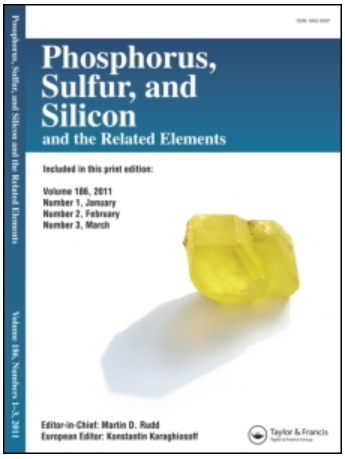

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Factors Determining the Stereochemical Structure of 2-(Phosphorus Substituted) Methylidene-thiazolidine- 4-ones in Solid State and in Solution

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Factors Determining the Stereochemical Structure of 2-(Phosphorus Substituted) Methylidene-thiazolidine-4-ones in Solid State and in Solution

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A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russian Federation

Regioselective synthesis of novel 2-(phosphorus substituted) methylidene-thiazolidine-4-ones ***5a–c*** *was performed via condensation of phosphorus-substituted acetic acid thioamides* ***4a–c*** *with dimethyl acetylenedicarboxylate. Thiazolidine-4-ones* ***5a,b*** *bearing thiophosphoryl or dithiophosphoryl moiety were obtained as E,Z-isomers while their analog* ***5c*** *with triphenylphosphonium group was formed as a Z, Z-isomer. The structures of thiazolidin-4-ones* ***5a–c*** *obtained were determined by single crystal X-ray diffraction. According to quantum-chemical calculations, the isomers observed in the solid state are thermodynamically more stable. In solution, thio- and dithiophosphorylated thiazolidinones* ***5a, b*** *undergo E,Z → Z,Z isomerization relative to* C^2 *carbon atom of the heterocycle proceeding via an imine–enamine mechanism.*

Keywords *ab initio* calculations; dimethyl acetylenedicarboxylate; isomerization; 2-(phosphorus-substituted)methylidene-thiazolidine-4-ones; regioselectivity; (thio)phosphoryl acetic acid thioamides

INTRODUCTION

Condensation of thioureas and malonothioamide derivatives with dimethyl acetylenedicarboxylate (DMAD) is known to be a convenient

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.
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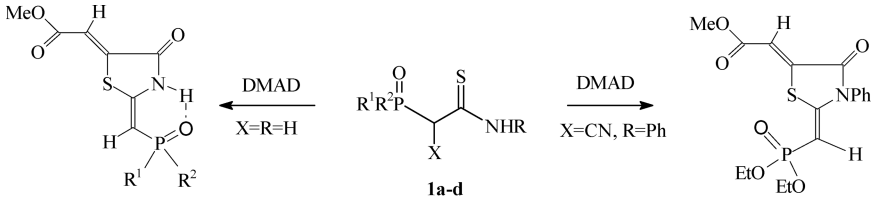
route to pharmacologically active 2-imino-5-methoxycarbonylthiazolidin-4-ones[1–7] and 2,5-bis(substituted methylidene)-thiazolidine-4-ones,[8,9] which are formed usually as a mixture of *Z*, *Z* and *E*, *Z* isomers. Recently we demonstrated that phosphoryl acetic acid thioamides **1a–c** or thioanilide **1d** also react with DMAD according to a similar condensation scheme yielding 2-(phosphoryl)methylene-thiazolidin-4-ones **2** and **3** in good to high yields (Scheme 1).[10]



1a, **2a**: R=H, R^1=R^2=OEt, X=H
1b, **2b**: R=H, R^1=R^2=Ph, X=H
1c, 2c: R=H, R^1=Ph, R^2=OEt, X=H
1d, **3**: R=Ph, R^1=R^2=OEt, X=CN

