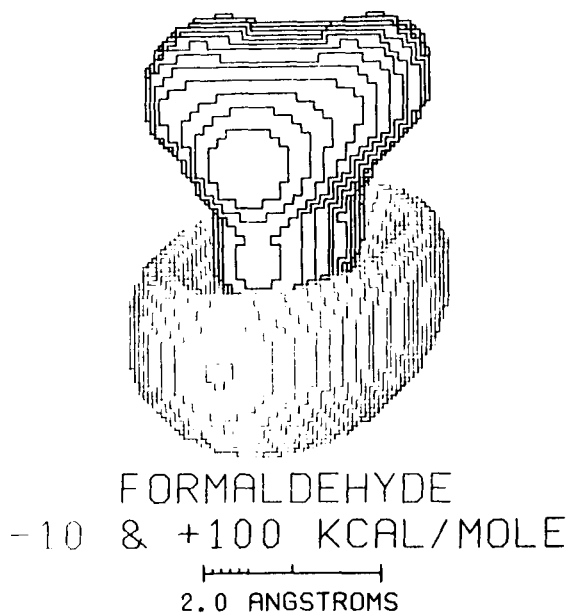
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−10 & +100 KCAL/MOLE

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Figure 8—*Electrostatic potential energy contour surface of formaldehyde.*

This program is a modified version of that used previously[4]. The resulting illustrations are produced by the computer line printer. This type of illustration is produced with much less computer time than is necessary for three-dimensional illustrations. It is advantageous to use this program to obtain a preliminary view of the various electrostatic potential energy contours of a molecule and to position the molecule properly for the full three-dimensional illustration. Also, for many symmetrical molecules, a two-dimensional view provides the same information as a three-dimensional view.

The electrostatic potential at any point in space is derived from a nuclear repulsion term and an integral representing the affinity of a proton for the various electrons of the atoms in a molecule. This integral determines how much of the nuclear charge is screened by the electrons associated with a particular atom. The repulsion term varies inversely with the distance from the nucleus while the attraction integral decreases exponentially. The numerical difference between these two terms is the net electrostatic potential energy.

A positive potential is always present near the nucleus of an atom because of the greater influence of the repulsion term. As one proceeds on a vector away from the atomic center, this term diminishes at a much larger rate than the attraction integral. Thus, the individual atoms of a molecule will always be identifiable by a region of positive potential about the nucleus.

An atom with excess electrons effectively screens the nucleus and possesses an affinity for a proton. This condition is demonstrated by a net negative potential in the immediate vicinity of the atom. Conversely, a deficiency in the electron population produces a larger than normal positive potential about the atom, resulting in an atmosphere repulsive to the proton.

Figure 8 is a composition illustration of the −10- and +100-kcal/mole electrostatic potential energy contour surfaces pertaining to formaldehyde. The molecule is oriented such that the molecular plane is parallel to the page, with the hydrogen atoms positioned at the top.

The area surrounding the carbon and hydrogen atoms is repulsive for an attacking proton. Although the hydrogens possess a slight excess of electrons, no center of negative potential is found in this region of the molecule. The carbon atom is deficient in electrons, creating a large positive potential, and the influence of this atom mitigates any negative potential generated by the hydrogen atoms.

The oxygen atom radiates a negative potential due to its excess electrons. As this contour surface of negative potential is penetrated, the potential progressively decreases until a minimum is reached. In this case, a minimum of −21 kcal/mole is found.

Because of the spherical symmetry of the *s* orbitals used in the at-

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[4] Upon request, Program VSS was supplied; it performs the calculations corresponding to Approximation II of Ref. 28.

