CHIMIA 49 (1995) Nr. 5 (Mai)

as an interactive platform is the users' workplace. Interactive work such as file editing, code writing and submitting of NQS batch jobs can be done on the front end.

The front end system is also manager for a large archive system and handles massive amounts of data. Its capacity amounts to more then 4 TBytes.

The CSCS local network is linked to the worldwide Internet community through *PTT-Telecom* leased SWITCH lines. These lines, linking CSCS to ETHZ, EPFL, CERN, and all Swiss universities, are currently rated at 2MBits/s.

If you are interested in more information or documentation, please feel free to contact us.

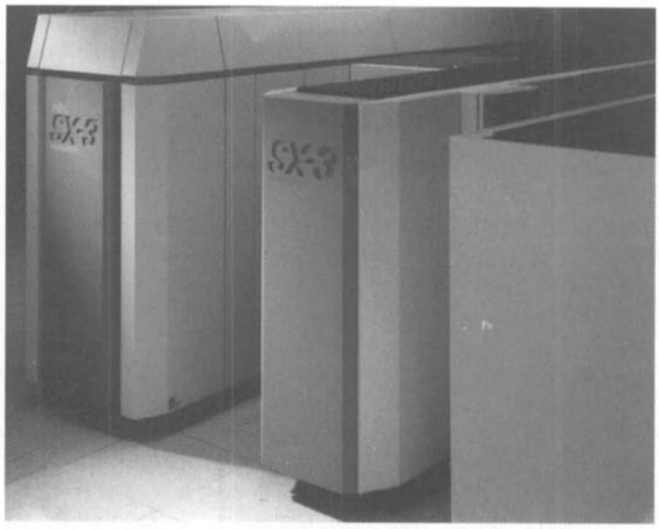

Fig. 2. NEC SX-3124R
vector computer

Chimia 49 (1995) 125–127

ISSN 0009–4293

Quantum Chemistry and Drug Design

Hans Ulrich Suter[a])*, **Djordje M. Marič**[a]), **Jacques Weber**[b]), and **Colin Thomson**[c])

Abstract. The state-of-the-art computational chemistry software, visualization tools and high performance computing infrastructure are employed to assist the design of new and more effective drugs. At present a project focuses on the quantitative structure activity relationships of antimalarial drugs.

1. Introduction

Computational methods today play an important role in modeling applications in molecular sciences such as chemistry and biology. In particular, drug design techniques based on computational tools recently have proved to be very efficient in predicting the potency of possibly active compounds among a large series of molecular systems [1]. In this article we concentrate on this specific field of drug design and mainly on its relationship with high performance computing. We also briefly describe the results of such an investigation we are currently carrying out on antimalarial compounds derived from the lead system artemisinin, known in China as the traditional medicament *Qinghaosu*.

The key steps in rationalizing and predicting the biological activity of a given molecule start invariably with the determination of the structure of this compound. Traditionally, this has been done using experimental techniques such as X-ray crystallography. Nowadays, however, progress in both computer hardware and computational chemistry methods is such that this determination can be performed theoretically with considerable reliability. Quantum chemistry is indeed in principle able to reproduce the structural parameters of molecules to a high accuracy (*i.e.* ± 0.01 Å on bond lengths and ± 2° on bond and torsion angles) provided that ample computational resources, such as those provided by a supercomputer, are available. The second step is more heuristic: how to correlate the structure, and possibly some molecular properties, with the biological activity of the compound? This is generally achieved using the approach of structure activity relationship (SAR) correlation, or quantitative SAR (QSAR) correlation if the relationship is of a quantitative nature. In other words, mathematical equations are developed to correlate biological effects of a set of compounds with their structural and molecular properties.

