DFT Study of the Arbuzov Reaction Mechanism between Ethyl Halogenides and
Trimethoxyphosphine

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The mechanism of the reaction between ethyl chloride or ethyl bromide with trimethoxyphosphine in a non-polar ($\varepsilon = 1$) and polar medium (methanol, $\varepsilon = 32.7$) was studied within the density functional theory (DFT) using MOLPRO program. It was shown that the reaction occurs in 2 stages: first, a nucleophilic attack of the carbon atom by phosphorus occurs, followed by the interaction of methyl of one of the methoxy groups with the halide. The limiting stage in all cases is the second stage of the reaction, the barrier of which is approximately 1.5 times higher than the barrier of the first. The reaction barriers are lower for the reaction of ethyl bromide, while the stabilization energies of the intermediate complexes and products are almost the same for chloride and bromide. Temperature in general has little effect on the reaction profile, with the exception of entropic destabilization of the initial complex. At the same time, the usage of a polar solvent accelerates the reaction process, lowering the barriers and stabilizing the intermediates, and can be recommended for carrying out the reaction.

Keywords: formation of C–P bond, density functional theory, reaction kinetics, solvent effect, temperature effect.

INTRODUCTION

The formation of the carbon–phosphorus (C–P) bond is of great importance for modern organic chemistry, as it is the basis for the synthesis of organophosphorus compounds (OPCs), among which there is a large number of biologically active substances and ligands of catalytically active metal complexes [1-5]. Some OPCs, in particular, phosphoric acid esters, appeared to be highly effective insecticides, such as chlorophos and others. In addition, OPCs include herbicides actively used in agriculture (glyphosate [6,7], ammonium glufosinate [8], and others).

At the same time, phosphine ligands are actively applied in catalytic reactions from various areas of organic synthesis: from cross-coupling (Sonogashira reaction) to selective homogeneous hydrogenation (reaction with Wilkinson catalyst) [9].

A powerful synthetic method that involves the use of OPCs is the Wittig [10,11] and Horner-Wadsworth-Emmons [12-17] reactions. These processes make it possible to carry out the

transition between different classes of organic substances – from carbonyl compounds to alkenes.

The Michaelis-Arbuzov reaction is very important for the creation of precursors for the above-mentioned reactions, actually become a convenient synthetic apparatus for obtaining R'–P(O)(OR)$_2$ phosphonates [18]. In its classical version, the Arbuzov reaction (Michaelis-Arbuzov reaction, Arbuzov rearrangement) is the alkylation of trialkyl phosphites with alkyl halides to form dialkyl phosphonates [19] (Fig. 1).

Nowadays, chemists make attempts to optimize the technology for obtaining precursors using the Arbuzov reaction, which requires an understanding of the physicochemical factors that affect the kinetics of this transformation. However, despite the importance of this aspect, no systematic studies of these reaction kinetics, including the impact of structure and composition of reagents, solvent and temperature, as well as other physicochemical factors that allow changing the kinetics of the reaction, have been conducted. And only one recent article provided calculation data for the reaction of (2-chloro/bromoethyl)benzene or methyl chloride/methyl bromide with trimethyl phosphite [20].

In this work, we present the first systematic theoretical study of the reaction of ethyl chloride/ethyl bromide with trimethyl phosphite from first principles using quantum chemistry methods, in order to analyze the influence of halogen nature, solvent and temperature on the kinetics of this reaction.
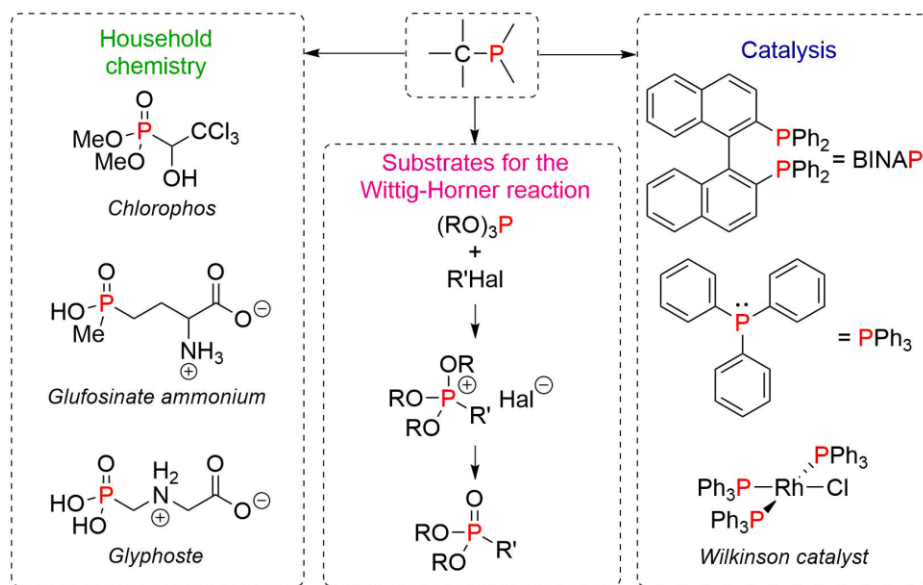