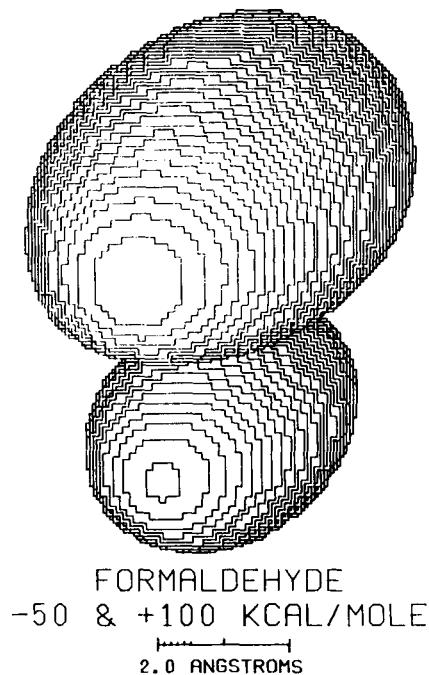FORMALDEHYDE
−50 & +100 KCAL/MOLE

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Figure 9—*Electrostatic potential energy contour surfaces of formaldehyde. The population coefficients for the carbon and oxygen atoms are reversed.*

traction integral, only one minimum is found; it is located on the molecular axis below the oxygen atom. The characteristics of this illustration are in agreement with those previously found (28) from two-dimensional contours.

The sensitivity of this method of producing molecular illustrations was evaluated by a means identical to that used for the electron cloud drawings. In the resulting illustration (Fig. 9), the molecule is positioned in the same manner as in Fig. 8. A large and significant change in the overall contour surface can be noted. Exchanging the atomic valence populations on the carbon and oxygen atoms results in a large net positive charge associated with the oxygen atom. This result is demonstrated by the enlarged contour surface representing +100 kcal/mole.

The negative potentials generated by the excess electrons on the carbon and hydrogen atoms combine to form a large negative lobe. In this figure, the negative contour represents −50 kcal/mole. Again, the minimum is found on the molecular axis, but it is positioned at the opposite end of the molecule. At this point, an electrostratic potential of −274 kcal/mole is found. At points in close proximity to the hydrogen atoms, the potential is positive as a result of the greater influence of the nuclear repulsion term. As the distance from these atoms increases, the energy rapidly decreases because of the overpowering effect of the large electron population in this region. Thus, the hydrogen atoms are embedded in the negative lobe in a lock-and-key fashion.

A comparative analysis of Figs. 8 and 9 reveals the acute sensitivity of this method of producing molecular illustrations. The potential energy calculations not only consider the probability of finding an electron at a particular point in space but also take into account the interaction of these electrons with the nuclei. The net result is the electrostatic force that an approaching molecule would encounter.

Further investigations were carried out on other small symmetrical

Table I—CNDO/2 Net Atomic Charges for Ammonia, Ammonium Ion, and Nitrogen Trifluoride

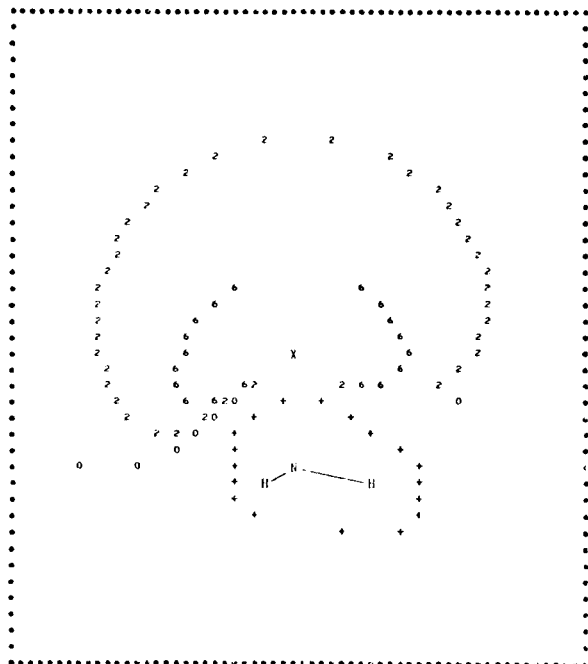| Ammonia		Ammonium Ion		Nitrogen Trifluoride	
Atom	Net Atomic Charge	Atom	Net Atomic Charge	Atom	Net Atomic Charge
N	−0.2458	N	−0.0750	N	0.3464
H-1	0.0819	H-1	0.2688	F-1	−0.1155
H-2	0.0819	H-2	0.2688	F-2	−0.1155
H-3	0.0819	H-3	0.2688	F-3	−0.1155
		H-4	0.2686		

