Development of Hybrid Web System for Supporting Process Research

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Recently, the role of computational chemistry is increasingly important, but unfortunately the field is still only for the specialist. On the other hand, as diffusion of internet technology, a lot of systems to solve chemical problems are spreading. Hence, for the purpose of promotion to open in-house system and database, a new system based on web technology has been established. The web system realized the new research environment in company, which easily access synthetic route design system, in-house reaction retrieval database, and property estimation system via unified graphical input editor.

Introduction

Today, computers are playing increasingly important roles in the fields of engineering and the natural sciences, with the field of chemistry being no exception. The following methodologies have been derived from the popularization of computers: information retrieval [1] is used to extract desired data from myriad information groupings pertaining to chemical reaction and chemical compound data compiled by previous researchers; informational chemistry [2] is used to predict specific trends and extract special characteristics from enormous amounts of raw data; and theoretical computations are used to predict reaction outcomes, chemical properties and other phenomena, based upon theoretical chemistry [3]. These branches of chemistry, which utilize computers, are generally referred to as computational chemistry [4]. Among all the categories included within computational chemistry, the recent emergence of combinatorial chemistry in particular, demonstrates a methodology that did not exist prior to the invention of the computer. Today, although combinatorial chemistry is most commonly used by pharmaceutical companies, with a gradually-increasing number of researchers employing this methodology, we must admit that computational chemistry is still a tool that is only used by a few specialists. One of the reasons why researchers have, so far, avoid-

ed using this methodology, is due to its low level of reliability. While computational chemistry is widely utilized as a means of enhancing our understanding of known chemical phenomena, there have only been a few cases reported thus far in which new phenomena have actually been discovered through the use of computational chemistry. Moreover, some discrepancies between calculated values and actual measured values are inevitable, whenever a computer is utilized in the calculation of physical properties. In order to improve the accuracy of calculated values, a substantial amount of computation resources are required. Thus, if a complex chemical compound is subjected to investigation via computational procedures, the accuracy of such calculations will be almost impossible to improve. Another reason behind the lackluster popularity of computer chemistry is that its effective employment requires the investment of a significant number of man-hours in preparatory procedures. For example, in order to perform a statistical analysis, a great deal of data must first be collected for use on the subjects of analysis. In addition, researchers need to obtain the requisite skills for operating the analytical system and must also possess the knowledge to correctly interpret the results. Therefore, in the current environment, when a company decides to utilize a particular computational chemistry methodology, they will usually attempt to engage in joint research

together with computational chemistry specialists.

Why has the reaction database retrieval system (referred to hereafter as the "reaction database") become so widely utilized among researchers? The answer is simple-because accurate results [6] are obtained and the operating procedures are extremely easy and convenient. The most important factors are that researchers do not need to understand the algorithms used for structural searching and that system operation itself is quite simple. These factors are obvious, since almost all of the commercially available chemical-related software packages incorporate some kind of graphical input interface for chemical structures.

Basic physical properties, such as the heat of reaction, LogP value and pKa value, can be predicted using off-the-shelf software. However, due to the aforementioned reasons, in most cases, researchers consign the work of performing these predictions to computational chemistry specialists, rather than introducing and implementing such software systems themselves. Therefore, we examined the use of the internet for both the simplification of data input / output operations and for the creation of an environment that would allow a large number of researchers to utilize the system independently. It is relatively easy to create a client-server system and to input, output and display molecular structures, using any internet web browser (including Internet Explorer and Netscape Navigator). In addition, the management of the entire system itself is relatively simple, with results that are not dependent upon the particular types of devices utilized by researchers. For these reasons, we consider the internet to be an ideal environment that will enable all company employees to access the various systems that have been developed by our company.

