A Novel Method for Characterization of Three-Dimensional Reaction Fields Based on Electrostatic and Steric Interactions toward the Goal of Quantitative Analysis and Understanding of Organic Reactions

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Received October 25, 1998

A novel characterization method named FRAU (Field-characterization for reaction analysis and understanding), which numerically characterizes field around molecules based on electrostatic and steric interactions with pseudoreactant, has been developed for giving numeric measures of factors controlling reactions. FRAU estimates three kinds of features (FRAU features), i.e., extent of reaction field, electrostatic features, and steric features. Power of the FRAU features as discriminators recognizing similarities and differences of characteristics of structures and roles of reagents in reactions have been examined by 39 reagents containing Mg or B atoms. Similarities in these features were analyzed with the help of a self-organizing map (SOM). Good correspondences were found between the features, structures, and the role of the reagents in reaction. The results show abilities of FRAU to give useful numeric characterization of reagents.

1. INTRODUCTION

The ultimate goal of our project is to realize quantitative prediction of reactions being able to answer to questions: what products will be given from arbitrary reactants under arbitrary conditions, how much will be the product ratio, and will the desired structure be given as a major product. These are important questions remained in synthetic chemistry. However, they have not been sufficiently answered yet by any reaction prediction systems,[1−3] because it is difficult to understand mechanisms of reactions which occur as a result of complicated interactions among many factors: structural and electronic features of reactants, reagents, catalysts, solvents, temperature, etc.

The first step of our project is classification of reactions based on these factors. The purpose of the classification is to find out factors that distinguish similarities and differences in reactions and to investigate degree of the contributions of these factors to the reactions. In the previous classification studies, Chen and Gasteiger classified reactions belonging to some kinds of reaction types (e.g., Michael reactions) using electronic features of reaction sites of reactants or products as discriminators,[4−6] and we classified reactions containing oxygen atoms in their reaction sites which were chosen from a reaction database at random, in which changes of electronic features of the oxygen atoms from reactants to products were used as discriminators.[7] The classification studies demonstrated that the electronic features[8−11] were useful and important measures for automatic classification of reactions, even though these electronic features were calculated by considering two-dimensional topological relationships between connected atoms.

Our next stage of the classification study is to take into account more detailed information such as reaction conditions and three-dimensional electronic and steric features in order to find out more accurate knowledge on factors and sites which highly control a reaction.

As one of tools for this stage, we have developed a novel characterization method named FRAU (Field-characterization for reaction analysis and understanding). The FRAU gives numerical information of a molecule in reaction fields based on steric and electrostatic interactions with pseudoreactant.

In a study of three-dimensional quantitative structure−activity relationships (3D-QSAR), Cramer et al. developed a rectangular three-dimensional lattice model named CoMFA for characterization of ligand based on interactions between the ligand and pseudoreceptor.[12] CoMFA analyzes relationships among activities and differences in interactions detected by a probe as the pseudoreceptor on the grid. Thus, CoMFA discusses differences in features on each grid among ligands aligned based on common structure. The size of rectangular set around the ligands depends on the size of ligands to be analyzed. In QSAR, ligands having large common skeleton and small different substituents are discussed; however, in analysis of chemical reactions, molecules (e.g., reactants and reagents) having various sizes and structures are discussed. In this meaning, it is hard to apply the CoMFA to analysis of reactions. For analysis of reactions, it is necessary to avoid alignment within a variety of molecules and to give a canonical representation of numerical characterization of the molecules.

Thus, on the basis of an idea of CoMFA, the FRAU has been originally and newly developed particularly for analysis of reactions. Strong points of FRAU are the giving of

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10.1021/ci9801567 CCC: $18.00
Published on Web 06/02/1999

