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On the Mechanism of a Modified *Perkin* Condensation Leading to α-Phenylcinnamic Acid Stereoisomers – Experiments and Molecular Modelling

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Summary. A modified *Perkin* condensation leading to α-phenylcinnamic acid stereoisomers affords predominantely or exclusively the (*E*)-isomer. Reaction duration, temperature, and polarity of the solvent affect the isomeric distribution only to a minor extent. However, geometry optimization of the stereoisomers by semiempirical quantum chemical methods revealed that their thermodynamic stabilities in the absolute minimum are the same. (*E*)-(*Z*)-isomerization under the conditions of the *Perkin* condensation resulted in an equilibrium mixture of nearly 1:1 composition, thus corroborating the results of the computations. Comparing the detailed potential energy maps of the isomers obtained at the semiempirical level of theory may explain the controversy. The (*Z*)-isomer has a structured potential energy surface with few but well-defined minima, whereas that of the (*E*)-isomer shows an extended flat plateau enabling this isomer to approach a minimum (which is close to the global one) right after its formation.

Keywords. Isomeric distribution; Potential energy surfaces; Semiempirical quantum chemical methods; Stereoselectivity.

Introduction

Cinnamic acid derivatives are important synthons in the production of lignins in higher plants [1]. They are members of the shikimic acid metabolic pathway, and their mechanism of formation is complex. Nevertheless, key reactions are condensations (mostly of the *Claisen* type [1]), just as in the laboratory synthesis (mostly of the *Perkin* type [2]). The usual *Perkin* reaction leads to the predominant or exclusive formation of the (*E*)-isomer. A modified *Perkin* condensation (Scheme 1) affords under certain conditions (low temperature, short reaction time) a mixture of (*E*)- and (*Z*)-α-phenylcinnamic acids with (*E*)-isomer predominating [3–5]. Early studies (see *e.g.* Ref. [6]) found this fact obvious, since the (*E*)-isomer was

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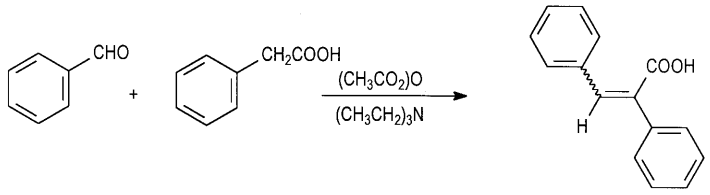


Scheme 1

considered to be thermodynamically more stable. Indeed, reactions for prolonged time periods afforded exclusively this isomer. However, when we started to model the two isomers in order to find a structural explanation for the large difference in the acidities of the stereoisomers, AM1 [7], MNDO [8], and PM3 [9] semiempirical quantum chemical calculations gave nearly identical heats of formation for the fully optimized structures of the isolated (*E*)- and (*Z*)-isomers [10]. Therefore, it seemed to be interesting to study the reaction from a mechanistic point of view, with the aim of exploring factors influencing the isomeric distribution. The thermal (under the conditions of the modified *Perkin* condensation) and photoinduced (*E*)-(*Z*) (and (*Z*)-(*E*)) isomerizations of the acids were also investigated. The isomerization reactions were explored experimentally as well as computationally.

Results and Discussion

The modified *Perkin* reaction provided an isomeric mixture with a predominance of the (*E*)-isomer. The maximum amount of the (*Z*)-diastereomer was 21%; it was obtained when the *Fieser* mixture was kept under reflux (about 150°C) for 35 min. A compilation of literature results revealed that any modification in the composition of reactants, temperature, and duration of reflux resulted in the preferential or in most cases exclusive formation of the (*E*)-isomer (Table 1).

Interestingly, full geometry optimization at the semiempirical quantum chemical level of theory on the isolated molecules gave similar stability data for the two isomers in the global minima. However, calculations also revealed that the dipole moments were different (Table 2).