The Internet and Chemistry

The internet was first established as part of a military study on distributed networks (ARPANET), conducted in 1969 by the US Defense Advanced Research Projects Agency, which enabled communications to occur, even if parts of the network structure itself had been damaged (**Table 1**). In the early stages, the internet was merely a network used for communications among four US organi-

zations (University of California at Los Angeles, Stanford Research Institute, University of California at Santa Barbara and University of Utah). In 1984, JUNET (Japan Unix Network) was established in Japan, heralding the beginning of networked communications within the country. The internet was first introduced in the field of chemistry in 1975, at the 170th national meeting of the American Chemical Society, during a symposium on computer networking and chemistry. In 1993, the American Chemical Society held CHEMCONF '93 (sponsored by the Chemistry Education Subcommittee), the world's first online electronic conference. Since that time, increasing numbers of chemistry-related conferences have been conducted online.

Although the tremendous utility of the internet shall not be the focus of our discussion, as numerous books have already been published on this topic, we shall merely state that the convenience afforded by the internet has led to its widespread utilization throughout all areas of chemistry [7]. By simply browsing the websites of national organizations, universities and institutes, one can obtain a tremendous amount of chemistry-related information (**Table 2**). Moreover, many chemical companies disclose corporate information on their websites, thus facilitating easy access to company profiles. For example, the website of the Liverpool University Chemistry Department contains links to more than 740 chemistry-related corporations [8]. As an example of one such open website, we shall introduce the website for Parameter Estimation for the Treatment of Reactivity Applications (PETRA) [9], which is currently under development by the research group of J. Gasteiger of Erlangen-Nürnberg University. The physiochemical properties that can be obtained from the PETRA website are useful in applications involving organic chemical reaction responses and QSAR (Quantitative Structure-Activity Relationship). This website utilizes the SMILES [10] format, allows the entry of chemical structural information and predicts the requested physical properties for chemical compounds. If SMILES format structural information is not known for the particular chemical compound, a structure editor can be utilized. After entry of the required parameters (**Fig. 1**), clicking the "Submit" button causes the predicted val-

ues to be displayed (**Fig. 2**). The computations are completed almost instantly for most organic chemical compounds. Furthermore, although the upper computational limit is 100 molecules, data for several molecular structures can be entered in

a single file, for the simultaneous estimation of physiochemical properties.

Input form of PETRA

Fig. 2 Results of PETRA

Table 1 Internet in Chemistry [7)]

Year	Event
1969	DARPA (Defence Advanced Research Projects Agency) established ARPANET.
1975	The 170th National Meeting of American Chemical Society (ACS) held Synposium on Computer Networking and Chemistry.
1983	DCA (Defense Communications Agency) and DARPA established TCP/IP protocol.
1988	In Japan network system, JUNET (Japan UNIX Network), was started.
1990	The first major internet worm was appeared.
1992	CERN (Centre Européen pour la Recherche Nucléaire) released the crient software, World Wide Web (WWW).
1993	NCSA (National Center for Supercomputing Application) released the first graphical viewer, *Mosaic*, for the WWW.
	Division of Chemical Education of ACS held Committee on Computers in Chemical Education (CHEMCONF '93), which was the first electric on-line conference in the world.
1994	The 1st International Chemometrics Society (INCINC '94) was held by North American Chapter of the International Chemometrics Society (NAmICS) and Elsevier.
	The 1st Electronic Computational Chemistry Conference (ECCC) was accomplished using Web mechanism alone.
1995	Electronic Conference on Trends in Organic Chemisty (ECTOC) was held through WWW, and were discussed using e-mail.

