EMERSON CENTER Newsletter

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EMERSON CENTER EXPANDS ITS INT'L BORDERS

Reported by Dr. Jamal Musaev,
Principal Scientist and Manager of the Emerson Center

The reputation of the Cherry L. Emerson Center is continuously growing among international scholars, partially because of its well-recognized Visiting Fellowship program, the high international reputation of its Subscribers, Director and Scientific Staff, and the state-of-the-art research activities on the Emerson Center's facilities. The Emerson Center is very proud that its Director, Prof. Keiji Morokuma, was elected the President of the prestigious International Academy of Quantum Molecular Sciences, in the year 2000.

Dr. Musaev & Prof. Hirao

In this aspect, my recent visit to Japan, the University of Tokyo, as a Visiting Professor of Intelligent Modeling Laboratory, helped to significantly promote the Emerson Center's position among Japanese scientists. During my two months stay in Japan, I visited nineteen Universities and R&D Laboratories (including Tsukuba and Okazaki National Research Centers, Toyota Technological Institute, Mitsubishi Chemical Inc., Universities of Keio, Kyoto, Nagoya, and more), and presented more than 25 scientific talks. As a result, we have set up the collaborative research activities between the Emerson Center's researchers and several Japanese research laboratories, including the Intelligent Modeling Laboratory (The University of Tokyo, Japan).

The Intelligent Modeling Laboratory (IML) was founded in 1996 with funding from the Japanese government. It is directed by Prof. K. Hirao, an internationally acclaimed scholar and the Vice-Dean of the School of Engineering, Univ. of Tokyo. IML includes more than 80 research groups and involves the following (to mention only a few) research projects:

- Molecular Structure and Simulation

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NEWS FROM THE ECEC MEETING

The Emerson Center Executive Committee (ECEC) met on Monday, September 9, 2002, to discuss issues related to the new school year. On the agenda were administrative issues including membership, income & expenses, and the EC newsletter. The new year subscription to the center has reached 17.25 shares, compared to 12 shares in the last academic year. Please refer to the Center's website: www.emerson.emory.edu for the current list of subscribers and users. The center's scientific staff presented a technical report on hardware and software purchases. Dr. Jamal Musaev, Manager of the center, reported to the committee on his trip as a visiting professor in the summer. Please see this page for report details. Plans for 2002-2003 were discussed including budget issues, the Visiting Fellows Program, and hardware upgrade of the center's equipment. A 5% increase to the subscriber fee was approved by the committee.

Biology Professor as New Subsriber to Emerson Center

The Emerson Center welcomes Dr. Rustom Antia, Associate Professor, Department of Biology, Emory University, to become the newest subscriber of the Emerson Center. Dr. Antia's research interests range over the population dynamics of microparasites and the immune responses they elicit. Dr. Antia describes his research interests as "encompassing a broad area of theoretical and empirical studies of the interaction between pathogens and the immune response. I use mathematical models and computer simulations in conjunction with experimental work to: (i) understand the complex and often counter-intuitive dynamics of pathogens and immune responses in vivo, (ii) estimate important biological parameters that are not directly measurable by experimentation, and (iii) generate empirical tests of different models and hypotheses. Almost all my theoretical work is based on experiments, mostly done in collaboration with other experimental immunologists at Emory and the CDC, and some done in my laboratory."

Letters from Fellows

I appreciate the five-month opportunity to join Professor Dennis Liotta and Dr. Jim Snyder and their molecular modeling group. During the last decade my computational interests were focused on hydrogen bonding in small, but biologically important models. These early studies carried out with MOPAC program demonstrated to me that even simple quantum-chemical calculations can provide both important insights into the nature of the organizing forces of biomolecules, and also reproduce essential aspects of their stereochemistry. Although over the last ten years dramatic progress in density functional computational chemistry as well as hybrid quantum mechanics/molecular mechanics methods has been made, for the evolving genomic era we need significant improvements in well parametrized force fields to properly reflect stereoelectronic interactions in massive biomolecules, primarily proteins. The Emerson Center Visiting Fellowship has given me the chance to use state-of-the-art biomolecular modeling software on modern Silicon Graphics workstations. The Tripos Sybyl program has proved to be the tool of choice for resolving the sophisticated problem of judging the bioactive conformation of an important drug at its protein target.

Dr. Marek R. Lozynski

I want to express my profound gratitude to Dr. Jim Snyder for his suggestions, his comments and, particularly, his personal guidance. I am indebted to Jim H. Nettles for helpful discussions on the detailed protocol of the calculations. I also want thank the staff of the Center for perfect service and enthusiastic assistance.

