ANLIZE: A molecular mechanics force field visualization tool and its application to 18-crown-6

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Summary

We describe a software tool that allows one to visualize and analyze the importance of each individual steric interaction in a molecular mechanics force field. ANLIZE is presently implemented for the Dreiding force field for use with the Cerius^2 software package, but could be implemented in any molecular mechanics package with a graphical user interface. ANLIZE calculates individual interactions in the force field, sorts them by size, and displays them in several ways from a menu of choices. This allows the user to scan through selected interactions to visualize which interactions are the primary determinants of preferred conformations. The features of ANLIZE are illustrated using 18-crown-6 as an example, and the factors governing conformational preference in 18-crown-6 are demonstrated. Users of molecular mechanics packages are encouraged to demand this functionality from commercial software producers.

Introduction

Molecular mechanics (MM) force fields are widely used as tools for geometry optimization and conformational analysis. The same force fields can also be used for molecular dynamics. Of the dozens of commercially available MM programs, only a few report information beyond the total steric energy of a molecule. Thus, MM force field programs are often used as 'black boxes' from which results are reported. Users are given little opportunity to understand the subtle interplay between force field terms and their parameters that combine to produce results of interest.

Molecular steric energy is a delicate function of conformation. MM predicts energetically favorable molecular conformations by using an empirical fit of molecular potential energy as a function of internal coordinates which is assumed to be transferable among a class of molecules. MM is used to perform conformational analysis by searching the multidimensional potential surface of a molecule to determine global and local minima which represent stable conformations. However, useful information beyond the total steric energy of a molecule can be obtained from the force field without undue computational or intellectual effort. Because the MM parameters are usually intuitive, the analysis of individual force field terms and interactions can be extremely illuminating. The typical MM force field contains a set of interaction expressions and associated parameters. For example, in most common force fields, the total steric energy is a sum of terms similar to the following:

$$U_{total} = U_{valence} + U_{nonbond}$$
$$= U_{stretch} + U_{bend} + U_{torsion} + U_{van\ der\ Waals} + U_{Coulomb} \quad (1)$$

where the valence interactions include the first three terms in the second line (bond stretching, angle bending, and torsion terms), and the nonbonded interactions include the van der Waals and electrostatic or Coulomb terms. In some more sophisticated force fields, the division, particularly of the valence terms, into a simple sum breaks down because of coupling terms that have been found to be desirable for some purposes. Force fields differ in the way interactions are divided into separate terms, in the functional forms chosen to describe the interactions, and in the values for the parameters used. However, the concepts

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demonstrated here are applicable to nearly all force fields, and the functionality of the program described here could be incorporated into any molecular mechanics program.

In applying the molecular mechanics method in our own work, we were frustrated using several commercial programs in that no tools were available to analyze and understand *why* a particular conformation was lower in energy than another. We wanted both qualitative and quantitative information about the individual contributions in Eq. 1 to help us understand the reasons *why* molecules adopt the structures they do. We wrote ANLIZE to display individual interaction terms for the MM program Cerius^2, a product of Molecular Simulations Inc. ANLIZE was written first as a stand-alone program running on a PC, and then as a facility that could be run from within the Cerius^2 environment. ANLIZE is written in C++ for the MM calculations and in Tcl/Tk for the user interface. Although ANLIZE uses the Cerius^2 molecular modeling environment as a front-end, almost any MM program could easily incorporate the methodology of ANLIZE, which is described below. The contributions to each component of the MM force field (bond stretching, angle bending, etc.) of a given conformation are sorted by size to reveal the location and nature of interactions in that conformation. ANLIZE displays the contributions in the Cerius^2 model window superimposed on a three-dimensional (3D) model of the molecule or molecular cluster. The necessary graphical tools are present in most MM programs to visually display similar information and should provide a powerful tool for the analysis of molecular interactions if this functionality were incorporated into commercial packages.

