Applications of Molecular Simulation Software SCIGRESS in Industry and University

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SCIGRESS is computer simulation software developed by Fujitsu that is capable of simulating the behavior of atoms and molecules. The drug design phase in the pharmaceutical industry requires experiments to verify the effectiveness of a design; however, it takes considerable time and costs if all the required experiments are performed without computer simulation. SCIGRESS can perform virtual experiments on a computer to help practical experiments, resulting in time and cost savings. SCIGRESS is often used for education in teaching organic chemistry in universities. In particular, students tend to misunderstand what the resonance of aromatic compounds actually means when they only listen to lectures and read textbooks. SCIGRESS can visualize aromatic compounds with 3D graphics and help people to have a correct understanding. This paper describes two applications of SCIGRESS for drug degradation prediction by Sanofi S.A. in France, a major pharmaceutical company in the world, and for teaching organic chemistry in Ulm University, a public university in Germany.

1. Introduction

In the manufacturing industry, experiments are used in the design phase of manufacturing for verifying the adequacy and safety of a design to identify any problem at an early stage, thereby preventing major rework during later stages. However, these experiments require substantial costs and time, and so it is essential to improve work efficiency to reduce them by carrying out virtual experiments on a computer as a substitute for practical experiments. Such technology is called "computer simulation." Computer simulation refers to a technology for representing real-world and hypothetical phenomena on a computer, based on scientific theories.

Fujitsu developed SCIGRESS,[1)] which is computer simulation software to resolve these issues in R&D that are faced by many enterprises in the manufacturing industry, especially those in the fields of chemistry, materials and pharmaceuticals. SCIGRESS is capable of reproducing and analyzing nanoscale properties and behavior based on theories of computational chemistry such as the molecular orbital method and molecular dynamics method. In particular, SCIGRESS is not only equipped with its own unique computation programs but also capable of interfacing with many other computation software applications developed by academic institutions and researchers around the world, which allows it to be applied to a variety of fields in the manufacturing industry. In addition, SCIGRESS is released for overseas markets including Europe, North America and Asia as well as Japan and many enterprises in the world are now making use of SCIGRESS in their materials research.

Application of SCIGRESS is not confined to the industrial field but extends to basic research and teaching in universities. Organic chemistry classes, in particular, often deal with chemical formula and phenomena that students find difficult to imagine through lectures and textbooks alone and many students are in fact prone to have a wrong interpretation. To address this issue, computer simulation can be used for 3D visualization on a computer screen of chemical formula and phenomena that are difficult to imagine, and this facilitates a correct understanding.

This paper presents two examples of application of SCIGRESS to the industrial and education fields, namely,

for the industrial use, applying SCIGRESS for prediction of drug degradation by Sanofi S.A., a major French pharmaceutical company, and for the educational use, applying SCIGRESS for teaching organic chemistry by Ulm University, a German public university.

2. Case of application of SCIGRESS in research on drug degradation prediction in pharmaceutical industry

Sanofi S.A., which is based in Paris, France, is the world's fourth largest multinational pharmaceutical enterprise in sales of prescription drugs. It is engaged in a wide scope of activities ranging from R&D, manufacturing and sales of prescription drugs to development of over-the-counter drugs and covers seven major therapeutic areas including cardiovascular, central nervous system, diabetes, internal medicine, oncology, thrombosis and vaccines.

2.1 Importance of research on drug degradation prediction

To ensure the effectiveness and safety of drugs, evaluation for quality assurance in the initial stage of drug development is necessary. Above all, degradation of active ingredients is a significant factor that determines the shelf life of a drug and any toxicity in any of the degradation products (substances generated as a result of degradation) may make the drug unsuitable for use. From the perspective of these issues, to prevent failures and major rework during later stages essentially requires the stability of active ingredients and formulations (substances suitable for use made by mixing active ingredients with excipients) to be evaluated in the drug design stage. What is especially important is to identify chemical properties including reactivity for evaluating stability of the active ingredients mixed with formulation ingredients.

2.2 Case of application of SCIGRESS

While experiments are required to determine these chemical properties of substances, experiments unavoidably involve trial and error, which involves substantial costs and time. To address this issue, computer simulation making use of the technique of computational chemistry can be carried out before conducting experiments to predict the chemical properties and stability of substances, and this not only significantly reduces the time for experiments but also opens up the possibility of discovering properties that cannot be identified by experiments.