**Dr. Marek R. Lozynski is Senior Lecturer at the Department of Chemical Technology, Poznan University of Technology, Poznan, Poland. He stayed at the Emerson Center from April 2002 to September 2002 with a fellowship provided by the Visiting Fellows Program at the Emerson Center.*

EMERSON CENTER VISITING FELLOWSHIP

The Emerson Center offers visiting fellowships to interested scientists throughout the year. Scientists from academic institutions all over the world who want to perform intensive research in computational chemistry, biology, physics, and math & computer sciences for one to several months are encouraged to apply. Travel expenses and stipends are available. Although fully independent research is not excluded, collaboration with an EC subscriber is desirable, and EC subscribers are encouraged to make recommendations. The deadline for Emerson Center Visiting Fellowship applications for summer 2003-summer 2004 is February 1, 2003. To formally apply, please submit:

- *1-2 page research proposal*
- *CV including publication list*
- *Amount of financial support needed*
- *Length of stay with an approximate start/end date*

Applications should be submitted to the Emerson Center (address on p. 4).

APPLICATION DEADLINE: FEBRUARY 1, 2003

My Stay at the Emerson Center as a Visiting Fellow

Dr. Laszlo Nemes, Central Research Institute for Chemistry

Hungarian Academy of Sciences, Budapest, Hungary

This past Spring-Summer I had the privilege to become a Visiting Fellow at the Emerson Center. This visit was the outcome of some two years of previous scientific contact with Professor Joel Bowman, and was initiated by a common interest in the application of the VSCF (vibrational self-consistent field) method to the fullerene (C_{60}) molecule. Actually during those two months I was given the opportunity to work in Professor Bowman's group on another interesting molecule, ketene (CH_2CO).

Dr. Laszlo Nemes and his wife in Savannah, Georgia.

I am very grateful to both Professor Bowman and Professor Keiji Morokuma for this invitation that I enjoyed to the full. I had an opportunity to get to know the Group, and in particular to collaborate closely with Professor Bowman and his Ph.D. student Tiao Xie. We spent many hours of discussion over the potential function of ketene and had started MULTIMODE calculations of its vibrational-rotational spectrum in the infrared spectral range. Through those discussions (sometimes quite intense and animated) I learnt new approaches to spectroscopic problems from the angles of molecular dynamics, oftentimes quite different from my own, ingrained way of looking at molecules. Thus the personal contact with Professor Bowman has been a unique learning opportunity for me.

I also owe my thanks to Dr. Jamal Musaev and Dr. Stephan Irle for their never failing help to me in the operation of the facilities at Emerson Center, as well as the personal help myself and my wife received from Ms. Jianli Zhao. And I am very proud of being included in the webpage for the Bowman Group created by the expert photography of Ms. Susan Browne.

We also enjoyed with my wife the trips we made in Georgia and to Tennessee, the lush woods in and around Atlanta and the possibility to get to know the Southern Soul.

Reports on Research Activities at the Emerson Center

The Emerson Center is supported, in part, by "subscribers" -- faculty members, research groups or departments who purchase shares in order to gain access to its resources for their research projects. EC scientific staff members are also encouraged to conduct scientific research in their own areas of specialty. In this issue, we have research reports from two research groups who uses the Emerson Center facilities for their research.

Geometry of Biradical Intermediates Engaged in B_{12} Enzyme Catalysis Revealed by Orientation-Selection ESEEM Spectroscopy

Research Report by Jeffrey M. Canfield & Kurt Warncke
Department of Physics, Emory University

We are using experimental techniques of pulsed-electron paramagnetic resonance (EPR) to determine the structure and dynamics of paramagnetic catalytic intermediates in a class of enzymes that use coenzyme B_{12} to perform radical-mediated catalysis. A useful property of the EPR spectra of these Co^{II}-radical pair intermediates in our frozen, disordered samples is that different positions in the EPR spectrum correspond to subsets of molecular orientations. Therefore, a high resolution EPR experiment, such as the electron spin echo technique, ESEEM, which is performed at a single magnetic field value, measures the electron-nuclear interactions for a subset of molecular orientations. In principle, this "orientation-selection" approach can lead to "single crystal-like" spectra, with all of the attendant information about atom geometries, but from a disordered sample!

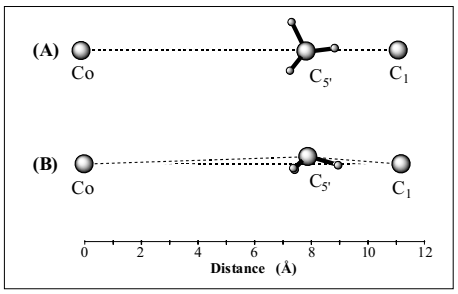


Figure. *Model for the structure of the Co(II), 5'-deoxyadenosine C5' methyl group, and C1 substrate radical center in the Co(II)-substrate radical pair state of ethanolamine deaminase. The positions of the atom centers are to scale, relative to the plane of the Co-C1 axis, which lies in the plane of the page. The distance scale is in the plane of the Co-C axis. View (B) represents a 90° rotation about the Co-C axis relative to view (A).*