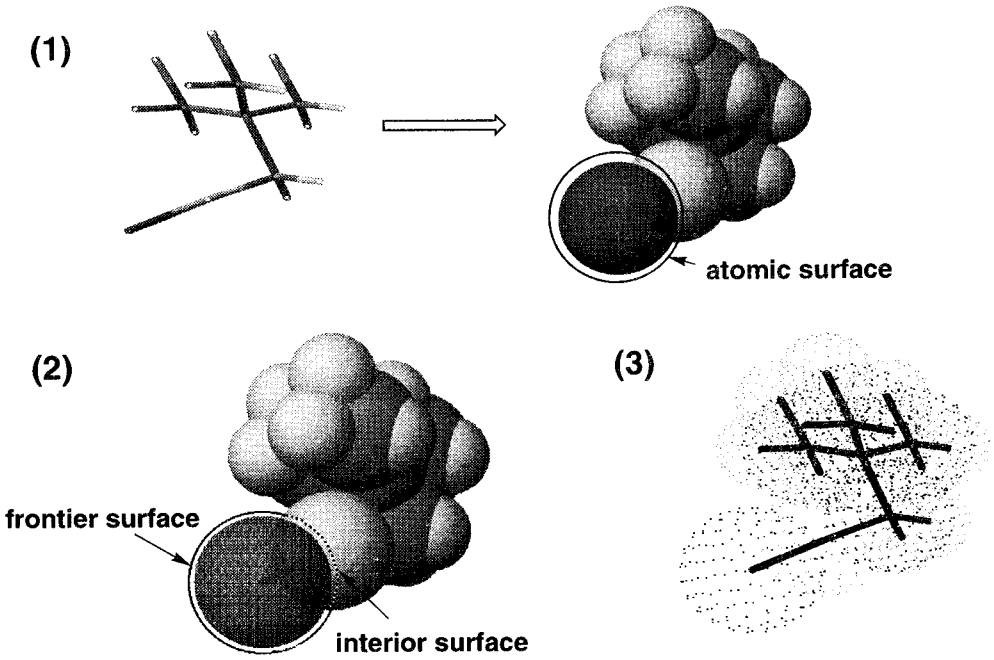

Figure 1. Process of field-characterization of FRAU. (1) A sphere is drawn around each atom. The sphere is for estimating interaction with a probe as a pseudoreactant on surface of the sphere. Radius of the sphere is equal to or longer than van der Waals radius. Surface of the sphere is called atomic surface. (2) Atomic surface overlapping a sphere of the other atom is called interior surface, and atomic surface except the interior surface is called frontier surface. (3) On the atomic surface dots are evenly set which are positions of a probe to detect features of the molecule.

numerical and *canonical* representations of features of molecules having any *sizes* and *substructures without alignment* of the molecules and dividing the features into *each factor* and *each site* of the molecules. Particularly, the point that FRAU can uniformly characterize three-dimensional field around a molecule having various sizes and substructures is noticeable to discuss chemical reactions, in which it is necessary to treat molecules having various sizes and substructures. In this meaning FRAU is a novel method for characterization of a molecule that is especially useful for discussing reactions.

The purpose of this paper is to introduce the FRAU by showing the procedures of characterization and the first results from FRAU with the help of a self-organizing map (SOM).

2. METHOD

2.1. Procedures of Characterization by FRAU. The first step of the characterization by FRAU is drawing a sphere around each atom of a molecule. The sphere is for estimating interaction with a probe as a pseudoreactant on surface of the sphere (Figure 1(1)). Radius of the sphere is equal to or longer than van der Waals radius of the corresponding atom. In FRAU, surface of the sphere around each atom is called *atomic surface*. Atomic surface overlapping with a sphere of the other atom is called *interior surface*, and atomic surface except the interior surface is called *frontier surface* (Figure 1(2)). The frontier surface is considered as an area that is mainly concerned in reactions.

On the atomic surface dots are evenly set (Figure 1(3)). The dots on the frontier surface are positions of the probe to detect features of the molecule. FRAU estimates three kinds of values: extent of reaction field (FF_{field}), electrostatic feature ($FF_{electro}$), and steric feature (FF_{steric}), which are called FRAU features (FF). The FRAU features are calculated for each atom in a molecule. The number of dots on the frontier surface of an atom is defined as FF_{field} of the atom:

$$FF_{field} = \text{the number of dots on the frontier surface}$$

Estimation of $FF_{electro}$ value is based on electrostatic interaction between unit charge as a probe on the dots that are counted as the FF_{field} and charge of every atom in the molecule. The $FF_{electro}$ is calculated by the following equation

$$FF_{electro} = \{\sum_{i=1}^{FF_{field}} \sum_{j=1}^{natom} 331.8417 \times charge(j)/r_{ij}\}/FF_{field} \quad \text{(kcal/mol)}$$

in which natom is the number of atoms in the molecule, $charge(j)$ is net charge of each atom, and r_{ij} is distance between the ith dot and the jth atom. Estimation of FF_{steric} value is based on the van der Waals interaction between an atom as a probe (ex. sp^3 carbon) on the dots that are counted as the FF_{field} and every atom in the molecule. The FF_{steric} is calculated by the following equation, which is from the MM3 force field:[13]

$$FF_{steric} = \left[\sum_{i=1}^{FF_{field}} \sum_{j=1}^{natom} \sqrt{\epsilon_i \times \epsilon_j}\left\{1.84 \times 10^5 \exp\left(-12.0/\frac{r_i + r_j}{r_{ij}}\right) - \left(2.25 \times \left(\frac{r_i + r_j}{r_{ij}}\right)^6\right\}\right]/FF_{field} \quad \text{(kcal/mol)}$$

in which natom is the number of atoms in the molecule, $\varepsilon_{i(or\ j)}$ is a parameter of MM3, which represents hardness of the atoms, $r_{i(or\ j)}$ is van der Waals radius defined in MM3,

and r_{ij} is distance between the probe atom on the *i*th dot and the *j*th atom.

2.2. Procedures of Examination of Power of FRAU. In order to demonstrate the power of FRAU features as discriminators recognizing similarities and differences of characteristics of structures and roles of molecules in reactions, the first results from FRAU for 39 reagents containing boron or magnesium atoms were investigated with the help of a SOM.

In the first step, in order to obtain molecular geometries and atomic charges to be used in FRAU, the geometries and electronic structures of the reagents were optimized by *ab initio* RHF/3-21G** molecular orbital (MO) calculations.[14] The reason why *ab initio* MO calculations were performed here was that accurate geometries and atomic charges of reagents were rather suitable to examine and discuss the power of the FRAU. Arbitrary computational level of theory is adaptable for geometry optimization and estimation of atomic charges according to purposes of FRAU users, namely, FRAU users can choice a computational level of theory that more rapidly optimizes geometry and estimates atomic charges.