Of course, a better, but very difficult, procedure would consist of a comprehensive description of 'what is happening' in the biological system under the effect of the drug. This includes the whole path followed *in vivo* by the drug from the intake up to its binding to the active site, and the chemical reactions which are induced by the drug or in which the drug takes part. Needless to say, the comprehensive knowledge of this complex process would enable one accurately to ration-

*Correspondence: Dr. H.U. Suter
[a]) Centro Svizzero di Calcolo Scientifico
Via Cantonale
CH–6928 Manno
[b]) Department of Physical Chemistry
University of Geneva, CH–1211 Geneva 4,
[c]) Department of Chemistry
St. Andrews, Scotland

CHIMIA 49 (1995) Nr. 5 (Mai)

as an interactive platform is the users' workplace. Interactive work such as file editing, code writing and submitting of NQS batch jobs can be done on the front end.

The front end system is also manager for a large archive system and handles massive amounts of data. Its capacity amounts to more then 4 TBytes.

The CSCS local network is linked to the worldwide Internet community through *PTT-Telecom* leased SWITCH lines. These lines, linking CSCS to ETHZ, EPFL, CERN, and all Swiss universities, are currently rated at 2MBits/s.

If you are interested in more information or documentation, please feel free to contact us.

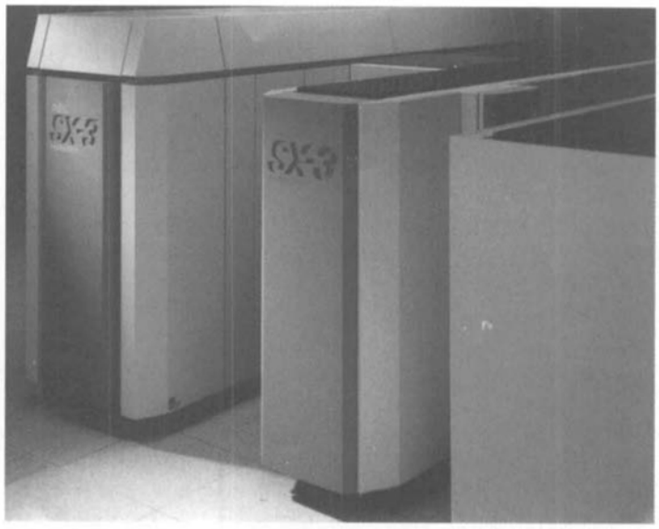

Fig. 2. NEC SX-3124R
vector computer

Chimia 49 (1995) 125–127

ISSN 0009–4293

Quantum Chemistry and Drug Design

Hans Ulrich Suter[a])*, **Djordje M. Marič**[a]), **Jacques Weber**[b]), and **Colin Thomson**[c])

Abstract. The state-of-the-art computational chemistry software, visualization tools and high performance computing infrastructure are employed to assist the design of new and more effective drugs. At present a project focuses on the quantitative structure activity relationships of antimalarial drugs.

1. Introduction

Computational methods today play an important role in modeling applications in molecular sciences such as chemistry and biology. In particular, drug design techniques based on computational tools recently have proved to be very efficient in predicting the potency of possibly active compounds among a large series of molecular systems [1]. In this article we concentrate on this specific field of drug design and mainly on its relationship with high performance computing. We also briefly describe the results of such an investigation we are currently carrying out on antimalarial compounds derived from the lead system artemisinin, known in China as the traditional medicament *Qinghaosu*.

The key steps in rationalizing and predicting the biological activity of a given molecule start invariably with the determination of the structure of this compound. Traditionally, this has been done using experimental techniques such as X-ray crystallography. Nowadays, however, progress in both computer hardware and computational chemistry methods is such that this determination can be performed theoretically with considerable reliability. Quantum chemistry is indeed in principle able to reproduce the structural parameters of molecules to a high accuracy (*i.e.* ± 0.01 Å on bond lengths and ± 2° on bond and torsion angles) provided that ample computational resources, such as those provided by a supercomputer, are available. The second step is more heuristic: how to correlate the structure, and possibly some molecular properties, with the biological activity of the compound? This is generally achieved using the approach of structure activity relationship (SAR) correlation, or quantitative SAR (QSAR) correlation if the relationship is of a quantitative nature. In other words, mathematical equations are developed to correlate biological effects of a set of compounds with their structural and molecular properties.

