FIRST EXAMPLE OF THE TISHCHENKO-TYPE REACTION IN THE GAS PHASE

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Introduction

Our team has many years of experience in studying gas-phase chemistry. We have developed simple and efficient method for generating gas-phase phenide anions with various substituents in the ring.[1] The formation of these anions can take place in the medium pressure part of the ESI ion source or in a collision cell. It is possible also to subject these anions to reactions with various gas-phase reagents, which are introduced with the curtain or collision gases.

In this poster, the results of the gas-phase reactions of the substituted phenide ions with methyl formate are reported. It was shown that the phenide ions substituted with electron-withdrawing groups react with methyl formate in the gas phase in a two-step reaction. The first step which proceeds according to the typical addition-elimination mechanism results in the formation of the anion of the respective benzaldehyde derivative with the negative charge located either in the aldehyde group (acyl anion) or in the benzene ring (phenide anion) in position *ortho* to an aldehyde moiety. In the second step the preliminary formed anion reacts with the second molecule of methyl formate yielding formally product of the second addition-elimination reaction. We focused our attention to the latter reaction and performed quantum chemical calculations.
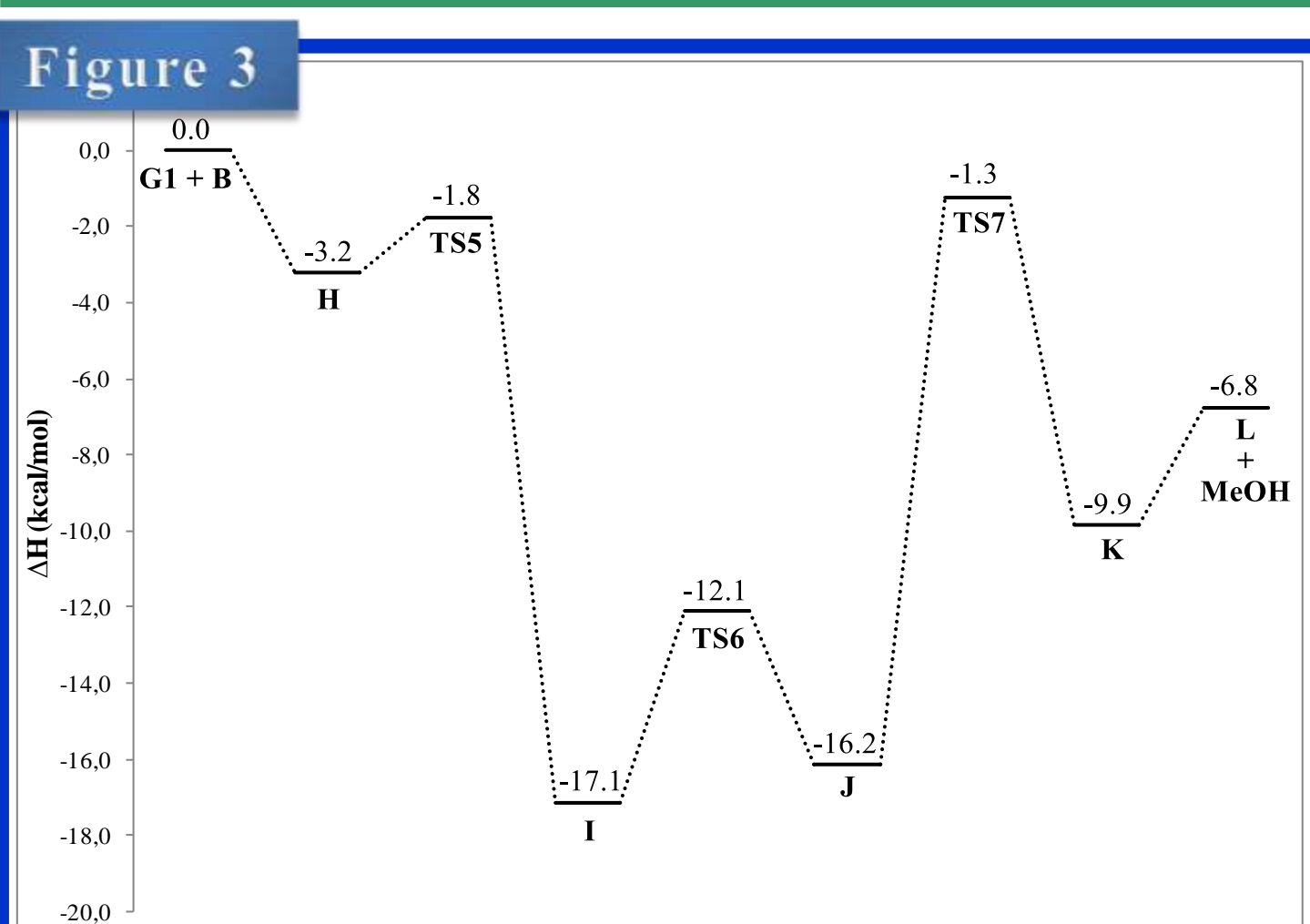
Experimental