Next, the FRAU features of each atom in the reagent molecules were calculated using the optimized geometries and atomic charges. In this paper, interactions with a probe on the surface of the sphere of which the radius is van der Waals radius were estimated. Unit charge (+1) was used as a probe for calculation of $FF_{electro}$, and sp^3 carbon was used as a probe for calculation of FF_{steric}. Incidentally, sp^2 carbon was also examined as a probe for estimation of van der Waals interactions and gave results of the same tendency as those which used sp^3 carbon. In this paper, the results which used sp^3 carbon are shown because isotropy of sp^3 carbon is more suitable as the probe to detect features. Various distances between the probe of the sp^3 carbon and the center of the atom being detected features were also examined. The best resolution was found when the center of the probe was on the frontier surface with van der Waals radius.

Then, contents and tendency in the calculated FRAU features were investigated by a SOM developed by Kohonen, called the Kohonen neural network.[15] Namely, using the FRAU features as discriminators, the reagents were classified by the Kohonen neural network, which projects input data in multidimensional space into a planar map (hereafter called Kohonen map or map) preserving topological relationships among the input data in the initial space. Boundaries among the classified groups of the data in the resulting planar map were recognized by **U**-matrix method.[16] We used the Kohonen neural network because good validity of the Kohonen neural network for classification of reactions has been being demonstrated by Chen, Gasteiger,[5−7] and us.[8] The results from the classification of reagents were analyzed based on similarities of molecular structures and roles of the reagents in reactions. Namely, relationships among the similarities of the FRAU features, molecular structures, and roles in reactions were examined.

3. RESULTS AND DISCUSSIONS

Figures 2−7 show the results from the examination. The input data to the Kohonen neural network are FRAU features of metallic atoms and atoms connected to the metallic atoms (140 atoms) in the 39 reagents.

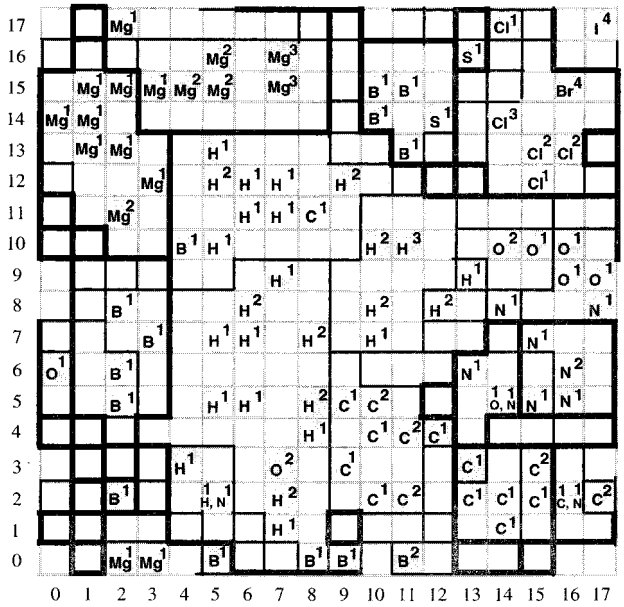

Figure 2. A Kohonen map analyzed by the kind of atoms. Each small square in the map is a neuron. Neurons obtaining the input data are colored gray and labeled by the atomic symbols with the number of the input data. The superscript figures mean the number of the input data obtained by the neurons. Black lines are boundaries recognized by U-matrix method. Bold black lines represent larger difference between neurons than the fine black lines. Actual shape of this map is a torus. Thus, the top of this map connects with the bottom, and the left edge connects with the right one. Coordinates in the map are for pointing out the position of a neuron in explanations and have no mathematical meanings.

3.1. Overview of the Results from Examination Based on Kinds of Atoms in a Kohonen Map. Figure 2 shows the result from examination based on kinds of atoms in a planar map resulting from the Kohonen neural network. Each small square in the map is a neuron, which has three-dimensional vectors corresponding to the three kinds of FRAU features, $FF_{electro}$, FF_{steric}, and FF_{field}. Those vectors were trained to simulate distribution of the vectors of the input data. After the training, a neuron obtains the input data that has the most similar vector, namely, each of the input data was set on a neuron having the most similar vector. Thus, the input data having similar FRAU features are gathered in the same or neighboring neurons. In Figure 2, neurons obtaining the input data are colored gray and labeled by the atomic symbols with the number of the input data. Black lines in the map are boundaries between neurons recognized by the **U**-matrix method. Bold black lines represent a larger difference between neurons than the fine black lines.[17] The actual shape of this map is a torus. For visualization the torus is cut along two perpendicular lines, and the surface is spread into a plane. Thus, the top of this map connects with the bottom, and the left edge connects with the right one. Coordinates along the axes are for assigning position of the neuron in the following explanation and have no mathematical meanings. In Figure 2 it is found that the same kind of atoms are gathered in the same or neighboring neurons.

