

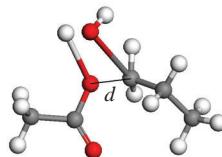
Alternativeness of ester synthesis reaction mechanism: a case study of propyl acetate

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The mechanism of the esterification reaction without the use of acid as a catalyst was examined using the AIMD method. A dissociative mechanism for the interaction of acid and alcohol without the formation of a transition state has been proposed.



Keywords: molecular dynamics, AIMD, DFT, esterification, propyl acetate.

The esterification reaction is one of the most studied chemical processes and is of great practical importance. The mechanism of nucleophilic substitution in the process of acid catalysis, proposed in 1895 by Fischer and Speier,¹ was accepted as the main one. Subsequently, with the development of quantum chemical methods, this mechanism was comprehensively studied by the Density Functional Theory (DFT) method,² which made it possible to quantitatively analyze the reaction path with the formation of transition states. Classical molecular dynamics is a very effective method for studying intermolecular interactions.³ Greater opportunities, including the investigation of alternative reaction mechanisms and the influence of the reaction medium, are achieved through the simultaneous use of classical molecular dynamics and DFT methods.⁴ In recent years, such approaches to studying the mechanisms of esterification and other organic reactions have yielded interesting and significant results.

For example, in the work of Huang *et al.*,⁵ some features of the mechanism of esterification and hydrolysis of esters were considered using the example of flavor compounds. The electronic features of the variants of transition states in the gas and liquid phases during the interaction of methanol with acetic acid in the presence of acetyl halides are presented in the cited articles.^{6,7} Two-step reactions in the presence of acid were proposed in the works of Shi *et al.*,^{8,9} using the DFT method and models of acid-catalyzed esterification of carboxylic acids and ester hydrolysis. In Salvatella's work,¹⁰ two reaction mechanisms with a sulfonylium cation and a methyloxonium cation were proposed for esterification during the interaction of sulfonic acid and alcohols in the gas phase. The effect of solvent on the mechanism of butyric acid monoglyceride ethanolysis was also studied by Huppes da Silva *et al.*¹¹ It has been confirmed that both in the gas phase and in solution the processes pass through one transition state with a certain and significant influence of internal hydrogen bonds.

Two mechanisms for the esterification of *p*-nitrobenzoic acid with *n*-butanol in pyridine, with and without diethyl chlorophosphate, were proposed by Zhang *et al.*¹² Other recent work has included analysis of esterification under other conditions, including heterogeneous catalysis. For example, in the work of Ostrovski *et al.*,¹³ the formation of heavy adducts during the esterification of acrylic acid under conditions of heterogeneous catalysis was studied by the DFT method. The esterification reaction of acetic acid and

ethanol in the presence of 'silica-propyl-SO₃H' catalyst was studied by Vafaeenezadeh *et al.*¹⁴ In their work, in particular, it was shown that the effect of the catalyst in the reaction does not consist in the transfer of H⁺ from the catalyst to the substrate and back, but in the formation of strong hydrogen bonds.

We also note the use of the Conductor-like Screening Model (COSMO),¹⁵ which allows for a detailed analysis of the effect of the solvent on the electronic structure of the reacting components. The successful application of COSMO for the esterification reaction was demonstrated in the work of Fermeglia *et al.*¹⁶ A certain limitation in their case is associated with the features of COSMO: the effect of the solvent is estimated through the approximation of the continuum of the environment by polarizability, described by the permittivity constant.

In our work, unlike most previous studies, the DFT method was also used, but implemented in combination not with classical, but with *ab initio* molecular dynamics (AIMD). In this work, the Materials Studio software package and its included DMol³ program were used.^{17–19} With this approach, the calculation of the electronic structure is carried out at each step of the movement of particles in the reaction medium, which makes it possible to model the process without using common experimental and theoretical potentials of interatomic interaction. The reaction of formation of *n*-propyl acetate was chosen as the object of modeling. To correctly describe the interactions and somewhat simplify further analysis, we excluded a number of factors, primarily the presence of a catalyst. The results obtained, as will be shown below, made it possible, under certain conditions, to propose a variant of the process mechanism that differs from the traditional nucleophilic substitution.

The dynamics of the motion of atoms and molecules in combination with the calculation of the electronic structure of the system makes it possible to observe the evolution of the state of the reaction medium at the atomic level. As already indicated, the interaction forces were calculated at each step of the movement of molecules. Accordingly, the choice of experimental/theoretical force field parameters was therefore excluded.

An ideal model for describing the reaction under consideration using the AIMD method can be represented as a cube with periodic boundary conditions, filled with molecules of acetic acid and *n*-propanol in given quantities, after a given reaction time.