All gas-phase reactions were performed using an API 365 triple quadrupole mass spectrometer (Applied Biosystems) equipped with a TurboIonSpray source. All spectra were recorded in a negative ion mode using electrospray ion source. Source parameters were as follows: capillary voltage –4.5 kV, nebulizer gas 12 and curtain gas 8 (arbitrary units), N_2 in both cases). Typical DP values were between 20 and 60 V, and FP values were between 180 and 300 V. To enable the use of different collision gases, the collision gas inlet was modified to allow introduction of the selected collision gas independently from the curtain gas. The ion molecule reactions in the collision cell were studied using appropriate gaseous reagents. The pressure of collision gas was set at 3 (arbitrary units). Collision cell parameters were set as follows: entrance potential (CEP) – 10 V, exit potential (CXP) 15 V. The collision energy (CE) during the reaction was set at 5 eV.

All quantum chemical calculations described in this work were performed using the Gaussian 09 software package. Starting geometries for geometry optimization were created using the GaussView 5.0 program. Reaction potential energy profiles and molecular properties were computed applying density functional theory methods, at the B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) level. Proton affinities (PA) of the anions at 298.15 K were calculated as the enthalpies of the reaction: AH = A[–] + H^{+}.

API 365 triple quadrupole mass spectrometer

Figure 2
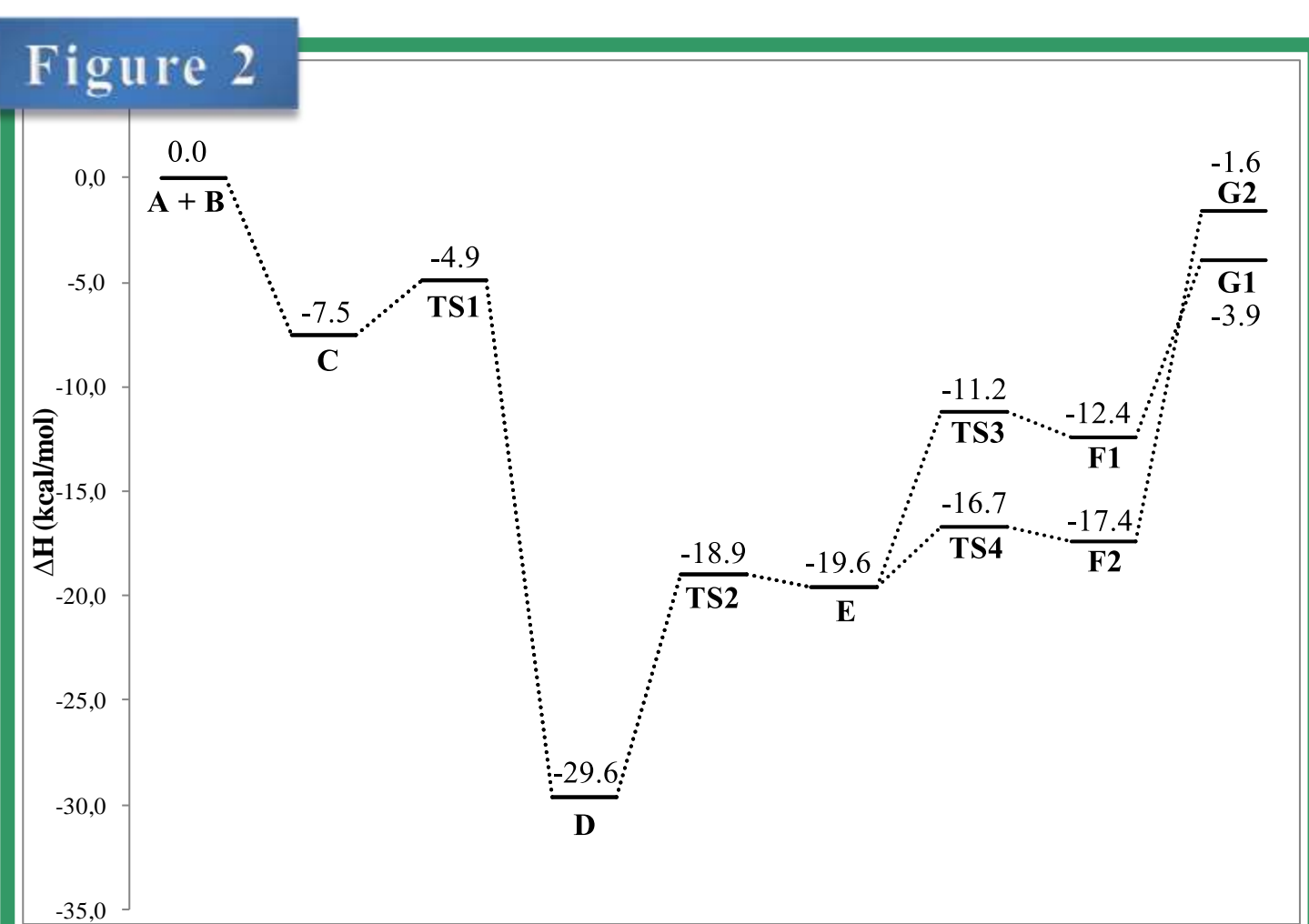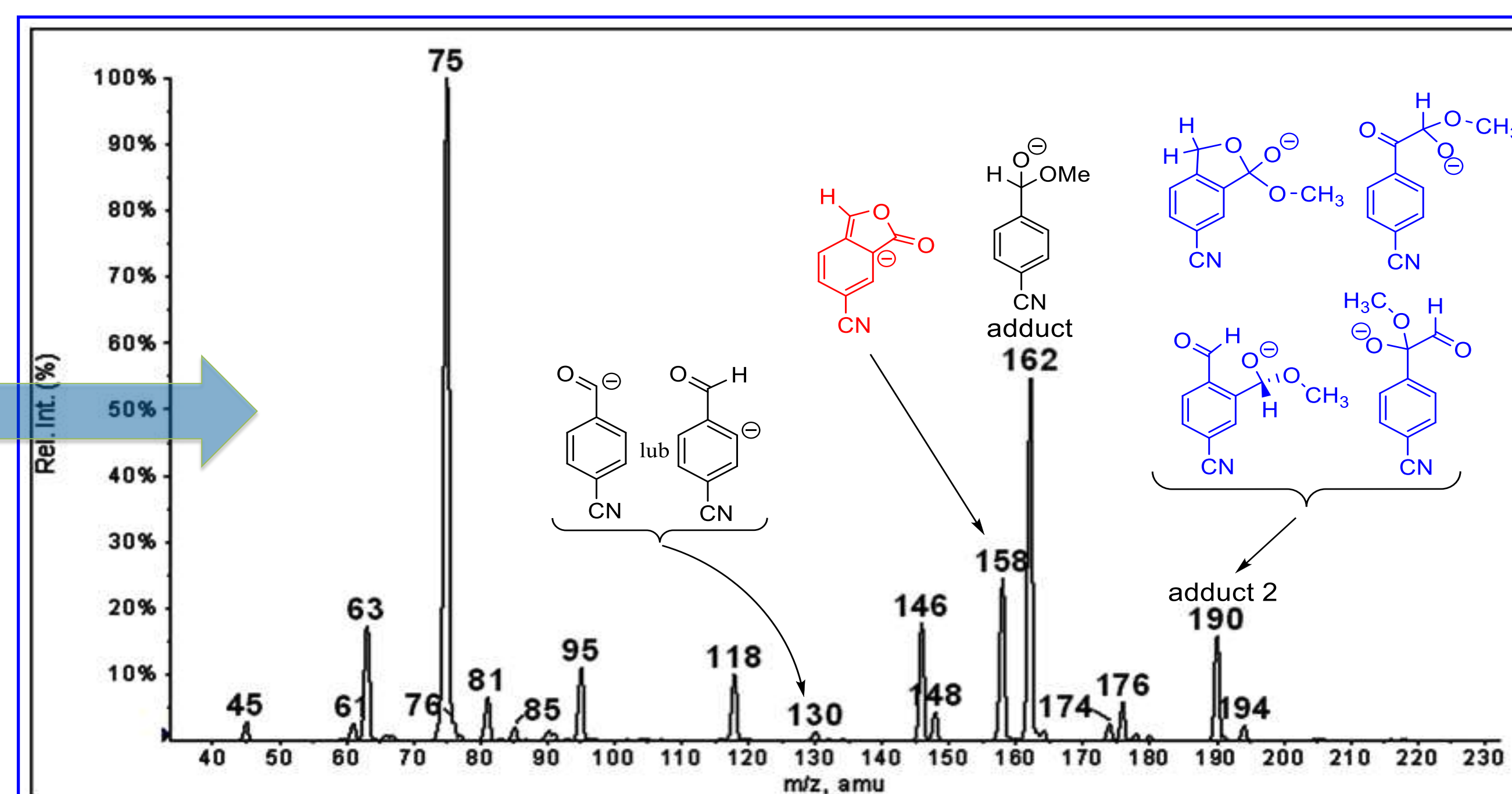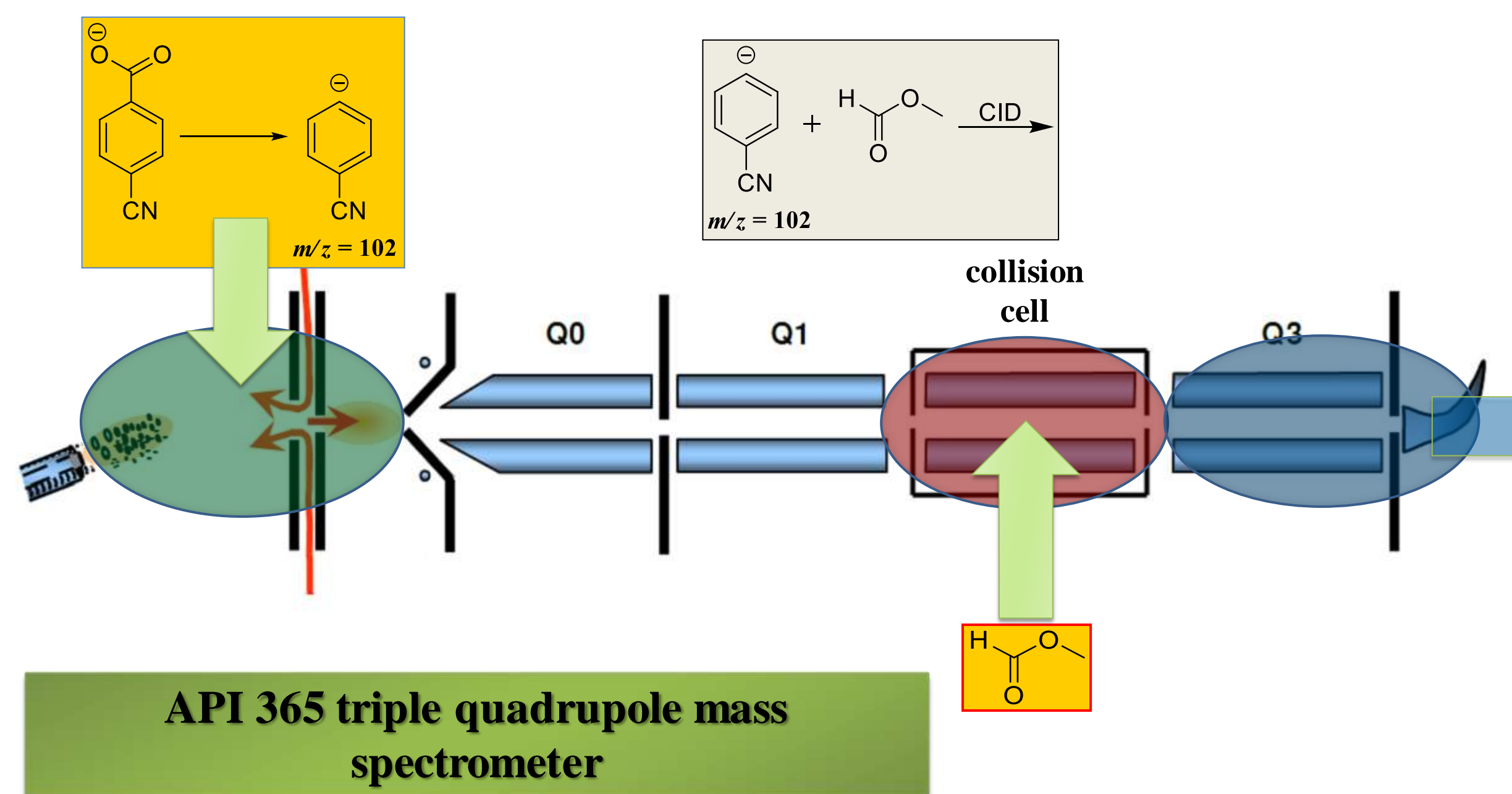
The mechanism of gas-phase addition-elimination reaction is very similar to this observed in a liquid phase, however in the elimination step a methanol molecule is eliminated, instead of methoxyl anion, which is eliminated in the condensed phase reaction. Moreover, during the gas-phase reaction two kinds of products are possible, which differ from each other by location of a negative charge in the molecule after the elimination of methanol molecule from the adduct. Due to its high basicity in the gas phase, the methoxyl anion which is eliminated from the adduct, takes off the most acidic proton from benzaldehyde derivative. Hence, two final products of the addition-elimination reaction are possible: an acyl anion (**G1** in Scheme 1) and the substituted phenide anion (**G2** in Scheme 1). To distinguish between these two anions quantum chemical calculations have been performed. Proton affinity of **G2** anion calculated by DFT methods is higher than for G1 anion, but using quantum chemistry composite methods (G3MP2, G4MP2), which are supposed to be more accurate, the reverse result was obtained (Table 1). On the basis of these calculations it is not possible to establish unequivocally which anion is mainly generated. It is very likely that both anions are formed in the addition-elimination reaction. Moreover, there are no kinetic and thermodynamic obstacles, which could adversely affect the formation of G1 and G2 anions (Figure 2).