Table 2 Web-site of National Institute and Society of Chemistry

Name	URL
The Chemical Society of Japan	http://www.chemistry.or.jp
The American Chemical Society	http://www.chemistry.org
The Royal Society of Chemistry	http://www.rsc.org
Die Gesellschaft Deutscher Chemiker	http://www.gdch.de
The Canadian Society for Chemistr	http://www.chemistry.ca
National Institute of Advanced Industrial Science And Technology	http://www.aist.go.jp
National Institute of Standards and Technology (NIST)	http://www.nist.gov/srd/chemistry.htm
The Royal Institution of Great Britain	http://www.ri.ac.uk
World Association of Theoretical Oriented Chemists (WATOC)	http://www.ch.ic.ac.uk/watoc
The QSAR and Modelling Society	http://www.qsar.org
Dutch National Center for Computer-Assisted Chemistry and BioInformatics	http://www.cmbi.kun.nl
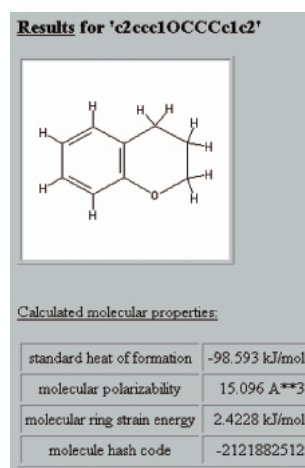
Web Integration System (Web-CC)

We have been seeking a client-server type of executing environment for our SYNSUP [11)] synthesis design system, which has been under development by our company for several years. Meanwhile, certain research requirements do exist, such as the creation of our own internal company databases containing information about organic chemical reactions and organic compounds, as well as predicted values for physical properties, such as LogP values. We have been evaluating various methods of providing an environment in which researchers can easily access such information. Although it is possible to utilize off-the-shelf software for each individual system, no single application existed that allowed for the retrieval of information from all systems. Thus, we have created a web integration system (referred to hereafter as Web-CC) that can be shared throughout our com-

pany via web browser, on our company intranet.

In Web-CC, the molecular structure of chemical compounds can be drawn using a common chemical compound input editor. The desired system can be selected for use from among an internal reaction database, a synthesis design system and a physical property estimation system (**Fig. 3**). To facilitate ease-of-use, the structural input editor was created based on Java (Sun Microsystems, Inc.). Bonding information for the chemical compounds that have been input via the editor, is transmitted to the web server and the retrieval results are output to the web browser. **Fig. 4** depicts a conceptual diagram of Web-CC.

Detailed information about the synthesis reaction design system, the reaction database and the physical property estimation system is introduced in the next section.
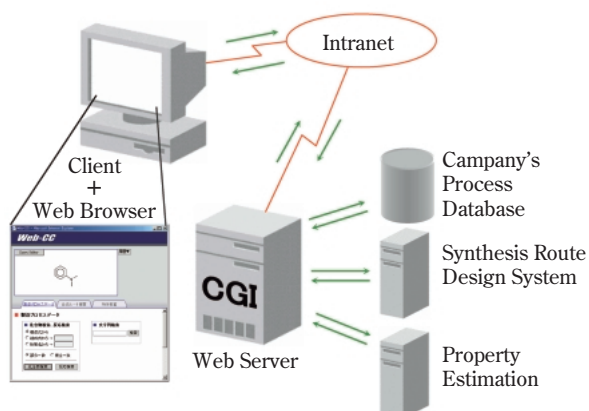

Fig. 3   Web-CC Front Page

Fig. 4   Image of Web Application System

Synthesis Design System

A thesis pertaining to the synthesis design system was released in 1969, for the first time in the world, by Corey and Wipke [12]. Since that time, a variety of synthesis design systems have been proposed [13]. In the broader sense, the term "synthesis

Table 3   List of Synthetic Route Design[13]