Of course, a better, but very difficult, procedure would consist of a comprehensive description of 'what is happening' in the biological system under the effect of the drug. This includes the whole path followed *in vivo* by the drug from the intake up to its binding to the active site, and the chemical reactions which are induced by the drug or in which the drug takes part. Needless to say, the comprehensive knowledge of this complex process would enable one accurately to ration-

*Correspondence: Dr. H.U. Suter
[a]) Centro Svizzero di Calcolo Scientifico
Via Cantonale
CH–6928 Manno
[b]) Department of Physical Chemistry
University of Geneva, CH–1211 Geneva 4,
[c]) Department of Chemistry
St. Andrews, Scotland

CHIMIA 49 (1995) Nr. 5 (Mai)

alize the mechanism of drug action, and, ultimately, to design new active compounds.

If we restrict ourselves to QSAR, which is by far the most popular approach in drug design, we have seen that correlations are sought between structural and physico-chemical properties of similar potential drugs and their activity. One obvious relationship may be expected between the solubility of a molecule, *e.g.* its ability to enter the solvent phase, and its biological activity. In other words, the more soluble the molecule, the better it should reach the active site in the biological system. This is the basic hypothesis of the well-known *Hansch* analysis [2], which correlates experimentally determined parameters for solubility with drug activity. This method has led to many successful QSAR investigations. Another approach consists of calculating the electronic structure of the molecule and of describing how the surrounding solvent phase would 'see' the molecule. This may be achieved by evaluating the gross charges of the various atoms of the system derived by a least-squares fit to the molecular electrostatic potential (MEP) calculated using a quantum chemical method. The MEP is a local property defined as the interaction energy of a positive charge (*i.e.* a proton) with the unperturbed molecule.

Another drug design approach is based on the so-called 'lock-and-key' model which is somehow related to the binding mechanism of the drug to the protein receptor. In this model, it is assumed that the interaction of the drug with the active site is the rate determining step in the mechanism. In this case, it is necessary to have some knowledge about the interaction site, such as the active part of an enzyme inhibited by the drug. One tries then to sterically fit the drug into a pocket of the site which is presumably active. This type of modeling drug-receptor interactions is performed interactively on graphical devices. As this approach is based on steric effects only, it should be replaced whenever possible by more efficient techniques that also take account of electronic effects.

2. *Qinghaosu* as Antimalaria Drug

The herb *Artemisia annua* (qing hao su) has been used for a long time in traditional Chinese medicine for the treatment of fever, headache, and malaria. In 1977 Chinese scientists were able to isolate and characterize the molecule, thereafter called *Qinghaosu* or artemisinin, responsible for the antimalarial activity of this herb. *Qinghaosu* is a sesquiterpene containing a 1,2,4-trioxane six-membered ring (*Fig.*).

Another substance exhibiting antimalarial activity and also containing the O–O peroxo moiety has been isolated from the Chinese plant *Artabotrys uncinatus* and was called *Yingzhaosu A*. Since the discovery of these compounds several laboratories have attempted to synthesize better drugs based on this structure. At the Department of Organic Chemistry of the University of Geneva, *e.g.*, the group of *C.W. Jefford* has synthesized several 1,2,4-trioxanes structurally resembling artemisinin in an attempt towards defining structure-activity relationships. As the first step in the collaboration with CSCS, the *Qing-*