Scheme 1

Table 1

ANION	B3LYP[a)]	M05-2X[b)]	G3MP2	G4MP2
G1 (acyl)	**369.0**	**368.7**	373.5	373.8
Δ	-2.3	-1.2	2	2.6
G2 (ortho)	371.3	369.9	**371.5**	**371.2**

a) B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d), b) M05-2X/6-311+G(3df,2p)//M05-2X/6-31G(d)

Figure 3

Due to the formation of two possible products in the gas-phase addition-elimination reaction (structures **G1** and **G2** in the Scheme 1), there are two different ways of the second addition-elimination reaction, in which different products are obtained (Scheme 2 and Scheme 3). The **G1** anion is supposed to react with another molecule of methyl formate producing the adduct **I** (Scheme 2). The reaction energy diagram corresponding to this reaction pathway is depicted in Figure 3. We were not able to model the direct elimination of methanol from anion **I**. In the course of the calculation, we observed that during the departure of the methoxy group from the adduct, this group is moved to the neighboring carbonyl group. The resulting anion **J** undergoes the elimination of methanol yielding finally anion **L**. The energies of all transition states are lower than the energy of the reactants so the formation of anion **L** is feasible. An alternative structure for anion L, i.e. with the negative charge located in the *ortho* position of the benzene ring (analogously to **G2**) has to be rejected because its proton affinity is about 19 kcal/mol higher than PA of the anion **L**.

