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Regioselectivity and Regiospecificity of Phosphorylation of (*Z*)- and (*E*)-4-Chloromethylene-2-phenyl-5(4*H*)-oxazolones. Effect of Solvation: Supramolecular Approximation

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Abstract—By the methods of quantum chemistry in supramolecular approximation, are considered stereochemical and energetic features of phosphorylation of 4-chloromethylene-2-phenyl -5(4*H*)-oxazolone *Z*- and *E*-isomers in gas phase and their solvates with acetonitrile of 1:*n* composition where *n* varies from 1 to 10. On the MNDO–PM3 level the phosphorylation with triphenylphosphine proceeds endothermally in two steps: nucleophilic addition in the first step and elimination of chlorine anion with formation of phosphonium salt in the second step. Solvation with acetonitrile leads to stabilization of phosphonium intermediate and decrease in heat of conversion. On both semiempirical and nonempirical levels occur regioselectivity of nucleophilic attack at the double C=C, but not C=O, bond and regiospecificity of transformation without inversion of initial configuration of the isomers owing to steric hindrances restricting rotation degree of freedom of $-CHClP^{+}Ph_3$ group. Therewith, elimination of chlorine anion is characterized by low activation barrier and occurs with donation negative charge from π-orbital of carbon atom in the 4 position of heterocycle on antibonding σ*-orbital of carbon–chlorine bond; two orbitals become practically coplanar in the transition state.

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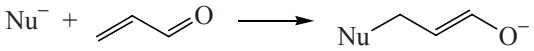
Nucleophilic addition at a double bond of simple olefins as a rule does not occur. However, nucleophile can add enough easily when resulting carbanion is stabilized by a positive substituent, best of all by a +*E* substituent, as, e.g., in the Michael reaction [1].



This mechanism is very effective for free anions NC^{-}, MeS^{-}, and R_2CH^{-}, because they possess highly positioned MO that provides well overlapping with π*-MO of double bond that increases at the polarization of the double bond by a +*E*-substituent, or by coordination of the olefin with an organometallic group, or at replacement of C^{β} carbon atom of the double bond by a heteroatom, or by solvation effects. As has been noted by us [2], supramolecular approximation allows together with substantial saving computation time (always deficient) to study dynamics of behavior of reagents at the consecutive extension of the solvate shell of solvent molecules, in contrast to existing solvation models fixing final result of calculation only.

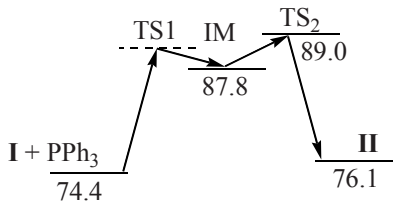
In this approximation we studied details of phosphorylation reaction with relatively weak (as compared with free anions) nucleophile triphenylphosphine of 4-chloromethylene-2-phenyl-5(4*H*)-oxazolone *Z*,*E*-isomers in gas phase and their solvates with acetonitrile in 1 : *n* ratio with *n* from 1 to 10, which in liquid phase experiment proceeds enough readily [3]. Choice of this reaction for theoretical study is defined by a possibility of observation of retention or inversion of configuration of the *Z*,*E*-isomers and elimination of chlorine anion in the same object. The *Z*,*E*-isomerism of phosphorylated compounds is also interesting in view of further obtaining of acyclic compounds with certain configuration for further cyclization; elimination of chlorine anion outside of solvate shell extends our preceding studies in the area of intramolecular chlorotropic isomerization of tri- and hexacoordinated phosphorus compounds (e.g., see [4] and literature cited).

In this work using the methods of quantum chemistry in supramolecular approximation we studied

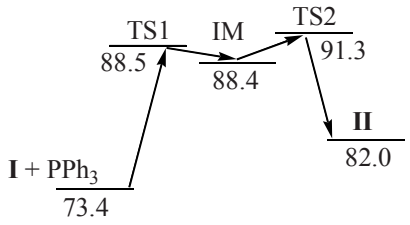
structures of initial, intermediate and final compounds and energetic characteristics of the reaction of phosphorylation of 4-chloromethylene-2-phenyl-5-(4*H*)-oxazolone *Z*,*E*-isomers and related solvates with acetonitrile of 1:*n* composition with n from 1 to 10. Calculations of structures were carried out with complete geometry optimization [5, 6]. The type of stationary point was elucidated from the form of Hessian by solving vibration problem. Search for transition states on MNDO-PM3 level was conducted by the method of difference vector [7,8] followed by refinement by means of the procedure of following for eigenvector [9].

