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Mechanism of the aminolysis of phenyl acetate: a computational study

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Dedicated to Academician Ivan Juchnovski on the occasion of his 70th birthday

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Density functional methods were applied in examining the possible mechanistic pathways for the reaction of phenyl acetate with ammonia. Transition state structures and energies were determined for concerted and neutral stepwise mechanisms. The general base catalysis of the process was also examined. The theoretical predictions reveal that the most favourable pathway of the reaction is through general base-catalysed neutral stepwise mechanism with the nucleophilic attack being the rate-determining stage. Comparisons are made with the energetics of the aminolysis for methyl formate and methyl benzoate. In the latter two esters, the energies of the first and second transition states, associated with the stepwise mechanism, are quite similar in magnitude. In contrast, in the case of phenyl acetate the transition state, associated with the nucleophilic attack (TS1), has distinctly higher energy than the elimination stage (TS2), and is the rate-determining stage of the reaction. The much lower energy of TS2 in phenyl acetate is attributed to the higher stability of the leaving group.

Key words: ester aminolysis, phenyl acetate, mechanism; density functional theory.

INTRODUCTION

The ester aminolysis is an important reaction for both biochemistry and organic chemistry. It is the usual process in the generation of amide functional groups in proteins and peptides [1–9]. The kinetics and mechanism of the reaction has been the subject of numerous experimental [10–19] and theoretical studies [20–33]. These studies have focused on the influence of various factors on the rate and mechanism of the reaction. The detailed understanding of the chemistry of the process – mechanism, reactivity, and catalysis – is, therefore, of importance for both chemistry and biology. The theoretical and experimental results obtained so far indicate that the reaction can proceed *via* two probable paths: concerted and step-wise neutral mechanisms. The particular mechanistic pathway for a pair of ester and amine would depend on the structure of reactants, the presence of excess amine, and the nature of solvent. The aim of the present study is to apply methods of computational quantum chemistry in studying the mechanism of ester aminolysis in the case of phenyl acetate. Ammonia was used as a model reactant.

Phenyl acetate and several ring-substituted derivatives have been popular models for a number of experimental studies on the aminolysis process [10e, 34–40]. Jencks and Carriuolo [34] investigated the reaction of phenyl acetate with several amines in aqueous solution and found out that the process proceeds under general base catalysis. Oleinik *et al.* [37] studied the kinetics of the aminolysis of *p*-nitrophenyl acetate and 2,4-dinitrophenyl acetate by a number of aliphatic amines in various solvents. The kinetic results indicated that the transition state associated with the rate-determining stage of the reaction varies from reactant-like to similar in structure to a tetrahedral intermediate depending on the nature of the participating ester or amine. Lee and co-workers [38] investigated the kinetics of the aminolysis of substituted in the aromatic ring phenyl acetates by benzyl amine in dimethyl sulfoxide solution. Rajarathnam *et al.* [39, 40] examined the kinetics of the aminolysis of *meta* and *para* ring-substituted phenyl acetates by imidazole in aqueous medium.

It was of interest to compare the energy profiles of the aminolysis of phenyl acetate with previously reported results for methyl formate [29a] and methyl benzoate [29d]. In this way it would be possible to assess the influence of aromatic substitution at both sides of the ester grouping on the energy characteristics of the aminolysis reaction.

COMPUTATIONAL METHODS

The computations were carried out with the Gaussian 98 [41] program package. Stable structures and transition states along the reaction pathway were fully optimised by applying B3LYP

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method [42, 43] in conjunction with the 6–31G+(d,p) [44, 45] basis set. The critical points were further characterized by analytic computations of harmonic vibrational frequencies at the same level/basis set. Transition state structures were located by the traditional transition state optimisation using the Berny algorithm [46] and then checked by intrinsic reaction coordinate (IRC) computations [47] at the same level of theory. Single point computations at the MP2/6–31+G(d,p) [48] and MP2/cc-pVTZ [49] level were performed for more precise energy predictions.

The effects of solvent were predicted by using the Polarized Continuum Model (PCM) [50] incorporated in the Gaussian package. Single point PCM//B3LYP/6-31+G(d,p) computations were performed for estimating the change in energy profile of the reaction in presence of water and the aprotic solvent acetonitrile. The standard dielectric constants for water and acetonitrile implemented in the Gaussian program were employed.