Functionality of ANLIZE

ANLIZE is invoked by piping its output into the Cerius^2 text window from the UNIX prompt. ANLIZE evaluates and sorts individual contributions of each of the force field terms in Eq. 1 and displays them in the default Cerius^2 model window. ANLIZE identifies a contribution by displaying a color-coded line superimposed on the 3D model of the molecule. The model can be rotated and zoomed using the usual Cerius^2 mouse commands. A line is colored according to which type of interaction it represents (arbitrarily chosen to be green for stretches, yellow for bends, white for torsions, purple for van der Waals interactions, and blue for Coulomb interactions); the line connects the atoms associated with the interaction (along one bond for a stretch, along two bonds for a bend, or along three bonds for a torsion, and connecting two atom centers for nonbonded interactions). Here we assume the electrostatic interaction is represented as that of atom-centered partial atomic charges. If bond dipoles are used, the line could be drawn connecting the bond centers. In addition to the color-coded line identifying the interac-

tion, additional information is optionally displayed as print, also color-coded for clarity: the energy of that contribution, the distance or angle which describes it, and/or the parameters of the force field for that term. The largest energy stretch, bend, torsion, van der Waals and/or Coulomb interactions are displayed first to allow a quick comparison of the relative magnitudes for each term of the force field. The user can then select the interactions to be displayed, display a text listing of the interactions, or display bar graphs or pie charts of the energy breakdown. These options are selected by toggling buttons in the ANLIZE control panel and are described below.

Selecting interactions to be displayed
The ANLIZE control panel uses an integer index to select which interaction (ordered by numerical size) is displayed. An index value of one represents the largest interaction energy for each term of the force field in Eq. 1, an index value of two is the second largest, and so on. The user can click the INCREASE or DECREASE buttons in the control panel to increment or decrement the force field index. The user can also quickly move to the highest and lowest index by clicking the HIGHEST or LOWEST buttons. When the index is changed, the program automatically updates the displayed interactions and the numerical information displayed on the screen.

The displayed information quickly informs the user of the significant interactions and their contribution to the total steric energy of the molecular configuration. One can also scan through the other interactions in ascending or descending order to identify areas of stability or strain. This method can be applied to obtain information on the bond stretches, angle bends, torsions, van der Waals and/or Coulomb interactions or any combination of the interaction types by selecting the appropriate boxes in the control panel.

Load new file
The load button brings up a list of the molecules or systems for which Cerius^2 has *.BGF files (the Biograf/Polygraf format which is the current default format). Any BGF file may be selected, loaded into Cerius^2, and analyzed.

Update window
The update button redraws the model window using newly selected options in the ANLIZE control panel. The window is automatically updated when the index is changed.

Report a text listing of the interactions
When the REPORT button is selected, ANLIZE reports a sorted text listing of all the interaction terms in the force field of the configuration. The information is

sorted by energy and gives the important information needed to cross reference the interaction with the model and to calculate the interaction energy. The text file includes separate sorted listings for each interaction type, the atom numbers and atom types, the value of the distance or angle on which the term depends, force field parameters used for that term, and the energy for the interaction term. Additional information, such as atom coordinates, could be easily added.

Display pie chart

Selecting PIE CHART produces the total energy breakdown for the contributions in a pie chart, quickly allowing the user to identify the relative contributions of each term of the force field as divided up in Eq. 1.

Display a plot of interaction terms

Selecting the PLOT button plots the energy of desired interaction terms versus index for each portion of the force field, allowing the user to quickly identify the relative magnitudes amongst the various components for each interaction type.

Comments

(1) Newer force fields that include coupling terms between the standard terms in Eq. 1 would need additional attention. Two alternatives have been suggested: (i) leave coupling terms as a new and separate term in Eq. 1 to be plotted and sorted separately; and (ii) divide coupling terms proportionally among the terms already listed in Eq. 1. We have not implemented either of these alternatives, but either one would provide more information than is currently available in MM calculations.