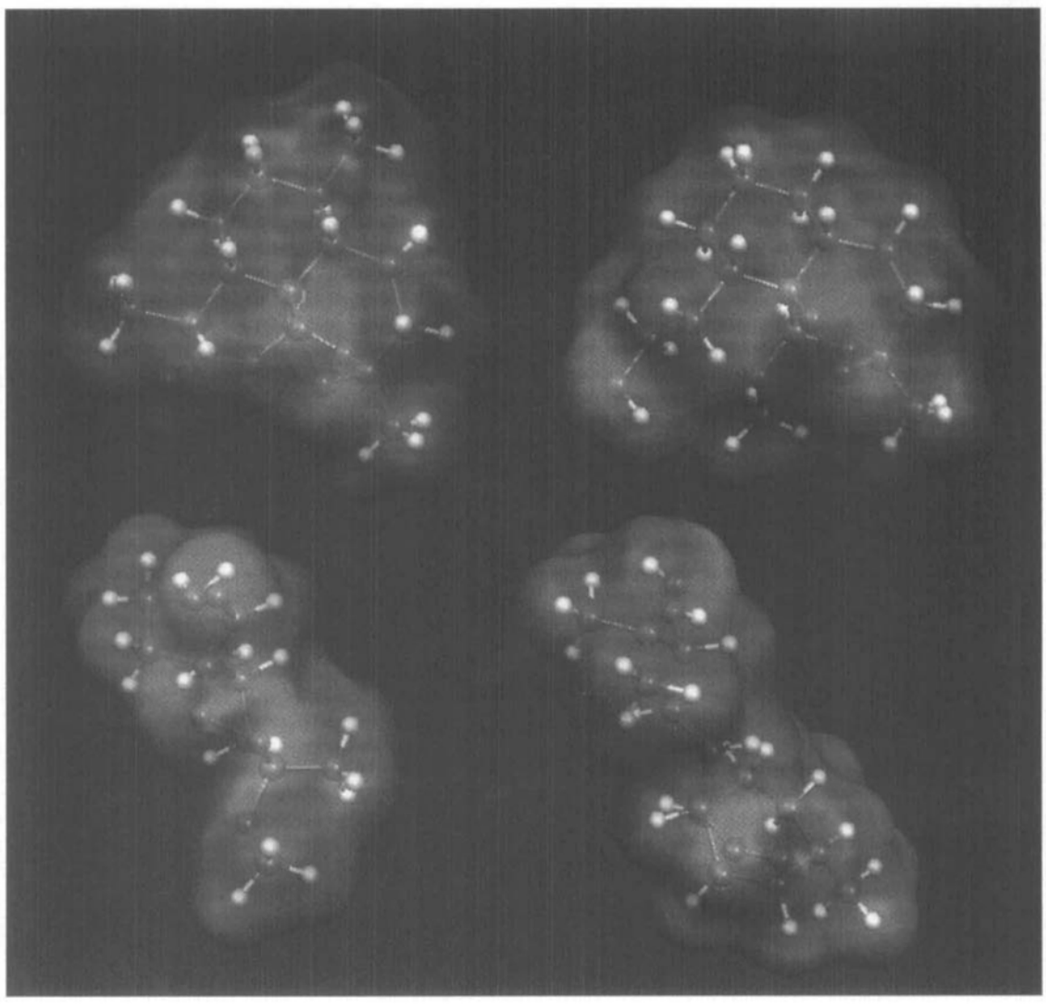

Figure. *The molecular electrostatic potential (MEP) given by a* Gaussian *92/DFT calculation and displayed with the MOLEKEL program.* The molecules are *Qinghaosu*, an active modification, an inactive modification, and *Yingzhaosu A*.

haosu and *Yingzhaozu A* systems have been theoretically investigated using quantum chemical methods.

3. Optimization of the Geometry

As discussed above, it is essential in QSAR studies to know the 3-dimensional structural parameters of the compounds investigated. Theoretical methods enable us today to calculate these parameters, *i.e.* to perform a molecular geometry optimization, at different levels of approximation. Molecular mechanics techniques, based on the use of classical force fields, present the advantage of limited computing effort, but they may be applied only to systems falling in the range of those employed for the parametrization.

Computational quantum chemistry methods are generally based on the *Born-Oppenheimer* approximation which assumes separability between the motions of the electrons from those of the nuclei. Therefore, the optimum molecular geometry is obtained from the minima of a potential energy surface given by the sum of the electronic (quantum) and nuclear (classical) energies. As the first one has to be calculated repeatedly for a series of positions of fixed nuclei, the problem may involve a substantial computing effort for large systems.