Fig. 1. The importance of the formation of the C–P bond for organic chemistry in various applied areas: organic synthesis, catalysis, agrochemistry and household chemicals.

RESULTS AND DISCUSSION

For the theoretical study of the reaction of ethyl chloride and ethyl bromide with trimethyl phosphite, the corresponding structural models were constructed, and within the framework of the

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density functional theory using the B3LYP functional [21-23], the transformation of the reagents into a phosphonate and the corresponding methyl halide was simulated. It was shown that the reaction occurs in 2 stages. The phosphorus atom, which is a part of trimethyl phosphite, has an electron pair, which at the first stage attacks the substrate – alkyl halide, as a result of which the halide ion gains mobility, becoming a good leaving group. At the second stage, the halide ion attacks one of the methoxy groups of the phosphonium salt with the formation of methyl halide and strengthening of the bond between oxygen and phosphorus (which is also energetically favorable due to the special property of phosphorus – oxygenophilicity) in the second expected product – phosphonate. The stages of the reaction under study are shown in scheme 1, and the structure of the corresponding transition states, products and intermediates is shown in fig. 2.
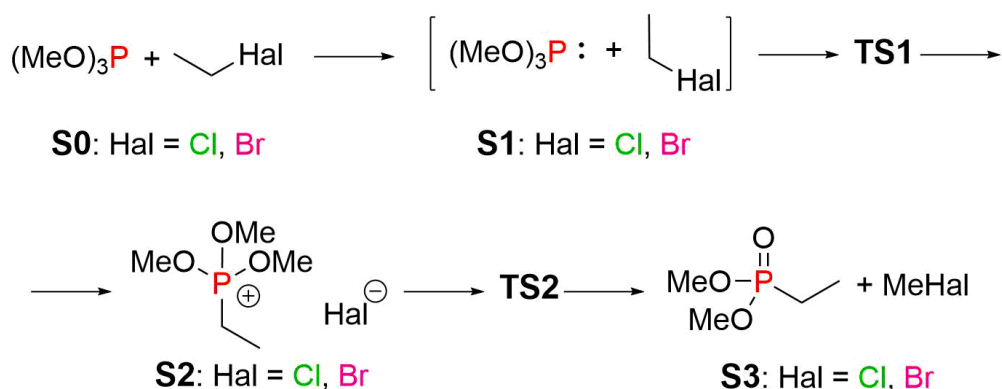
Scheme 1. Stages of the Arbuzov reaction between ethyl halides and trimethyl phosphite.
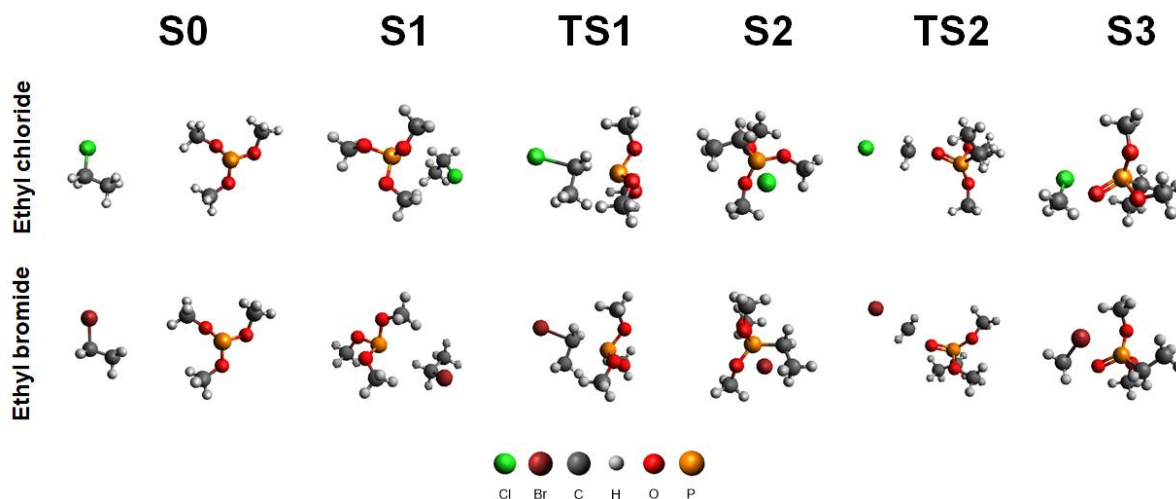