(2) It is important to note that for bond stretching, angle bending and torsion terms which are typically parameterized to be nonnegative, an examination of an ANLIZE PLOT need only focus on the largest contributions. However, for van der Waals and Coulomb interactions which can be either positive or negative, both ends of the PLOT need to be examined. This caution should be exercised in examining interactions in the model window. In fact, we suggest that users first look at the plot for van der Waals and Coulomb interactions to verify the number of large negative and large positive contributions before scanning the nature of these interactions in the model window; otherwise the large negative interactions may be forgotten.

(3) The current version of ANLIZE implements only the Dreiding force field (which is particularly simple in terms of atom types and number of parameters) and uses the BGF (Biograf/Polygraf) file format for input and output. The program could easily implement other force fields and file formats, making it a powerful tool in comparing the predictions of different force fields used in MM calculations. However, it is our opinion that this implementation should be done by each company which markets an MM program rather than a separate facility marketed by third parties. If enough users demand this type of tool, users will have available an additional versatile tool for probing the details of intramolecular and intermolecular interactions and will be able to gain a deeper understanding of molecular structure and function.

(4) The value of ANLIZE is dependent on the intuitive and logical breakdown of steric energy into physically important interactions as in Eq. 1. ANLIZE allows one to visualize (i) which types of interactions are important in a particular configuration; (ii) which individual terms are important; and (iii) the sensitivity of results to individual parameter values in the force field. To the extent that a force field has physically nonintuitive terms, ANLIZE may lose its logical value; however, ANLIZE could still be used to determine the size and importance of these terms.

Results and Discussion

We now present an example of how ANLIZE can be used to identify the chief contributing interactions for conformational preference in 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane). 18-Crown-6 (18C6) is of interest in molecular recognition as an ionophoric ligand for the selective complexation of K^+ ion in preference to Cs^+ ion, for example [1]. 18C6 has often been examined using MM with and without bound ions [2–8]. Specificity is shown because the macrocyclic cavity is only large enough to bind ions one at a time and because different ions bind with varying affinities, usually because of varying ion size. Crown ethers are often used as a paradigm for ligand–host interactions in general and as a prototype of the more complicated interactions of enzymes and other biological systems.

18C6 poses a challenge to the MM method because the isolated macrocyclic ring is so flexible. There are perhaps several hundred distinct conformations of 18C6 within a few kcal/mol [8]. The binding of 18C6 is suspected to be due to electrostatic interactions between polar ether oxygen atoms and metal ions. However, the intramolecular Coulomb repulsion between oxygens is expected to affect the conformational energetics of free 18C6. We have used ANLIZE to investigate this hypothesis.