The basic problem of quantum chemistry is thus to calculate electronic energies and wavefunctions. In the *Hartree-Fock-Roothaan* approximation, which has long been used to this end, the major difficulty is due to the large number of two-electron integrals to be calculated, which scales approximately as the fourth power of the number of electrons.

Semi-empirical methods are less demanding in terms of computer resources, but they are more approximate as they neglect part of these integrals. An example is provided by the PRDDO method which has been described in a previous *Crosscuts* issue [3].

In some cases, it may be important to go beyond the *Hartree-Fock* approximation by taking account of correlation effects, which may be performed in the *ab initio* formalism using perturbation theory such as the 2nd-order *Moller-Plesset* (MP2) method. An interesting alternative is provided by Density Functional Theory which is now a widely accepted approach to introduce correlation, especially for transition metal systems.

The *Table* presents some structural parameters and the approximate computer time requested for a full geometry optimization of artemisinin derivatives. The computer time is strongly dependent on the level of calculation. Molecules of the size of *Qinghaosu* may be calculated at CSCS using methods which go beyond the *Hartree-Fock* level. This is a prerequisite as the *Table* shows that the *Hartree-Fock* calculation predicts a bond distance which is 10% in error, while the semi-empirical (PM3) calculation leads to large discrepancies for bond and torsion angles.

Table. *Four Geometrical Parameters of* Yingzhaosu A (45 Atoms and 148 Eectrons) *and Estimated Computational Time for a Geometry Optimization on the* NEC-SX-3 *with the* Gaussian *92/DFT Program*

Method	Distance [Å]	Angle 1 [°]	Angle 2 [°]	Angle 3 [°]	Time
PM 3	1.546	113.1	112.1	–59.6	min
RHF/6-31G*	1.389	108.6	109.7	–81.1	6 h
BLYP/6-31G*	1.505	107.1	108.6	–78.7	10 h

Currently, density functional methods are the best suited for geometry optimization of molecules of the size of artemisinin. However, progress in hardware and software technologies suggest that correlated *ab initio* calculations may also be carried out in the future for such systems.

4. Visualization

After geometry optimization, it is useful to visualize the main content of the results. This is very useful for such molecules of biological interest, as this enables the user to fully grasp the main features of the system, as its size, 3D conformation, wavefunctions, *etc.* The MOLEKEL program developed by the University of Geneva and CSCS [4] turned out to be very useful to this end. Indeed, the use of molecular models is essential in chemistry, as exemplified by the famous stick (*Dreiding*), ball-and-stick and space-filling models. The advantage of computer graphics resides in its capability to visualize features which are not representable by mechanical models. In addition, it enables us to display properties obtained from quantum chemical calculations, such as the MEP.

5. Structure Activity Relations

It is an essential step now to correlate the results of quantum chemical calculations with biological activities. This is a task where much space is left for the drug designer to use his chemical insight. It is also obvious that here the computer may play an important role, for instance by providing tools derived from artificial intelligence. Some recently reported investigations use neural networks to find descriptors based on physico-chemical properties calculated on molecular surfaces [5].

We have performed some preliminary studies in this direction by using neural networks to project 3D MEPs on 2D surfaces so as to more easily compare the main features of the MEPs calculated for the various systems and to elaborate some correlations with their biological activities. Ultimately, this procedure should lead to predicting which are the most potent antimalarial compounds among a given series.

It may be thus expected that such investigations provide some help in the rationalization of the mechanism of action these drugs and, ultimately, contribute to the development of novel pharmaceutical substances.

[1] W.G. Richards, *Pure Appl. Chem.* **1994**, 1589.
[2] C. Hansch, *Acc. Chem. Res.* **1969**, 232.
[3] D.S. Marynick, A. Dereckskei-Kovacs, S.K. Estreicher, M.A. Roberson, D.M. Maric, *Crosscuts* **1994**, *3/2*, 1.
[4] P. Flükiger, Ph.D. thesis 2561, University of Geneva, 1992.
[5] J. Zupan, J. Gasteiger, 'Neural Networks for Chemists: An Introduction', VCH, Weinheim, 1993.