別記様式第３号　　　　　　　　　　　　　　　　　　　　　　　　　　　　　課程博士用

豊橋技術科学大学長　殿

平成 _10_ 年 _12_ 月 _15_ 日

審査委員長　スヲニナ

論文審査及び最終試験の結果報告書

このことについて，下記の結果を得ましたので報告いたします。
記

学 位 申 請 者	Eugen Deretey	学籍番号	第 _957270_ 号
申 請 学 位	博 士（工 学）	専 攻 名	機能材料工学専攻
論 文 題 目	Analysis of Macrocyclization Reaction（大環化反応の解析）		
公開審査会の日	平成 _10_ 年 _12_ 月 _11_ 日		
論文審査の期間	平成 _10_ 年 _4_ 月 _22_ 日～平成 _10_ 年 _12_ 月 _14_ 日	論 文 審 査 の 結 果	合 格
最 終 試 験 の 日	平成 _10_ 年 _12_ 月 _11_ 日	最 終 試 験 の 結 果	合 格

論文内容の要旨

The Ph.D. thesis of Mr. Eugen Deretey of Rumania consists entirely from computational work applied to a topical reaction system from synthetic organic chemistry. The computational work models reactions relevant to the synthesis of erythromycin A, an efficient antibiotic with its chemical structure based on a fourteen-membered cycle. The erythromycin synthesis was reported by Woodward et al. in 1981 through a ring closure reaction of the properly protected seco acid. The model computations on the system are performed using empirical, semi-empirical, and non-empirical or ab initio techniques of computational chemistry. In the initial stage, the search in the conformational space is carried out with the Conflex procedure in combination with the MM2 energy function. The conformational search was performed with limits of 6.7 and 10 kcal/mol for the reactive seco acid and the macrocyclic cyclic lactone, respectively. Analysis of the steric energy components was also carried out. Then, the study concentrates on transition-state search for the lactonization in order to provide a deeper insight into the reaction mechanism and the related model calculations are performed at a sophisticated ab initio level - the geometry optimizations using the Hartree-Fock SCF approaches HF/6-31G* and HF/6-31+G**. The reaction energetics is further checked with the second orderd Møller-Plesset perturbation theory MP2/6-31G* in order to evaluate the electron-correlation effects. The correlated approaches reduce the activation energies significantly. Interesting linear relationships are found for various geometrical parameters from the HF/6-31G* and HF/6-31+G** methods. The transition-state search is verified by application of the intrinsic-reaction coordinate technique. However, this high-level theoretical tools can be applied to small molecules only. Thus, the transition states for the reactive seco acid are to be compute at semi-empirical level. In particular, two most recent methods are employed, viz. the PM3 and SAM1 semi-empirical methods. The advanced SAM1 method produces lower activation energies. The computed data allow for some interesting conclusions on the reaction mechanism. For example, the starting step is represented by an elongation of the (O=)C-S bond. Though some of the bonds in the transition state are relaxed, the hydrogen atoms themselves are bonded. In the transition state the hydrocarbon backbone is close to the lactone structure. The semi-empirical structure findings agree with the ab initio ones.

審査結果の要旨

The thesis deals with an attractive problem from synthetic organic chemistry and applies adequate affordable computational tools in order to support and interpret the observed facts and supply details not accessible by experiment. The committee members pointed out several interesting questions from both theoretical and experimental sides: possible influence of various protecting groups and structural simplification in the model used, equilibrium vs. non-equilibrium conditions in the experiment, effects of reaction concentrations, possible polymerization, comparison of the Hartree-Fock and correlated treatments, further expansion of the basis set, semiempirical parameters for the S atom. The work brings a distinctive and substantial novelty and expands the present insight into the reaction behavior of the reactive seco acid in the ring closure process; it helps to understand the high reaction specificity. The considerably extensive conformer search should assure that the produced set contains all important folded conformers. Energy components responsible for stabilization of properly shaped conformers are analyzed and classified. The reaction kinetics is interpreted at the level of the activated-complex theory, i.e., the highest technically possible description of the rate processes involved. The energetics is studied by both, semi-empirical and non-empirical techniques, again representing the upper limit of the chemical theory applicable at present. The work supplies independent computational support for the double activation mechanism of the ring closure. This up-to-date description also gives an instructive example of the potential and limitations of the contemporary computational chemistry in exploring potential energy hypersurfaces. The committee has unanimously concluded that the candidate had performed an original research with a sufficient degree of independency and that his submitted thesis corresponds to the present scientific standard in the field and adds new significant results. The related results are contained in two published journal articles (J. Mol. Struct. - Theochem; Quant. Struc.-Activ. Relat.), one paper in international-conference proceedings (Fundamental Principles of Molecular Modeling, Plenum Press), and one journal article accepted for publication in J. Mol. Struct. - Theochem (the candidate is co-author of several additional published works, too). In conclusion, the committee unanimously recommends the award of the doctoral degree.
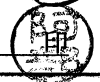
審査委員　スヲニナ　　伊藤浩一　　西山久雄
　　　　　阿部英次　　大澤映二　　　　　　　　　　印

（注）　論文審査の結果及び最終試験の結果は「合格」又は「不合格」の評語で記入すること。