3.2. Results from More Detailed Examination of the Kohonen Map. Figure 3 shows the results from examination of the contents of distribution of magnesium, boron, hydrogen, and carbon atoms based on characteristics of structures and roles of the reagents in reactions in the same map as

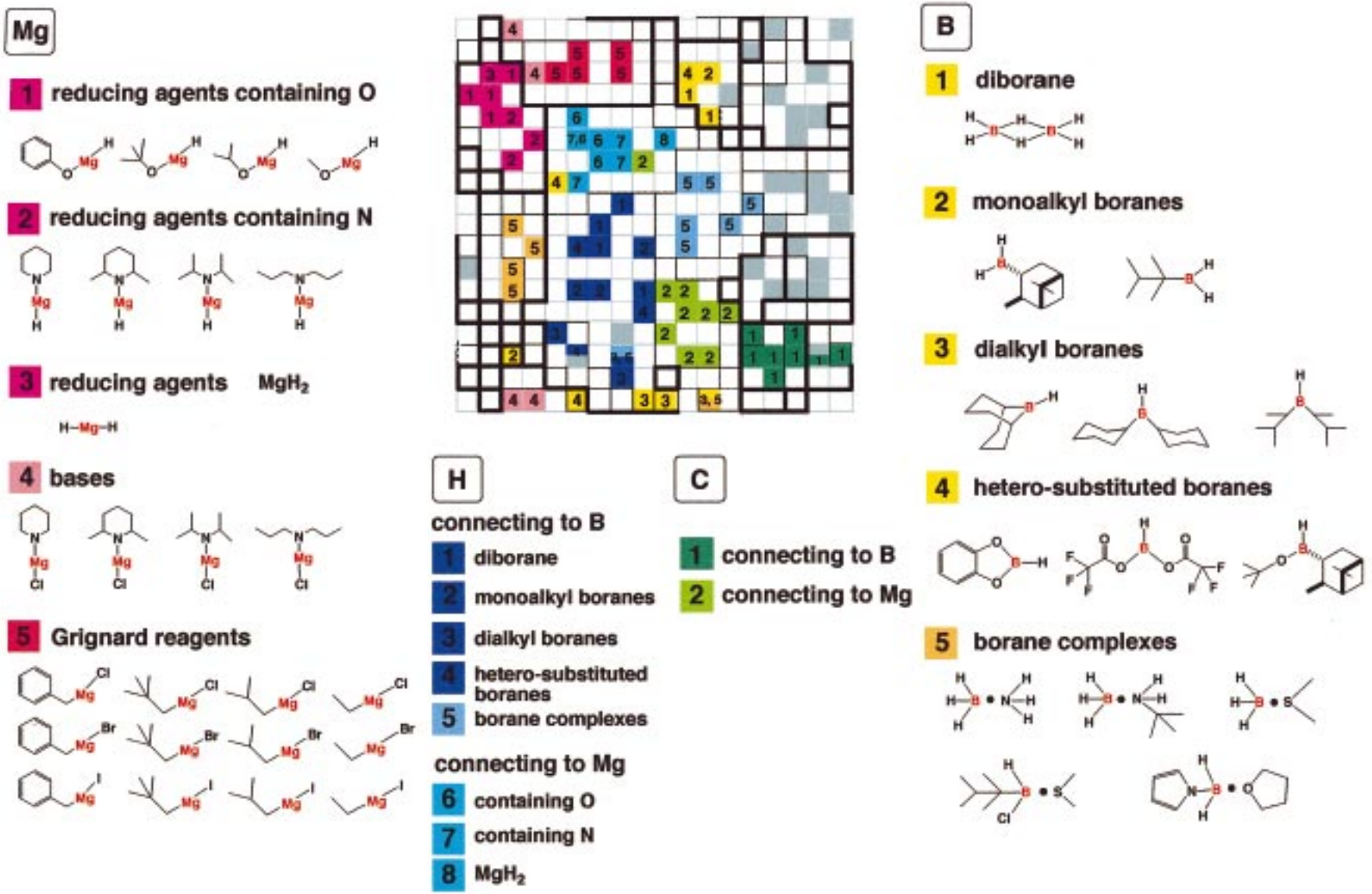

Figure 3. A Kohonen map analyzed by similarities of molecular structures and roles of reagents in reactions.

Figure 2.[18] Neurons obtaining magnesium, boron, hydrogen, and carbon atoms are colored, respectively, pinkish, yellowish, bluish, and greenish.

Magnesium atoms mainly gather on the upper left side of the map. These are clearly grouped into reducing agents (Mg-1, -2, and -3) and the other ones (Mg-4 and -5). The reducing agents consist of three groups: Mg-1 (connecting to oxygen atoms), Mg-2 (connecting to nitrogen atoms), and Mg-3 (magnesium hydride). Reagents of Mg-4 are magnesium salts of R_2NH known as bases, and reagents of Mg-5 are magnesium salts of R_3CH known as Grignard reagents. Groups of Mg-4 and Mg-5 are nearly distributed. This is reasonable because Grignard reagents can be considered as strong bases. From the point of view of similarities of an alkyl group, those of Mg-4 are close to those of Mg-2, and those of Mg-5 are close to those of Mg-1. This indicates that factors other than features of substructure determine the boundaries.

Then, to examine which FRAU features (FF_{field}, $FF_{electro}$, FF_{steric}) determine the boundaries, the neurons on the map were colored according to the size of the value of the FRAU features on the corresponding neuron as shown in Figure 4. Correspondence of gradient between the value and the color on the map are shown in the color bar in the right side of Figure 4.

