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Conformations of 2–Phenyl–3–Pyridylpropenoic Acid (α–Phenyl Pyridylcinnamic Acid) Dimers – A Computational Study

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Conformations of 2–Phenyl–3–Pyridylpropenoic Acid (α–Phenyl Pyridylcinnamic Acid) Dimers – A Computational Study#

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Abstract

Motivation. Cinnamic acid analogs are not only important parts of the shikimic acid metabolic pathway of higher plants but it is possible to assemble, particularly from those containing oxygen or nitrogen heteroatoms, various patterned structures kept together with CH...O or CH…N hydrogen bonds. The fundamental unit of these structures is the acid dimer, *e.g*., the dimer of *E* and *Z*–2–phenyl–3–pyridylpropenoic acids of this study, which may exist in many conformations. As a preparation for a detailed conformational analysis of the patterned structures, it was decided to study the conformational behavior of these acid dimers, containing the N heteroatom in all possible positions of the aromatic ring. The conformational behavior of any cinnamic acid analogs in the dimeric form has not been studied before.

Method. The conformational search module of the HyperChem package was used for the conformational analysis of the acid dimers with the PM3 semiempirical method. Calculations were performed for isolated dimers, *i.e*., without solvent.

Results. The conformational search identified many conformers of the acid dimers. Although their numbers amounted to hundreds, they were found to fill the conformational space unevenly, in a highly symmetric nature. The distribution patterns were typical for the stereoisomers, but resembled to each other irrespective to the position of the nitrogen atom.

Conclusions. It was proved to be possible to study the conformational behavior of cinnamic acid analogs in their dimeric forms for the first time. Large number of conformers was identified and they were found the fill the conformational space in a patterned way.

Keywords. α–Phenyl pyridylcinnamic acid dimers; semiempirical method; PM3; conformational search; conformer distribution.

Abbreviations and notations

E2' – *E*–2–phenyl–3–(2'–pyridyl)propenoic acid	Z2' – *Z*–2–phenyl–3–(2'–pyridyl)propenoic acid
E3' – *E*–2–phenyl–3–(3'–pyridyl)propenoic acid	Z3' – *Z*–2–phenyl–3–(3'–pyridyl)propenoic acid
E4' – *E*–2–phenyl–3–(4'–pyridyl)propenoic acid	Z4' – *Z*–2–phenyl–3–(4'–pyridyl)propenoic acid

Dedicated on the occasion of the 65th birthday to Danail Bonchev. Presented in part at the Internet Electronic Conference of Molecular Design 2004, IECMD 2004.

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1 INTRODUCTION

Cinnamic acid derivatives are important intermediates in the shikimic acid metabolic pathway of higher plants. They also have interesting structure–forming properties *via* strong OH...O hydrogen bonds (in acids [1]) in solution and C–H...O close contacts (in acids [1] and also in esters [2]) in the solid state. Upon replacing the phenyl group with heteroatom–containing aromatic ring, like a pyridyl group in position 3, further possibilities for aggregate formation opens *via* (aromatic)C–H...(pyridyl)N intermolecular hydrogen bonds [3].

Theoretically, intramolecular C–H...N bonds may also appear to make certain conformers predominant. These interactions in various 2–furyl– and 2–pyridyl–substituted 3–phenyl propenoic acids have already been investigated computationally [4]. In order to make *ab initio* calculations feasible the systems were simplified: monomeric acids were used instead of the dimers, even though the latter are known to be typical forms of appearance even in the gas phase. This type of simplification seems to be general [5–7], to our knowledge conformational analysis by computations for dimeric acids has not been performed yet. After studying the potential energy surfaces of these simplified systems [4] one can envisage various conformers. As expected, numerous conformers will be revealed when the more realistic dimers are studied instead of the monomers.

In this paper we present computational results regarding the conformational behavior of *E*– and *Z*–2–phenyl–3–pyridylpropenoic acid dimers. For this analysis we used the PM3 semiempirical quantum chemical method.

2 MOLECULES AND METHODS

2.1 Molecules Studied

The model compounds were the *E* and *Z*–2–phenyl–3(X'–pyridyl)propenoic acids (X = 2, 3 or 4) (Figure 1). The abbreviated names look like E2' where the first letter is the stereochemical designation, the number with prime is the position of the pyridyl nitrogen.