Fig. 2. Structure of intermediates, transition states and reaction products of the formation of phosphonate and methyl halides according to the Arbuzov reaction: **S0** – isolated reactants, **S1** – reactant complex, **TS1** – first transition state, **S2** – intermediate complex, **TS2** – second transition state, **S3** – reaction products.

The reactions under consideration are modeled both in the gas phase with permittivity $\varepsilon=1$ and in a highly polarized solvent presented by methanol that is frequently used for this reaction

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with a high permittivity ε=32.7 applying the COSMO model [24]. The reaction in the gas phase can also be considered as a reaction in a non-polar or low-polar solvent. Quantum-chemical calculations show that the reaction scheme and structures of intermediates in non-polar and polar media are very similar.

In the structure of the first transition state **TS1** of the Arbuzov reaction, the bond between the halogen atom and the carbon atom coordinated by three substituents – two hydrogen atoms and a methyl group – is broken. In this case, the C–P bond is formed. In the second stage of the reaction, a bond is formed between the halogen atom and the carbon atom surrounded by three hydrogen atoms and initially belonging to trimethyl phosphite. In this case, we observe the destruction of the carbon-oxygen bond. The bond of the phosphorus atom with the oxygen atom is strengthened. It is interesting to note that the bond lengths between the key reaction atoms weakly depend on the polarity of the solvent: it noticeably affects only the length of the P=O bond. The bond lengths between the key atoms in the optimized structures of the starting materials, the proposed intermediates and the products are shown in fig. 3.

Fig. 3. Lengths of C–P and P–O bonds in key intermediates and reaction products in the gas phase and methanol.

In the preactivation complex **S1**, the C–Hal bond lengths are longer than for isolated reactants when the reaction is carried out in a solvent – methanol. In this case, as a rule, longer bonds are more easily ruptured.

The C–P bond lengths in intermediate **S2** obtained from both chloroethane and bromoethane have similar values and, therefore, the strength is of the same order of magnitude both in the gas phase and in methanol.

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When changing the gas phase to the solvent, the C–P bond in the **S3** product becomes shorter by 0.3–0.4 Å for both substrate types. Probably, the polar product is solvated by polar methanol, and the C–P bond is strengthened compared to the gas phase, which makes the formation of the reaction product more favorable.

The methyl groups bound to the oxygen atoms presumably feel mutual repulsion and are capable of rotation, which makes the equivalent P–O bonds unequal, resulting in isolated trimethyl phosphite **S0** and intermediate **S2** acquiring an asymmetric structure. This can also explain the different lengths of the P–O bonds in the structure of product **S3**. The P=O bond in product **S3** is expectedly shorter and stronger than the P–O bond.