Referring Figure 4 with Figure 3, the major factor determining the boundaries between reducing agents and the other ones is found to be the $FF_{electro}$ values. The order of the $FF_{electro}$ values was Mg-1, -2, and -3 (reducing agents) < Mg-4 (bases) < Mg-5 (Grignard reagents). $FF_{electro}$ values of magnesium atoms of Grignard reagents (Mg-5) were higher than those of bases (Mg-4). Since $FF_{electro}$ is a measure of electrostatic interaction energy with +1 unit charge in this case, a molecule containing magnesium atom having higher $FF_{electro}$ value can be considered as a stronger base. Thus, this result indicates that reagents of Mg-5 are stronger bases than those of Mg-4. It is suitable for nature inherent in the reagents. Furthermore, the results show that the $FF_{electro}$ is one of considerable measures determining the role of these reagents in reactions.

The area of magnesium atoms (the horizontal axis is from 0−7, the vertical axis is from 11 to 17, and 0) is closed up with their molecular structures in Figure 5. This shows that molecules were grouped, in more detail, according to their similarities of types of alkyl groups connecting to methylene in Grignard reagents, those connecting to nitrogen atom in bases and reducing agents, and those connecting to oxygen atom in reducing agents, respectively. Grignard reagents were grouped into those having a phenyl group, those having a methyl group and those having an isopropyl group or *tert*-butyl group. Investigation of their FF_{steric} values shown that the order of the sizes was methyl group < phenyl group < isopropyl and *tert*-butyl groups. The same tendency was found for the reducing agents including oxygen. This order corresponds with those of their sizes of hindrance in the field. For bases and reducing agents including nitrogen, respectively, those having diisopropyl amine were close to those having 2,6-dimethylpiperidine, those having di-*n*-propylamine were near to them, and those having piperidine were near but somewhat separated from the group of di-*n*-propylamine. Their FF_{steric} values were also investigated, and

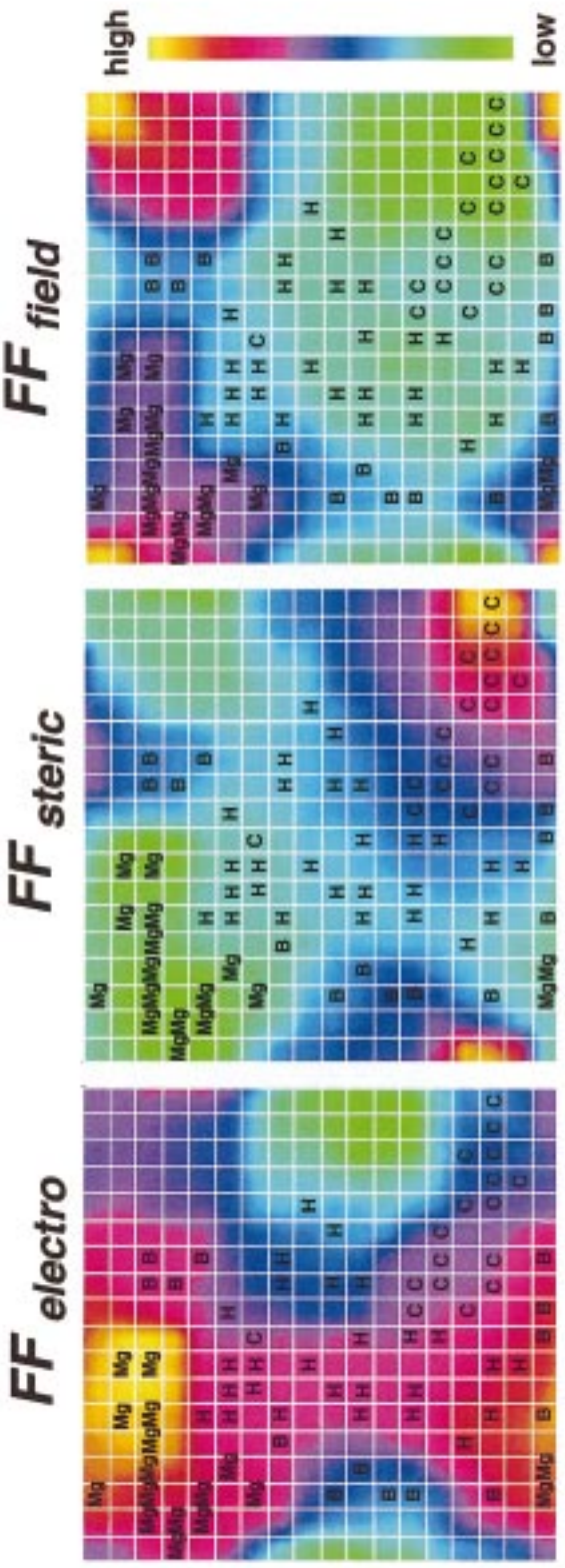

Figure 4. Kohonen maps colored according to the value of the FRAU features (FF_{field}, $FF_{electro}$, FF_{steric}) on the corresponding neuron. Yellow and green represent the highest and the lowest values, respectively, as shown in color bar in the right side.