System	Algorithm*1)		Execution*2)		Purpose*3)		
	E	L	I	B	RD*4)	RP	SM
AIPHOS[14]	✓	✓	✓		✓		
CAMEO	✓		✓			✓	
CASINO		✓	✓		✓		
CASP	✓		✓		✓		
CHIRON			✓				✓
CICLOPS[15]		✓		✓	✓	✓	
COMPASS	✓	✓	✓		✓		
CONAN		✓	✓		✓✓		
COSYMA	✓		✓		✓		
EROS[16]		✓		✓	✓	✓	
FLAMINGOES		✓	✓		✓	✓	
ICAR	✓	✓	✓			✓	
KOSP[17]	✓	✓		✓	✓		
HOLOWin	✓		✓		✓✓	✓	
LHASA[18]	✓		✓		✓		✓
LILITH		✓	✓		✓		
MASSO		✓	✓		✓		
PASCOP	✓		✓		✓		
PEGAS		✓	✓		✓	✓	
PSYCHO	✓		✓			✓	
RESYN	✓		✓		✓		
RAIN		✓		✓	✓	✓	
SAS		✓	✓		✓✓		
SCANCHEM	✓		✓		✓	✓	
SECS	✓		✓		✓		
SESAM			✓				✓
SOPHIA	✓	✓		✓		✓	
SOS	✓		✓		✓✓		
SPEK	✓		✓		✓		
SST			✓				✓
STORM	✓	✓	✓		✓		
STRAKS	✓		✓		✓✓		
SYNCHEM	✓			✓	✓		
SYNGEN[19]		✓		✓	✓	✓	
SYNSUP[11]	✓			✓	✓		
TOSCA	✓	✓	✓		✓	✓	
TOSP[20]	✓			✓	✓		
TRESOR	✓		✓		✓		
WODCA[21]		✓	✓		✓	✓	✓

*1) E : Empirical, L : Logical

*2) I : Interactive, B : Batch

*3) RD : Retrosynthetic Design, RP : Reaction Prediction,
   SM : Starting Material Search

*4) ✓✓ : Key reaction design, others : Precursor design

design system" is a general name used to refer to any of the following types of systems: precursor design types; key reaction design types; starting material design types; and reaction prediction types. Both precursor design types and key reaction design types are retrosynthesis design systems, in which precursors are designed based upon the target product. The key reaction design system focuses particularly upon reactions that form the important skeleton for the creation of a target chemical compound. The starting material system is used to design starting material candidates based on the skeleton of the target product. The reaction prediction system is used to predict the reaction products of the compound that has been input (**Table 3**).

In this paper, we present an overview of a precursor design system, which we refer to as a synthesis design system.

A synthesis design system is composed of modules that are used to perform the following operations: recognition of the chemical compound structure; design of precursor candidates; and verification of the proposed precursors and reaction feasibility. There are two basic types of system execution procedures. In the "interactive" procedure, every time the system needs information, the user is prompted to enter either information about each precursor, or the information necessary to lead the system to a precursor. The second type of execution procedure is "batch," in that once target information about a chemical compound has been entered, the system continues to propose candidate precursors, one after the other, until the requirements specified at the time of input have been fulfilled (i.e., starting chemical compound, number of steps, etc.) (**Fig. 5**). Design methods can also be classified into two types: a method in which known reactions are exactly reproduced (Empirical) and a method in which precursors are proposed through generalizations of reactive sites and bonding conversion information (Logical) (Table 3). The proposed precursors vary, depending upon the particular design method used. Many of the synthesis design systems are of the empirical type, with typical systems including LHASA [18] and SYNSUP. Empirical design methods involve organizing reactions in a manner similar to the way in which reactions are classified in

common textbooks. As well, this method provides reaction rules for each reaction. The system recognizes the reaction center structure (synthon or retron [22]), which is described in the abovementioned reaction rules, from the target molecule, then performs transforms to derive the proposed precursors.
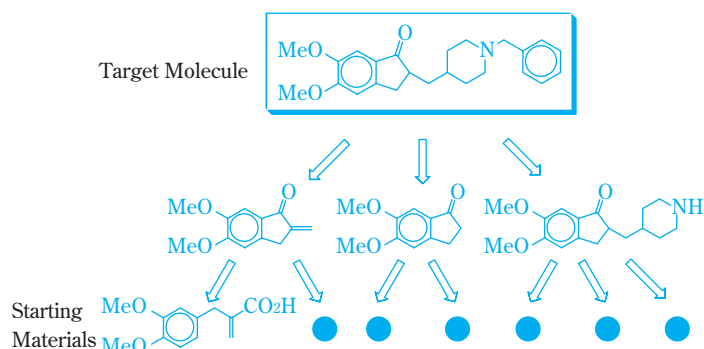
Fig. 5 Retrosynthesis