2.2 Method of Conformational Search

We considered three dihedral angles for one acid molecule (six for the dimer). They correspond to the rotation of the phenyl (phe), the pyridyl (pyr) and the carboxylic (ac) groups. The OH group was used up in the (carbonyl)O…HO hydrogen bond pair. The length of these hydrogen bonds were fixed during optimization, thus, the dimers remained together on changing the 2×3 dihedral angles followed by geometry optimization. Therefore, the dimer conformer is described by six coordinates. The conformer distribution can be visualized in a 3D coordinate system by depicting one molecule of the dimer at a time.

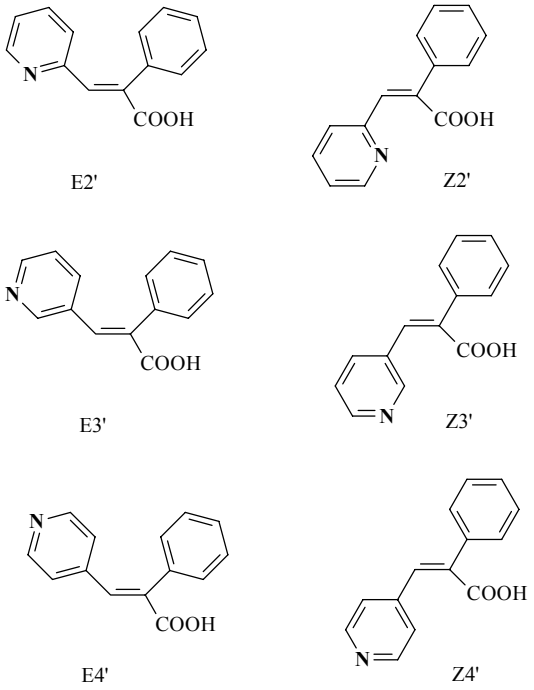


Figure 1. The molecules studied.

The optimization module of the HyperChem package works in the following way. The dimer is optimized until 0.01 gradient. Then, the dihedral angles are changed in a random way and the generated new structure for the dimer is optimized until the gradient equals or smaller than 0.01. Using a minimum structure random dihedral changes take place again and optimization follows. The low–energy unique conformations are stored, while high–energy or duplicate structures are discarded. Lacking clear–cut termination criteria, the conformational search was considered to be over, when the number of conformers remained unchanged for 24 hours.

3 RESULTS AND DISCUSSION

Results concerning the acid dimers are displayed, discussed and compared for the stereoisomers separately, giving the conformer distributions for all possible nitrogen positions. Then, examples for the major conformer classes are shown.

3.1 Conformer distributions for the *E* isomers

The conformer distribution of each component molecule is depicted in a 3D coordinate system from the viewpoint of the dihedral angle belonging to the rotation of the phenyl group (phe1 or phe2 = *x* axis, ac1 or ac2 = the *y* axis and pyr1 or pyr2 = *z* axis) (Figures 2–4). This type of visualization offers the easiest possibility for classification.