Different reaction product responsible for the *m/z* 158 peak (Figure 1) should be formed in the reaction of anion **G2** with methyl formate. We expected that analogously to the reaction of the starting cyanophenide ion formylation of the benzene ring via addition-elimination reaction should take place (Scheme 3). The DFT calculations show that such process is energetically possible (Figure 4). The energies of all intermediates and transition states are located below the energy of reactants or – in the case of **TS10** and **TS11** – are only slightly higher.
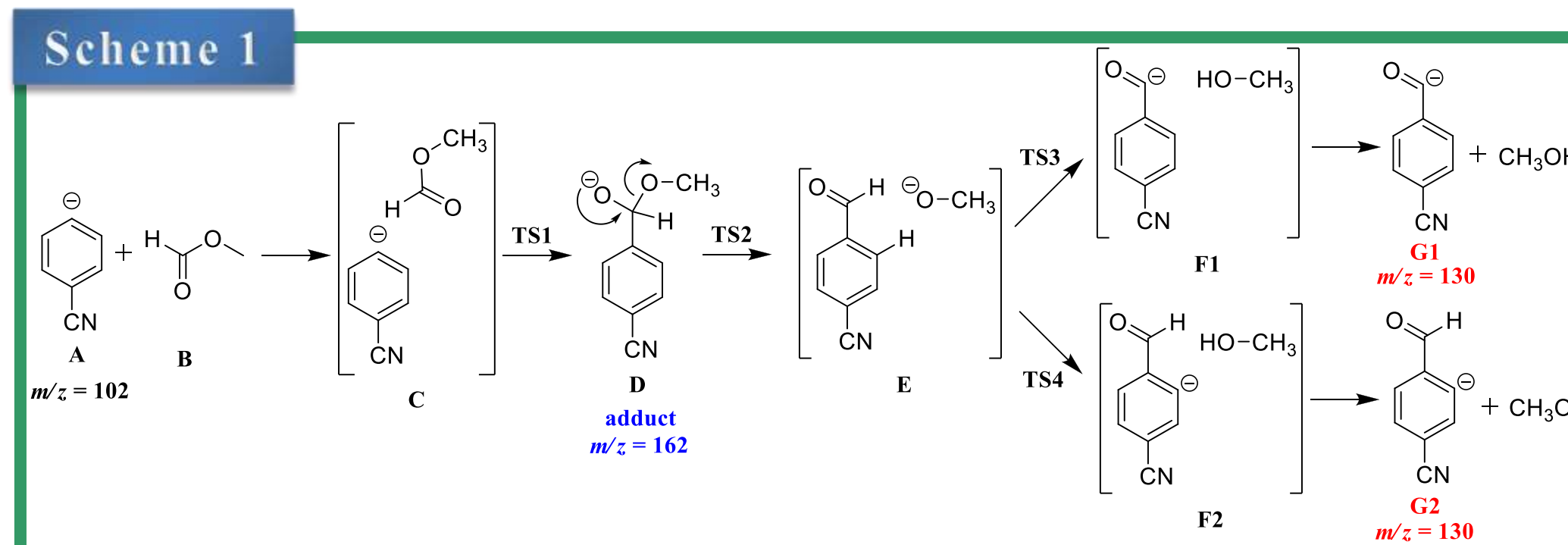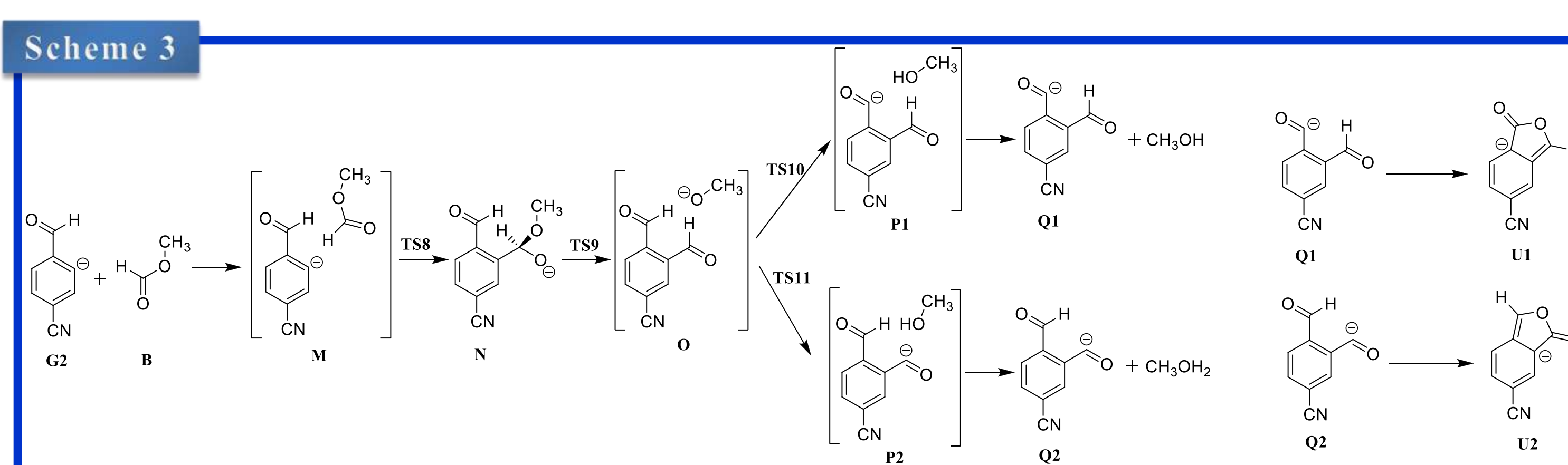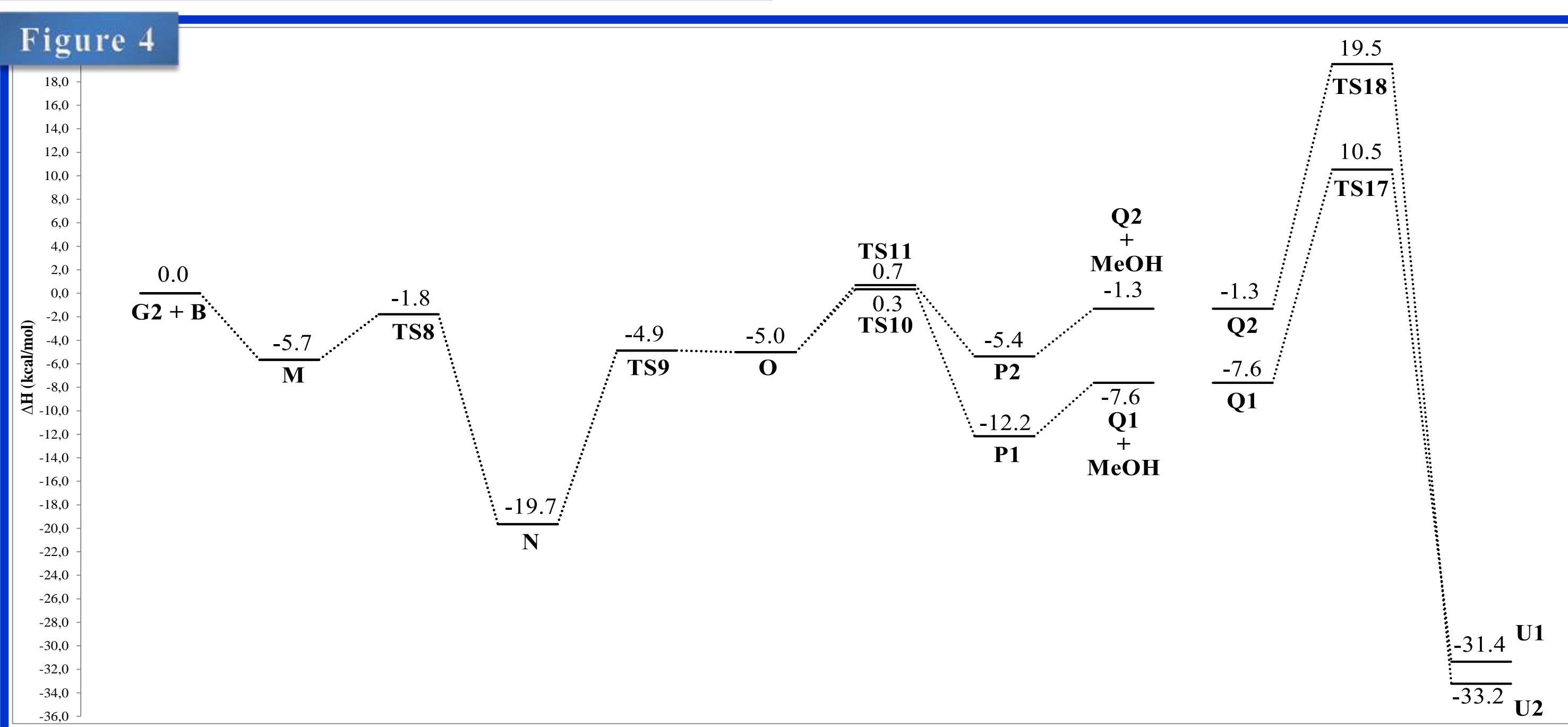
Scheme 2