Stability of *Z*,*E*-isomers and regioselectivity of addition of triphenylphosphine to 4-chloromethylene-2-phenyl-5(4*H*)-oxazolone I. Electronic characteristics of the oxazolone **I** *Z*,*E*-isomers calculated by semiempirical and non-empirical methods are listed in Table 1. According to the calculations, the oxazolone **I** *Z*,*E*-isomers are kinetically stable compounds. Despite slightly higher stability of *Z*-isomer, experimentally oxazolone **I** was isolated as *E*-isomer only [10], that is connected with the conditions of crystallization of polar molecules from a non-polar solvent [11]. With the higher deshielding of vinyl proton of *E*-isomer are in agreement only the data of semiempirical calculation, which also point to positive charge at methylene carbon atom C^{β}. For the further discussion of reactivity of oxazolone **I** it is important to reach similarity in the results obtained for atomic coefficients in LVMO regardless the calculation method. From these calculations follows that values of atomic coefficients at the C^{β} and C^{5} reaction centers of α-enone fragment C^{β}=C–C^{5}=O of oxazolone **I** *Z*,*E*-isomers (orbital control) unequivocally points to the attack of "soft" nucleophile, in our case of triphenylphosphine, at methylene, not carbonyl, bond and addition of triphenylphosphine at C^{β} atom despite total negative charge on this center obtained in calculations of higher level, ab initio and density functional.

Regiospecificity of formation of *Z*,*E*-isomers of phosphonium salt II. We considered separately reaction of triphenylphosphine with oxazolone **I** *Z*- and *E*-isomers on the MNDO–PM3 level for elucidation of the possibility of regiospecific formation of configurations of the final compound, phosphonium salt **II**. The results of calculations of the reaction of phosphorylation of oxazolone **I** *Z*- and *E*-isomers are depicted in schemes (1a) and (1b), respectively (the energy hereinafter is given in kcal mol^{-1}).



(a) *Z*-isomer



(b) *E*-isomer

(1)

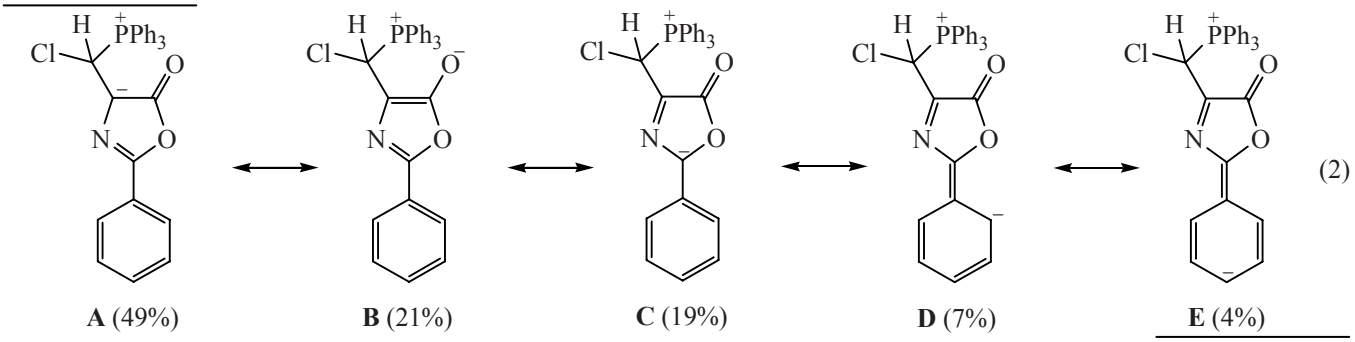
Table 1. Electronic parameters of oxazolone **I** *Z*- and *E*-isomers calculated by methods of quantum chemistry

Calculation mathod	Isomer	–*E*, au	π* LUMO			*q*, au		
			–ε, au	a_{ij}[a]		C^{β}	C^{5}	H^{b}
				C^{β}	C^{5}			
MNDO	*Z*	94.370506	1.4400[c]	–0.550	0.246	0.124	0.352	0.096
	E	94.370099	1.3004[c]	–0.607	0.283	0.125	0.354	0.107
RHF/6-31G**	*Z*	1045.846302	1.1728	–0.643	0.035	–0.136	0.292	0.225
	E	1045.842030	1.1739	–0.629	0.069	–0.132	0.291	0.216
B3LYP/6-31G**	*Z*	1049.680471	0.8882	–0.688	0.080	–0.155	0.202	0.148
	E	1049.677107	0.8897	–0.705	0.113	–0.149	0.203	0.144

[a] Atomic coefficient for MO. [b] Vinyl hydrogen atom, δ_H, ppm ($CHCl_3$): 5.30 (*Z*), 7.25 (*E*) [10]. [c] eV.