SCHEME 1

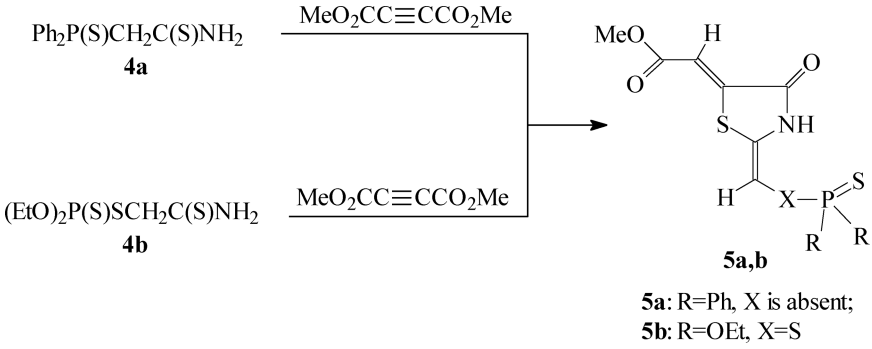
In contrast to the condensation of nonphosphorylated malonothioamide derivatives with DMAD,[8,9] compounds **1a–d** react with DMAD regioselectively and yield a single isomer of the final heterocycle, which is the thermodynamically more favorable according to quantum-chemical calculations.[10] The type of isomer depends on the substituent *R* at the nitrogen atom of thiocarbamoyl group in the starting compound **1a–d**. Thus, condensation of thioamides **1a–c** (R=H) resulted in the formation of only *E*, *Z*-isomers of thiazolidines **2a–c**, while the reaction of thioanilide **1d** (R = Ph) led to the formation of **3** as *Z*, *Z*-isomer. The structures of these compounds were unambiguously confirmed by X-ray crystallography. According to the X-ray data, the *E*,*Z* isomers of **2a–c** are stabilized in a solid state by strong intramolecular hydrogen bonds P=O···HN, which define their structure. According to the NMR spectroscopic analysis, in $CDCl_3$ and C_6D_6 solutions phosphorylated thiazolidin-4-ones **2a–c** exist also as the *E*, *Z*-isomers, showing one singlet in the ^{31}P NMR spectrum and one set of signals in the ^{1}H and ^{13}C NMR spectra in the same solvent. During the time of observation, no changes were recorded in these spectra. Moreover, the independence of the NH-chemical shifts on the concentration in the ^{1}H NMR spectra of these compounds in $CDCl_3$ and C_6D_6 indicates the conservation of the intramolecular H-bonds, which stabilize the *E*, *Z*-isomers in solution.[10] At the same time, when the *E*,*Z*-isomer of compounds **2a–c** is dissolved in CD_3OD, $CD_3C(O)CD_3$, or DMSO-d_6, the solutions display the ^{31}P

NMR signals corresponding to two isomers with one of the signals substantially dominating (84–96%) *ca*. 10 min after solution and becoming the minor over time. Therefore, in these solvents, the *E*,*Z*-isomers of the thiazolidin-4-ones **2a–c** undergo isomerization at the C^2 carbon atom of the heterocycle.[10]

Taking into account that regioselectivity of the above condensation, the stability of the products, and their behavior in solution are associated with the formation of intramolecular P=O···H-bond, it was of undoubted interest to determine the stereochemical result of condensation with DMAD for phosphorus substituted acetic acid thioamides bearing thiophosphoryl, dithiophosphoryl, or phosphonium group, i.e., groups that are less inclined to form H-bonds or principally do not form hydrogen bonding.

RESULTS AND DISCUSSION

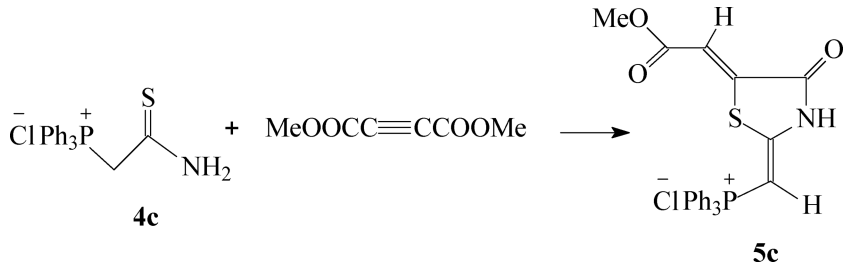
The reaction of both thio- and dithiophosphoryl thioacetamides **4a,b** with DMAD in $CHCl_3$ (RT, 6 h) was found to proceed similarly to the condensation of thioacetamides **2** bearing the phosphoryl moiety and to give *E*, *Z*-isomers of thiophosphorylated thiazolidin-4-ones **5a,b** in high yields, as illustrated in Scheme 2.



SCHEME 2

In the case of thioacetamide **4c** with a phosphonium group, the condensation also proceeded regioselectively and, as expected, yielded the final NH-heterocycle **5c** as *Z*, *Z*-isomer (Scheme 3).