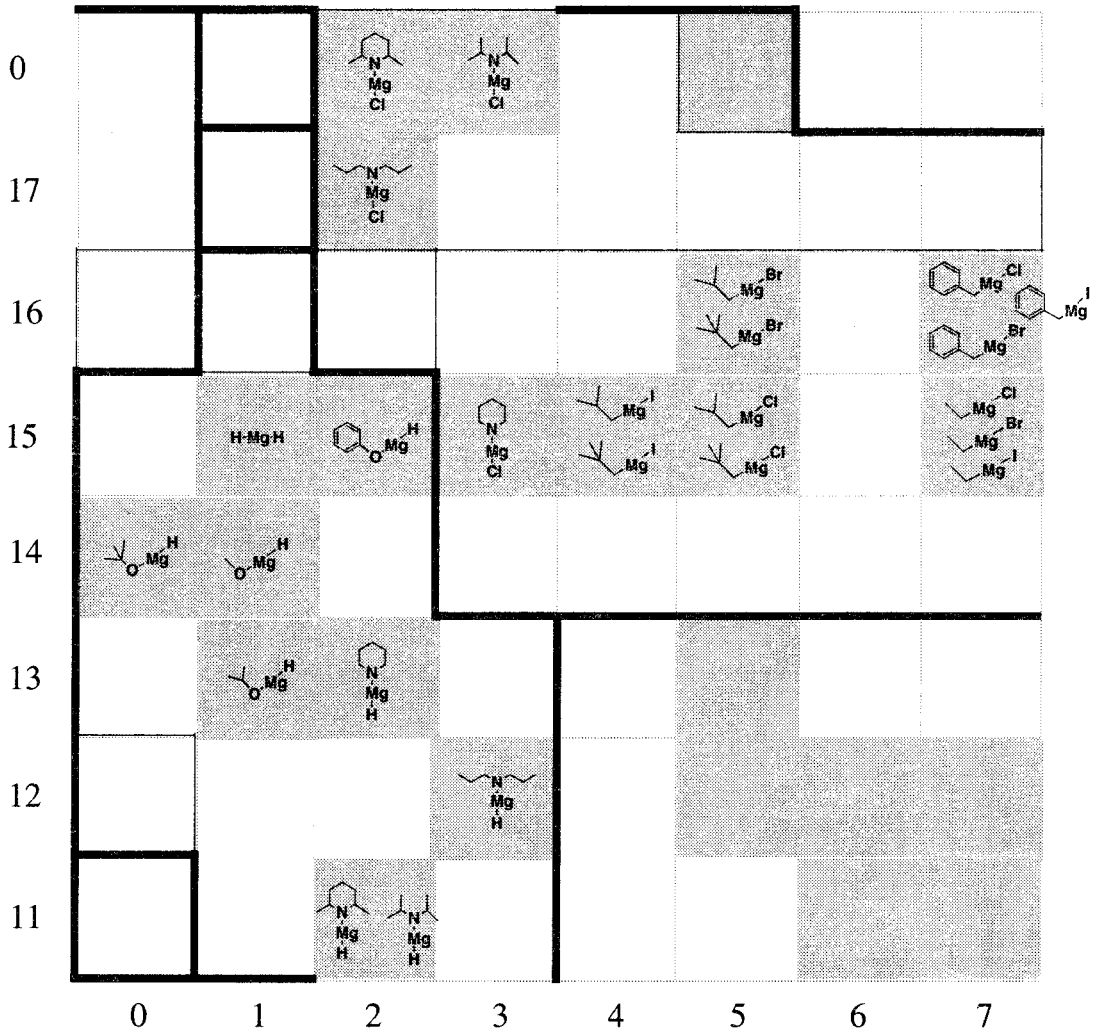

Figure 5. Part of a Kohonen map. An area of magnesium atoms is focused on.

the order of the sizes was shown as pyperidine < di-*n*-propylamine < 2,6-dimethylpiperidine and diisopropylamine. This also corresponds with those of their sizes of hindrance in the field.

Boron atoms were dispersed in the map as shown in Figure 3. For boron atoms, $FF_{electro}$ values were clearly different between borane complexes and the others as shown in Figures 3 and 4. $FF_{electro}$ values for borons of borane complexes (B-5) (colored violet in Figure 4) were lower than those of the others (colored pink in Figure 4). This difference is caused by the difference of type of bonds.

Hydrogen atoms connecting to metals were distributed in the center of the map. Figure 3 shows that they were separated by the kind of metals to which the hydrogen atoms connect: hydrogen atoms connecting to boron atoms (H-1, -2, -3, -4, and -5) and connecting to magnesium atoms (H-6, -7, and -8). Examination of $FF_{electro}$ values of neurons obtaining hydrogen atoms connecting to boron atoms shows that values for hydrogens connecting to boron atoms in complex boranes (colored violet in Figure 4) were lower than those of others. This is the same tendency as that of boron atoms.

Carbon atoms connecting to metals were distributed in the right bottom of the map. Figure 3 shows that they were also separated by the kinds of metals to which the carbon atoms connect: carbon atoms connecting to boron atoms (C-1) and carbon atoms connecting to magnesium atoms (C-2). Figure 4 shows that three kinds of FRAU features for carbon atoms evenly contribute to determine boundaries between them. $FF_{electro}$ and FF_{field} values for C-1 were lower than those for C-2, while FF_{steric} values for C-1 were higher than those for C-2.

