HAMOG: Molecular graphics program for chemistry, biochemistry, molecular biology and enzyme research

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HAMOG is a computer graphics program written in C for personal computers. Clear menus and a context-sensitive help option make the program easy to operate for occasional users. HAMOG provides a flexible environment for displaying and manipulating molecules and molecular systems. Special functions allow the investigation of structure–activity relationships of biologically active molecules. These include the calculation of molecular electrostatic potentials and fields, the superposition of molecules and the calculation of steric accessibilities. The visualization and manipulation of protein structures immediately readable from the Brookhaven Protein Data Bank files are also possible using HAMOG. The construction of any peptide or protein structure is very simple.

Keywords: molecular graphics; peptide generation; molecular electrostatic potential, molecular electrostatic field, superposition

INTRODUCTION

In chemistry and biochemistry many useful packages exist for the graphical representation and handling of molecular structures. Most of these require "higher" computer systems, for instance, workstations. The Halle molecular graphics program HAMOG does not. It was written for chemists, biochemists and researchers who are interested in molecular modeling and structure–activity relationships and who use personal computers in their work.

HAMOG is a graphics program capable of visualizing any kind of chemical structure on a 16- or 32-bit personal computer. It is configured for all elements of the periodic system. Because it can display simultaneously a maximum of 20 molecules altogether consisting of up to 10,000 atoms, the user can construct and manipulate not only single structures but molecular systems as well. The program offers special functions to analyze the structure–activity relationships of biomolecules. Furthermore, the construction of any kind of peptide or protein structure turns out to be particularly simple. The generation,[1–3] and manipulation of peptides and proteins is menu driven. By inputting a nucleotide sequence, several standard structures of RNA molecules may be visualized. Structures can also be generated by converting cylindrical into Cartesian coordinates.

Clear menus and context-sensitive help functions are available for all options, which are selected by arrow keys or by mouse, so that HAMOG is well suited also for beginners and for occasional workers. (See Tables 1–8.) The user may change all menu colors and all of the parameters[4] of a molecular graphic, such as the color index in a graphics display and covalent or van der Waals radii.

GRAPHICAL REPRESENTATION OF MOLECULES

For the graphical representation of molecules, their (Cartesian) coordinates are required. Even if there are no X-ray analysis data or calculated coordinates of the desired molecules available, HAMOG will provide everything necessary for the construction of molecules.

A useful feature allows the user to input internal coordinates describing the spatial arrangement of molecules. For this, suitable standard bond lengths and angles are used. The input pattern is due to the mode of bonding an atom to the preceding one in terms of bond lengths, bond angles and dihedral angles. It is not necessary to input data for hydrogen atoms; HAMOG has an automatic hydrogen generation function that renders the correct completion of free valences by hydrogen atoms. Alternatively, Cartesian and X-ray coordinates can be entered directly. The program immediately converts internal and X-ray coordinate files into Cartesian coordinate files.

To perform only slight manipulations, single atoms can be simply substituted by other atoms in the graphics mode. It is not necessary to input further information, such as a connection table. The simple structure of the Cartesian-coordinate files is a good prerequisite for further calculations (for instance, as input data to energy calculation programs, or for manipulations). An extended fragment library

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Table 1. Main screen and its submenus

Load	Loading of Cartesian, internal, X-ray and cylindrical coordinates
	Loading of computed MEP- or VDW-pictures
	Loading of atomic point charges
	Loading of files of the Brookhaven Protein Data Bank
	End of HAMOG
	Go to DOS
Input	Input of Cartesian, internal, X-ray and cylindrical coordinates
	Input of atomic point charges
	Input of definitions for dihedral angles
Edit	Modifying coordinates, charges, dihedral angle definitions, atomic parameters (atomic radii, bond radii, color of atoms), color of the menus a.o.
Graphics	Go to the graphics
	Change of graphics mode and linewidth
	Change of other graphics parameters
Save	Saving of Cartesian coordinates
	Saving of the connection table
	Saving of the definition of dihedral angles
Print	Print of Cartesian coordinates
	Print of atomic point charges
	Print of bond lengths and dihedral angles
Biomolecule	Input of peptides by choosing the amino acid sequence from the corresponding menu
	Input of RNA standard structures