Sanofi S.A. uses SCIGRESS for predicting the degradation of active ingredients. **Figure 1** shows a workflow of degradation prediction.[2)] The dotted line box indicates the computation performed by SCIGRESS, which specifically uses three functions:

- Molecular conformational analysis
- Calculation of Fukui indices
- Energy calculation of hydrogen abstraction

First, conformational analysis detects stable molecular structures for which computation is to be performed. Calculating Fukui indices for the molecular structure helps to identify reactive sites on the molecule. **Figure 2** shows an example of computation of reactivity of aspirin by using SCIGRESS. The degrees of reactivity are indicated by different colors and the white area indicated by the arrow shows the most reactive site on the molecule. Meanwhile, calculating the hydrogen abstraction energy provides information about reactivity to radicals (unstable atoms and molecules that have one or more unpaired electrons and are in a very reactive state).

As a result of applying the functions of SCIGRESS, we have successfully obtained the following information before conducting experiments.

- Chemical vulnerabilities of active ingredients themselves
- Chemical compatibility of active ingredients with excipients

Chemical vulnerabilities of active ingredients point to chemical weaknesses found in advance that may cause the active ingredients themselves to generate impurities regardless of formulation. Chemical compatibility of active ingredients with excipients allows the stability and interactions of a mixture of active ingredients with excipients to be checked in advance. These pieces of information are very useful for actual formulation design.

As described above, chemical stability of active ingredients and formulations can be predicted at an early stage of drug development by using SCIGRESS for in silico research, and this has resulted in considerable cost and time savings. These pieces of information have been confirmed to be correct results in pre-formulation

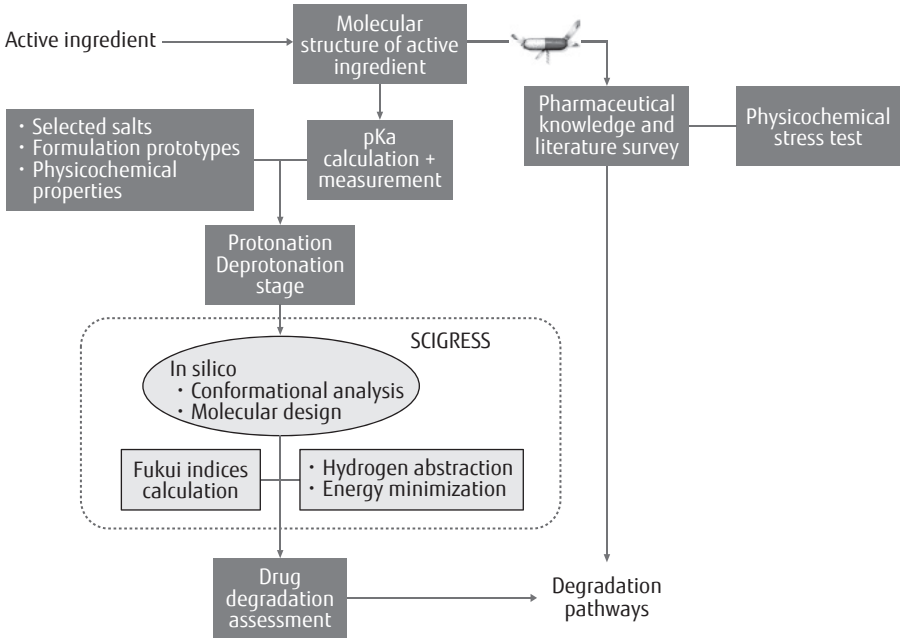

Figure 1
Workflow of degradation prediction.

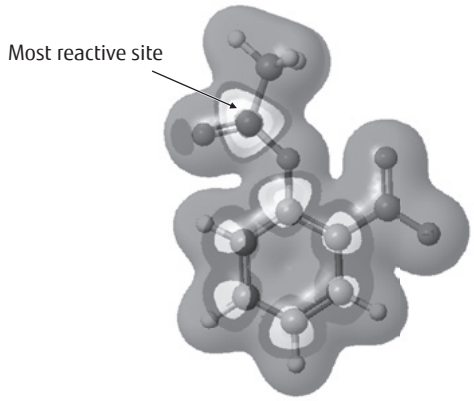

Figure 2
Result of computation of reactivity of aspirin (antipyretic-analgesic) by SCIGRESS.

research (research in which experiments are used for evaluating the stability and physicochemical properties of active ingredients), the first phase of formulation that follows, and play an important role as part of risk assessment of formulations. In addition, they are used for predicting toxicological risks caused by generation of impurities. In this way, SCIGRESS is essential software for predicting the degradation of active ingredients.