Table 1. Isomeric distribution of α-phenylcinnamic acids at various temperatures and reaction times based on literature data

T/°C	*t*/min	*benz*[a]/mol	Ac_2O[b]/mol	*phac*[c]/mol	Et_3N[d]/mol	(*E*)/(*Z*)
30[e]	90	0.74	0.30	0.20	0.20	100/0
30[e]	90	0.74	0.30	0.20	0.20[i]	100/0
65[e]	180	0.74	0.30	0.20	0.40	100/0
65[e]	180	0.74	0.30	0.20	0.40[i]	100/0
140[f]	35	0.18	2.10	0.11	1.50	96/4
150[g]	35	0.30	0.21	0.18	0.15	79/21
150[h]	330	0.40	0.84	0.40	0.29	100/0

[a] Benzaldehyde; [b] acetic anhydride; [c] phenylacetic acid; [d] triethylamine; [e] Ref. [11]; [f] Ref. [6]; [g] Ref. [4]; [h] Ref. [5]; [i] added dropwise during the reaction

Table 2. Standard heats of formation and dipole moments for the α-phenylcinnamic acid diastereomers calculated by semiempirical quantum chemical methods

	MNDO		AM1		PM3	
	$\Delta H_{f,298}$/kJ · mol^{-1}	μ/D	$\Delta H_{f,298}$/kJ · mol^{-1}	μ/D	$\Delta H_{f,298}$/kJ · mol^{-1}	μ/D
(*Z*)	−115.1	1.81	−100.5	1.80	−98	1.75
(*E*)	−113.9	2.10	−98.6	2.54	−97.6	2.00

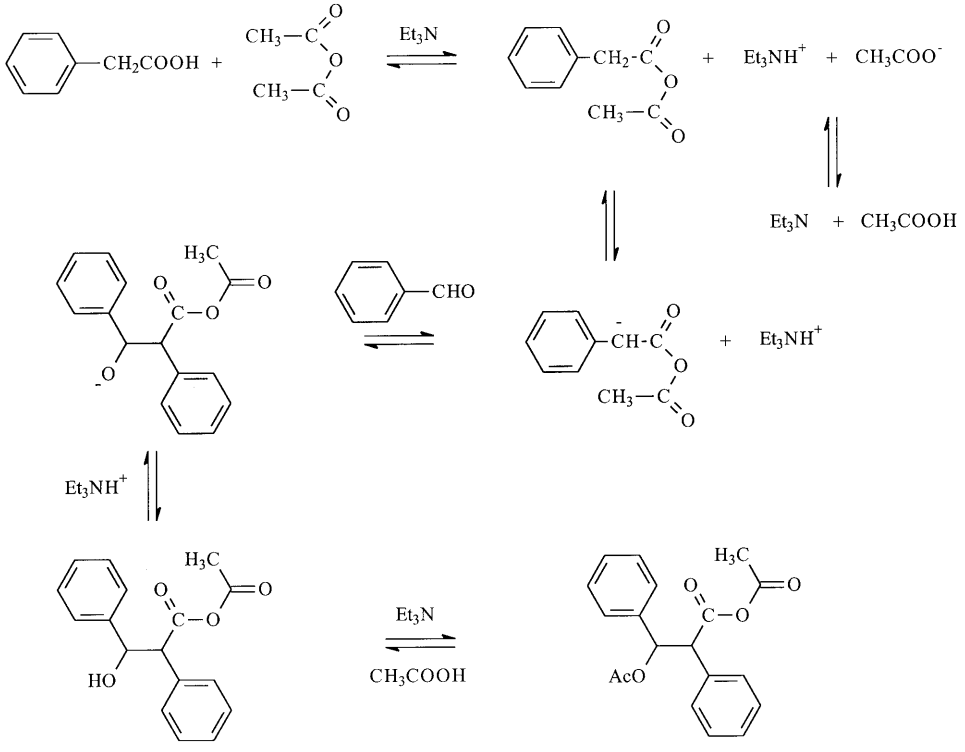
Table 3. Isomeric distribution in solvents of different dielectric constants, dipole moments, and boiling points at various reaction times (the reactions were carried out under reflux)

Solvent	*t*/min	(*E*)/mol%	(*Z*)/mol%
Fieser mixture[a] (b.p.: app. 150°C)			
	35	78.9	21.1
H_2O (b.p.: 100°C, $\varepsilon^{(20)}$: 80.1)			
	180	94.4	5.6
Diethyl ether (b.p.: 35°C, $\varepsilon^{(20)}$: 4.34, $\mu^{(20)}$: 1.15)			
	180	100	0
Dibutyl ether (b.p.: 142–143°C, $\varepsilon^{(20)}$: 3.08, $\mu^{(20)}$: 1.18)			
	40	100	0
Diglyme (b.p.: 162°C, $\mu^{(25)}$: 1.97)			
	180	100	0
Benzene (b.p.: 80°C, $\varepsilon^{(25)}$: 2.275, $\mu^{(20-60)}$: 0)			
	180	100	0
Xylene (isomeric mixture; b.p.: 138–142°C, $\varepsilon^{(20)}$: 2.37 $\mu^{(20)}$: 0.30)			
	30	100	0
	180	98.1	1.9
	360	97.9	2.1
Decalin (isomeric mixture; b.p.: 192°C, $\varepsilon^{(20)}$: 2.19, $\mu^{(25)}$: 0)			
	35	94.2	5.8
	360	87.4	12.6
	540	90.5	9.5