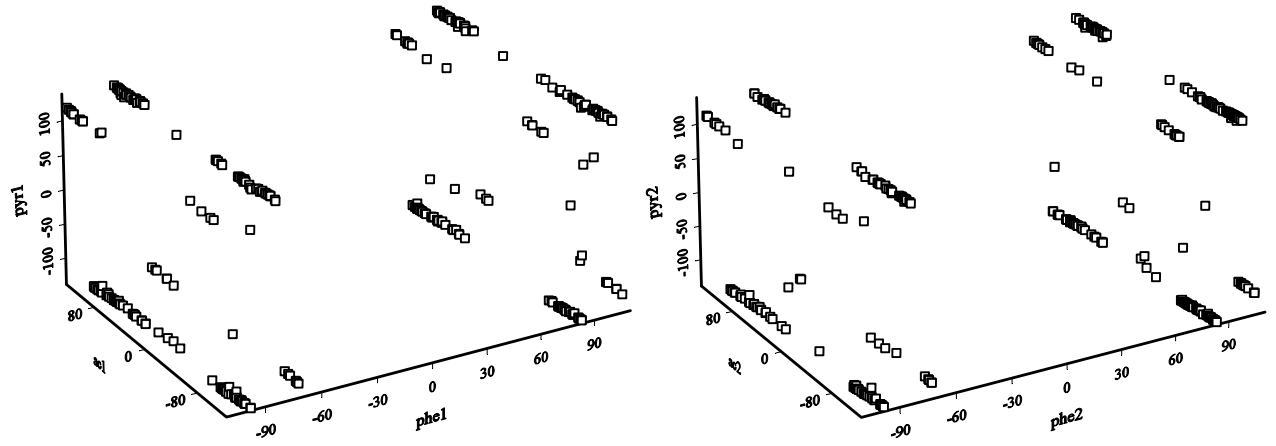


Figure 2. Conformer distributions for the component acids of the E2' dimer.

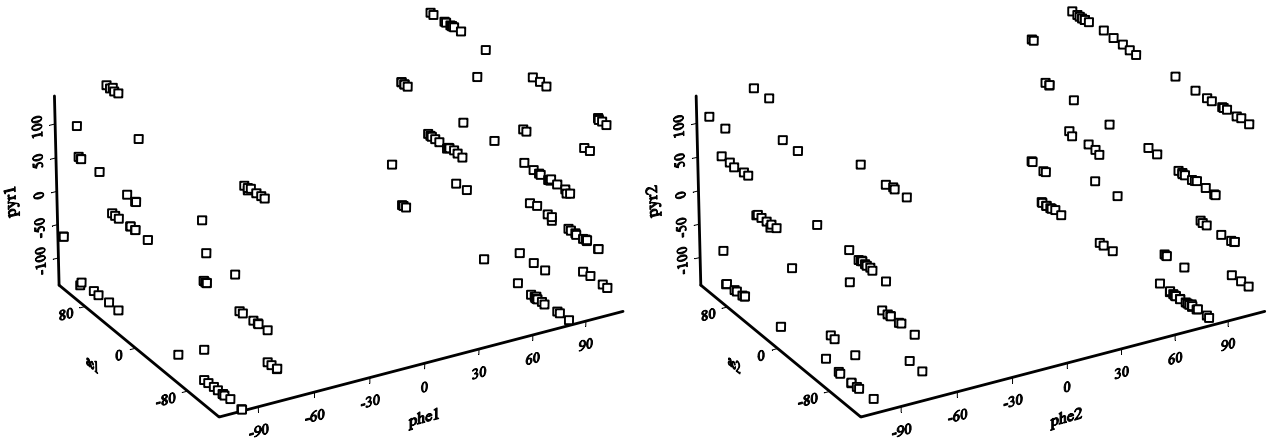


Figure 3. Conformer distributions for the component acids of the E3' dimer.

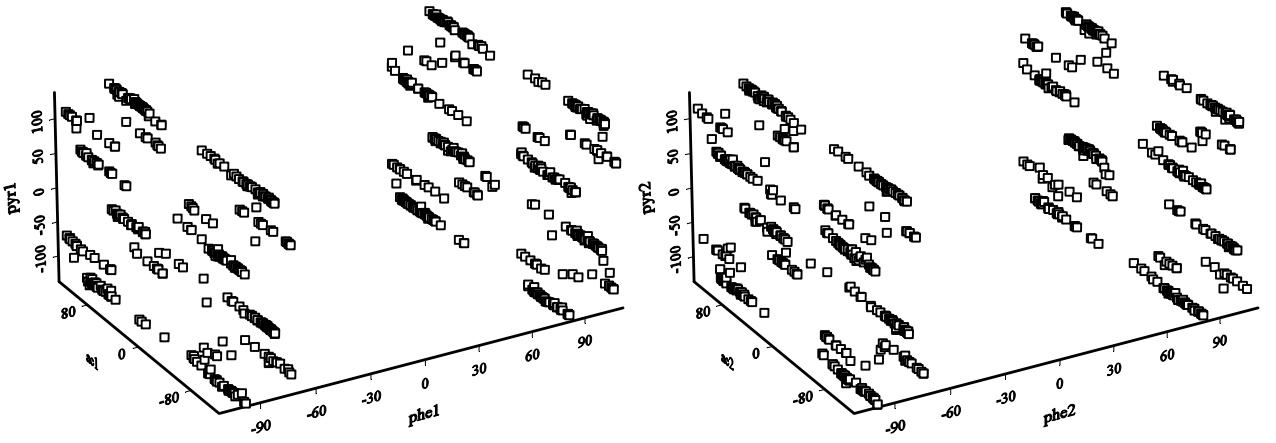


Figure 4. Conformer distributions for the component acids of the E4' dimer.