In practice, the modest orientation selection afforded by the electron-electron dipolar interaction in our system requires the collection of ESEEM at several magnetic field values across the spectrum, and a computation-intensive strategy for extraction of the geometric information. We have developed a novel approach of global simulation of the magnetic field-dependent ESEEM. The matrix-based algorithms are coded in Matlab (v. 6, MathWorks), and Emerson Center computers are used in the computations. Recent results [*J. Phys. Chem. B* 2002, **106**, 8831] have revealed the geometry of reactant centers in the Co^{II}-substrate radical pair state of the B_{12} enzyme, ethanolamine deaminase from *Salmonella typhimurium*, as shown in the Figure. The results provide insight into the principal nuclear coordinates involved in radical rearrangement and hydrogen atom transfer reactions in the enzyme. This work is supported by the NIH (DK54514).

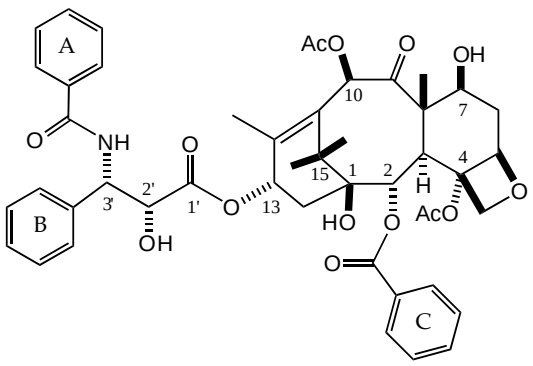
Molecular Modeling of Taxol Bioconformation & Photoaffinity Labels in β-Tubulin

Reported by Marek Lozynski (EC Visiting Fellow)
Jim Snyder and Dennis Liotta, Department of Chemistry

Taxol (**1**, paclitaxel) is a naturally occurring antitumor drug, introduced into the clinic in the late 80's and targeted to breast and ovarian cancers. For biologists it is a member of a growing family of natural products that selectively stabilizes a polymeric form of tubulin, namely microtubules. For the synthetic chemist, Taxol is a highly functionalized, chiral molecule with eleven sterogenic carbons containing the rigid, tetracyclic diterpenoid baccatin core as its centerpiece.

From the viewpoint of the computational chemist, Taxol is a polycyclic baccatin scaffold decorated with four side chains at C-2, C-4, C-10 and C-13. The latter incorporate ten single bonds contributing to the considerable conformational flexibility of the molecule. The longest C-13 side chain is particularly rich in molecular conformations due both to its length and the lack of steric constraints around the seven single bonds. Overall, the presentation by Taxol of three benzene rings (A, B and C) and a hydrophobic region of the core (C-15(Me2)) is important for binding four hydrophobic domains at the ligand-controlling cleft of the tubulin protein.

The rational design of new Taxol analogues would be facilitated if the three-dimensional structure of the bioactive conformer (i.e. the conformer encapsulated within the β-tubulin binding site) could be determined and correlated with its pharmacological properties. Ideally, a future generation of anti-cancer drugs would contain the necessary 3-D features of Taxol without its structural complexity. Recently, on the basis of combined NMR and electron-crystallographic studies on Taxol and the α,β-tubulin dimer, it has been proposed that the drug binds to a hydrophobic pocket in a T-shaped conformation. Molecular modeling shows that nearly the entire, "Emory-born" T-molecule is embedded in a 7 Å deep and 10 Å wide binding cavity. Because competitive models exist, we decided to employ molecular dynamics simulation followed by aggregate optimization to validate the proposed structure by comparison with experimental photolabeling results. Four such experiments that identify specific peptides and individual residues in β-tubulin were taken as the basis for our molecular modeling studies. All of the experiments incorporated radiolabeled rings (i.e. tritium) and a photoreactive center in rings A and C. Three studies employed phenyl azides at the same phenyl rings,



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--EC Extends Borders, Continued from page 1

- Development of Fundamental Techniques for Large Scale Parallel Computation
- Intelligent Material Design
- High-Precision Three-Dimensional Bio-Structure Modeling
- Development of a Software System for Analyzing Protein Structure and Function
- Seismic response simulation of transportation facilities, and more.

Similar to the Emerson Center's Visiting Fellowship program, IML has set up an active exchange program (with other institutions of Japan and overseas) for collaborative research. I am pleased that they have chosen EC's research staff to be one of them.

Our colleagues in Japan and research staff at the Emerson Center are planning to jointly elucidate the problems of the catalytic nitrogen fixation, the application of small clusters and nano-structures to important catalytic processes, the search for more effective drugs against peroxynitrite related diseases (such as heart diseases, cancer, and apoptotic cell death in leukemia and aortic smooth muscle cells), and the search for an effective drug delivery systems based on nano-technology.