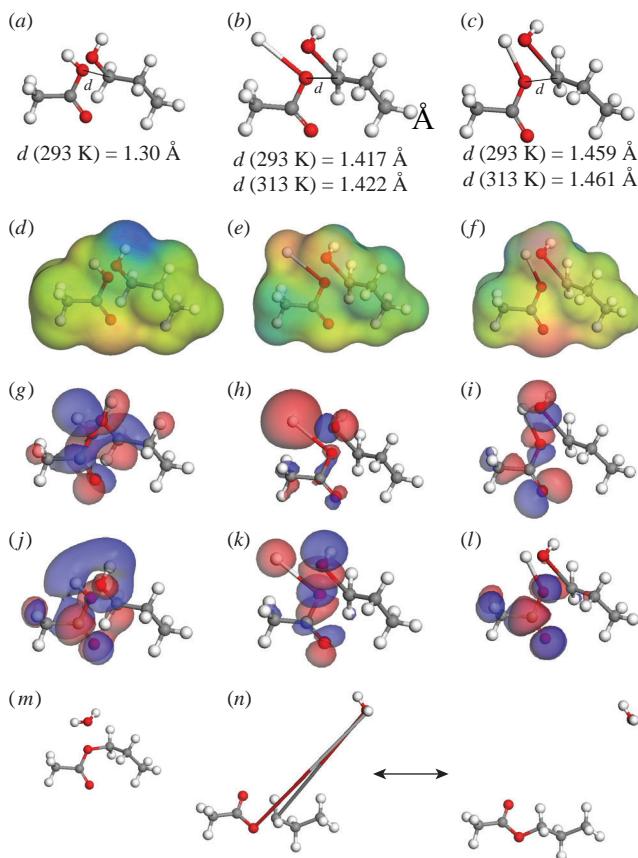


Figure 1 Evolution of (a)–(c) interatomic distances, (d)–(f) COSMO surfaces, (g)–(i) HOMO orbitals and (j)–(l) LUMO orbitals in molecules of acetic acid and *n*-propanol brought into close contact after AIMD calculations for (a),(d),(g),(j) 0 fs (starting point), (b),(e),(h),(k) 40 fs and (c),(f),(i),(l) 80 fs. (m),(n) The movement of a water molecule away from the resulting ester molecule.

Preliminary analysis has shown that quite powerful modern software and hardware do not provide enough time for the molecules to meet in a configuration favorable for the esterification reaction.

Therefore, for the initial configuration, the molecules of acetic acid and *n*-propanol were brought closer to each other from the side of their functional groups, carboxyl and hydroxyl, respectively, to a distance of $d = 1.30\text{ \AA}$ between the oxygen bonded to the hydrogen and the carbon bonded to the hydroxyl group [Figure 1(a)].

Next, for a temperature of 293 K and an interaction time of 2 ps, the calculation was carried out using the AIMD method with a step of 1 fs. The PBE functional was used in the all-electron approximation of the DND numerical basis (version 4.4) in COSMO with a permittivity constant of the environment equal to 13. It was found that when molecules of acetic acid and *n*-propanol interact at a distance closer than 1.30 \AA , the esterification reaction begins, and at greater distances, the molecules do not interact chemically, *i.e.*, electrons do not move from molecule to molecule, but move together with the nuclei of the atoms of the molecules.

The evolution of the COSMO surface is shown in Figure 1(d)–(f). It can be clearly seen how the color of the charge density surface changes from blue (positive charge) to red (negative charge). The evolution of the HOMO and LUMO orbitals is also shown in Figure 1(g)–(l). The complex nature of the orbitals at the starting point transforms into the standard state of two molecules as the process of electron redistribution occurs during the chemical reaction.

AIMD calculations were also performed for elevated temperature to evaluate its effect on the reaction. Figure 1(b),(c) shows the distances between molecules after 40 and 80 fs at temperatures

of 298 and 313 K. With a small change in interatomic distances in such a short time, it should be emphasized that an increase in temperature has virtually no effect on the formation of a carbon–oxygen bond in the resulting *n*-propyl acetate molecule.

The simulation results show that at the very beginning of the interaction of molecules, a proton is separated from the carboxyl group of the acetic acid molecule and the hydroxyl group is separated from the *n*-propanol molecule. At this stage, the proton does not interact with the hydroxyl group, but dissociates in the opposite direction from the *n*-propanol molecule. Accordingly, the hydroxyl group of the *n*-propanol molecule also dissociates, breaking away from the propyl residue. Note also that already at a very early stage a covalent bond is established between the oxygen of the carboxyl group of acetic acid and the propyl residue. Further evolution of the system leads to the movement of the water molecule away from the resulting ester molecule. Subsequently, the water molecule tends to move away from the ester molecule and for a time of 2 ps is at a distance of more than 10 Å from it [Figure 1(m),(n)].

Thus, the chemical interaction of acetic acid and *n*-propanol occurs according to a mechanism involving the dissociation of both acetic acid and *n*-propanol. Such an unusual mechanism of esterification is additionally substantiated by energy characteristics: the total energy of the system decreases monotonically during the process, that is, the formation of ester corresponds to the minimum of energy. The reaction enthalpy value of 2.6 kcal mol⁻¹ calculated by the DFT method and the value of 3.9 kcal mol⁻¹ calculated from experimental data²⁰ are in satisfactory agreement.

An obvious limitation in the implementation of such a mechanism is the preliminary forced approach of the carboxyl and hydroxyl functional groups of the reactants. Therefore, it can be assumed that the indicated mechanism will be implemented with a rather low probability (with a certain fluctuation), which increases with increasing density of the reaction medium. At the same time, it is known that alternative mechanisms can be realized under different conditions, but their contribution to the overall course of reactions may be insignificant.

As a result, we investigated the mechanism of esterification occurring without acid catalysis. It is known that in this case the reaction is extremely slow and the possibility of acid catalysis is associated only with the dissociation of one of the reactants (acid). Nevertheless, within the framework of AIMD modeling, we were able to show that the esterification process without a catalyst can proceed according to an alternative option presented in the article and different from the nucleophilic substitution mechanism accepted in the literature. Under normal conditions (atmospheric pressure and room temperature), the proportion of such interactions via this alternative mechanism is small, and the reaction is practically inhibited (if autocatalysis due to acid dissociation is excluded). The probability that this mechanism is realized increases, for example, with increasing pressure. Accordingly, then the esterification reaction can proceed at a noticeable rate without the participation of hydrogen ions as a catalyst. Thus, the AIMD method made it possible not only to analyze the interaction in the reaction medium, but also to propose an alternative mechanism for the esterification reaction (using the example of propyl acetate) and evaluate the conditions for its implementation.

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In commemoration of the 300th anniversary of Saint Petersburg State University’s founding.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.041.

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