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# Structural features of pyridylcinnamic acid dimers and their extended hydrogen-bonded aggregations

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## HIGHLIGHTS

- *E*-3-(*x*-pyridyl)propenoic acids ($x = 2$, 3 or 4) were synthesized.
- The structure forming abilities were investigated.
- Energies and bond lengths of C—H···N H-bonds were determined.
- Conformational behaviour of the acids and the zwitterionic forms were studied.

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## ABSTRACT

The conformational as well as the structure-forming properties of *E*-3-(*x*-pyridyl)propenoic acids ($x = 2$, 3 or 4) have been studied with a combination of computational and spectroscopic methods. IR spectroscopy revealed that in the solid state the zwitterionic species predominate, while NMR measurements showed that dimers, kept together by strong C=O···H—O hydrogen bonds, were formed in a dipolar aprotic solvent (DMSO). In concentrated solution, extended aggregation occurred through the cooperative effect of (aromatic) C—H···N weak hydrogen bonds. Conformational search was performed at the HF/6-31G(d,p) level of theory. Comparison with experimental values as well as benchmarking calculations at several different levels of theory to probe the performance of the methods, B3LYP/6-31G++(d,p) method was found to be able to provide reasonable geometries as well as quantitative formation energies for the dimers and the tetramers, too.

## Introduction

For some time, the family of cinnamic acid and its heteroatom-containing derivatives has been in the focus of our interest, due to their structural features allowing short- as well as long-range ordering in the liquid and the solid state as well [1–9]. They are also important pharmacologically, they act as enzyme inhibitors in cancer research [10], as new type of drugs against multiple resistant TBC bacteria [11], and as important intermediates in the chemical synthesis of pharmacologically active compounds [12,13].

In our previous studies, the combination of spectroscopic methods and molecular modelling was applied successfully for the characterisation of the structure-forming interactions taking place in solution as well as in the solid state for furyl- [6] and thienyl-substituted cinnamic acids [9]. It was shown that the fundamental unit of the acids was the dimer, kept together by strong hydrogen bonds between the carboxylic groups, while the aggregation of the dimers occurred *via* weaker CH···X (X: O or S) interactions. Although these close contacts are weak, they are numerous, making the total interaction strong. Thus, they are crucial in keeping the molecular crystals together. Through applying computations, it was possible to pinpoint the most probable positions for the hydrogen bonds and to give reasonable estimates for their geometric parameters; however, energetic aspects were not touched. For the N-containing derivatives, only simple geometry optimizations were performed at the semiempirical level of theory [14–16] – assuming again that the dimer is the fundamental unit – since we were not successful in the syntheses of the molecules.

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Since then, we have found ways for the preparation of some of the pyridyl-containing derivatives and now, the combined experimental and computational approach has become feasible. Results of this work is communicated in the followings.

## Experimental

### *The molecules and their syntheses*

Our choice for model compounds were the isomers of pyridylcinnamic acid: *E*-3′-(2-pyridyl)propenoic acid (**E2P**), *E*-3′-(3-pyridyl)propenoic acid (**E3P**), *E*-3′-(4-pyridyl)propenoic acid (**E4P**) and their sodium- and hydrochloride salts (Fig. 1). Although these molecules were rarely studied, simple NMR shift assignments and conformational analysis at low theoretical level have been done [17,18], and they were of help in checking the success of our synthetic work.

The model compounds were prepared by the Knoevenagel–Doebner condensation [19,20], taking place between the proper pyridine carboxaldehyde and malonic acid (Fig. 1) under basic conditions.

Details of the synthesis are as follows. Two equivalents of malonic acid were dissolved in four equivalents of pyridine at 50 °C; then, a catalytic amount of piperidine ($c_{\text{piperidine}} = 0.01$ mol/L) was added to the reaction mixture. It was necessary to add traces of hydroquinone to the reaction at the beginning, to prevent radical polymerisation, probably taking place at higher temperatures. One equivalent of freshly distilled *x*-pyridinecarboxaldehyde ($x = 2$, 3 or 4) was then added dropwise at 50 °C, under vigorous stirring. After the addition of all components, the solution was stirred for an additional hour at 50 °C, to complete the condensation step; then, the mixture was heated to reflux for additional 5 h. It was needed for the complete decarboxylation of the intermediates, the 2-(*x*-pyridyl)methylenemalonic acids. The **E3P** and **E4P** compounds started to precipitate from the reaction mixture at the end of the first hour; however, the solution for the **E2P** synthesis, stayed clear over the time of the reaction.