RESULTS AND DISCUSSION

As already emphasized in the introductory section, the experimental and theoretical results accumulated so far showed two most likely pathways for the ester aminolysis reaction: concerted and neutral stepwise mechanisms. Theoretical computations have revealed that a step-wise mechanism involving the formation of zwiterionic intermediates is unlikely [29b]. These two possibilities are explored here in studying the reaction of phenyl acetate with ammonia. The manner of attack by the nucleophile differs in the two mechanisms. For the concerted pathway, the initial nucleophilic attack is along the C–O ester bond, while for the stepwise route the reaction begins with an orientation of an N-H bond from NH_3 along the carbonyl C=O bond.

Concerted mechanism

In the case of the concerted pathway the reaction consists of one step, in which all bond-forming and breaking processes occur in concert. The nucleophilic ammonia molecule attaches to the eletrophilic carbonyl carbon atom from the ester, accompanied by a proton transfer from the ammonia molecule to the oxygen atom of the ester C–O single bond. Thus, the transition state for the concerted mechanism (designated **CTS**) involves simultaneous creation of a C–N bond, cleavage of the C–O bond and a proton transfer from ammonia to the oxygen atom. The transition structure involved in the concerted pathway of the aminolysis of phenyl acetate is presented in Fig. 1. The main vectors of the imaginary vibrational frequency of the transition state **CTS** are also shown in Fig. 1 and correspond to a proton transfer between the nitrogen and the oxygen atoms and to the cleavage of the C–O ester bond, and the formation of the C–N bond. The distance between the carbonyl carbon and the ester oxygen in the transition state structure is significantly longer, 2.044 Å, than in the reactant phenyl acetate, 1.378 Å. The nitrogen-carbon bond is close to formation with a distance of 1.605 Å in **CTS** compared with 1.369Å in the product acetamide.

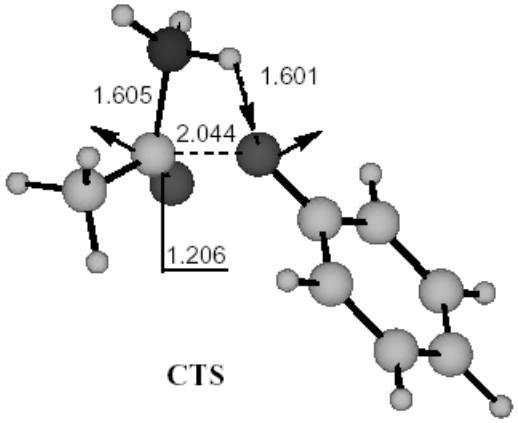

Fig. 1. B3LYP/6-31+G(d,p) optimised structure for the concerted transition state structure **CTS** for the uncatalysed aminolysis of phenyl acetate. The arrows in the transition state structure **CTS** indicate the normal coordinate with an imaginary frequency.

Stepwise mechanism

The stepwise pathway for the aminolysis of phenyl acetate is an addition-elimination process accompanied by proton transfer processes that maintain the neutrality of the structures. The transition state structures along the stepwise pathway of phenyl acetate aminolysis are presented in Fig. 2.

The first step of the reaction is the addition of an N-H bond from the ammonia molecule to the carbonyl double bond in phenyl acetate and formation of a tetrahedral imtermediate (Fig. 2). This addition takes place through a transition state **TS1**. The main vectors of the imaginary vibrational frequency for **TS1** are shown in Fig. 2 and correspond mainly to a proton transfer from the nucleophile NH_3 to the carbonyl oxygen. The hybridisation of the electrophilic carbonyl carbon atom converts from sp^2 to sp^3 during the process. The C=O double bond becomes longer (1.335 Å for **TS1**) and an alcohol-amine is obtained as an intermediate. A new C–N bond is created with a length of 1.560 Å in the transition state **TS1**.