The structures of the compounds **5a–c** isolated after the work-up procedure as crystalline solids (see the Experimental section) were unambiguously confirmed by single crystal X-ray diffraction. According to the X-ray data (random sampling of at least four crystals), thiazolidin-4-ones **5a**,**b** were formed with *E*, *Z*-configuration at the double bonds,



SCHEME 3

i.e., *trans*-orientation of the phosphorus-containing substituent and the ring sulfur atom and *cis*-orientation of the carbomethoxy group relative to the latter one (Figures 1 and 2, respectively). In contrast, heterocycle **5c** displays *Z*, *Z*-configuration at these double bonds (Figure 3). The principal geometric parameters in all molecules under investigation (see Table I) are close to typical values of nonphosphorylated thizolidine-4-one derivatives[6,7,11–13] and those bearing the phosphoryl group.[10] In particular, the 5-methoxycarbonyl group in **5a–c** is also characterized by *Z*-orientation stabilized by intramolecular (O)C=O···S contact with S···O distance varying in the range of 2.769(2)–2.823(2) Å. These contacts are characterized by a pronounced degree of directionality with O(5)S(1)C(2) angle varying in the range 163.5(1)–164.8(1)°. Therefore, this contact can be interpreted as

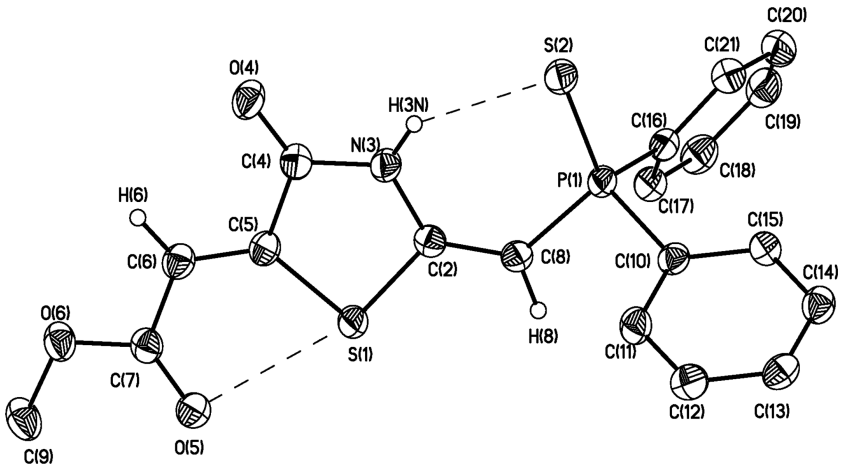


FIGURE 1 View of *E*, *Z*-**5a** in the crystal; thermal ellipsoids are drawn at 50% probabilty level.

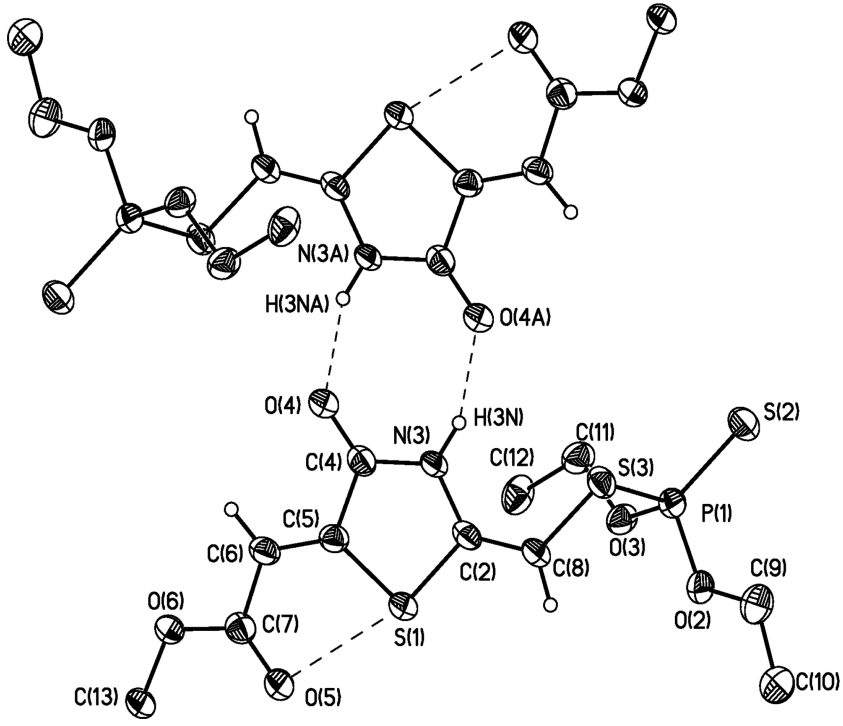


FIGURE 2 View of the N—H···O bonded dimer of *E*, *Z*-**5b**; thermal ellipsoids are drawn at 50% probability level.

a charge transfer from the oxygen-lone pair to the S-C antibonding orbital.

