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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 construct, especially from those containing e.g., 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. In order to prepare for a detailed conformational analysis of the patterned structures, it was decided to study the conformational behaviour of these acid dimers, containing the N heteroatom in all possible positions of the aromatic ring. Curiously, their conformational behaviour, moreover, of any cinnamic acid analogs in the dimeric form, has not been studied before.

Method. For the conformational analysis of the acid dimers the conformational search module of the HyperChem package was used, applying the PM3 semiempirical code.

Results. Applying the conformational search module many conformers of the acid dimers could be identified. 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 to conformational behaviour of cinnamic acid analogs in their dimeric forms for the first time. Moreover, the large number of conformers could be handled and patterns of their distribution could be identified.

Availability. The software used for the calculations (HyperChem) is a commercial product.

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

Abbreviations and notations

E2P32'PY, *E*-2-phenyl-3-(2'-pyridyl)propenoic acid	Z2P32'PY *Z*-2-phenyl-3-(2'-pyridyl)propenoic acid
E2P33'PY, *E*-2-phenyl-3-(3'-pyridyl)propenoic acid	Z2P33'PY *Z*-2-phenyl-3-(3'-pyridyl)propenoic acid
E2P34'PY, *E*-2-phenyl-3-(4'-pyridyl)propenoic acid	Z2P34'PY *Z*-2-phenyl-3-(4'-pyridyl)propenoic acid

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)O intermolecular hydrogen bonds [3].

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Theoretically, intramolecular C-H...N bonds may also appear making 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 these 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], 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. Expectedly, numerous conformers will be revealed when the more realistic dimers are studied instead of the monomers.

In this contribution computational results regarding the conformational behaviour of *E*- and *Z*-2-phenyl-3-pyridyl propenoic acid dimers are reported. For the analysis the PM3 semiempirical quantum chemical code was applied.

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 E2P32'PY where the first letter is the stereochemical designation, the numbers without prime are the positions on the propenoic acid, the number with prime is the position of the pyridyl nitrogen, P and PY stand for the phenyl and the pyridyl groups, respectively.

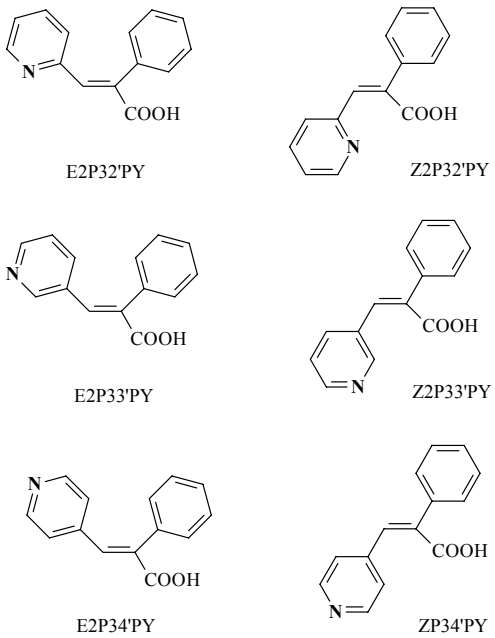


Figure 1. The molecules studied

2.2 Computer Software

Conformational analysis on the isolated dimers was performed with the conformational search module implemented in the HyperChem 7.0 package [6] choosing the PM3 semiempirical quantum chemical method [7,8] to keep computations tractable.

2.3 Method of Conformational Search

We picked 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 optimisation, thus, the dimers remained together on changing the 2x3 dihedral angles followed by geometry optimisation. Now, the dimer conformer is described by six coordinates. The conformer distribution can be visualised in a 3D coordinate system by depicting one molecule of the dimer at a time.

The optimisation module of the HyperChem package works in the following way. The dimer is optimised until 0.01 gradient. Then, the dihedral angles are changed in a random way and the generated new structure for the dimer is optimised until the gradient equals or smaller than 0.01. Using a minimum structure random dihedral changes take place again and optimisation 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 visualisation offers the easiest possibility for classification.

Many conformers could be identified. For E2P32'PY 323, for E2P33'PY 161 and for E2P34'PY 823 conformers were found. 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 phe 2) 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 [±80°–±110° (phe); ±130°–±140° (pyr)] for E2P32'PY, in the [±80°–±110° (phe); ±45° or ±140° (pyr)] for E2P33'PY and [±80°–±100° (phe); ±45° or ±140° (pyr)] for E2P34'PY. The distribution of conformers is highly symmetric for each compound.