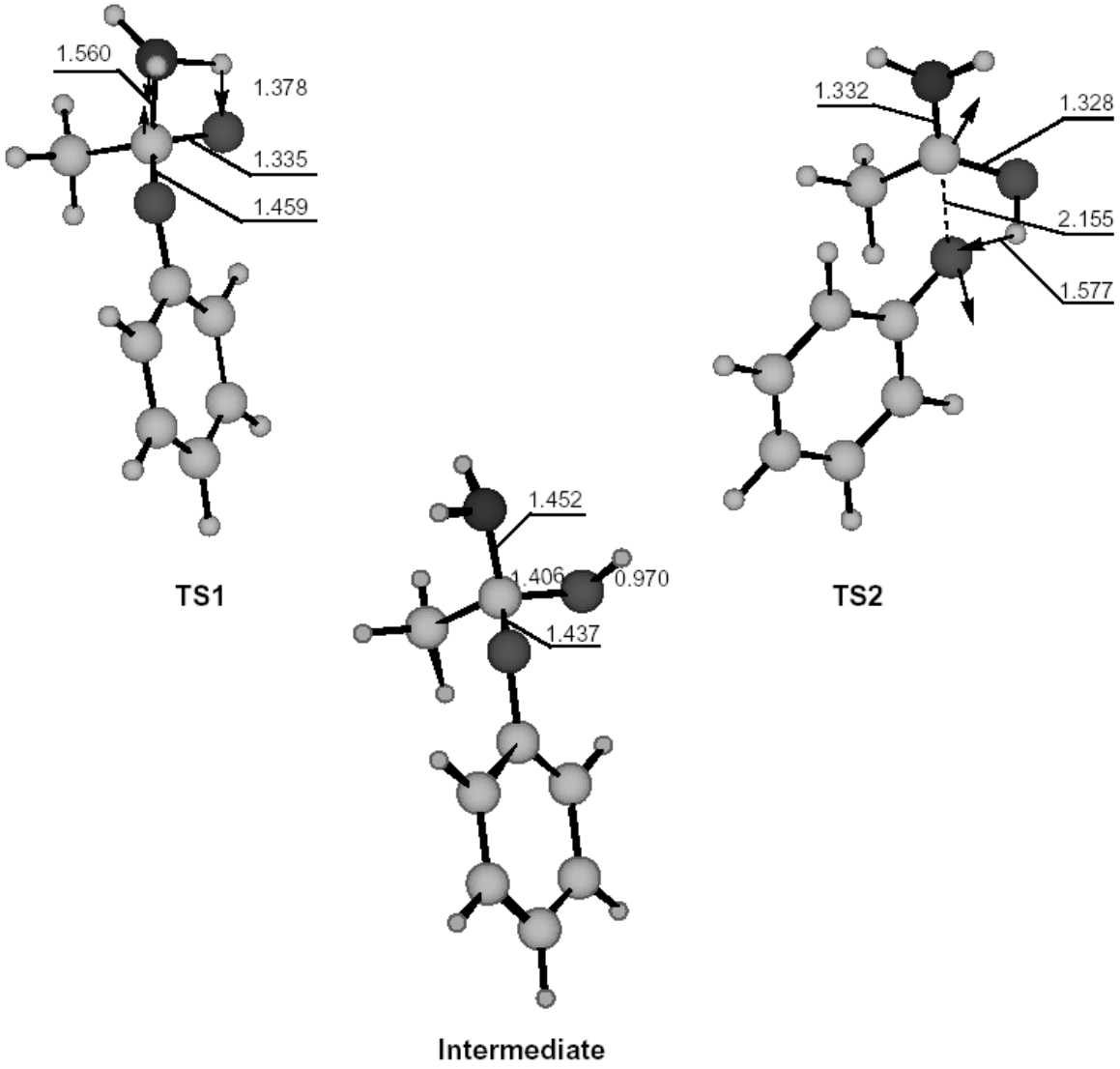

Fig. 2. B3LYP/6-31+G(d,p) optimised structures of the intermediate and transition states for the stepwise pathway of the uncatalysed aminolysis of phenyl acetate. The arrows associated with the transition state structures **TS1** and **TS2** indicate the respective normal coordinates with imaginary frequency.

The second step of the reaction is the conversion of the tetrahedral intermediate into aminolysis products. The intermediate converts to the products acetamide and phenol through the transition state **TS2**. This stage of the process involves the breaking of the C–O ester single bond and simultaneous restoration of the C=O bond following a proton transfer between the two oxygen atoms. The main components of the transition vector for the second transition state (**TS2)** correspond to the proton transfer process and cleavage of the ester C–O ester single bond (Fig. 2).

The relative energies of the structures along the concerted and stepwise pathways computed at different levels of theory are summarized in Table 1. It can be seen that the DFT computations predict the concerted mechanism to be more favourable than the stepwise pathway. The higher-level MP2 quantum mechanical computations show the same trend. The presence of a solvent, simulated here by PCM//B3LYP/6-31+G(d,p) computations (Table 1), does not significantly affect the energetics of the process. The theoretical predictions for the effect of CH_3CN and H_2O reveal that the overall trends in the energy profile of the aminolysis of phenyl acetate are not affected significantly by these solvents. These theoretical findings are in qualitative agreement with earlier results for the aminolysis of methylthioacetate [25] and methyl formate [29a]. The latter studies showed that the energies of the transition states for the stepwise and concerted pathways are quite close.