The area of the carbon atoms (the horizontal axis is from 9 to 17, the vertical axis is from 1 to 5) is closed up with their molecular structures in Figure 6. This shows that carbons were grouped into secondary carbons, which belong to magnesium atoms, and tertiary carbons and quaternary carbons, which belong to boron atoms. There are two differences in degree of alkyl substitution for carbons and types of the connected metals. It is not obvious which difference mainly determined the boundaries in this case; however, the degree of alkyl substitution for carbon also might somewhat contribute the distribution, because the order of sizes of FF_{steric} values is secondary carbons < tertiary carbons < quaternary carbons as shown in Figure 4, even though magnesium atom, to which every secondary carbon connects is bigger than boron atom, to which every tertiary or quaternary carbon connects. Thus, this distribution corresponds with their differences of size of hindrance around the carbon. Furthermore, these were grouped according to their similarities of alkyl groups.[18] The distribution is because of differences of sizes of hindrance around the carbons, and

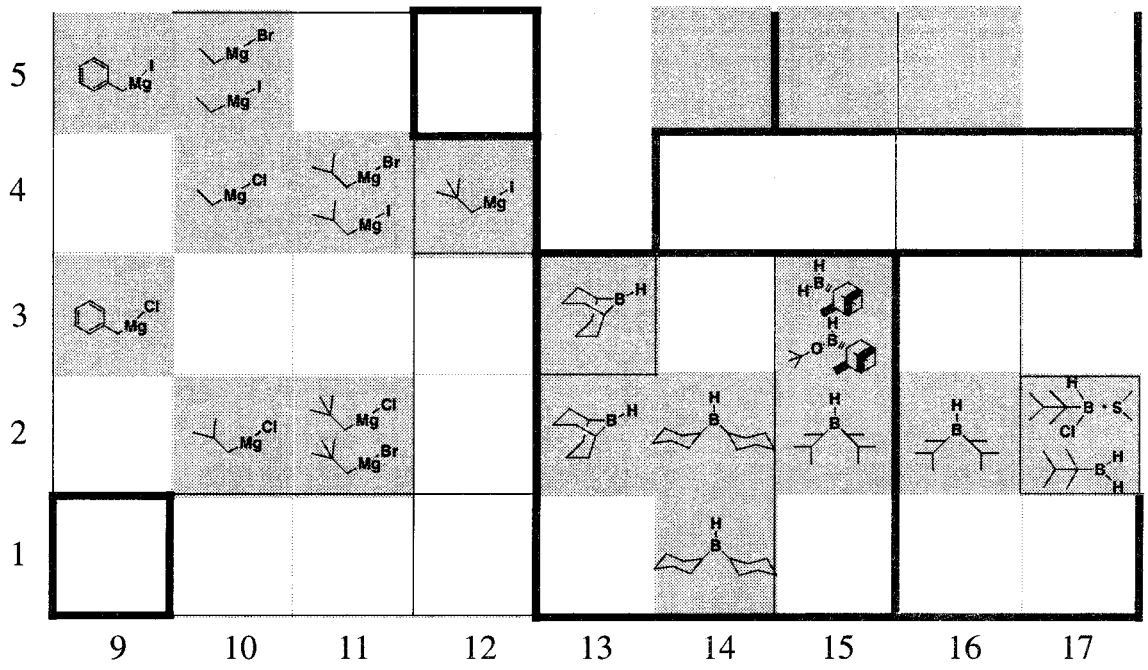

Figure 6. Part of a Kohonen map. An area of carbon atoms connecting to metals is focused on.