To understand the reason why one conformation is lower than another in 18C6, one must examine the contributions of 42 bond stretches, 60 bending angles, 72 torsions, and 741 van der Waals and 741 Coulomb interactions. Using the Dreiding force field and atom-centered partial atomic charges calculated using the charge equilibration method of Rappé and Goddard [9], the lowest energy conformation is one of C_i symmetry [10], in agreement with the predictions of the AMBER force field [11] and crystal structure [12].
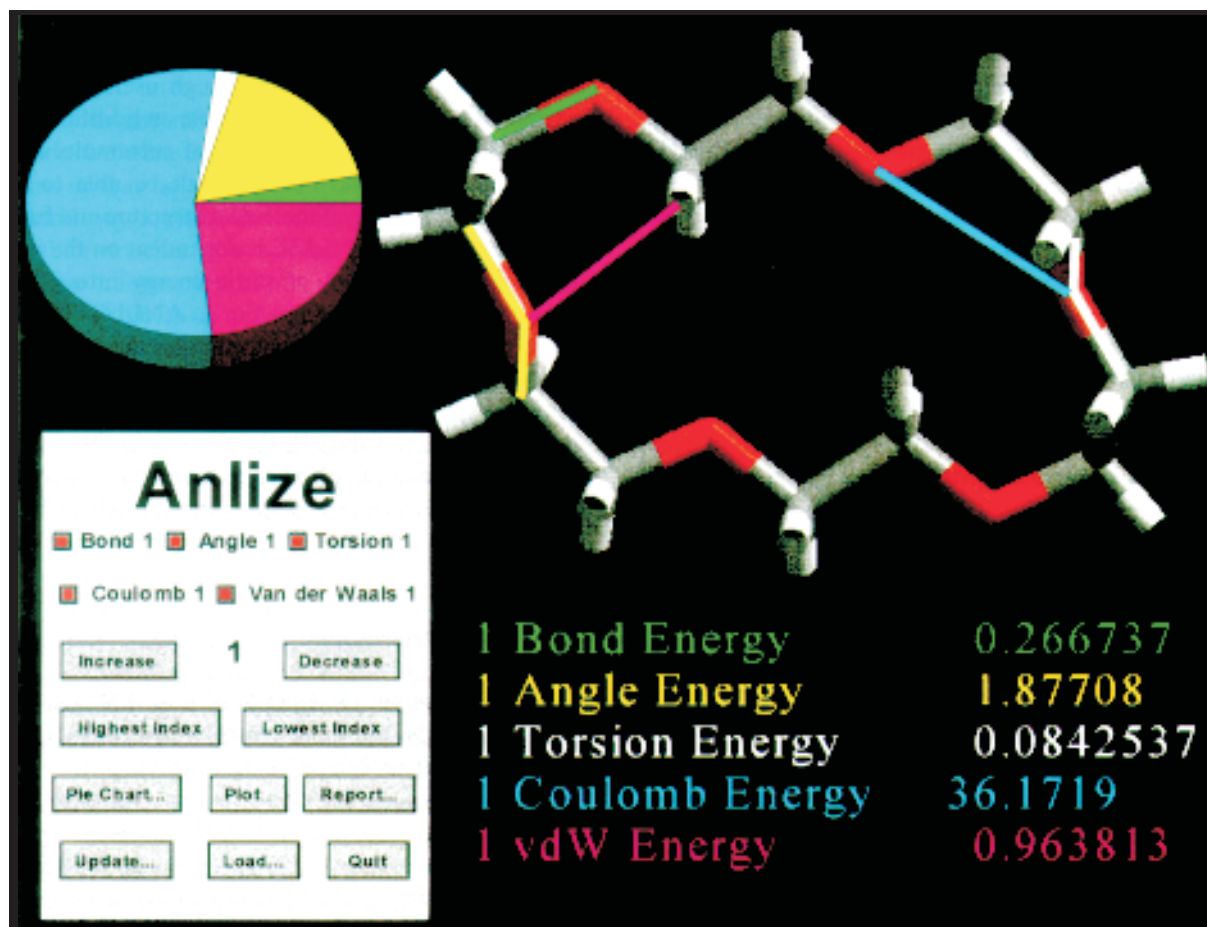
132

Fig. 1. Example of information from the ANLIZE control panel, pie chart output and the Cerius² model window showing ANLIZE output for 18C6 in its lowest energy conformation, with the largest interactions of all five types indicated. These results are from the Dreiding force field with charges determined by the charge equilibration algorithm of Ref. 9.

