電子状態シミュレーションによる分子形状解析

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Introduction: Molecular recognition is a process of forming a specific pair of molecules. This process is a key step in e.g. biological ligand-receptor binding. The driving force to yield the complex is due to intermolecular interactions. Although they arise from quantum mechanical nature of electrons in molecules, empirical potential energy functions are frequently employed for large systems where positions of atoms are their variables.

When a docking geometry is computationally optimized or is experimentally elucidated, the easiest way of quantitative interpretation would be to introduce the concept of molecular shape. Usually the shape is defined by van der Waals radii of atoms. It is further used to define molecular volume, which can be a good measure investigating chemical nature of pores in porous materials.

Conceptual importance of molecular shape is well known in biochemistry: the lock-and-key model is a fundamental model for understanding ligand-receptor interactions. A simple but fundamentally important question about molecular shape is "how the quantum mechanical intermolecular interactions can be modeled by molecular shape". This issue seems important because the concept of molecular shape can be regarded as one of the coarse-grained pictures of complicated quantum mechanical interactions. In this paper, we develop a computational scheme of defining molecular shape with the use of ab initio electronic structure calculations. Our objectives are to investigate chemically important topological features of molecular shapes and to characterize them quantitatively.

Figure 1: Illustration of the computational surface-probing method.

Computational Algorithm and Method: Molecular shape can be regarded as one of the molecular properties. It is well known that an electronic property such as electric dipole moment, electric susceptibility, etc. is defined as a response to an applied external field. For a given perturbation (λ), the energy is expressed by the Taylor series such as

$$E\left(\lambda_1, \lambda_2, \cdots, \lambda_N\right) = E(0) + \sum_{i=1}^{N}\left[\frac{\partial E}{\partial \lambda_i}\right]_{\lambda=0}\lambda_i + \frac{1}{2!}\sum_{i=1}^{N}\sum_{j=1}^{N}\left[\frac{\partial^2 E}{\partial \lambda_i \partial \lambda_j}\right]_{\lambda=0}\lambda_i\lambda_j + \cdots\cdots \qquad (1)$$

where $E(0)$ is the energy without perturbation. For example, dipole moment corresponds to the first order response of molecular energy to the electric perturbation. Therefore a consistent definition of molecular shape would be to consider energy response to an appropriate perturbation.

Here we propose to define molecular shape by computing quantum mechanical energy for interaction between a target molecule and a probe atom (see Fig. 1). From the interest in biological systems and chemistries in aqueous solution, we focus on interaction related to the hydrogen bond. This is done by choosing H^+ and O^{2-} as probe atoms. For a target molecule fixed in the 3D space, electronic-structure calculations are repeatedly carried out for a probe atom on each grid in the same space. By displacing it in the predefined 3D box, energy mapping can be achieved. By extracting an isoenergy contour for an appropriate threshold, we can obtain a surface defining molecular shape. The present method can be called "the computational surface-probing method".

In the present study, interaction energies were calculated by using the MP2 method with the cc-pVDZ basis set. Geometries of target molecules (H_2O, CO_2 and C_2H_2 in this paper) were firstly optimized, and then calculations were repeated for the "target + probe" system where a probe atom was displaced on the uniform 3D grids. The 2 dimensional contours shown below were obtained for the 50×50 grids on the molecular plane of each target. As a probe, we considered H^+ and F^-. The latter ion was used as an alternative to O^{2-}. This is because convergence difficulty was encountered in SCF calculations in case of the O^{2-} probing. The energy contour map was drawn by calculating binding energies (stabilization energies) where the separated limit was referred to.