Figure 10—*Electrostatic potential energy contours of ammonia. Key: +, 100 kcal/mole; 0, 0.0 kcal/mole; 2, −2 kcal/mole; 6, −6 kcal/mole; and X, minimum energy of −13.4 kcal/mole.*

molecules (ammonia and nitrogen trifluoride) to assess the accuracy, specificity, and sensitivity of this method. Nuclear coordinates were derived from tables of standard bond lengths and angles. Due to the symmetry of these molecules, two-dimensional contour maps were drawn in the interest of expediency and efficiency of computer utilization (Figs. 10 and 11). The net atomic charges assigned to the atoms of each molecule are listed in Table I. Each map represents a molecular symmetry plane containing the nitrogen atom and the hydrogen or fluorine atom on the right. The atomic symbol shown at the left represents two atoms, one above and one below this plane.

In Fig. 10, a large negative lobe is found in proximity to the nitrogen atom. The single lone pair of electrons associated with this atom is re-
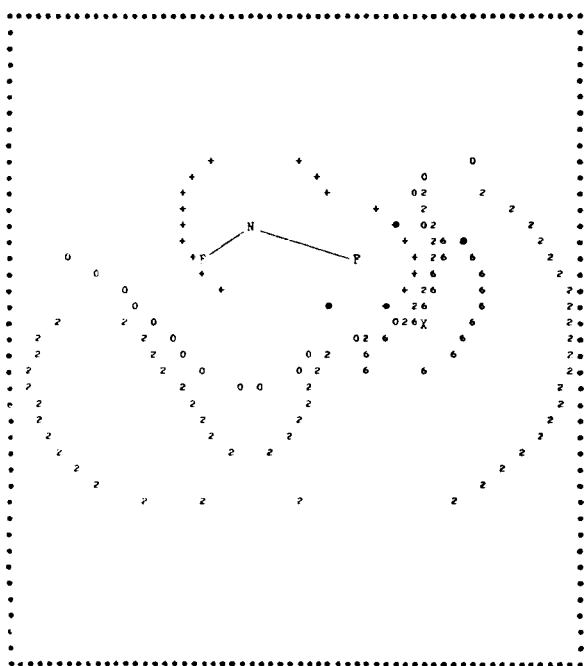

Figure 11—*Electrostatic potential energy contours of nitrogen trifluoride. Key: +, 100 kcal/mole; 0, 0.0 kcal/mole; 2, −2 kcal/mole; 6, −6 kcal/mole; and X, minimum energy of −9.0 kcal/mole.*
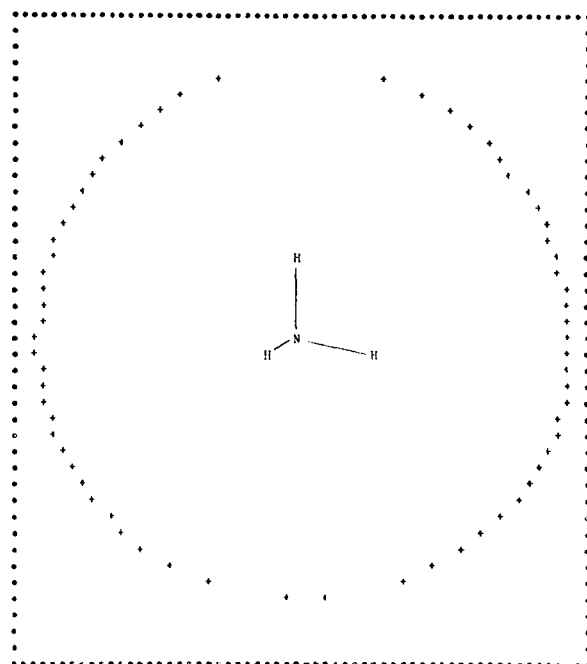

Figure 12—*Electrostatic potential energy contour of the ammonium ion. Key: +, 100 kcal/mole.*

sponsible for this energy well. A minimum value of −13 kcal/mole is located at its center.