In all cases under consideration, the transition states have a trigonal-bipyramidal structure, which is typical for nucleophilic substitution reactions. The structures of the transition states and the corresponding imaginary vibration frequencies are shown in fig. 4.
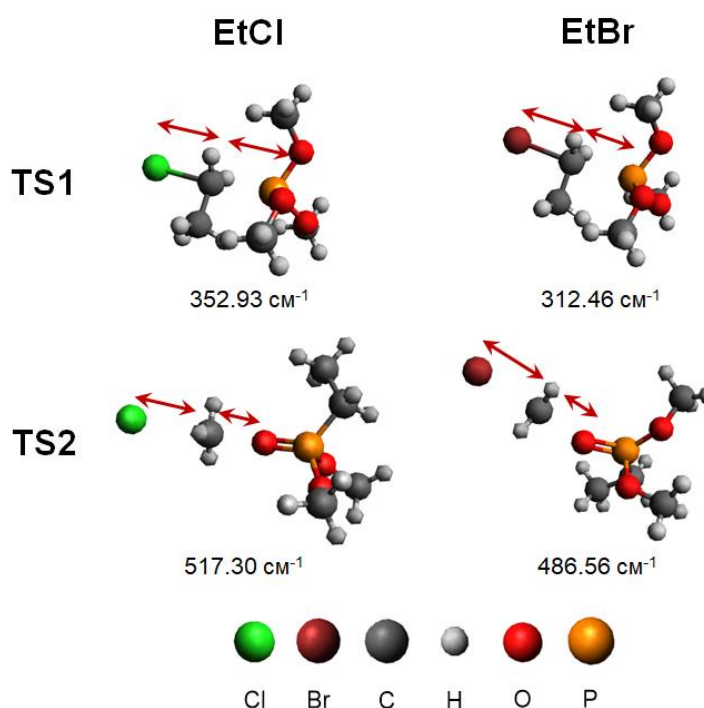

Fig. 4. Transition states, values and directions of imaginary oscillation frequencies corresponding to transition states.

When a quantum-mechanical calculation under the assumption of the proposed mechanism was carried out, we found that the zero-point energy (ZPE) has a weak effect on both the energy barriers of both stages of the Arbuzov reaction and on the energies of the intermediates and products. The electron energy at 0 K taking into account the ZPE, as well as the values of the thermodynamic functions obtained by quantum-chemical methods for the reaction in the gas phase and solvent at a temperature of 298.15 K and a pressure of 1 atm, are presented in table 1 and table 2, respectively.

Table 1. Thermodynamic characteristics of intermediates and products of the Arbuzov reaction

Substrate	Stationary point	ΔE, kcal/mol	ΔE+ZPE, kcal/mol	ΔH, kcal/mol	ΔG, kcal/mol
EtCl	**S0**	3.44	2.94	4.42	−10.53
	S1	0.00	0.00	0.00	0.00
	TS1	44.90	44.14	44.50	44.66
	S2	2.47	4.62	5.55	4.85
	TS2	75.86	74.04	73.54	75.53
	S3	−18.35	−17.81	−17.09	−18.23
EtBr	**S0**	2.43	2.16	4.07	−12.26
	S1	0.00	0.00	0.00	0.00
	TS1	37.99	37.77	38.54	37.41
	S2	2.63	4.88	5.93	4.82
	TS2	56.11	55.25	55.03	56.19
	S3	−22.21	−21.50	−20.89	−21.76

Table 2. Energies of intermediates and products of the Arbuzov reaction in methanol. The reference level in each case is the **S1** complex.

Substrate	Stationary point	ΔE, kcal/mol	ΔE+ZPE, kcal/mol	ΔH, kcal/mol	ΔG, kcal/mol
EtCl	**S0**	1.64	1.39	3.91	−13.85
	S1	0.00	0.00	0.00	0.00
	TS1	36.33	36.23	38.05	34.30
	S2	−9.17	−7.49	−5.37	−9.82
	TS2	52.62	51.55	52.48	50.75
	S3	−19.71	−19.00	−17.78	−20.31
EtBr	**S0**	0.93	0.64	2.57	−13.84
	S1	0.00	0.00	0.00	0.00
	TS1	32.55	32.67	33.35	32.51
	S2	−11.96	−10.20	−8.53	−12.24
	TS2	37.39	37.12	37.25	37.66
	S3	−21.62	−21.05	−20.37	−21.60