These data point to closeness in their energetics including heat effect of reaction. The reaction proceeds in two steps: in the first step is formed phosphonium intermediate (IM), in the second one phosphonium salt **II**. Transformation of phosphonium intermediate proceeds by partial rotation of $CHClP^+Ph_3$ group due to steric hindrances from triphenylphosphonium group. Torsion angle $\tau(XC^{\alpha}C^{\beta}P)$, where X = N, O for respectively *Z*- and *E*-isomer, decreases (Fig. 1), which in the region of 51° is accompanied with cleavage of C^{β}–Cl bond (see below) and promotes regiospecific transformation of the intermediate with retention of configuration of parent isomer. Thus, practically, at phosphorylation of isolated oxazolone **I** (it is isolated as *E*-isomer only [10]) the phosphonium salt **II** is formed as *E*-isomer exclusively.

Phosphonium intermediate (IM) and transition states (TS1) and (TS2). The results of calculation of geometry, charge and energy characteristics of the phosphonium intermediate and transition states for *E*-isomer of oxazolone **I** are listed in Table 2. The intermediate is stabilized phosphonium betain with the negative charge delocalized over both the heterocycle and side fragments including carbonyl and phenyl ring. Its structure can be represented by a set of unsaturated structures **A–E** in the scheme (2).



(2)

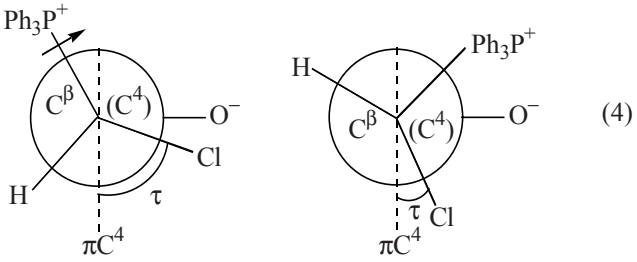
Contribution of each canonical structure s_i to the chloride ion elimination is taken proportional to the value of the charge difference on the negative center of the structures of intermediate and salt and is calculated from relation (3):

$$s_i = |\Delta q_i|/\Sigma|\Delta q_i|, \quad (3)$$

where $\Delta q_i = q_i(\text{intermediate}) - q_i(\mathbf{II})$, $i = \mathbf{A},..., \mathbf{E}$ (Table 2).

Although the larger part of transfer (49%) of negative charge at the transformation of the intermediate occurs from C^4 atom of heterocycle connected with $-C^{\beta}HClP^+$ group (structure **A**), atom C^4 nevertheless remains practically planar (SC^4=359.1°). Note that in the cases of substituents in 2 position incapable of delocalization of extra negative charge (non-stabilized ylidebetains), in part, in the case of unsubstituted in 2 position derivative leads to increase in relative weight of structure **A** and in this connection to noticeable pyramidation of C^4 carbon atom (SC^4 = 351.8°). Total charge transfer from structures **B** and **C** is comparable with those from structure **A** while **D** and **E** structures in this respect are less important.

A feature of structure of the intermediate is location of C^{β}–Cl practically in the plane of azalactone heterocycle in *cis* position to carbonyl group, as shown in scheme (4).



(4)

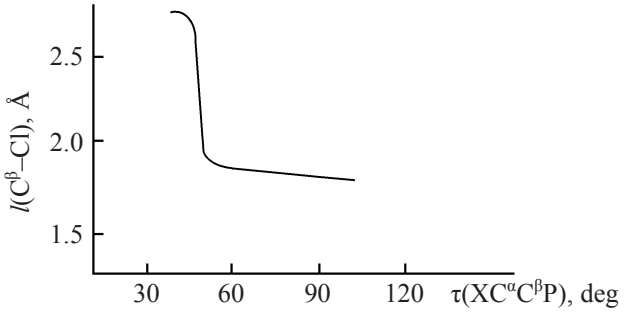


Fig. 1. Carbon–chlorine bond length plotted against rotation angle of $-C^{\beta}HClP^+Ph_3$ group.