The following two methods are well known as being typical of the generalized reactions used in logical precursor design systems. The first is a method developed by researchers Ugi and Dungundji, in which a given reaction is expressed in a form of a matrix. [23] The researchers represent reactants and products using matrices that contain values corresponding to the bond order and the free valence electrons for each atom. The reactions are described as matrices derived from the differences between matrices of reactants and products. This method was first utilized in CICLOPS [15] and was then implemented in EROS [16] and WODCA. [21] The second method utilizes a unique line-shaped notation developed by Hendrickson, which is now employed in SYNGEN. [19] Hendrickson paid particular attention to the carbon atoms at the reactive site and proposed a method in which a reaction is represented only by the following two parameters: changes in the types of carbon atom bonds and changes in the bond order. This method allows precursor generation to be performed from 114 reaction units. In logical systems, while there is a strong possibility that new reactions can be proposed through the abovementioned generalizations, the problem also exists that many reactions having low feasibility will be proposed, as well.

Many of the synthesis design systems have been

developed in universities and research institutes, with some systems being accessible by the public. In addition, some systems have already been released to the market (**Table 4**). Most of these systems are client-server type systems and certain ones can execute from internet sites. However, since none of these internet sites are free, users must pay for execution.

**Table 4** Commercially Available Synthesis Design

System	Supplier	URL
WODCA	Molecular Networks	http://www.mol-net.de
ChemSpire	row2technologies	http://www.row2technologies.com
Arthur	SYNTHEMATIX	http://www.synthematix.com/arthur.html
AIPHOS/KOSP	Fujitsu	http://software.fujitsu.com/jp/chem/html/inquire.html

## Web-CC Synthesis Design System

Our company utilizes 3 types of synthesis design system: SYNSUP, an empirical system; WODCA, a logical system; and AIPHOS, [14] a hybrid empirical-logical system. From among these systems, we have chosen SYNSUP and AIPHOS for incorporation into Web-CC. SYNSUP is an empirical system that has been under development by Bersohn [24] since 1971 and on which Sumitomo Chemical has been working jointly since 1984. SYNSUP is capable of proposing highly feasible synthesis routes. Another special feature is its ability to handle stereoselective reactions, as it can recognize asymmetric centers. We have created input/output application software for various user devices, as well as an application environment for email. [25] With respect to AIPHOS, our company has been participating in its development since the inauguration of the CCP1 (Computer Chemistry Program 1) project in 1990 (a joint development project involving collaboration among government, industry and academic sectors). AIPHOS is an empirical system to which logical attributes have been added, thus allowing users to extract a knowledge base from the reaction database. Although we currently utilize our unique client-server system, as well as TOSP [20] and KOSP, [17] which are derived from AIPHOS, we have now cre-

ated an integrated input/output interface for use with Web-CC.