3. Case of application of SCIGRESS in organic chemistry classes in university

Ulm University is a public university in the city of Ulm in the state of Baden-Württemberg of South Germany. The University, which was founded in 1967, has faculties of natural sciences, medicine, engineering and computer sciences, mathematics and economics. It is ranked 22nd in a ranking of the world's top 100 universities under the age of 50 by Times Higher Education and is at the world's highest level in the fields of opto-electronics, RF circuit design and microelectronics. At Ulm University, about 30 PCs in the computer lab have SCIGRESS installed for classes in summer and winter. In addition, the PCs are made available to students 24 hours a day to let them study by themselves anytime.

3.1 Issues with teaching aromaticity in classes

Aromaticity in chemistry refers to a property common to some compounds with a ring structure represented by benzene and has been known for a long time to be distinctive and unique. For that reason, aromaticity is one of the most fascinating topics of chemistry and sometimes used as an example to

enhance students' motivation for learning organic chemistry. However, careless teaching of the basic concept of aromaticity, e.g., concept of resonance, may lead to a wrong interpretation by many students that resonance is some kind of dynamic process of switching single and double bonds. If undergraduate students have a wrong idea about resonance, they may not be able to correctly understand more complicated reaction mechanisms in graduate studies. That is why ensuring that students have a correct understanding of the basic concept in undergraduate chemistry education is an important issue.

The following presents a successful case in which SCIGRESS is used in undergraduate chemistry classes to give students a correct understanding from the very beginning of organic chemistry learning.

3.2 Theory for understanding aromaticity

In 1865, Friedrich August Kekule proposed that the structure of benzene was composed of a six-membered ring of carbon atoms with alternating single and double bonds. Subsequently, molecular orbital theory (MO theory), introduced around 1932, presented a concept that electrons did not belong to individual bonds but existed in molecular orbitals extending over several atoms in a molecule. This led to the idea that the structure of benzene was not based on alternating single and double bonds but all bonds were equivalent and intermediate between single and double bonds.

Then, the Hückel molecular orbital method (HMO method) proposed by Erich Hückel deduced the rule of aromaticity. With benzene, there are six π molecular orbitals (π-MOs), of which three are bonding (orbitals that form a π-bond) and the other three are anti-bonding (orbitals that break a π-bond). With all of the six π electrons in bonding π-MOs, benzene is highly stable. It has been shown that, generally, compounds with a planar ring structure and $(4n + 2)$ π electrons in cyclic conjugation (n is a positive integer including 0) are stable and have aromaticity. The Frost-Musulin diagram on the left in **Figure 3** represents relative energies of π-MOs and shows that bonding π-MOs have low energy levels and are stable and anti-bonding π-MOs have high energy levels and are unstable.

3.3 Case of application of SCIGRESS

At Ulm University, SCIGRESS is used in classes for students to deepen their understanding of these theories on aromaticity.

For example, use of SCIGRESS for molecular orbital calculation for benzene provides a π-MO diagram as shown on the right in Figure 3. Visualizing π-MOs of benzene as a 3D diagram like this allows people to simply verify the shapes, symmetry and nodal planes, as well as energy, of π-MOs. Above all, this diagram clearly shows that electrons are distributed among atoms when orbital phases are the same between carbon atoms and that electrons do not exist between atoms (nodal planes are formed) when the phases are opposite. In addition, the three bonding π-MOs and three anti-bonding π-MOs for six electrons can be easily distinguished by color.

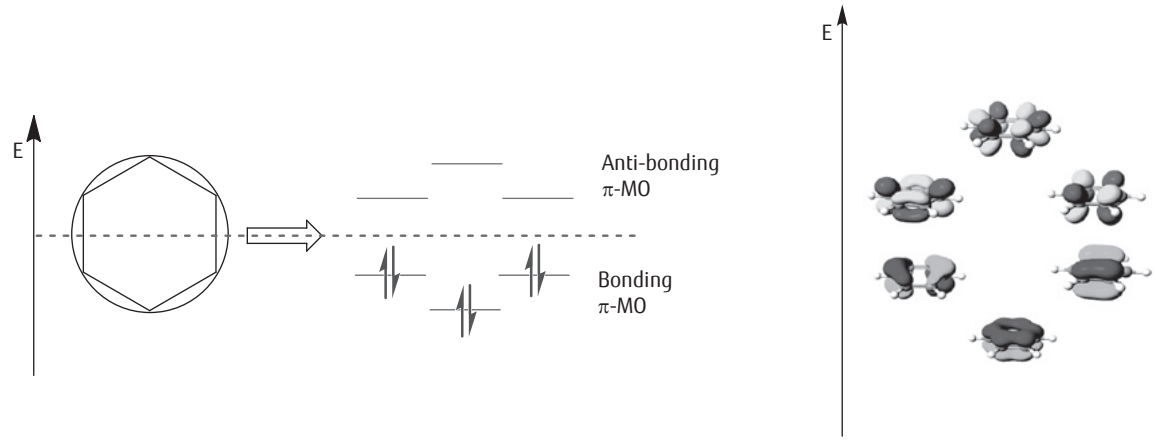

Figure 3
Frost-Musulin diagram of benzene (left) and corresponding π-MO diagram by SCIGRESS (right).