Calculations show that the proposed preactivation complex **S1** is stable only when considering electronic energy (ΔE), electronic energy with correction for zero-point oscillations (ΔE+ZPE) and enthalpy (ΔH), while it is the entropic contribution that destabilizes it compared to isolated reactants. In practice, this may mean that an increase in temperature leads to mutual repulsion of the reactants in the mixture and increases the corresponding barrier **TS1**, which in this case should be calculated with respect to **S0**. Accordingly, in the gas phase and in the solvent it increases by approximately 10 and 13 kcal/mol, respectively. Thus, a decrease in the mobility of the reactants in the medium or the use of moderate temperatures if possible (heating is in any case necessary to overcome the reaction barriers) can have a favorable effect on the first stage of the reaction. In addition, the use of a catalyst can be especially important for this stage both for the purpose of generally lowering the reaction barrier and for fixing the initial reactants near each

other within the preactivation complex.

For the gas phase, the main difference between the reactions with chloroethane and bromoethane is in the energies of the transition states, while the energies of the reactants **S0** and stable intermediates **S2** are virtually identical for them. The transition states **TS1** and **TS2** formed during the Arbuzov reaction, as well as the final products **S3** for the substrate containing chlorine, have higher energies than the corresponding derivatives with bromine. The activation energies of each of the two stages when bromoethane is introduced into the virtual reaction turned out to be lower than for the system with chloroethane as a reactant. A possible explanation is that nucleophilic substitution reactions occur more easily for bromine than for chlorine, since in the gas phase bromine is less nucleophilic and softer compared to chlorine and is therefore a better leaving group.