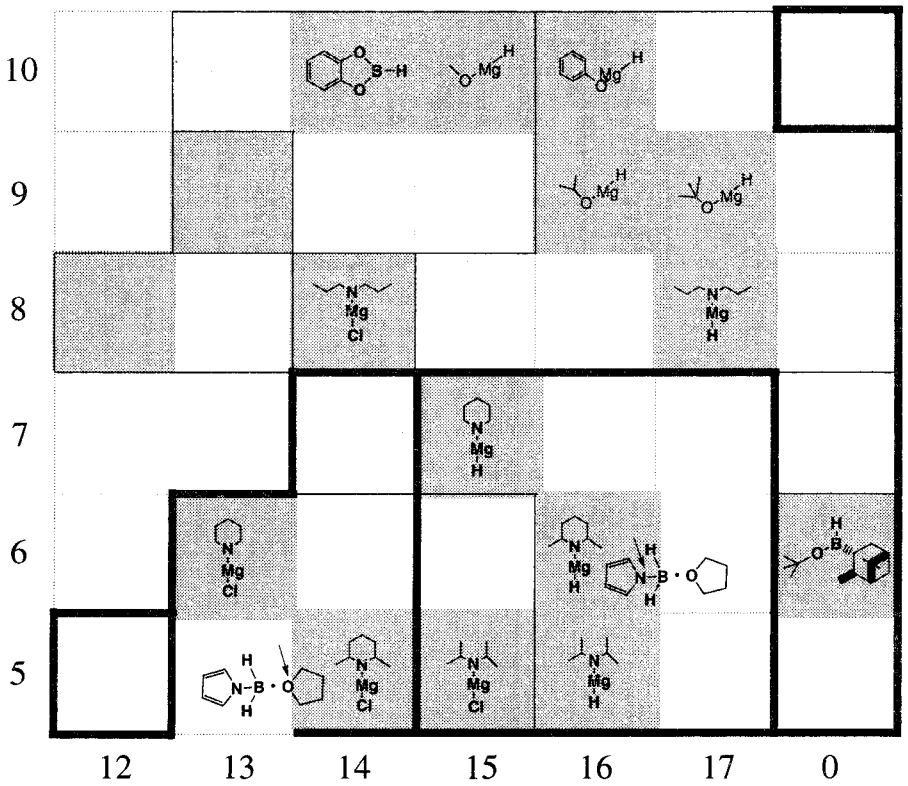

Figure 7. Part of a Kohonen map. An area of nitrogen and oxygen atoms is focused on.

these results are suitable to knowledge of chemists. However, only one of the Grignard reagents, benzyl magnesium bromide ($PhCH_2MgBr$) was set in a neuron far from this area ((8, 11) position on the map as shown in Figure 2). The reason has not been cleared yet.

Figure 7 shows distributions of nitrogen and oxygen atoms, which were not described in Figures 3 and 4. The nitrogens and oxygens were roughly separated, and they were roughly grouped into reducing agents and bases. Some of molecules including amines were distributed according to the similarity of substructure of alkyl groups around nitrogen atom. However, the distribution was less clear than the other atoms such as magnesium. One of the reasons why this ambiguous separation was given is that they have no definitive factor to determine the boundaries. In other words, factors of nitrogen and oxygen atoms might be not major to determine and explain the differences among these reagents. Another reason is that the number of data for nitrogen and oxygen atoms are rather small to get statistical results, since sizes of q_error value (measure of differences between weight vector of a neuron and the input vector set on the neuron) for nitrogen and oxygen atoms were somewhat large.

3.3. Current and Future of FRAU. The results show that the FRAU features discriminated similarities and differences of structures and roles of the reagents. The distribution on the map also reflected the similarities and differences of hindrance around a molecule. More detailed investigation of a power of FRAU to distinguish the similarities and differences of hindrance and stereochemistry will be done in future.

These results also show that FRAU features of magnesium atom are better as discriminators to distinguish the similarities of structures and roles of the reagents than those of nitrogen or oxygen atoms, and any FRAU features used as discriminators here did not distinguish clearly similarities and differences in borane reagents. A study for finding out better discriminators using FRAU features, for example, combination of suitable features, is now going on and will be shown in our future papers.

As described in Section 1, the philosophy and algorithm of FRAU essentially has no restriction in sizes and substructures of molecules to be calculated. However, in the current version, types of substructures which can be treated depend on whether corresponding parameters for calculating van der Waals energy in MM3 exist or not, and sizes of a molecule which can be treated depend on which computational method is used for obtaining molecular geometries and atomic charges within the limit of computational costs for practical use. Types of parameters for calculating van der Waals energy are now being increased to treat many types of reagents, reactants, and products, and appropriate computational methods to obtain molecular geometries and atomic charges will be examined in more detail.

4. CONCLUSION

The first results from examination of FRAU demonstrate good correspondence between the FRAU features and characteristics of structure as well as roles of reagents in reactions. Strong points of FRAU are the giving of numerical and canonical representations of features in three-dimensional molecular field having any size and substructures without alignment of the molecules and to divide the features into each factor and each site of the molecules.

In this paper, the FRAU was introduced as an application to reactions focusing on reagents. Taking account of these results as additional information in the previous classification studies will make it possible to more exactly classify reactions, automatically. That is one of which we are aiming.

ACKNOWLEDGMENT

This work was partly supported by Grant-in-Aid for Scientific Research on Priority Areas (No. 283, "Innovative Synthetic Reactions") from Monbusho. H.S. gratefully acknowledges financial support by the President's Special Research Grant from RIKEN and for that I had been working as a Special Researcher in the Basic Science Program in RIKEN.

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(13) Parameters and a mathematical scheme for van der Waals energy calculations are of MM3 '96 from QCPE.
(14) Program package GAMESS was used for MO calculations. (See: Schmidt, M. W.; Baldridge, K. K.; Boats, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupui, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.) Mulliken charges were used as the atomic charge for calculations of $FF_{electro}$.
(15) Kohonen, T. *Biol. Cybern.* **1982**, *43*, 59. Kohonen neural network program used in this study is one module of TUT_SOM, which is a program package developed by K. Funatsu in Toyohashi University of Technology. TUT_SOM includes two neural network programs (Kohonen neural network and counterpropagation neural network), two programs for recognition of boundaries among weight vectors on Kohonen map (U-matrix and Potential functions methods), and several convenient graphic viewers of the results given by the above programs.
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(17) The U-matrix treatment was executed by the TUT_SOM.
(18) The reason why some equivalent atoms (e.g., boron atoms in diborane) are on the different neurons is that the current FRAU does not perfectly evenly set dots on the frontier surface although the values of the FRAU features of the equivalent atoms are very close. This problem is to be refined in future.

CI9801567