Table 2. Calculated characteristics of intermediate and of transition states in the reaction of phosphorylation of oxazolone **I** and phosphonium salt **II** *Z*, *E*-isomers in the absence of solvating and for $M\times10$ CH_3CN[a] solvates

Method	MNDO–PM3 (*E*-isomer)					RHF/3-21G**	
Parameter[b]	**I**+PPh_3	TS1	IM	TS2	**II**	(*E*)–**II**	(*Z*)–**II**
–*E*, au	177.3009 (177.3041)	177.2817	177.2818 (177.2829)	177.2771	177.2920 (177.2973)	2066.2166	2066.2236
μ, D	2.4 (2.8)	5.0	8.4 (11.7)	10.6	4.9 (6.0)	9.8	14.1
ν_{im}, cm^{-1}	–	–51	–	–120	–	–	–
$l(C^4–C^\beta)$, Å	1.340 (1.340)	1.374	1.448 (1.442)	1.390	1.334 (1.334)	1.322	1.318
$l(C^\beta–Cl)$, Å	1.664 (1.663)	1.723	1.756 (1.779)	2.010	2.582 (2.587)	2.880	2.938
$q(C^4)$, au	–0.18 (–0.18)	–0.37	–0.50 (–0.56)	–0.45	–0.08 (–0.07)	–0.05	–0.04
$q(C^2)$, au	0.15 (0.15)	0.10	0.04 (–0.03)	0.03	0.16 (0.16)	0.27	0.29
q(O=), au	–0.28 (–0.28)	–0.21	–0.38 (–0.48)	–0.41	–0.28 (–0.29)	–0.25	–0.20
$q(C^o)$, au	–0.05 (–0.05)	–0.07	–0.08 (–0.11)	–0.08	–0.05 (–0.05)	–0.02	0.02
$q(C^p)$, au	–0.07 (–0.07)	–0.08	–0.10 (–0.10)	–0.10	–0.07 (–0.07)	–0.00	0.00
q(Cl), au	0.12 (0.12)	0.04	–0.00 (–0.01)	–0.43	–0.72 (–0.76)	–0.82	–0.84

[a] In parentheses (columns 2, 4 and 6) are given the characteristics of structures polarized by solvate shell consisting of 10 acetonitrile molecules. [b] Total energy is given without accounting for the contribution of zero vibrations; Mulliken and Loewdin charges are given for PM3 and 3-21G** methods, respectively.

Therewith, the dihedral angle τ between C^β–Cl bond and and π-orbital of the heterocycle C^4 atom is about 90°, that does not provide noticeable transfer of extra negative charge of beatin on the antibonding σ*-orbital of C^β–Cl bond; the bond length of the latter 1.756 Å (Table 2) remains comparable with the standard value.

Structure of the addition reaction transition state (TS1) is characterized by the following relative positions of triphenylphosphine (P) and oxazolone (C^β) reaction centers: $l(P\cdots C^\beta)$ 2.192 Å, $\angle PC^\beta C^4$ 111.6° and $\tau(PC^\beta C^4N)$ 77.6° attesting approach by triphenylphosphine of the vinyl fragment terminal side practically orthogonal to its plane, partially from the side of vinyl hydrogen The TS1 and TS2 Hessians are positive and contains one imagine part each, –51 and –120 cm^{-1}, respectively (Table 2). Transition state TS2 for chlorine anion elimination is formed by rotation in the intermediate of $C^\beta HClP^+Ph_3$ group around C^β–C^4 bond (Fig. 1, scheme 4) at the action of electrostatic interacttions between triphenylphosphonium group and negative charges, in part, on the carbonyl oxygen. Rotation occurs while C^β–Cl bond and π-orbitals at C^4 carbon atom of heterocycle achieve almost coplanar position (21.3°, scheme), that provides maximal transfer of electron density from the latter (and from conjugated with the latter centers in the structures C–F) on the antibonding σ*-orbital of C^β–Cl bond, increase in its length to 2.010 Å (Table 2) and further withdrawal of chlorine anion.

Table 3. Energetic parameters of solvates (*E*)-IM·*n*CH_3CN, calculated by MNDO–PM3 method

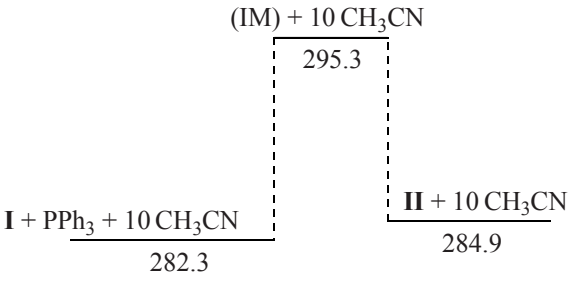
Parameters[a]	*n*				
	0	5	6	8	10
E, au	–177.282	–259.017	–275.372	–308.072	–340.776
ΔH^f_{298}, kcal mol^{-1}	88.38	199.45	216.37	257.42	295.34
E^s, kcal mol^{-1}	0	–5.0	–11.3	–16.7	–25.2
E^s/n, kcal mol^{-1}	0	–1.0	–1.9	–2.4	–2.5

[a] $E^s(M\cdot nCH_3CN) = \Delta H^f_{298}(M\cdot nCH_3CN) - \Delta H^f_{298}(M) - n\cdot\Delta H^f_{298}(CH_3CN)$, where M = **I**, **II**, (TS1), (TS2), (IM).