At the same time, the energy barriers for the reaction carried out using a solvent in both cases were lower than for the reaction carried out in the gas phase. In general, this is an expected result, since the reaction involves the rupture and formation of polar bonds. In this situation, the polar environment favors the stabilization of intermediates. It is especially interesting that polar methanol significantly stabilizes the intermediate product of the Arbuzov reaction – **S2**. Therefore, the real decrease in the energy barrier of the second stage of the reaction is not so significant and is about 10 kcal/mol for chlorine and 4 kcal/mol for bromine, which is also expected due to the lower polarity of bromine-containing intermediates. It is interesting that phosphonate **S3**, unlike **S2**, is almost equally stabilized in the gas phase and methanol for chloroethane and bromoethane. Thus, it can be concluded that increasing the temperature in these reactions has little effect on the thermodynamics of the process and is necessary only to overcome kinetic barriers. At the same time, the usage of polar media improves the reaction kinetics by reducing the corresponding reaction barriers and significantly stabilizing the intermediate complex **S2**. In addition, approaches associated with reducing the mobility of the reagents, for example, by increasing the viscosity of the solvent while maintaining a sufficient diffusion rate or fixation of the reagents, can be favorable for carrying out the first stage of the reaction. Finally, the use of a catalyst can be recommended both for reducing the kinetic barriers of the reaction and for spatial fixation of the reagents in close proximity to each other at the first stage.
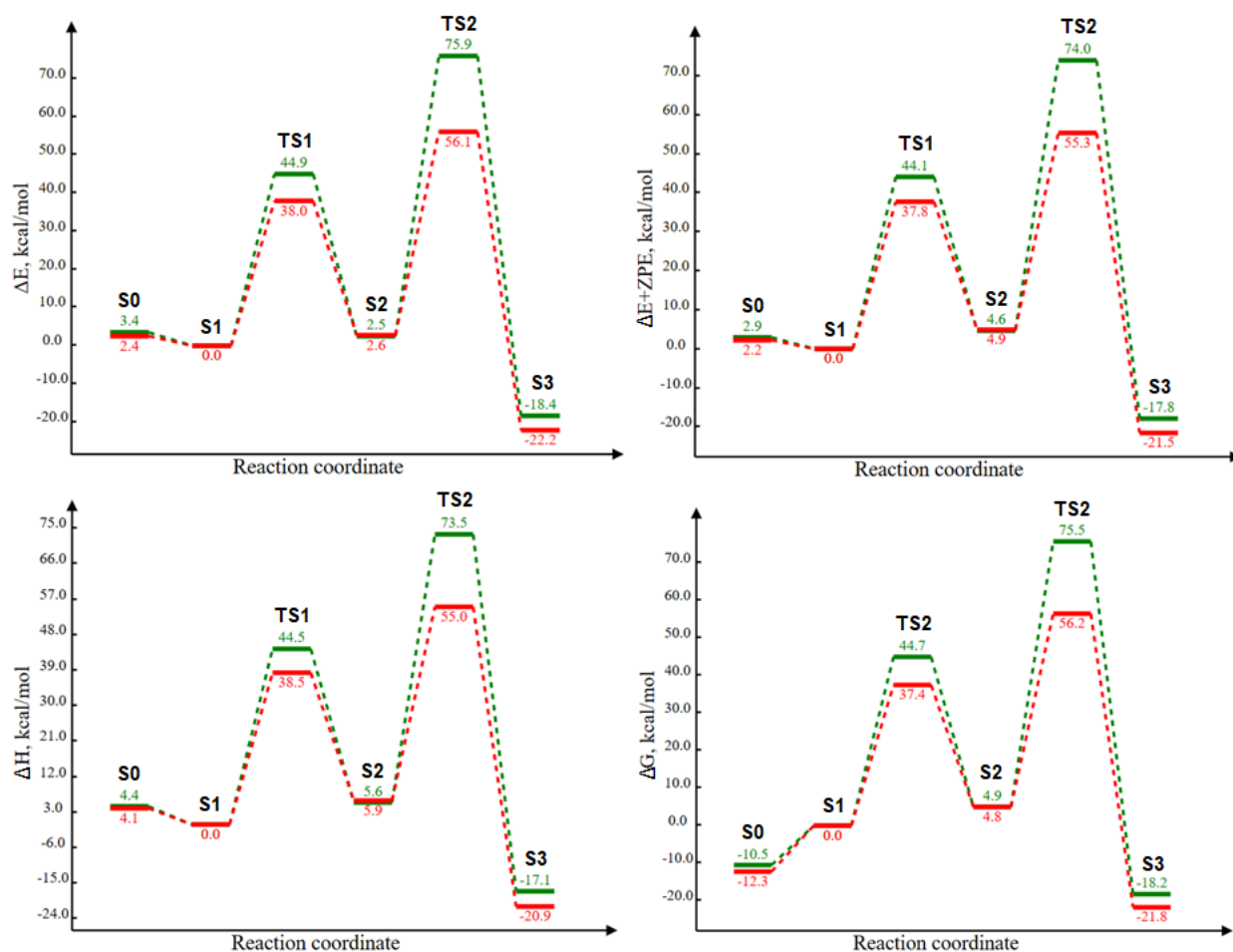
Fig. 5. Energy profiles of the Arbuzov reaction carried out in the gas phase (green – chlorine, red – bromine).
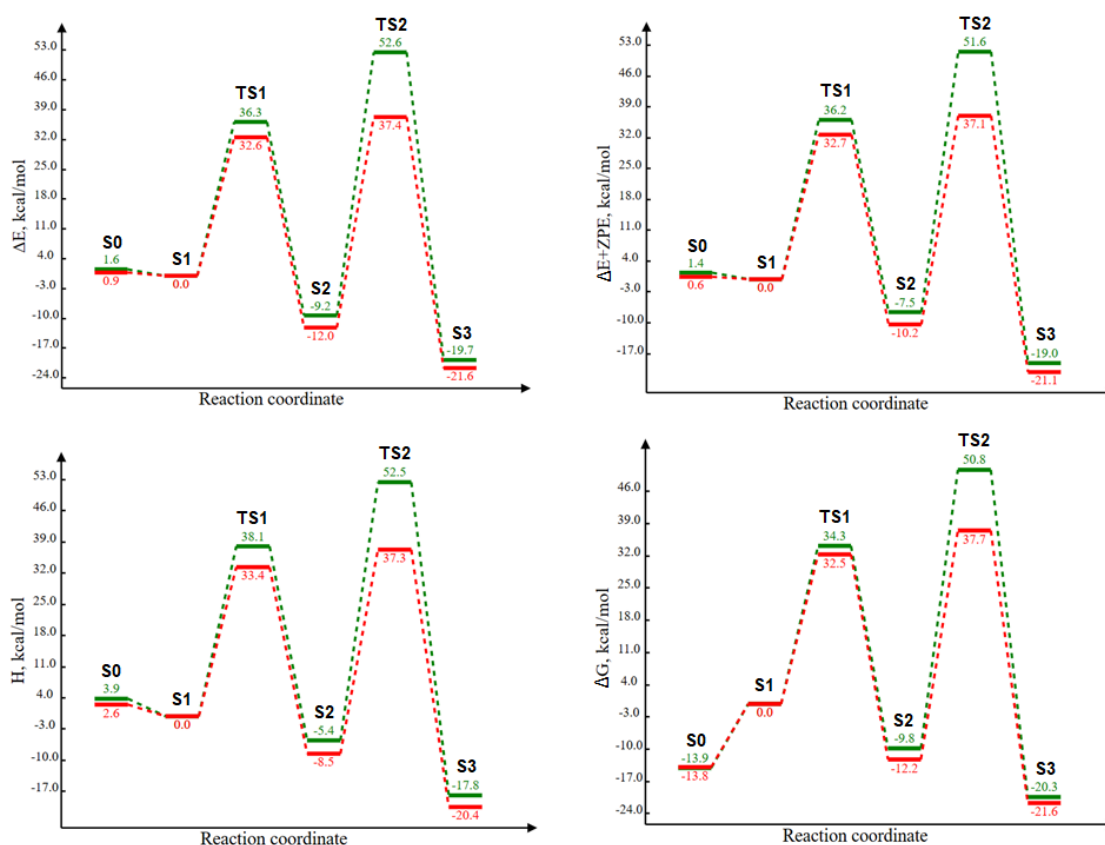
Fig. 6. Energy profiles of the Arbuzov reaction carried out in a polar medium – methanol (green – chlorine, red – bromine).