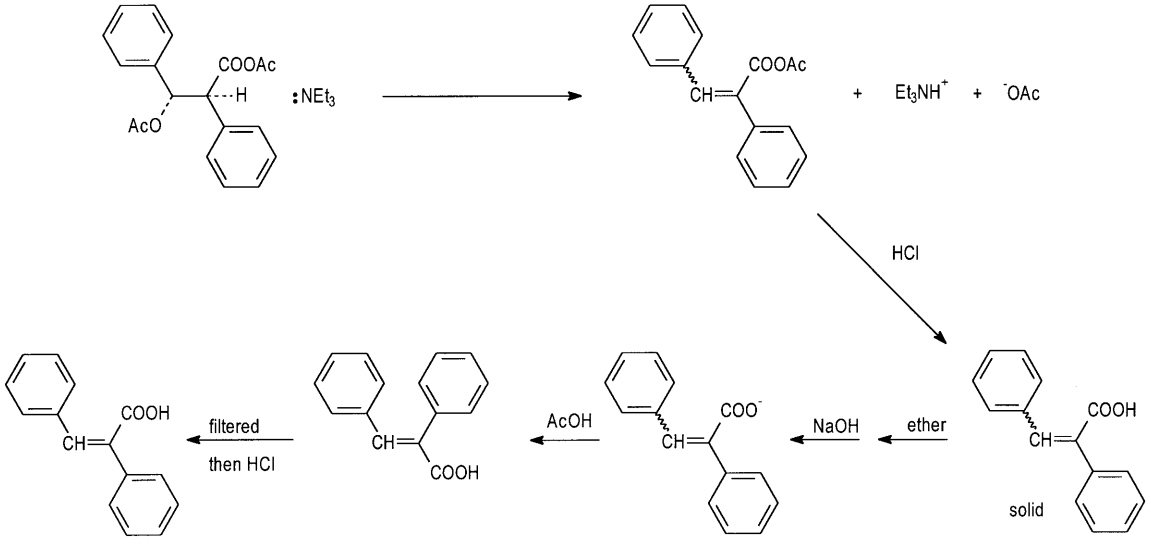
[a] See experimental part

In order to explore the possible effect of the different dipole moments upon the reaction, solvents of different properties (varying dielectric constant and/or hydrogen bonding capability) were used. However, the amount of the (*Z*)-isomer did not increase. Moreover, the exclusive formation of the (*E*)-isomer can be considered typical. The (*Z*)-isomer was formed (in small amounts even under these circumstances) when high temperature, long reaction time, and nonpolar solvent were used or the solvent was capable of hydrogen bonding (Table 3).

However, isomerization reactions, starting from either the (*E*)- or the (*Z*)-isomer, resulted in a thermal equilibrium mixture containing 55 mol% (*E*)- and 45 mol% (*Z*)-isomer under the conditions of the modified *Perkin* reaction, and UV irradiation produced a photo-equilibrium mixture of 61 mol% (*E*)- and 39 mol% (*Z*)-isomer. These experiments nicely corroborated the results of the semiempirical calculations.



Scheme 2



Scheme 3

Thus, the real reason of the predominance of the (*E*)-isomer in the formation reaction is not due to different thermodynamic stabilities of the stereoisomers.

The modified *Perkin* condensation consists of two parts: (1) nucleophilic addition of the mixed anhydride formed from acetic anhydride and phenylacetic acid to the carbonyl group of benzaldehyde *via* base catalysis (Scheme 2)

Table 4. Absolute configurations of the diastereomers and those of the products after *anti*-elimination

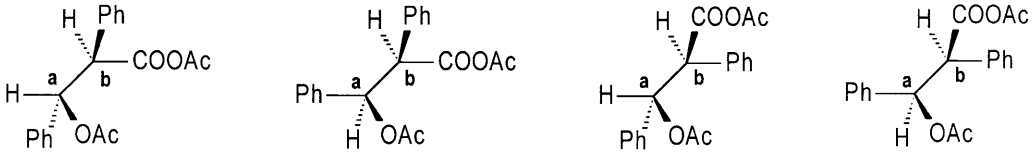
	Chiral centres (cf. Fig. 1)		Product after elimination
	a	*b*	
1	(*S*)	(*R*)	(*Z*)
2	(*R*)	(*R*)	(*E*)
3	(*S*)	(*S*)	(*E*)
4	(*R*)	(*S*)	(*Z*)

and (2) elimination of acetic acid and hydrolysis of the product anhydride (Scheme 3).