Table 2. GRAPHICSCREEN, the graphics main menu. Some standard functions are not written in the menus. One can get these functions with "hot keys," for instance: rotation, translation, zoom, change of rotation angle, translation step and zoom step

Viewmode	Change of graphics mode (Table 3)
Computations	Computing molecule parameters (Table 4)
Modify	Modifying molecule parameters (Table 5)
Design	Clear / add / substitute atoms or fragments (Table 6)
Potential/Field	Computing molecular electrostatic fields and potentials
	Computing atomic point charges (Table 7)
Stereo	Stereo graphics (Table 8)
Molfit	Superposition of two molecules
Into XY-Plane	Lay molecule onto the x–y plane
Numbers	Labeling atoms by numbers
Hydrogens	Display molecule with or without hydrogen atoms
Mark	Marking molecules (these molecules are always shown together with the actual one)
Mouse	Switching mouse cursor on/off
Help	Get context-sensitive help

Table 3. Menu VIEWMODE

Line	Line representation of bonds
VDW-Radii	Pseudo space-filling representation by drawing colored dots on the surface of the molecule
Quickfill	Pseudo space-filling representation: atoms as colored circles; bonds are invisible
Stick-and-Ball	Atoms as small colored circles, bonds as sticks
Spacefill	Space-filling model
Fastwrite	Fast rotation of small molecules
Atom Radius	Pseudo space-filling of single atoms as colored dots on the atom surface

with a large number of basic organic structures makes it possible to construct even larger molecules; the user may enlarge this library. Furthermore, HAMOG is able to use files of the Brookhaven Protein Data Bank to directly input coordinates. The user may choose whether the whole structure or merely the backbone conformation of a protein is displayed.

The program provides different modes for the graphical representation of mol-

ecules. (See Table 3.) In all cases the nature of the atoms is characterized by corresponding colors. To simultaneously distinguish between several structures the carbon framework is displayed in different colors. A special option allows users to adapt HAMOG for monochromic display.

The standard display mode is the line representation. Here the option FAST-WRITE allows real-time rotation of small molecules. The stick-and-ball display of structures gives a good spatial impression. Masked atoms or bonds are not visualized. Several pseudo space-filling displays are also offered. A true calotte representation needs additional calculation time depending on the desired screen resolution; however, even in the mono-representation, it gives a very good spatial impression.

Most structural manipulations can also be performed in the stereo-mode. (See Table 8.) Stereo-mode means that red–blue (red–green) glasses or, a more desirable arrangement, a stereo mirror (stereo prism) are used to view the appropriate stereo-pair representations. The following display modes are available in stereo-mode: line, stick-and-ball and pseudo space-filling.

Table 4. Menu COMPUTATIONS

Coordinate	Display of Cartesian coordinates of a selected atom
Bond Length	Calculation of the bond length or a distance between two selected atoms
Bond Angle	Calculation of the angle between three selected atoms
Dihedral Angle	Calculation of the dihedral angle between four selected atoms
atm. Charges	Display of the atomic point charge of the atom
Accessibility	Investigation of the sterical accessibility of a desired atom
H...X Bond	Testing for intra- and intermolecular hydrogen bonds

Table 5. Menu MODIFY

Coordinate	Changing Cartesian coordinates of a selected atom
Bond Length	Changing bond length or distance between two selected atoms
Bond Angle	Changing angle between three selected atoms
Dihedral Angle	Changing dihedral angle between four selected atoms
atm. Charges	Changing the atomic point charge of an atom
Predef. Dihedr.	Changing, saving, or redefining of torsional angle files
Break Bond	Deleting a bond between two atoms
Make Bond	Creating a bond between two atoms
Search Bonds	Recalculating the bonding matrix

Table 6. Menu DESIGN

Add Atom	Addition of an atom to a molecule
Add Fragment	Addition of a molecular fragment from the fragment library to the molecule
H-Addition	Generation of all hydrogen atoms
ELP-Addition	Completion of free electron pairs at the selected atom
Delete Atom	Erasing a selected atom from the molecule
Delete Fragment	Erasing a fragment from the molecule
Substitution	Substitution of one atom by another (change of atom kind)
Library	Display of all fragments from the fragment library