New Location for Emerson Center Apartment

The Emerson Center Apartment for Visiting Fellows will move to Emory's Clairmont Campus on Nov. 1, 2002. We will have to a 2-bedroom/2-bathroom apartment there. This move will offer better living conditions for our Visiting Fellows while providing them easy access to campus. The apartment will be fully furnished, with cable TV and internet access.

The Center also makes the apartment available to other short-term visiting faculty on campus when there is a vacancy. The rent, which includes all utilities and local telephone service, is $660 per room per month, or $30 per day if less than 30 days. Please contact Jianli Zhao at 727-0867 for more information.

--Lozynski Research Report, Continued from page 3

while a fourth utilized a benzophenone unit linked to Taxol's C-7 alcohol. To mimic geometric control of the reactivity of the various photolabels, we examined all possible rotamers of the azido-substituted derivatives in individual molecular dynamics and energy minimization calculations.

The resulting complexes of substituted Taxol and β-tubulin strongly support the T-conformation, while rejecting other models including the so-called "hydrophobic collapse" conformer. The relatively high photoincorporation yield for one experiment and the high regioselectivity of another is easily rationalized by appealing to both hydrophobicity and hydrogen bond concepts as the organizing forces behind the photolabeling reaction.

The Emerson Center Fellowship, of course, was the key factor in permitting these studies to be carried out. As a complement, the biomolecular software facilities of the Emerson center, in part, allowed us to perform the molecular dynamics calculations quickly followed by perfect visualization of the results. In the nearest future we anticipate submitting the work for publication.

New & Upgraded EC Software Packages

Stephan Irle and Jamal Musaev, Emerson Center

As the Emerson Center's subscribers' interests become more and more diverse, the list of installed application software packages at the Center continues to grow. Recently, we have installed numerical computational tools such as Matlab, Mathematica and IDL. Smaller tasks using these software packages can be solved interactively on our main server, euch4e, or on one of several older workstations. However, numerically intensive calculations should be running under LoadLeveler, using the scripts /libs/scripts/matlabrun (for Matlab) or /libs/scripts/mathrun (for Mathematica) and a user-generated input file which consists of otherwise interactively typed commands. These software programs can also display information graphically either directly at the Emerson Center or remotely at an X-windows capable terminals in your laboratories. IDL can be run only interactively and is started using the script /libs/idl/idl/bin/idl.

On the quantum chemical software side, we very recently installed CADPAC 6.5 and thereby mainly expanded the list of available density functionals unique to this code (Handy's HCTH, HCTH147, B97, PBE and PBE0 functionals). From this package, the TDDFT calculations for frequency dependent polarisabilities, excitation energies and gradients and dispersion coefficients are available as well. Other features include intermolecular perturbation theory (IMPT), distributed multipole moments and polarisabilities by numerical integration, and distributed polarisabilities by the LeSueur-Stone algorithm. The code has been made considerably faster as compared to the old CADPAC 4 version and provides a valuable alternative to the functionals available in GAUSSIAN. The new CADPAC 6.5 program can be run under LoadLeveler on our SP3 by using the script /libs/scripts/cadpac6. Other upgrades were made to the following software packages: Jaguar 4.1, MacroModel_7.2, Sybyl_6.8, and MOLPRO 2002.1.

TINKER, a classical molecular dynamics software package, has now been installed also for our IBM SP3 nodes in addition to the previously available SGI version. The TINKER molecular modeling software is a complete and general package for molecular mechanics and dynamics, with some special features for bio-polymers. TINKER has the ability to use any of several common parameter sets, such as AMBER94/96, CHARMM27, MM2(1991), MM3(2000), OPLS-AA and OPLS-UA. Included are a variety of novel algorithms such as a new distance geometry metrization method that has greater speed and better sampling than standard methods, Elber's reaction path methods, and several of our Potential Smoothing and Search (PSS) methods for global optimization. TINKER has many more features suitable for structural analysis and it is very easy to extent by using an extensive library of FORTRAN routines. The User has to create a LoadLeveler .cmd file specifying which module to run according to the syntax as given on the TINKER homepage http://dasher.wustl.edu/tinker/.

RATFOR is a minor addition to the Center's arsenal of compilers. It is a preprocessor for FORTRAN code that allows to use C-like flow expressions. Statements on a line may be separated by a ";". Statements may be grouped together with braces {}. Do loops do not require statement numbers because {} defines the range, etc. The Fortran relational operators .gt.,.ge,.ne., etc. may be written >,<=,!=,etc. In addition to installing RATFOR, the GNU GCC/G++/G77 family of compilers has been upgraded to version 3.1.

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