The next example shows the use of SCIGRESS for visualizing electrophilic aromatic substitution reactions, which are the most important of chemical reactions of benzene. Electrophilic aromatic substitution reactions are chemical reactions in which an electrophile (electron-deficient ion or compound) reacts with π electrons of an aromatic compound to replace mainly a hydrogen atom. Accordingly, the reactions are likely to occur in a site with a high density of π electrons. Here, comparison of reactivity between benzene, pyridine and pyrrole is taken as an example.

Unlike benzene, pyridine and pyrrole contain a nitrogen atom in the ring structure. While benzene and pyridine are based on a six-membered ring, pyrrole is based on a five-membered ring.

As shown in the top diagrams of **Figure 4**, benzene has six π electrons symmetrically distributed on six carbon atoms. Pyridine, like benzene, has six π electrons distributed among six atoms but more π electrons are on the nitrogen atom, which has higher electronegativity, and the density of π electrons on carbon atoms is lower than that of benzene. Therefore, the reactivity of pyridine in electrophilic aromatic substitution reactions is lower than that of benzene. While pyrrole also has a nitrogen atom, six π electrons are distributed among five atoms and the density of π electrons on carbon atoms is higher than that of benzene. This means that the reactivity of pyrrole in electrophilic aromatic substitution reactions is higher than that of benzene.

Quantum chemical calculations of these compounds by using SCIGRESS provide an electrostatic potential on the iso-electron density surface, as shown in the bottom diagrams of Figure 4. They clearly show that the π electron site of the pyrrole ring has an area with high electron density (white area in the diagram) larger than that of the benzene ring, leading to higher reactivity than that of the benzene ring, and that the π electron site of the pyridine ring does not have an area with high electron density, hence it has a lower reactivity than that of the benzene ring. In addition, the nitrogen atom site of pyridine has an area with the highest electron density reflecting the lone-pair electrons (shaded area in the diagram), indicating the basicity or nucleophilic center of pyridine. The nitrogen atom site of pyrrole has an area with high partial positive charge (shaded area in the diagram), indicating the N-H acidity of pyrrole.

In this way, use of SCIGRESS to show graphical information on a computer screen allows students to understand aromaticity more directly and comprehensively.

4. Conclusion

This paper has presented two cases of application of SCIGRESS in the industrial and education fields. SCIGRESS is playing very important roles in the two fields and expectations for it are expected to increase further from now on.

In the future, we plan to add functions mainly to handle new materials and to improve display and analysis features. Moreover, we intend to offer analysis

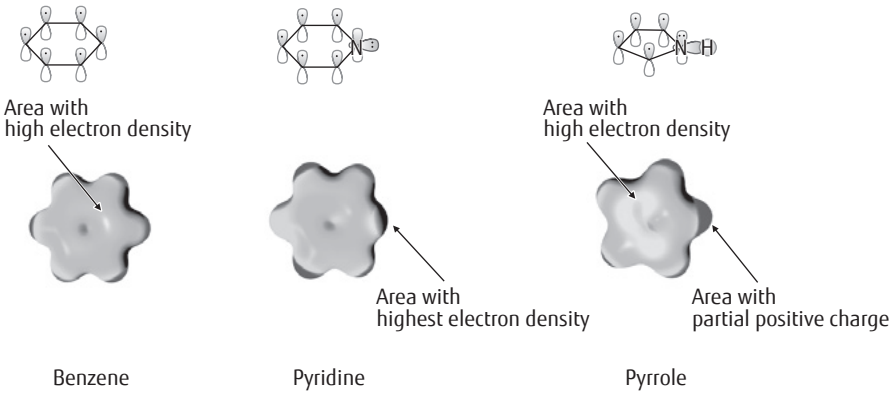

Figure 4
Orbital diagrams of benzene, pyridine and pyrrole (top) and corresponding electrostatic potential diagrams by SCIGRESS (bottom).

and education services in which Fujitsu's specialized staff directly helps customers with their research and education.

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