Pyridine was removed from the reaction mixture on a rotary evaporator; then, the residue was diluted with cold diethyl ether, filtered, and washed twice with cold diethyl ether. The yield was 82–93%, and only the *E* isomer was formed. Due to the poor solubility of the compounds in any solvents except dipolar aprotic ones like DMSO (dimethyl sulfoxide) or DMF (N,N-dimethylformamide), they can be obtained with purity up to 99% without further purification. The sodium salts were prepared by the addition of one equivalent of NaOH in water, for each pyridylpropenoic acid. The hydrochloride salts were prepared with similar titration, *i.e.*, with the addition of one equivalent of concentrated hydrochloric acid in water. The molecules prepared, are shown in Fig. 2.

### *Spectroscopic measurements*

IR (infrared) measurements were carried out on a Bio-Rad FTS-40 FT-IR spectrometer, working in the reflection mode, using 1% of the sample in KBr (spectroscopic grade, Aldrich Chem. Co.) for the solid state and 0.1 mol/L solution in DMSO (Spectroscopic grade, Aldrich Chem. Co.) at 0.2 mm liquid thickness in quartz cuvette. 256 scans were collected for the spectra at 4 $\text{cm}^{-1}$ resolution.

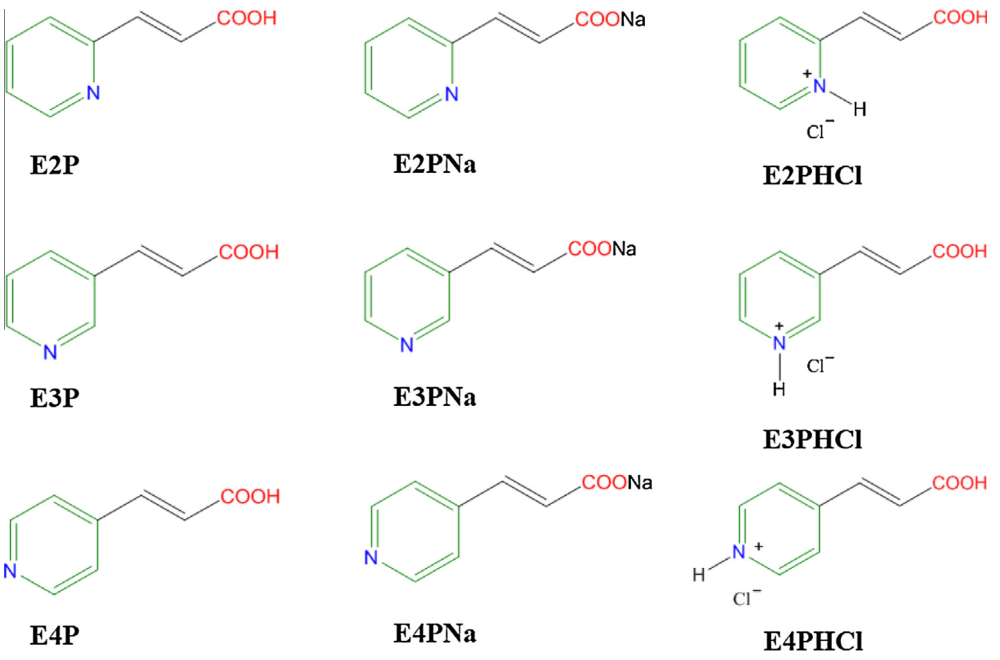

**Fig. 1.** The modified Knoevenagel–Doebner condensation.

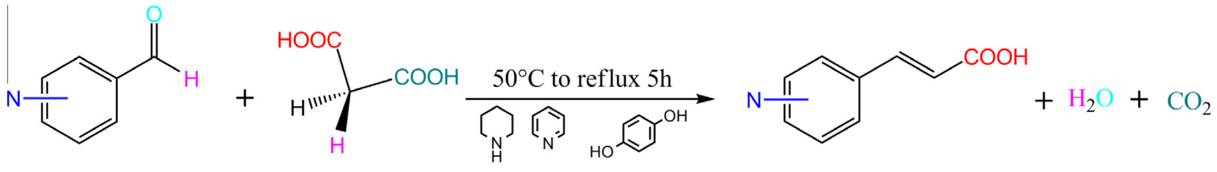

**Fig. 2.** The molecules studied.