Fig. 6 depicts a portion of the Web-CC output image of proposed precursor results from the first step of the SYNSUP process for Ethyl 1-methyl-1H-indole-2-carboxylate. In this system, any related information can be easily viewed on the results output screen, using hyperlinks. For example, users can display reference data pertaining to a particular reaction at each step of the synthesis route proposal results (**Fig. 7**). The results output screen also displays the names of reference documents and the reaction schemes described within.
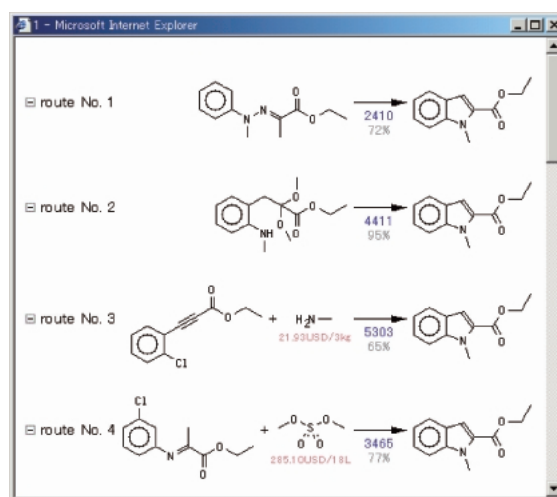
Fig. 6 Output Image of SYNSUP
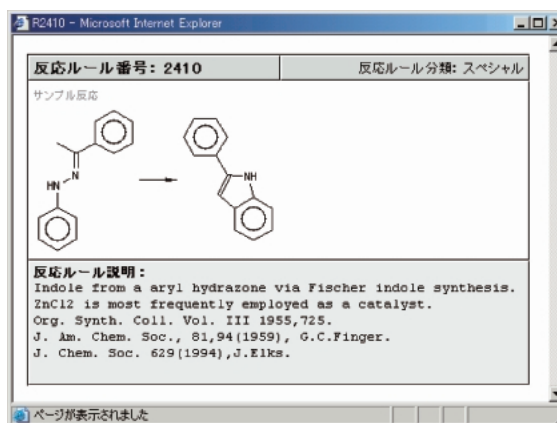
Fig. 7 Reference data in SYNSUP

Existing Reaction Databases

There are already a number of commercially available reaction database systems on the market. These systems consist of a variety of data vol-

umes, as well as collections of original data (**Table 5**). Up until the present time, we have been releasing, registering and managing reaction data and chemical compound data obtained on our own, using these commercially available databases. Although most commercially available databases possess outstanding functionality with respect to the retrieval of chemical compound and reaction data, they are difficult to customize in terms of linking to other systems and handling image data.

Table 5   Commercially Available Reaction Database System

System	Supplier	URL
ISIS/Host	MDL	http://www.mdli.com
SciFinder	CAS	http://www.cas.org
ChemFinder	CambridgeSoft	http://www.cambridgesoft.com
ACD/ChemFinder	ACD/Labs	http://www.acdlabs.com

In-House Web-CC Reaction Database

We have developed our own unique method for obtaining more detailed information from our in-house Web-CC reaction database. This method involves the creation of hyperlinks from existing data to related information (i.e., key words), through the use of the web browser's hyperlink function. When using the information retrieval function of the in-house reaction database, users can choose either an Exact Match or a Substructure Search (Fig. 3). **Fig. 8** depicts an example of the results produced for a Substructure Search with the N, N-Dimethylaniline structure.
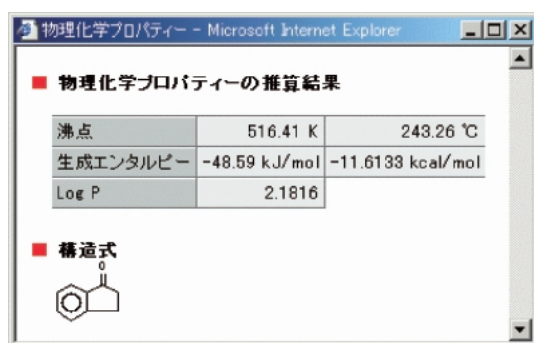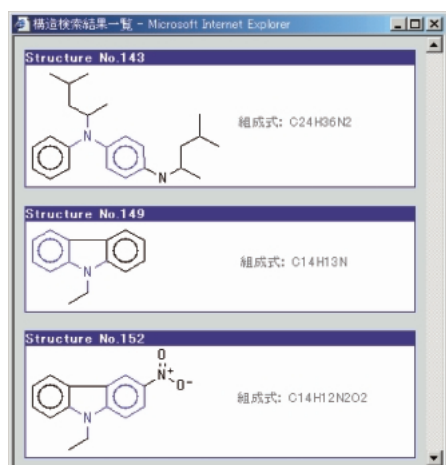