Table 1. Relative to reactants energies in kcal/mol for the stationary point structures along the concerted and stepwise mechanisms for the uncatalysed and catalysed aminolysis of phenyl acetate

Structure [a]	B3LYP/ 6-31+G(d,p)	MP2/ 6-31+G(d,p)// B3LYP/ 6-31+G(d,p)	MP2/ cc-pVTZ// B3LYP/ 6-31+G(d,p)	MP2/ cc-pVTZ// B3LYP/ 6-31+G(d,p)	PCM// B3LYP/ 6-31+G(d,p)	B3LYP/ 6-31+G(d,p)	MP2/ 6-31+G(d,p)// B3LYP/ 6-31+G(d,p)	MP2/ cc-pVTZ// B3LYP/ 6-31+G(d,p)
	Uncatalysed in gas phase			Uncatalysed in solvent		Catalysed in gas phase		
				CH_3CN	H_2O			
CTS	32.33	30.61	30.56	29.71	27.40	22.31	18.83	18.83
TS1	42.19	38.44	36.88	43.11	40.12	18.43	12.47	11.18
TS2	25.18	27.33	26.98	25.30	20.67	6.53	4.78	4.43
P	–5.49	–0.93	–2.08	–7.30	–13.88	–5.49	–0.93	–2.08

a - See text for symbols.

General base catalysis

The catalytic effects of a second ammonia molecule on the concerted and stepwise mechanisms of the aminolysis of phenyl acetate were next examined. The potential energy surfaces for the two reaction pathways were searched by applying the B3LYP/6–31+G(d,p) method. The theoretically estimated energies of the transition states for the concerted and stepwise pathways for the catalysed aminolysis of phenyl acetate are given in the last column of Table 1. In the case of ester aminolysis, the activation barriers were earlier found to result mainly from unfavourable proton transfer geometries [21]. This deduction is also supported by the present computational results for the directions of the transition vectors, characterizing the **CTScatal, TS1catal** and **TS2catal** structures. These structures are shown in Fig. 3 and reveal that all steps along the concerted and stepwise pathways involve proton transfers. The role of the catalyst in the process is to facilitate the proton transfer, thus lowering the energy barrier. In the case of the general base-catalysed aminolysis the stepwise mechanism has lower activation barrier (18.43 kcal/mol) than the concerted pathway (22.31 kcal/mol). The higher level calculations confirm that conclusion.

The energies of principal critical structures along the reaction pathways for the uncatalysed and catalysed aminolysis of methyl benzoate are illustrated in Fig. 4.

Comparison of the aminolysis process for methyl formate, methyl benzoate and phenyl acetate

As mentioned earlier, one of the aims of this study is to analyse the factors that determine the different energetics of the aminolysis reactions of aliphatic and aromatic esters. In the latter, the phenyl ring can be directly bonded to the carbonyl functionality, as in the case of methyl benzoate, or at the site of the ester oxygen atom in the phenyl acetate. In a previous study [29d] we showed that, in general terms, the ester aminolysis follows similar energy profiles for methyl esters of aliphatic (methyl formate) and aromatic (methyl benzoate) acids. In these esters the energy differences between the concerted and stepwise mechanisms are relatively small, approximately 2 kcal/mol in the case of methyl formate and 3 kcal/mol for the methyl benzoate aminolysis in the gas phase. The present theoretical computations for the aminolysis of phenyl acetate predict an energy profile with a pronounced difference between concerted and stepwise pathways. In all three cases the catalytic role of a second ammonia molecule makes the stepwise mechanism energetically more preferable. In the two previously studied systems (methyl formate and methyl benzoate), the two transition states **TS1** and **TS2** for both uncatalysed and catalysed processes have very similar energies at different level of computations. As can be seen from Fig. 4 the nucleophilic attack is definitely the rate-determining stage for both uncatalysed and catalysed aminolysis of phenyl acetate. This feature can be associated with the higher stability of PhO^- compared to CH_3O^- as leaving groups.