Zimmermann et al. have shown that the condensation reaction is elimination controlled [6]. There is no reason to assume that preferential formation of any of the four possible intermediates takes place. Assuming *anti*-elimination, the intermediates are able to produce both stereoisomers (Table 4).

Semiempirical quantum chemical calculations on the possible intermediates (Fig. 1) revealed that the heats of formation are very close to each other, and their dipole moments are similar (Table 5). This means that the different distribution of the final stereoisomers of the reaction did not result from differences in the stability or dipole moments of the intermediates. It is not necessary to assume *syn*-elimination to account for any of the isomers either.

A comparison of the stability data of the intermediates and the α-phenylcinnamic acid stereoisomers reveals that the elimination reaction is endothermic. Strictly speaking, this holds only for gas-phase reactions; nevertheless, it should be



1 **2** **3** **4**

Fig. 1. Structure of intermediates (before elimination) in the modified *Perkin* condensation (**a**, **b**: stereocentres)

Table 5. Standard heats of formation and dipole moments for **1**–**4** obtained by the AM1 method

	$\Delta H_{f,298}$/kJ · mol^{-1}	μ/D
1	−659.7	4.58
2	−654.6	5.24
3	−654.5	5.24
4	−659.7	4.58

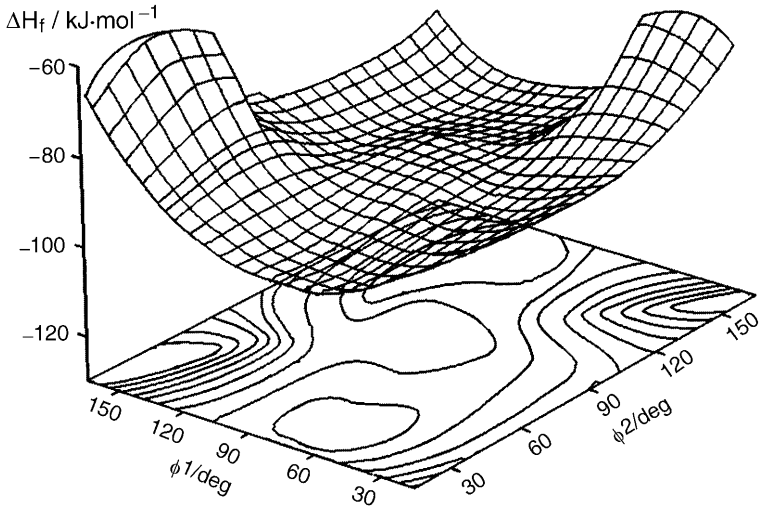


Fig. 2. Potential energy map of (*E*)-α-phenylcinnamic acid calculated by the AM1 method

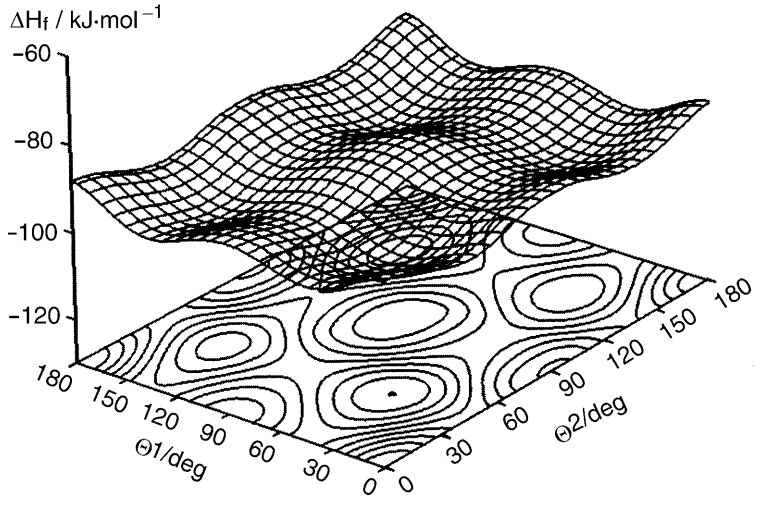


Fig. 3. Potential energy map of (*Z*)-α-phenylcinnamic acid calculated by the AM1 method

approximately valid in our system as well. Thus, the transition state is product-like, and the potential energy surfaces of the products may therefore be used in explaining stereoselectivity towards the (*E*)-isomer.