THEORETICAL AND COMPUTATIONAL DETAILS

The modeling of the mechanisms of the Arbuzov reaction between ethyl chloride/ethyl bromide and trimethyl phosphite was carried out within the framework of the density functional theory (DFT) using the MOLPRO software package [25] with the use of the hybrid exchange-correlation functional B3LYP [21-23], which is often used for research in organic chemistry due to the high-quality description of the geometric and energy parameters of the systems. The atomic basis set cc-pVDZ [26] was used to describe the wave function. To find the reaction mechanism, the geometry of the structures was optimized by searching for minima corresponding to intermediates and saddle points corresponding to transition states. To confirm the type of steady states and find the corresponding thermodynamic characteristics (enthalpy, entropy, Gibbs free energy) at a temperature of 298.15 K and a pressure of 1 atm, vibrational frequencies were calculated in the harmonic approximation. The reaction was modeled in the gas phase ($\varepsilon=1$) and in methanol ($\varepsilon=32.7$), as one of the most polar solvents used for this reaction, using the COSMO solvation model [24]. Quantum-mechanical calculations were performed on the Lomonosov-2 supercomputer [27].

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CONCLUSIONS

The mechanism of the Arbuzov reaction is proposed using the interaction of chloro- and bromoethane with trimethyl phosphite as an example. This reaction is a successive double nucleophilic substitution with the formation of the corresponding trigonal-bipyramidal transition states. It was found that temperature does not have a strong effect on the energy barriers and stability. The intermediate product **S2** of the reaction in the gas phase is destabilized with respect to **S1** and **S3**. At the same time, when the reaction is carried out in methanol, the polar compound **S2** is solvated and its energy decreases relative to the preactivation complex **S1** and reagents **S0** due to the polarity of the solvent. The preactivation complex **S1** can be destabilized compared to isolated reagents **S0** due to the entropic contribution, therefore, it is recommended to reduce the mobility of the reagents and use moderate temperatures. It can also be recommended to use a catalyst not only to directly lower the reaction barriers, but also to fix the initial reagents in the preactivation complex. In the gas phase, bromine is less nucleophilic and, being a better leaving group than chlorine, has greater mobility. In methanol, the characteristics of the intermediates for chlorine and bromine converge with the exception of **TS2**, and a general decrease in the reaction barriers and intermediates is also observed. Thus, the use of a polar solvent promotes the reaction and can be recommended for its acceleration.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Graphical abstract:

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