Many conformers could be identified. We found 323 conformers for E2', 161 conformers for E3', and 823 conformers for E4'. It is to be seen that they are unevenly distributed in the conformational

space. The conformers cannot be classified according to their dihedral angle corresponding to the rotation of the carboxylic group (ac1 or ac2), but there are typical dihedrals corresponding to the rotations of the phenyl (phe1 and phe2) and the pyridyl (pyr1 or pyr2) groups. Actually, they are not very different for the component acids. The overwhelming majority of the conformers fall in the ranges of [±80°–±110° (phe); ±130°–±140° (pyr)] for E2', in the [±80°–±110° (phe); ±45° or ±140° (pyr)] for E3' and [±80°–±100° (phe); ±45° or ±140° (pyr)] for E4'. The distribution of conformers is highly symmetric for each compound.

3.2 Conformer distributions for the *Z* isomers

Here, just like with the other stereoisomer the conformer distribution of each component molecule is depicted in a 3D coordinate system, but now, from the viewpoint of the dihedral angle belonging to the rotation of the carboxylic group (ac1 or ac2 = x axis, phe1 or phe2 = the y axis and pyr1 or pyr 2 = z axis) (Figures 5–7). For these stereoisomers this type of visualization gives the easiest possibility for classification.

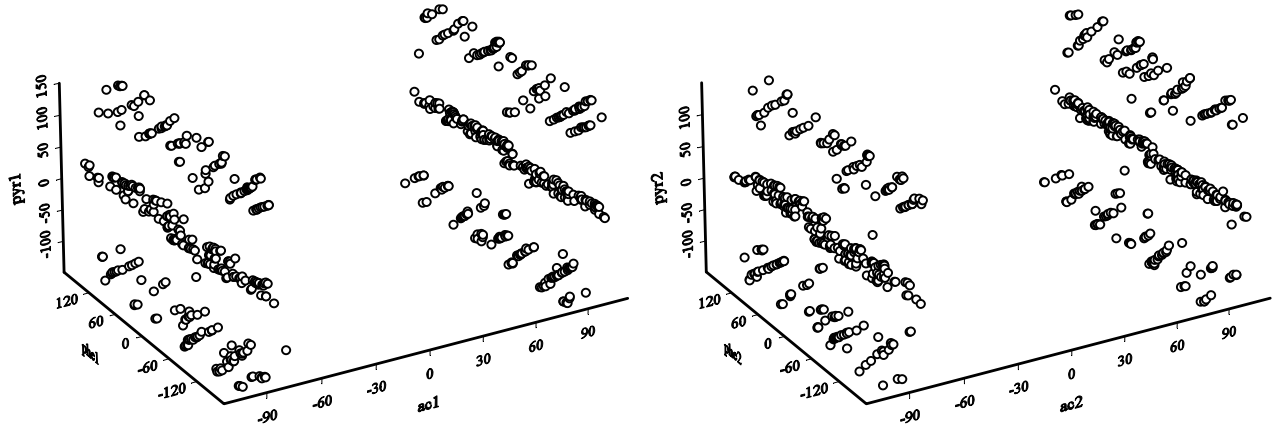


Figure 5. Conformer distributions for the component acids of the Z2' dimer.