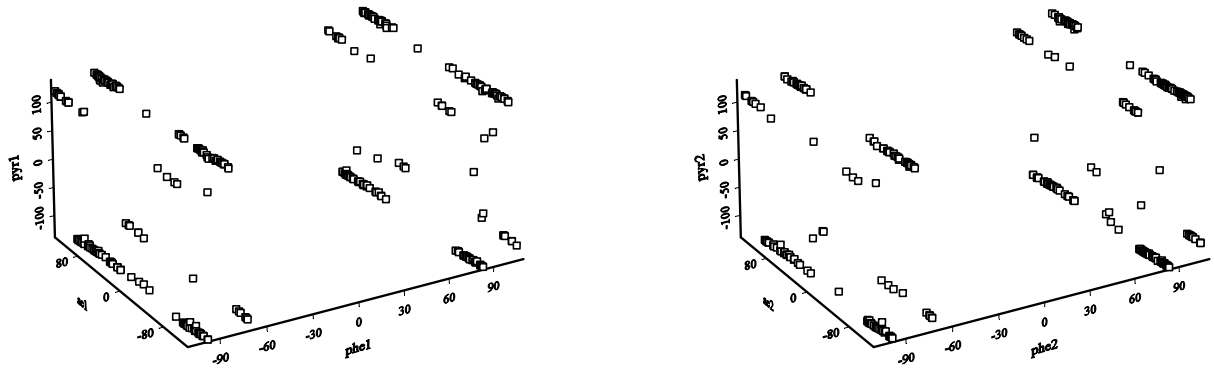


Figure 2 Conformer distributions for the component acids of the E2P32'PY dimer

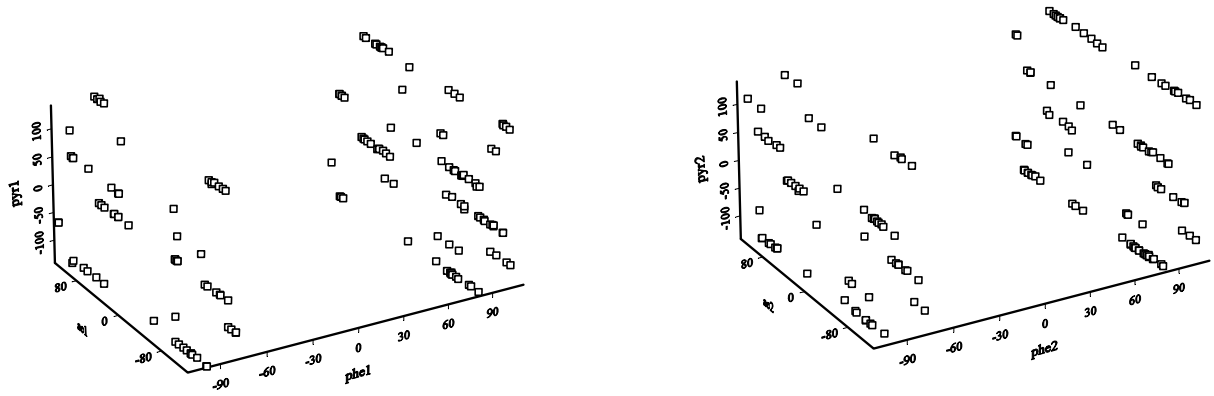


Figure 3 Conformer distributions for the component acids of the E2P33'PY dimer

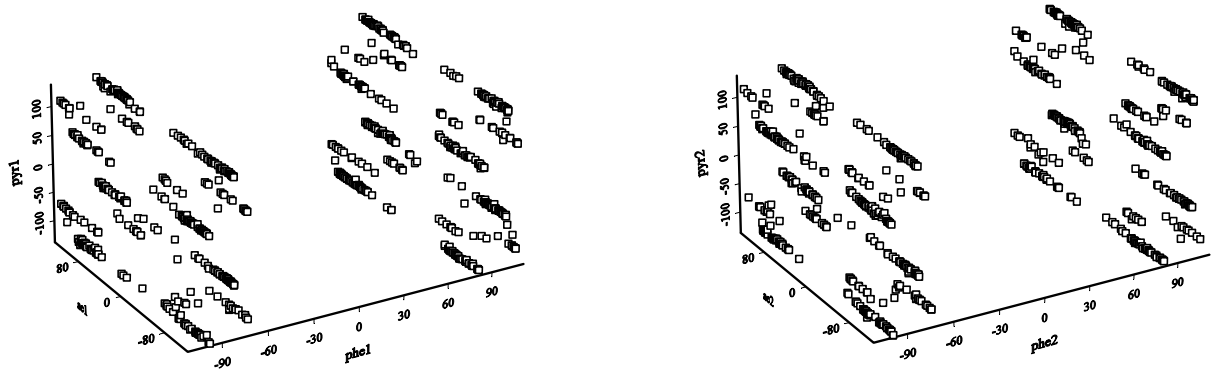


Figure 4 Conformer distributions for the component acids of the E2P34'PY dimer

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 visualisation gives the easiest possibility for classification.

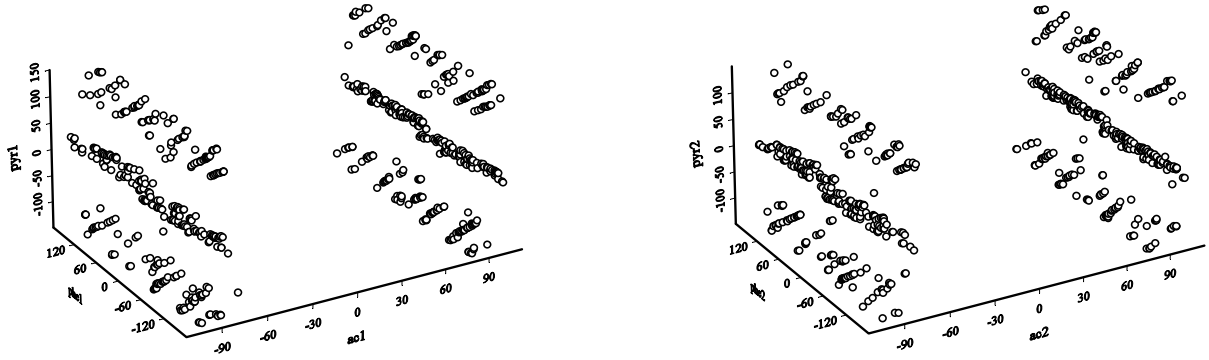


Figure 5 Conformer distributions for the component acids of the Z2P32'PY dimer

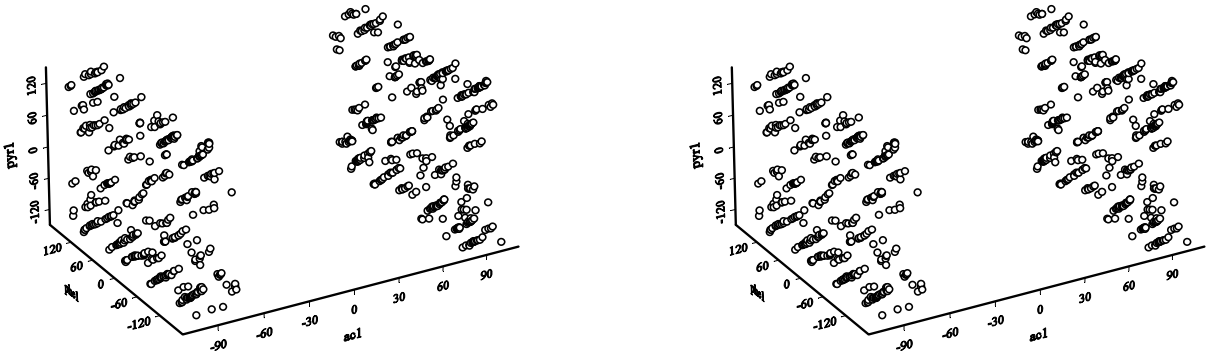


Figure 7 Conformer distributions for the component acids of the Z2P33'PY dimer

The number of conformers for the *Z* stereoisomers is mostly much larger than those of the *E* counterparts. For the Z2P32'PY 745, for the Z2P33'PY 851 and for the Z2P34'PY 719 (this was the only exception, when the number of conformers for the two stereoisomers was comparable) conformers were found. 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 overwhelming majority of the conformers fall in the [±90°–±110° (ac); 0°–±40° or ±120°–±140° (pyr)] for E2P32'PY, in the [±75°–±110° (ac); ±50°–±70° or ±120°–±150° (pyr)] for E2P33'PY and [±75°–±110° (ac); ±50°–±70°or ±100°–±130° (pyr)] for E2P34'PY.