The contours associated with nitrogen trifluoride show a marked difference from those corresponding to ammonia. In the latter compound, the peripheral atoms are more electronegative than the nitrogen, resulting in a net reduction in the electron population of the central atom. The negative energy contours in Fig. 11 are in the neighborhood of the halogen atoms. Each of these negative lobes possesses a minimum electrostatic potential energy of −9 kcal/mole.

A unique situation is observed in that the negative lobe of each fluorine atom merges at a point below the molecule on the symmetry axis. This region of low potential makes the entire lower portion of the molecule vulnerable to electrophilic attack.

The third illustration in the series (Fig. 12) represents the electrophilic potential energy contours of the ammonium ion. The net atomic charges for these atoms are also listed in Table I. To produce this figure, a proton was added to the ammonia structure on the symmetry axis.

The resulting contour diagram illustrates only a positive potential: no negative values are found in the environment of this ion. The effect of adding a single positive charge to ammonia results in a profound change in the magnitude of the potential energy. A comparison of Figs. 10 and 12 reveals the radius of the +100-kcal/mole contour to be increased approximately threefold, indicating the widespread influence of the positive charge. This cation is effectively shielded from electrophilic agents as a result of this positive field created by its charge, consistent with known chemical facts.

It can be seen that the electrostatic potential energy can be utilized as a sensitive molecular probe where changes or pertubations occur such as electronic shifts or protonation causes large, visually portrayable effects in these three-dimensional illustrations.

It was felt to be judicious to apply these considerations to large molecules such as morphine, meperidine, and alphaprodine; the results are reported in a subsequent paper.

CONCLUSIONS

Nonperspective, three-dimensional, computer-derived and drawn illustrations of small molecules were presented by a consideration of various molecular parameters.

Initially, the commonly used isoelectron density contours were considered and produced clear illustrations compatible with chemical, configurational, and molecular reasoning. However, the illustrations drawn from the computer-generated elements were rather insensitive to electronic changes. A somewhat more accurate and more sophisticated method of molecular parameter calculations was attempted with the deorthogonalized CNDO/2 eigenvectors. This method also produced clear

illustrations very similar to the isoelectron density contours without any increase in sensitivity to electronic alterations.

The electrostatic potential energy was then investigated for its utility to produce either two- or three-dimensional aspects of molecules. These isoelectrostatic energy contours produced pictorially clear illustrations with the additional characteristic of sensitivity to electron shifts and an attacking proton in these molecular projections.

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Three-Dimensional Molecular Illustrations II: Isoelectrostatic Energy Contour Spheres of Influence Applied to Narcotic Molecules

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Abstract □ A computer-generated method using quantum mechanics was applied to the calculation and subsequent plotting of nonperspective three-dimensional illustrations of molecules in vacuo. The purpose was to generate isoelectrostatic energy contour spheres for larger molecules and current drugs. The molecules chosen, morphine, meperidine, and alphaprodine, possess similar pharmacological properties. Minor configurational manipulation of the meperidine and alphaprodine molecules was made to approximate the spatial configuration of the rigid morphine molecule so that direct comparisons were possible. Common areas of reactivity, potential energy minima, net atomic charges, spatial regions, and near neighbor influences are considered.

Keyphrases □ Molecular structure—three-dimensional illustrations of narcotic molecules calculated and plotted with computer-generated method using electrostatic energy contours □ Narcotic molecules—three-dimensional illustrations of molecular structure calculated and plotted with computer-generated method using electrostatic energy contours □ Electrostatic potential energy—considered in depicting three-dimensional illustrations of molecular structure of narcotic molecules

In this study, molecular projections utilizing electrostatic potential energy contours were prepared for morphine, meperidine, and alphaprodine. These narcotic agents were chosen because their large molecular sizes show that the methods developed are adaptable to large molecular systems characteristic of most medicinal agents. Moreover, although the spatial configurations of the molecules are dissimilar, they possess common pharmacological properties. The molecular illustrations derived from the electrostatic potential energy function show that these molecules possess common regions of reactivity in their molecular environments.

BACKGROUND

The stereochemical configuration of compounds possessing narcotic activity was presented (1–5) and reviewed (6). Another study (7) dealt