Figure 1 shows a collection of ANLIZE information from the Cerius² model window for the first index value of the lowest energy conformation of 18C6 and illustrates how ANLIZE displays the largest energy contributions to the stretch, bend, torsion, van der Waals and Coulomb interactions simultaneously. 18C6 is displayed in cylinder
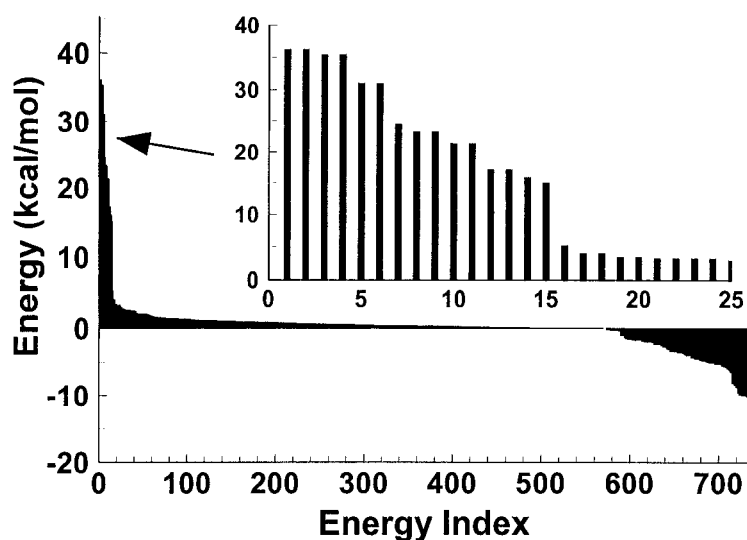

Fig. 2. Example of output from the ANLIZE plot option showing Coulomb interactions of 18C6 sorted by size. These results are from the Dreiding force field with charges determined by the charge equilibration algorithm of Ref. 9.

mode with oxygens colored red, carbons gray, and hydrogens white. Superimposed on this model are color-coded lines representing the largest interactions of each type. The largest stretch interaction is shown as a green C-C bond in the upper left of the molecule. The largest bend interaction is a bent yellow line on adjacent C-C-O bonds at the extreme left. The largest torsion is marked by three white bonds (C-C-O-C) at the upper right. The largest van der Waals interaction is indicated by a purple line connecting O and H atoms at the left. The largest Coulomb interaction is indicated by a blue line connecting two O atoms in the upper right. Note that the Coulomb interaction energy is by far the largest of these, over 36 kcal/mol. The largest torsion contribution is only about 0.084 kcal/mol, showing that all torsions are near their ideal angle.

The ANLIZE control panel is shown at the lower-left portion of Fig. 1. This panel controls the display of information. One can toggle on/off each type of interaction. The optional pie chart in the upper-left corner shows the total energy breakdown. The colors of the pieces in the pie chart correspond to the assigned interaction colors. Notice the large Coulomb contribution to the total energy (the blue pie piece). This contribution is largely due to the 15 O-O Coulomb repulsion terms. The largest such interaction is indicated by the blue line between the two oxygen atoms in the display as mentioned. The bond stretch and torsion contributions to the total steric energy are easily seen to be negligible.

When the Coulomb interaction is selected and the PLOT button is pressed, a plot similar to Fig. 2 is displayed. The graph displays interaction energies versus index. This graph allows the user to quickly identify the relative energies of the various terms. For the 741 Coulomb interactions of 18C6, the 15 O-O repulsions are particularly large (see the inset to Fig. 2). Individual interaction terms can be examined by returning to the Cerius[2] model window (default) and incrementing the index while inspecting the interactions as displayed on the model. The PLOT can also display stretches, bends, torsions, van der Waals terms, or combinations of these.

The 10 largest Coulomb terms for this conformation (Conformation #1) as reported by the ANLIZE REPORT feature are listed in Table 1, along with the corresponding terms for two other conformations (#2, the next highest one as determined by Sun and Kollman using AMBER [8], and #14, the D_{3d} conformation found when 18C6 is complexed with K^+ ion). Each entry in this table consists of an identification of what kind of interaction it is (Cou, meaning Coulomb), the index number (1 is the largest), the atom numbers and atom types (O_3 is sp[3] oxygen), the distance between atoms (in Å), and the energy of the interaction (in kcal/mol). Note that the 10 largest Coulomb interactions for all three conformations are O-O repulsions. The molecule can twist around the 18 ring