According to calculations, (*Z*)-, (*E*)-4-triphenylphosphoniomethylene-2-phenyl-5(4*H*)-oxazolone chlorides (**II**) are planar (the heterocycle, its methylene and phenyl substituents are in the same plane), while chloride anion is located in the orthogonal plane between C^β and P atoms. *E*-isomer, as commonly (see [11]) is by 4.4 kcal mol^{-1} (RHF/3-21G**) is less stable than *Z*-analog (Table 2).

Effect of solvation. In the absence of solvation the activation energy and formation energies of both phosphonium intermediate are almost equal: the difference is 0.1 and 2.9 kcal mol^{-1}, respectively, for *E*-isomer (scheme 1). Probably, due to polarization of transition states at solvation this difference falls to minimum, and therefore we were unable to fix solvated transition states even for 1:1 solvates. Actually, from the data in Table 2 follows that additional polarization of oxazolone **I**, intermediate and salt **II** due to solvate shell of 10 acetonitrile molecules equals 0.4, 3.3, and 1.1 D, respectively. Registered changes in the dipole moment of these structures are connected with redistribution of electron density due to polarization by solvate shell, which for, e.g., of solvated intermediate leads to increase in the C^β–Cl bond length to 1.779 Å and makes easier further elimination of chloride ion at the formation of salt. Fig. 2 depicts a typical supramolecular structure if solvate (parent molecule)·10CH_3CN as graphic image of optimized *Z*-matrix. Selected shortest intermolecular contacts are: H···N≡ 2.68, H···Cl 2.58, H···O= 1.81 Å. Torsion angle τ($PC^\beta C^4O$) is sensitive not only toward nintramolecular interactions but also toward intermolecular interactions and slightly increases (to 106.7°) as compared with not solvated intermediate (103.9°).

Energy changes at the transformation of solvated structures *M*×10CH_3CN is shown in scheme (5).



(5)

The transformation is characterized by decrease both in activation energy of nucleophilic addition to approximately 13 kcal mol^{-1}, and in heat of reaction, to 2.6 kcal mol^{-1} for *E*-isomer [compare schemes (1) and (5)]. Data in Table 3 demonstrate saturation effect for specific solvation energy of intermediate (*E*)-IM (solvation energy per one molecule of solvate shell) at stepwise extension of solvate shell. It is seen that the

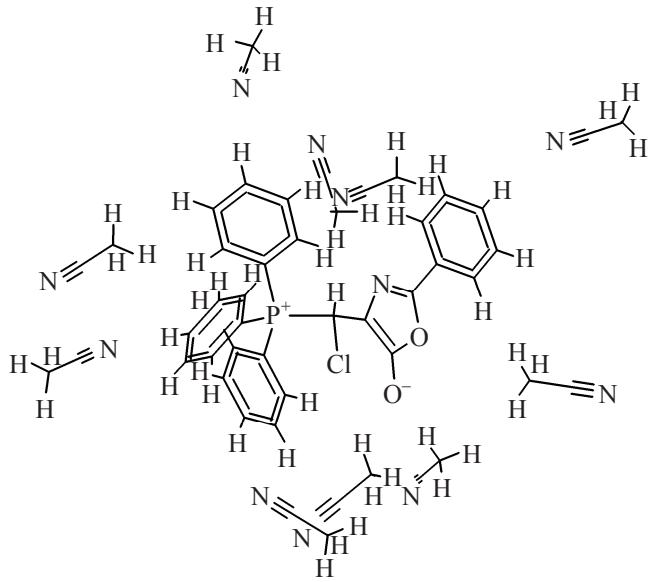


Fig. 2. Structure of solvate shell of 10 acetonitrile molecules in the case of phosphonium intermediate of oxazolone **I** *E*-isomer (IM)×10CH_3CN.

shell consisting of 10–15 acetonitrile molecules is optimal one for the maximal stabilization of phosphonium intermediate.

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