In the cases of methyl esters of aliphatic and aromatic acids, the concerted mechanism is energetically slightly more favourable for the uncatalysed process, but the stepwise pathway is preferred when general base catalysis is available. The small energy differences between concerted and stepwise processes are, very possibly, behind the experimentally established shifts upon substitution between the two mechanistic pathways in certain ester systems [16]. In contrast, in the case of phenyl acetate the energy differences between the two mechanisms are well pronounced as can be seen from Fig. 4.

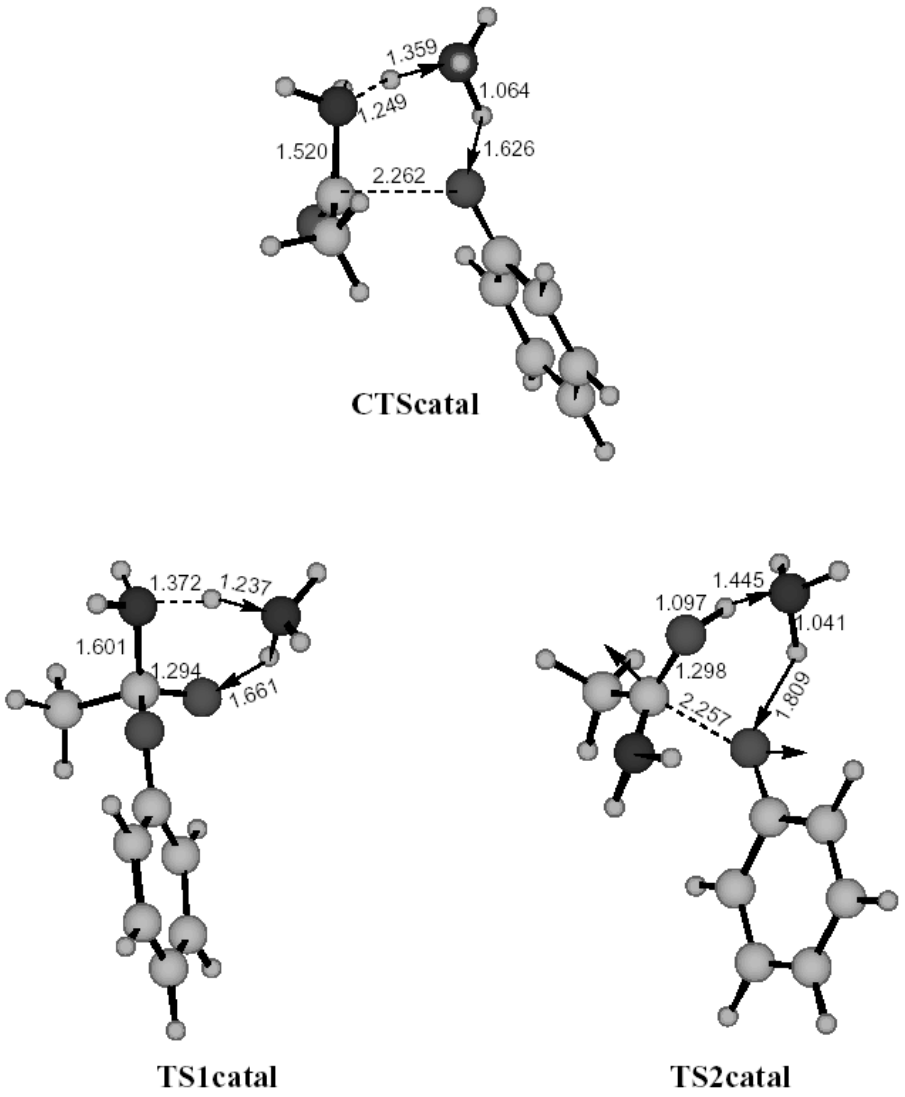

Fig. 3. B3LYP/6-31+G(d,p) optimised structures of the transition states for the catalysed aminolysis of methyl benzoate. The arrows in the transition state structures **CTScatal, TS1catal** and **TS2catal** indicate the respective normal coordinates with one imaginary vibrational frequency.