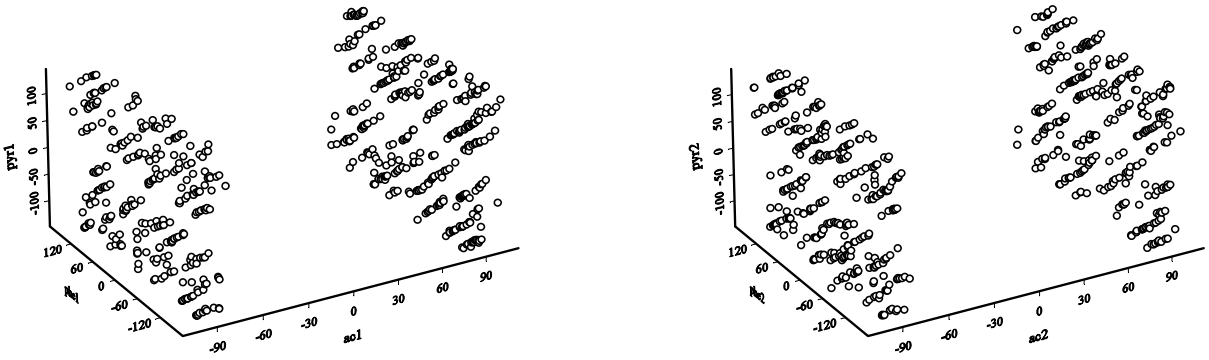
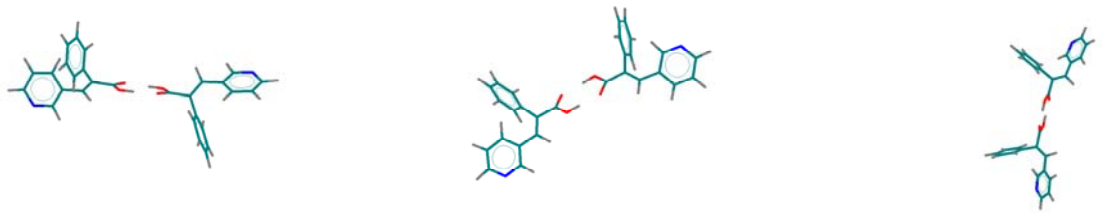


Figure 7 Conformer distributions for the component acids of Z2P34'PYR

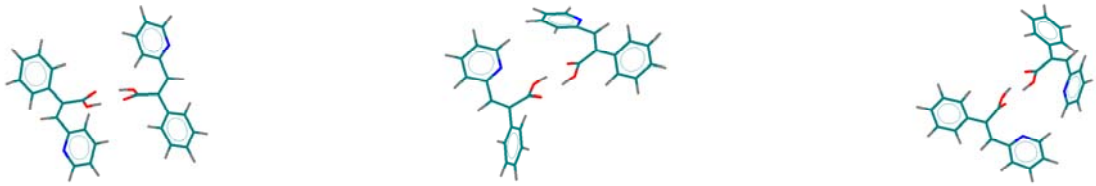
3.3 Representatives of conformer classes

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 are given for both stereoisomers in Figures 8 and 9. If we concentrate on the position of the conjugated double bonds (olefinic double bound and the conjugated double bond in the pyridyl ring) we may distinguish between *s-trans* and *s-cis* arrangements [9]. All their combinations occur among the conformers identified.



(a) (b) (c)

Figure 8 Representatives of the conformer classes for the *E* isomer (a) *s-cis–s-cis*, (b) *s-trans–s-cis*, (c) *s-trans–s-trans*



(a) (b) (c)

Figure 9 Representatives of the conformer classes for the *Z* isomer (a) *s-cis–s-cis*, (b) *s-trans–s-cis*, (c) *s-trans–s-trans*

4 CONCLUSIONS

It was proved to be possible to study to conformational behaviour 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.

Acknowledgment

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Biography

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 Laurate 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 summarised in over

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