Figure 4

Scheme 3

Figure 5

Searching for the optimal geometries of anions **Q1** and **Q2** we observed and unexpected "*in silico* reaction" in which these two species were converted into much more stable anions **U1** and **U2** corresponding, respectively, to the 5-cyanophthalide and 6-cyanophthalide anions (Scheme 3). Performed calculations showed that **U1** anion is 23.8 kcal/mol more stable than **Q1**. In the case of **Q2** and **U2** anions this difference is 31.8 kcal/mol. Search for the transition states of these two reactions showed however that the activation energy barrier of both of them is quite high and equals to 18.6 kcal/mol for **Q1** to **U1** transformation and 20.8 kcal/mol for the second reaction. These results show that direct transformation of ions **Q** into **U** is possible but should be rather slow.

Looking for another pathways leading to the **U1** or **U2** ions from the adduct of methyl formate to anion **G2** we considered a variant of the Tishchenko reaction (Scheme 4). It turned out that the migration of a hydride anion from the adduct **N2** (N and N2 adducts differ in conformation) and consequent elimination of methanol can proceed with very small energy barrier. In the first step of the bicyclic product formation, the Cannizzaro disproportionation reaction occurred within the adduct yielding ion **R**. Subsequently, an intramolecular attack of the anion, in which a negative charge is localized at the oxygen atom, to the carbonyl group occurs and the new adduct **S** is formed. The elimination of methanol molecule from the adduct **R** is a final step of the gas-phase version of Tishchenko reaction which ends with phthalide anion **U2**. It has to be noted that this mechanism leads solely to **U2** anion and it is not possible to rationalize the formation of the **U1** isomeric ion via Tishchenko reaction mechanism.

Obtained products and transition states are located below the energy of reactants and, additionally, the process is highly exothermic (Figure 5). Without doubts, this reaction should proceed much faster than the reactions leading to the anions **L**, **Q1** and **Q2**. With high degree of certainty it can be concluded that the anion **U2** obtained in Tishchenko reaction (observed in mass spectrum of reaction as signal at *m/z* 158) is the major/final product of the reaction of anion **G2** with methyl formate.