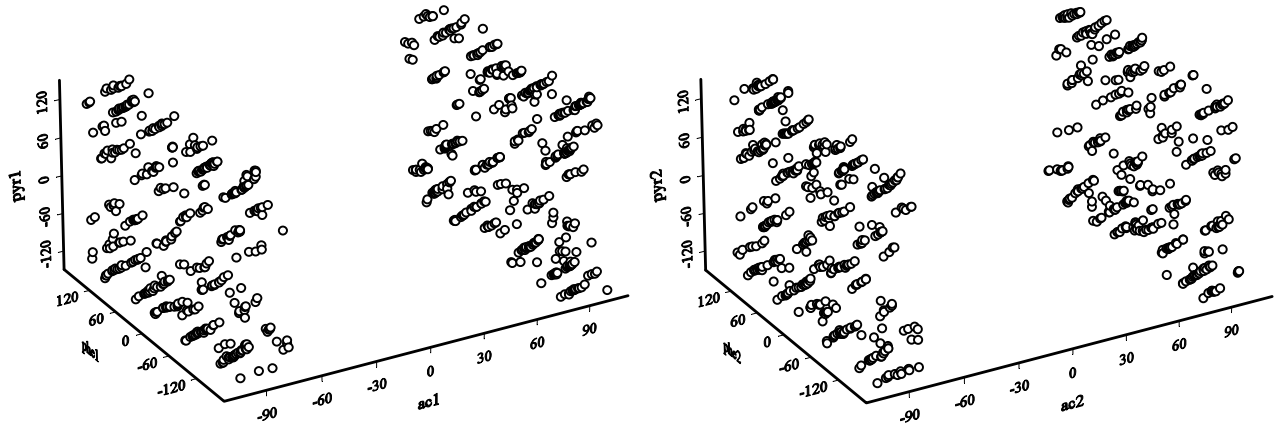


Figure 6. Conformer distributions for the component acids of the Z3' dimer.

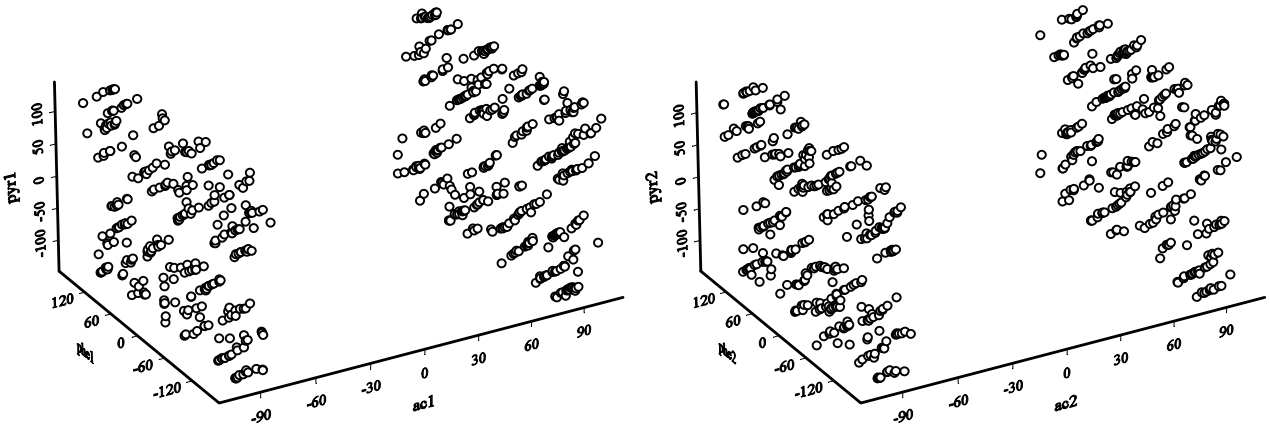
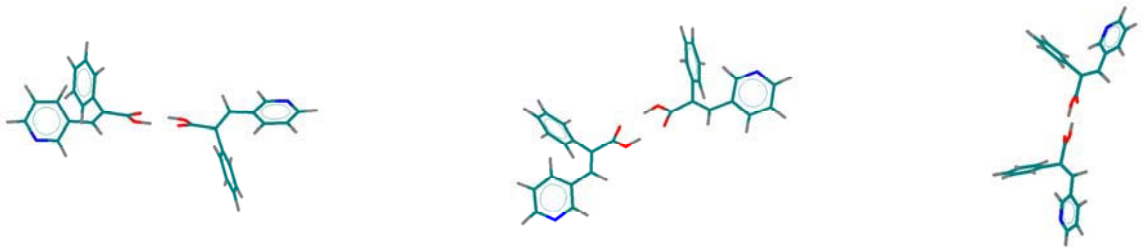