Fig. 8   Results of Substructure Retrieval

Physical Property Estimation

Chemical compounds possess a variety of physical properties. These physical properties include: fundamental physical data (heat of reaction, boiling point, melting point, viscosity) required for the design of chemical industry processes; new physical properties used for molecular design (for example, the viscosity and glass transition temperature needed for a new polymer); physical properties used for studying the quantitative structure-activity relationship (QSAR) of biologically active substances (for example, LogP, molecular refractivity, dipole moment); and conceptual physical properties (Hammett's σ value and electronegativity). The physical properties possessed by a single molecule may occasionally differ from those possessed by an assembly of the same molecules.

Physical property estimation methods in the area of computer chemistry can be roughly classified into two types. One such method allows for the estimation of physical properties through the following procedures: an entire system (either a single molecule or a molecular assembly) is divided into fragments; molecular weights are then determined for each fragment; and lastly, the total is obtained from the results of the individual fragment molecular weight determinations (using either linear or non-linear regression analysis). The other such method utilizes theoretical computations, such as MM, MO and MD, to estimate physical properties. The former of these two methods is known as quantitative structure-property relationship (QSPR). The use of QSPR results in the proposal of a variety of variables (Topological, [26] Electronic [27] and Geometrical descriptors [28]). A particular physical property can easily be estimated through QSPR, once the estimation equation has been determined. This method has therefore become publicly available on many internet websites. As an example of such usage within a corporate environment, a certain pharmaceutical company discloses on the internet, their estimated values for the physical property parameters (LogP, pKa, logD, polar surface area and molecular refractivity) required for quantitative structure-activity relationships. These values are obtained through the use of their own prediction system, created in combination with commercially available software [29].

Physical Property Estimation Using Web-CC

Fig. 9 depicts a screen displaying the estimation results for physical property values of 1-Indanone; the boiling point, enthalpy of formation and LogP value. A known estimation method was programmed and utilized for the predictive equation.

Results of Property Estimation

Unintentional Disclosure of Internal Company Information

Today, myriad information can easily be obtained from a multitude of different websites throughout the internet. Although the internet is a great convenience, additional caution is required when external websites are utilized during internal company research and development work. Detailed information pertaining to any operations that involve the internet, such as which particular requests are made from which devices, may be logged on external web servers. In other words, the mere process of accessing external websites in order to retrieve information, means that confidential internal information may also be unintentionally disclosed outside the company, at the same time. In addition, even the packaging and company-wide distribution of any system that has been developed internally involves the risk of a potential leak of the system itself, outside the company. The release of the Web-CC system, which we have developed internally, only onto our intranet, has great benefits in terms of the protection of internal company information, as the intranet is not accessible outside of our company. Moreover, we have implemented a variety of measures to protect data confidentiality, such as recording the access and information retrieval logs.

Conclusion

Taking into consideration the rapid evolution of computer hardware, we expect that in the future, the role of computer chemistry will take on even greater importance in the area of corporate research and development. Therefore, the establishment of a new environment for this field is one of the most important duties for computer chemistry specialists. This new environment must be designed so that the usage of computer chemistry systems is not limited only to certain company specialists, but can be utilized by as many internal researchers as possible.

Prior to our development of Web-CC, our factory sector had actually demonstrated a greater desire for a new system than had our research sector. This is because our factory sector was hoping that the new system would allow our research sector to be able to conduct even better research and faster development of new products, since they could take advantage of information received directly from our factories. We sincerely hope that our Web-CC system will be capable of accommodating all of their needs.

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