Scheme 4
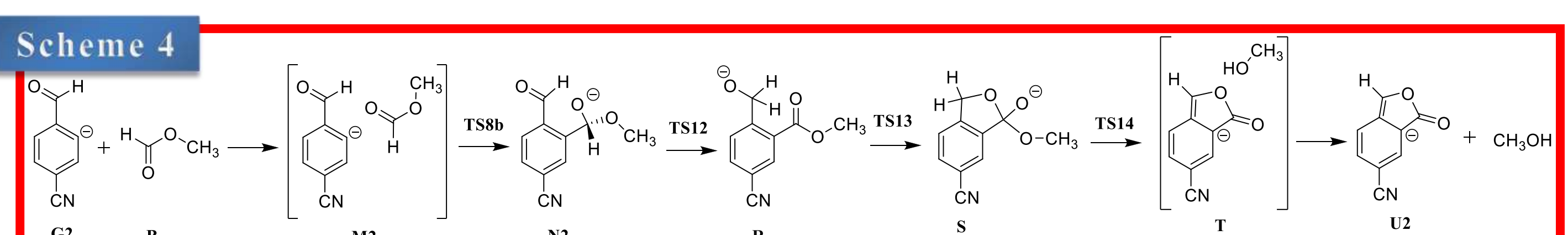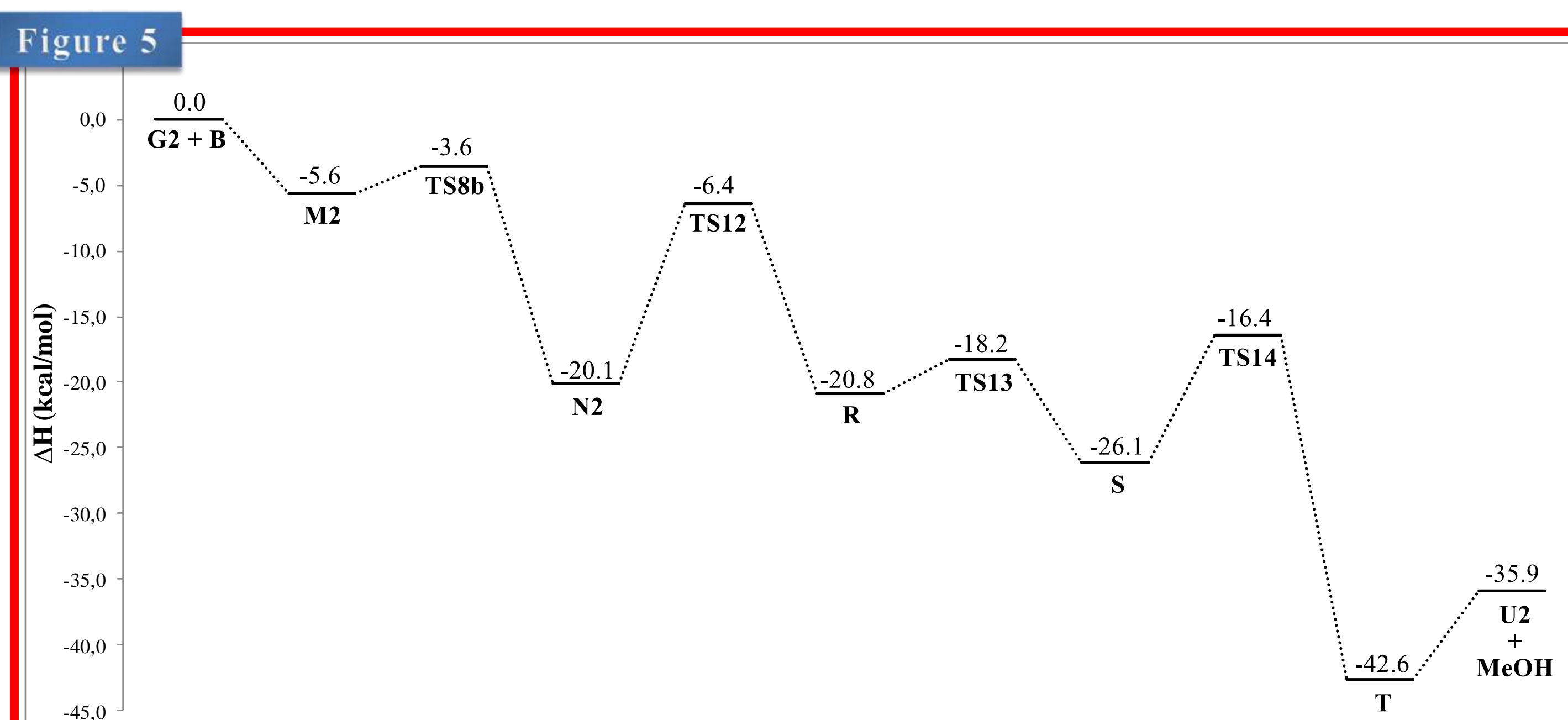
Conclusions

It was shown that the phenide ions substituted with electron-withdrawing groups react with methyl formate in the gas phase in a two-step reaction. In the second step the preliminary formed anion reacts with the second molecule of methyl formate yielding formally product of the second addition-elimination reaction. In the reaction an acyl anion the derivative of phenylglyoxal can be formed. The reaction of the *ortho*-formylphenide anion can lead either to the anion of phthalic aldehyde or – according to the Tishchenko reaction mechanism – to the respective phthalide anion. Theoretical calculations strongly suggest that the formation of the latter product is most likely. This is the most thermodynamically stable anion and on the reaction path leading to its formation there are no high activation energy barriers. These results show that it is very likely that we observed the first example of the Tishchenko-type reaction in the gas-phase.

References

1. T. Bienkowski, W. Danikiewicz; Rapid Commun. Mass Spectrom. **17**, 697-705 (2003).