Table 7. Menu POTENTIAL & FIELD

Potential Plane	Calculation of molecular electrostatic potential (MEP) in a selected area
Potential Surfc	Calculation of MEP at enlarged van der Waals sphere surface of molecule
Field Plane	Calculation of the molecular electrostatic field (MEF) in a chosen area
Field Surface	Calculation of MEF at enlarged van der Waals sphere surface of molecule
DIFF-MEP Plane	Calculation of difference-MEP of two molecules in a chosen area
DIFF-MEP Surfc	Calculation of difference-MEP of two molecules at enlarged van der Waals sphere surface of outer molecule
Pointpotential	Calculation of the point potential in a common point of space
atm. Charges	Calculation of atomic point charges

Table 8. Menu STEREO

Line-Pair	Line representation as a stereo pair (viewing with a stereo mirror or a stereo prism)
Red-Blue	Stereo-line representation for viewing with red–blue glasses
Red-Green	Stereo-line representation for viewing with red–green glasses
Stick-and-Ball	Stick-and-ball representation as a stereo pair (using a stereo mirror or a stereo prism)
Quickfill Pair	Pseudo space-filling model as stereo pair (using a stereo mirror or a stereo prism)
Spacefill Pair	Space-filling model as stereo pair (using a stereo mirror or a stereo prism)

MANIPULATING AND MODIFYING MOLECULES

All standard manipulations, such as rotations, translations and scalings, are easy to accomplish. In stereo mode HAMOG renders possible the movement of a molecule along the z-axis, in addition to the usual translations (driven by mouse or arrow keys) in the x–y plane. The atoms of a molecule are numbered according to the order in which they are input. These atom numbers, which may be monitored at any time, form the basis of all calculations and manipulations.

By inputting two, three or four atom numbers and choosing the desired atoms with the mouse, bond lengths and angles and dihedral angles can be calculated and modified. Analogous intermolecular parameters may be varied, too. Definitions of dihedral angles (always four atom numbers) can be saved, so that structures that are repeatedly modified will be easy to manipulate. A further function shows all of the topical atom numbers of the molecule, both in mono- and stereo-mode. By inputting three atom numbers, each molecule can be placed on the x–y plane. With this option it is easy to compare several familiar molecules.

For many problems a test for inter- and intramolecular hydrogen bonds seems to be interesting. With a special option the molecule or molecular system is tested for the existence of hydrogen bonds. These bonds are graphically stressed and their corresponding binding lengths are displayed.

All of the bond lengths, bond angles and dihedral angles of a molecule can be automatically displayed or documented with the help of a printer. Current graphics can be dumped by the Print Screen function and by a special printer routine, which is especially suitable for the reproduction of line representations in the mono- or stereo-modes, respectively. The program also contains a plotter routine that allows not only simple plotting in line and stick-and-ball (shadowed and solid) styles, but also colored plots, the selection of the light source direction and perspective drawings.

CALCULATION OF MOLECULAR ELECTROSTATIC POTENTIALS AND MOLECULAR ELECTROSTATIC FIELDS USING HAMOG

For many questions in biochemistry and pharmacology—or rather, in various fields of physical chemistry—the calculation of molecular electrostatic potentials (MEPs) or molecular electrostatic fields (MEFs) for the analysis of structure–activity relationships is a helpful method. Molecular electrostatic potentials or fields reflect the interaction behavior of a molecule with a proton in the simplest approximation,[5,6] which in most cases is completely sufficient. HAMOG may help the user discover the atoms of a molecule that are favored for an electrophilic or nucleophilic attack (negative or positive MEP). Knowledge of the electronic charge distribution in a molecule is prerequisite for calculations of MEP and MEF. For the charge distribution calculation a number of more or less suited semi-empirical quantum chemical methods (or empirical proceedings) are available.[7,8] If required, *ab initio* methods should be applied for more exact calculations. This, however, is rarely necessary for an initial analysis of structure–activity relationships.