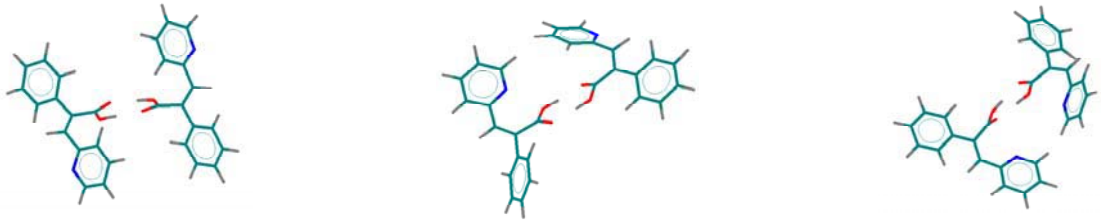
Figure 7. Conformer distributions for the component acids of Z4'.

The number of conformers for the *Z* stereoisomers is mostly much larger than those of the *E* counterparts. We found 745 conformers for Z2', 851 conformers for Z3', and 719 conformers for Z4' (this was the only exception, when the number of conformers for the two stereoisomers was comparable). These conformers are also unevenly distributed in the conformational space with much clearer and significantly more symmetric pattern than was seen for the *E* isomers. They cannot be classified according to their dihedral angle corresponding to the rotation of the phenyl group (phe1 or phe2), but there are typical dihedral ranges corresponding to the rotations of the carboxylic (ac1 and ac2) and the pyridyl (pyr1 or pyr2) groups. Again, they are not very different for the component acids. The majority of the conformers falls in the ranges of [±90° to ±110° (ac); 0° to ±40° or ±120° to ±140° (pyr)] for Z2', in the [±75° to ±110° (ac); ±50° to ±70° or ±120° to ±150° (pyr)] for Z3' and [±75° to ±110° (ac); ±50° to ±70°or ±100° to ±130° (pyr)] for Z4'.



(*a*) (*b*) (*c*)

Figure 8. Representative conformers for the *E* isomer (*a*) *s–cis–s–cis*, (*b*) *s–trans–s–cis*, (*c*) *s–trans–s–trans*.



(*a*) (*b*) (*c*)

Figure 9. Representative conformers for the *Z* isomer (*a*) *s–cis–s–cis*, (*b*) *s–trans–s–cis*, (*c*) *s–trans–s–trans*.

3.3 Representatives of conformer classes

Due to the large number of conformers it is not possible to represent them as overlaid structures. In order to show the feasible structural variations representative examples for better visualisation are given for both stereoisomers in Figures 8 and 9. If we concentrate on the relative steric positions of the planes of the olefinic double bound and the pyridine ring, we may distinguish between *s–trans* and *s–cis* arrangements [11]. All their combinations occur among the conformers identified.

4 CONCLUSIONS

It was proved to be possible to study the conformational behavior of cinnamic acid analogs in their dimeric forms for the first time. Moreover, the large number of conformers could be handled and the highly symmetric patterns of their distributions could be identified.

Both stereoisomeric dimer types showed considerable conformational mobility, however, generally, the *Z* isomers proved to be more flexible. Here, the rotation around of phenyl group is virtually unrestricted, just as that of the carboxylic group for the *E* isomer. These observations are somewhat surprising because due to continuous conjugation across each molecule of the dimer all–planar arrangement could be expected. Nevertheless, conformational mobility explains that in the crystal structures of cinnamic acid derivatives planar sheets are found [12] and the dimers for the acids and the monomers for the esters are kept together by hydrogen bonds within the plane.

Acknowledgment

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Biographies

István Pálinkó is associate professor of physical organic chemistry at the University of Szeged, Szeged, Hungary. He obtained a Ph.D. degree in physical organic chemistry from the Hungarian Academy of Sciences. Before getting the degree he was a predoctoral fellow with Professor G. V. Smith at the Southern Illinois University, Carbondale, USA. The postdoctoral research was with Nobel Laureate G. A. Olah at the University of Southern California, Los Angeles, USA. Dr. Pálinkó has collaborated on various projects with Professors Ken Seddon, Janos B. Nagy and Dr. Fujio Mizukami. His professional interest lies in heterogeneous catalysis, studying hydrogen bonded systems with experimental and theoretical methods and molecular modeling. Results achieved on these fields are summarized in over 160 scientific papers and numerous presentations on international scientific meetings.