Results and Discussion: Fig. 2 shows isoenergy contour map of H_2O. The result indicates that the space can be divided into two parts: one is a region of positive energy corresponding to repulsive interaction. It roughly corresponds to a while region in Fig. 2. This region may be called "repulsive shape". It may be approximately represented as superposition of circles centered on atoms when H^+ is used as a probe: three circles on O and two H atoms can be distinguished. For the F^- probe, the repulsive shape is an ellipsoid rather than a circle. The area of the repulsive region is larger for the F^- probe than for the H^+ probe. This may be interpreted as reflecting a difference between ionic radii of H^+ and F^-.
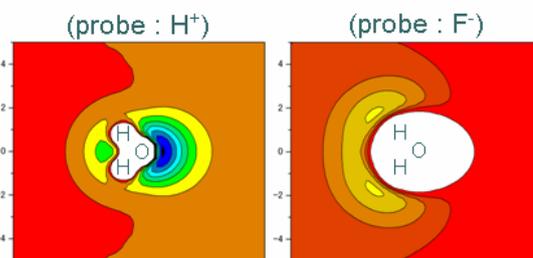
Figure 2: Isoenergy contour of H_2O probed by the H^+ (left) and F^- (right) ions.

Another part of the energy contour is a region of negative energy (the colored region). This may be called "attractive shape" of the target molecule. An interesting feature of the attractive shape of H_2O is existence of an interaction site near the oxygen atom. From its topological feature, it appears assignable to the oxygen lone pair orbital. This supports that, when interaction sites are determined for deriving empirical potential energy functions, they should be centered on, at least, three atoms (O and two H) and a site corresponding to a lone pair. In the attractive region probed by F^-, we see two energy minima near the hydrogen atoms. This is reasonable to represent an interaction in hydrogen bonding between the electropositive (H) and electronegative atoms (F).

Fig. 3 shows contour maps of CO_2. Similar to H_2O, we see interaction sites around two oxygen atoms for the H^+ probe. Reflecting differences of chemical interaction between the C-H^+ and O-H^+ pairs, the radii of the carbon and oxygen atoms are different. The energy contour probed by F^- indicates that CO_2 has no closed energy minima. Thus its shape consists of only repulsive region.

Fig. 4 depicts energy contours for acetylene. When it is probed by H^+, energy minima appear on both sides of molecular axis. This seems to be related to the π orbital of acetylene. This feature implies that topological shape of a chemically important orbital can be extracted by the present computational procedure. For the F-probed contour, we see two interaction sites near two hydrogen atoms although the energy stabilization is appreciably small in comparison with that obtained for the H-probed contour.

As seen in the above examples, it is evident that molecular shapes probed by ions show interesting topological features of molecules and look chemically important. The contour is nothing but a potential energy surface, which has clear physical meaning and quantitatively reflects chemical interactions: location and depth of energy minima directly reflect the nature of the ion-molecule interaction. For further applications, numerical analyses of molecular shapes need to be developed.
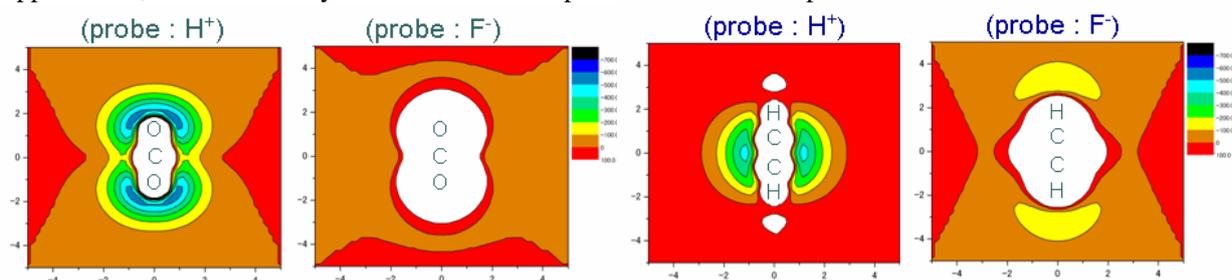
Figure 3: Isoenergy contour of CO_2 probed by the H^+ (left) and F^- (right) ions.

Figure 4: Isoenergy contour of C_2H_2 probed by the H^+ (left) and F^- (right) ions.