For the charge distribution calculation of common molecules we applied the electronegativity equalization procedure of W.L. Jolly and W.B. Perry.[9,10] However, charges calculated by any method can be read by HAMOG and used to calculate MEPs and MEFs. The Jolly-Perry method allows one to compute the partial charges of all atoms of the periodic system in a very short time. In contrast to the original calculation procedure, which involves solving a system of equations, we developed, therefore, an iterative computation method of unknown partial charges at the atoms. This method keeps the intrinsic advantages of the original approach. Very little free memory is needed to solve the corresponding equations; in that way it is possible to perform charge calculations, even of very large molecular structures (with more than 1 000 atoms) in a very short time.

Using the program, MEPs and MEFs may be calculated at any plane inside and outside of a molecule or at the 1.7-fold van der Waals radius of the external atoms of a molecule. The negative modeling of an unknown receptor for known molecules represents the calculation of MEPs on the van der Waals surfaces of molecules. This representation corresponds to the reflection of the interaction behavior with a substrate, as it can possibly "be seen" from the viewpoint of a receptor. Frequently the MEP gives only insufficient evidence regarding the interaction behavior of molecules with their environments. The MEP reflects the interaction energy with a monopole. Compared to it, one can regard the MEF as the interaction between a molecule and a dipole. By calculating gradients of MEPs in all three space directions, HAMOG offers the possibility of computing the MEF and of representing all information, such as the value and direction of the field in one graph. Color Plate 1 shows, for example, a molecular electrostatic field in a selected plane. The color of the circles shows the value of the field at this point in space. Simultaneously this value is represented by the length of the line starting from the circle. The direction of the field in the x–y plane and the z-direction is indicated by the course (direction) and color of the line. Each circle represents

the positive charge of an imaginary dipole; each line represents the dipole's negative charge. For molecules with similar biological properties and analogous modes of action it is necessary to compare their structures with their respective MEPs and MEFs. By a superposition[11,12] of selected atom pairs in two molecules, the molecules can be put into correspondence with as small a standard deviation (rms) as possible. In addition to calculating the MEPs of both molecules, the user can also calculate the difference in MEPs. If the two potentials are compared according to their signs (Color Plate 2), conclusions can be drawn regarding the areas that may be responsible for the biological activity of the molecules. For further information the difference between two potentials according to the value can be calculated at the same time.

CALCULATION OF STERIC ACCESSIBILITY

HAMOG also enables the user to calculate steric accessibilities (SA) of the atoms of a molecule.[13] The comparison of several molecules with similar properties regarding the steric accessibility of given reactive atoms allows one to draw conclusions about their potential reaction abilities. For the calculation of SAs 2 500 points are distributed symmetrically among the van der Waals surface of the atoms considered. A model reactant (for instance H^+ or H_2O) is placed at each of these points as a van der Waals sphere, and it is tested whether this sphere (reactant) overlaps the other van der Waals spheres of a molecule. If it does, the point is considered inaccessible; otherwise it is considered sterically accessible. The absolutely accessible area is calculated and may be graphically represented.

HARDWARE AND SOFTWARE REQUIRED FOR HAMOG

HAMOG runs on all IBM PC/AT/PS/2 or compatible computers with MS-DOS 3.X (or a later version), or in OS/2's DOS-Box. A hard disk and an 80×87 coprocessor is optional, but recommended. The program requires 512K of RAM, of which HAMOG will use about 250K. A graphics card of one of the following types (or their equivalent) is necessary:

- IBM EGA or compatible, 640×350, 16 colors
- IBM VGA or compatible, 640×480, 16 colors
- Super-VGA (Tseng Chipset), $800 \times 600 (1024 \times 768)$, 16 colors
- CGA (Schneider PC 1512, 16 colors supported)

CONCLUSION

The HAMOG package provides a wide range of representation and manipulation functions for the investigation of molecules and molecular systems on personal computers. The program contains special options for studying the structure–activity relationships of biomolecules, including, for instance, the calculation of molecular electrostatic potentials and fields, steric accessibilities, comparisons of molecular electrostatic potentials and superposition of different molecules.

Work in progress includes the development of interfaces to force-field programs like PIMM, MM2P and ECEPP. The HAMOG package is available from the CLB editorial office.[14]

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