TABLE 1
THE 10 LARGEST STERIC INTERACTIONS IN 18C6

Type/index	Atom numbers and types		Distance (Å)	Energy (kcal/mol)
Conformation #1				
Cou 1	13 O_3	10 O_3	2.9400	36.172
Cou 2	4 O_3	1 O_3	2.9400	36.172
Cou 3	10 O_3	7 O_3	3.0937	35.389
Cou 4	16 O_3	1 O_3	3.0937	35.389
Cou 5	16 O_3	13 O_3	3.6599	30.990
Cou 6	7 O_3	4 O_3	3.6599	30.990
Cou 7	13 O_3	4 O_3	4.4862	24.558
Cou 8	13 O_3	7 O_3	4.8573	23.351
Cou 9	16 O_3	4 O_3	4.8573	23.351
Cou 10	10 O_3	4 O_3	4.9722	21.388
Conformation #2				
Cou 1	13 O_3	10 O_3	3.1676	35.876
Cou 2	10 O_3	7 O_3	3.1676	35.876
Cou 3	16 O_3	1 O_3	3.1676	35.876
Cou 4	4 O_3	1 O_3	3.1676	35.876
Cou 5	7 O_3	4 O_3	3.1676	35.876
Cou 6	16 O_3	13 O_3	3.1676	35.875
Cou 7	13 O_3	7 O_3	5.0269	22.606
Cou 8	10 O_3	4 O_3	5.0270	22.606
Cou 9	13 O_3	1 O_3	5.0271	22.606
Cou 10	16 O_3	4 O_3	5.0271	22.606
Conformation #14				
Cou 1	7 O_3	4 O_3	3.0540	27.401
Cou 2	13 O_3	10 O_3	3.0540	27.401
Cou 3	10 O_3	7 O_3	3.0540	27.401
Cou 4	16 O_3	13 O_3	3.0540	27.401
Cou 5	16 O_3	1 O_3	3.0540	27.401
Cou 6	4 O_3	1 O_3	3.0540	27.401
Cou 7	16 O_3	4 O_3	5.2127	16.053
Cou 8	13 O_3	7 O_3	5.2127	16.053
Cou 9	10 O_3	4 O_3	5.2128	16.053
Cou 10	16 O_3	10 O_3	5.2128	16.053

torsions to any of three energetically equivalent positions (gauche+, gauche−, and trans), giving scores of possible conformations. The energy of each local minimum is then reached primarily by the bending of angles from their strain-free value and bond stretching to avoid large Coulomb repulsions and, to a smaller extent, van der Waals repulsions. However, the Coulomb repulsion is by far the largest contributor to the steric energy of a given conformation [10]. This analysis confirms the fact displayed in Fig. 1 that the Coulomb interaction is the most important determiner of molecular conformation in 18C6.

Conclusions

We have demonstrated that the ability to sort, display, and examine individual contributions to the total steric energy for a molecular conformation in a given force field reveals a wealth of information about the nature of conformational preference described by that force field. We

134

have written the ANLIZE program to provide this ability in the Cerius[2] environment. In particular, we have shown that ANLIZE clearly reveals that the O-O repulsions are the major determiner of the conformational preference of isolated 18C6 when described by the Dreiding force field [10]. The functionality of ANLIZE is clearly useful in revealing the details of intramolecular interaction in any molecule or molecular cluster. In the future, with increased computational power, the functionality of ANLIZE can be adapted to interactively monitor the dynamical nature of interactions in molecular dynamics simulations or to examine previously veiled details of ligand–receptor interactions.

Cerius[2] users who wish to use ANLIZE can download the software from the ANLIZE homepage at the URL http://chemwww.byu.edu/research/shirts/anlize.html. Comments should be directed to randy_shirts@byu.edu. After experiencing the ability to analyze details of the steric energy contributions in molecular conformations, we encourage practitioners of molecular mechanics to demand this kind of functionality from commercial vendors.

Acknowledgements

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