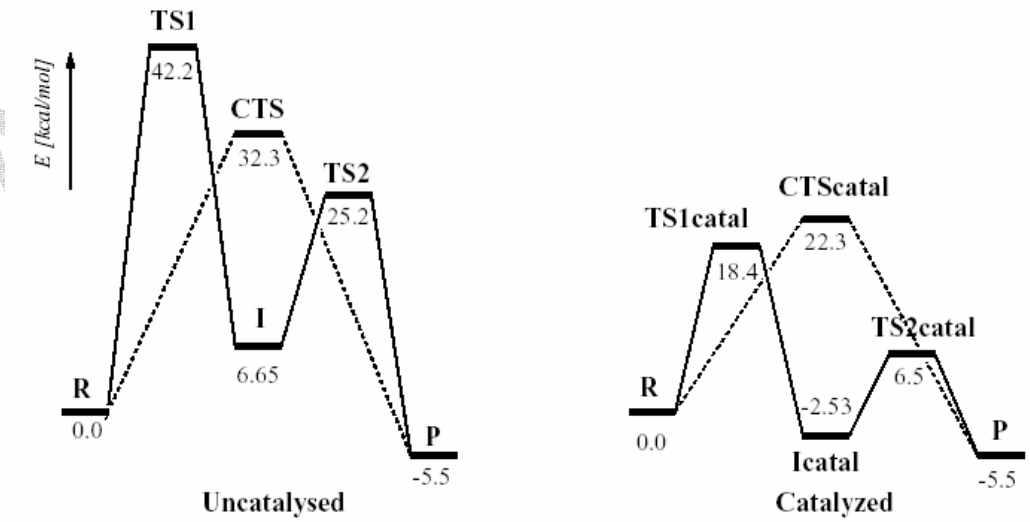

Fig. 4. Energy diagram for the uncatalysed and catalysed aminolysis of phenyl acetate from B3LYP/6-31+G(d,p) computations.

CONCLUSIONS

Density functional methods were applied in examining the possible mechanistic pathways for the reaction of phenyl acetate with ammonia. Transition state structures and energies were determined for concerted and neutral stepwise mechanisms. The general base catalysis of the process was also examined. The theoretical predictions reveal that the catalytic process results in considerable energy savings and the most favourable pathway of the reaction is through general base-catalysed neutral stepwise mechanism with the nucleophilic attack being the rate-determining stage. The structure and transition vectors of the transition states indicate that the catalytic role of ammonia is realized by facilitating the proton transfer processes. Comparisons are made with the energetics of the aminolysis for methyl formate and methyl benzoate. In the latter two esters, the energies of the first and the second transition states, associated with the stepwise mechanism, are quite similar in magnitude. In contrast, in the case of phenyl acetate the transition state, associated with the nucleophilic attack (**TS1**), has distinctly higher energy than the elimination stage (**TS2**), and is the rate-determining stage of the reaction. The much lower energy of **TS2** in phenyl acetate is attributed to the higher stability of the leaving group.

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ТЕОРЕТИЧНО ИЗСЛЕДВАНЕ НА МЕХАНИЗМА НА АМИНОЛИЗАТА НА ФЕНИЛАЦЕТАТ

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(Резюме)

Проведено е теоретично изследване на механизма на реакцията на аминолиза на фенилацетат. Стабилните структури и преходните състояния в хода на реакцията са оптимизирани на ниво B3LYP/6-31G+(d,p) за синхронен и стъпков механизъм, след което са охарактеризирани чрез изчисляване на хармоничните вибрационни честоти на съответното ниво/базисен набор. Преходните състояния са проверени чрез IRC изчисления. За по-точно определяне на енергията на състоянията са проведени MP2/6-31+G(d,p)//B3LYP/6-31+G(d,p) и MP2/cc-pVTZ//B3LYP/6-31+G(d,p) изчисления. Ефектът на разтворителя е изследван чрез метода PCM (Polarized Continuum Model). Проведени са PCM//B3LYP/6-31+G(d,p) изчисления във водна среда и в присъствие на апротонен разтворител ацетонитрил.

Получените резултати показват, че енергетично най-изгоден е процесът на базично катализирана аминолиза, протичащ в 2 стадия (стъпков механизъм), като скорост-определящ е първият етап на нуклеофилна атака и формиране на тетраедричен интермедиат. Направено е сравнение в енергетиката на аминолизата на метилбензоат и метилформиат. За двата метилови естери на мравчената и бензоената киселини енергиите на първото и второто преходни състояния, свързани със стъпковия механизъм, са близки. При фенилови естери на оцетната киселина първото преходно състояние (TS1), свързано с нуклеофилната атака, е доста по-високо енергетично от второто (TS2), което е свързано с етапа на елиминиране. По-ниската енергия на TS2 при аминолиза на фенилацетат може да се обясни с по-голямата стабилност на напускащата група в този случай.