The potential energy maps of the two diastereomers differ considerably. They were obtained by rotating the phenyl groups around the σ-bond between the olefinic carbon and the phenyl carbon atoms (ϕ^1 and θ^1 correspond to position 3 (β-position) for the (*E*)- and (*Z*)-isomers, respectively, and ϕ^2 and θ^2 correspond in a similar way to position 2 (α-position). The potential energy surface for the (*E*)-isomer contains extensive low-energy regions close to the absolute minimum throughout (Fig. 2). This table-like surface contains ridges of very small heights

between the shallow valley-like minima. There are maxima when the hydrogens on the phenyl groups approach each other.

In contrast, the potential energy surface for the (*Z*)-isomer is complex with several local minima (Fig. 3). The absolute minima of both stereoisomers are very close to each other. Large portions of the surface are in the higher energy region (saddles, ridges, local maxima).

Consequently, the reason for the preferential formation of the (*E*)-isomer is of kinetic origin. After formation, this molecule easily finds an arrangement close to the absolute minimum, whereas it is more difficult for the (*Z*)-isomer to find minimum conformations.

Conclusions

Using the modified *Perkin* condensation leading to α-phenylcinnamic acid isomers as a model reaction it has been demonstrated that experimental and computational methods together are able to give a move complete account of the observed stereochemical features than any of them alone. Applying the two different approaches in combination, the controversy between the isomer distribution in the condensation reaction and that in the (*E*)-(*Z*)-isomerization was resolved, and an explanation of the observed experimental facts could be given.

Experimental

Condensation reaction

First, the reaction was performed following the recipe of *Fieser* [4]. It involved heating a mixture of 2 cm^3 benzaldehyde, 2.5 g phenylacetic acid, 2 cm^3 acetic anhydride, and 2 cm^3 triethylamine for 35 min. The mixture of products was precipitated with 4 cm^3 of conc. HCl. The solid material was dissolved in diethyl ether and then washed with 3×10 cm^3 of 3% NaOH solution. The two isomers from the alkaline solution were obtained by selective precipitation. Acidifying with acetic acid to $pH = 5$ afforded the (*E*)-isomer, further lowering the *pH* to 1 with conc. HCl the (*Z*)-isomer. The crude products were crystallized from diethyl ether (m.p.: (*E*): 446.5 K, (*Z*): 409.5 K, close to the values published in the literature [4]).

In another set of experiments, duration and temperature of reflux were altered by variation of the solvent. Usually, 100 cm^3 of solvent was used to enforce the properties of the solvent on the reaction mixture (the quantities of the other components remained unchanged). Duration of reflux was varied from 35 min to 9 h in some cases. Products were isolated and separated as described above.

Thermal and photoinduced isomerization reactions

Thermal isomerization was performed in the *Fieser* mixture, *i.e.* 0.5 g of (*E*)-α-phenylcinnamic acid were added to a 1:1 mixture of acetic anhydride and triethyl amine (2 cm^3 each), and the system was kept under reflux for 168 h. For determining the isomeric composition, samples were withdrawn for GC-MS analysis at certain time intervals [12].

Photoinduced isomerization was performed with the help of an immersion mercury vapour lamp (Hanau GmbH, intensity maximum at $\lambda = 253.1$ nm). The reaction was performed at room temperature in a jacketed flask (water was used for controlling the temperature) under a nitrogen atmosphere on 1 g of (*E*)-α-phenylcinnamic acid dissolved in 500 cm^3 of diethyl ether. The duration of illumination was 30 h, and analysis was performed by means of the GC-MS method.

Computational methods

Geometry optimizations for the individual molecules were performed by semiempirical quantum chemical methods (MNDO, AM1, and PM3) included in the Spartan [13] or MOPAC93 [14] package. The gradient norms were always less than 0.1, and the force matrices were found to be positive definites verifying that minima were found.

Potential energy maps were computed for both isomers using the AM1 [7] routine in the Spartan [13] package. In creating a detailed surface the two phenyl groups were rotated by 1° increments, and potential energies were calculated for each conformer. The carboxyl group was allowed to assume an optimal conformation before energy calculation. Thus, fairly detailed maps were obtained. Potential energy values of 32580 points were calculated.

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