In the case of **5a**, the *E*, *Z*-isomer is stabilized by an intramolecular N—H···S hydrogen bond with N···S distance of 3.165(2) Å. Furthermore, in addition to the intramolecular N—H···S bond in the crystal, molecules *E*, *Z*-**5a** are assembled into centrosymmetric dimers via rather strong C(8)-H(8)···O(5) interaction. The H(8)···O(5) distance is equal to 2.09 Å, which can affect the strength of intermolecular interaction.

As one can expect, there is no similar specific interaction that can be the reason of *E*, *Z*-isomer stabilization in the case of **5b**, where the phosphorus atom and the double bond are separated with the additional sulfur atom. In this case the stabilization of the *E*, *Z*-isomer is achieved via formation of N(3)-H(3N)···O(4A) intermolecular H-bond with N(3)···O(4A) distance of 2.879(2) Å.

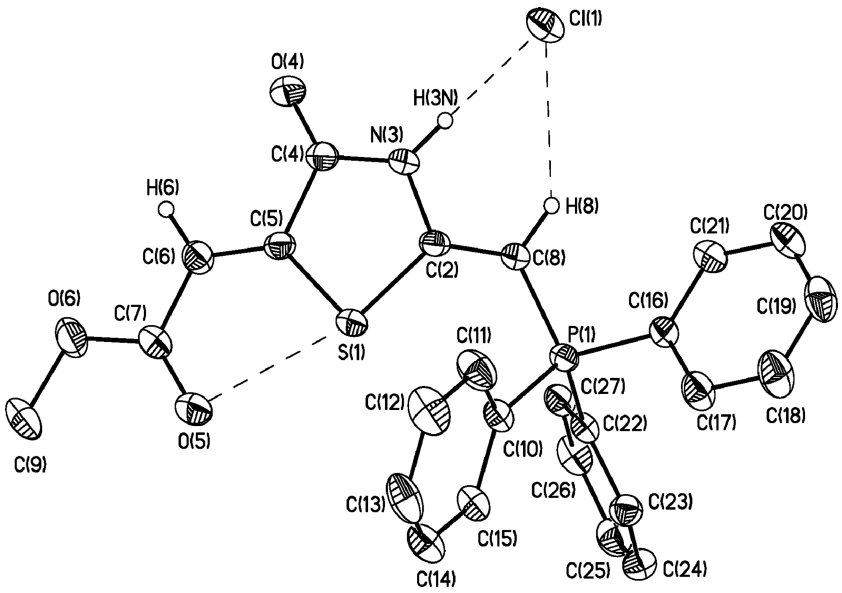


FIGURE 3 View of Z,Z-**5c** in the crystal; thermal ellipsoids are drawn at 50% probability level.

In the crystal of Z,Z-**5c**, the isomer is stabilized by interionic H-bonds formed by the ring NH-proton and the hydrogen atom H(8) of the C(2)–C(8) double bond with the chlorine anion. The corresponding N(3)···Cl(1) and C(8)···Cl(1) distances are equal to 3.101(2) and 3.501(2) Å, respectively.

Considering that stabilization of a particular isomer can be the consequence of crystal packing effects, we performed DFT calculations of E,Z and Z,Z isomers of compounds **5a** and **5b**. Calculations for both compounds (PBE/TZ2P) revealed that E,Z-isomers observed in the solid state correspond to energy minima. At the same time, the differences in energy between E,Z and Z,Z forms for **5a** and **5b** are significantly different. For thiazolidinone **5b,** in which no specific intramolecular interactions occur, the E,Z-isomer is more stable by 1.2 kcal/mol, while for **5a** the difference in energy is 6.9 kcal/mol. The reasons of such a pronounced stabilization of E,Z-**5a** are believed to be the same as that occurs for its phosphorylated analogs E,Z-**2**. Although P=S···H–N intramolecular H-bond must be significantly weaker than the corresponding P=O···H–N bond in E,Z-**2** (see ref. [14]), we cannot exclude that the corresponding P=S···S–C intramolecular interaction would be also weakened or even absent. Despite a shortened S(1)···S(2)

TABLE I Selected Bond Lengths (Å) and Angles (°) in *E,Z* Isomers of 5a-c and in *Z,Z*-2a

	E, *Z*-**5a**	*E*, *Z*-**5b**	*E*, *Z*-**5c**	*Z*,*Z*-**2a**
S(1)-C(2)	1.779(2)	1.766(3)	1.762(4)	1.768(1)
S(1)-C(5)	1.740(2)	1.741(3)	1.763(4)	1.745(1)
C(2)-N(3)	1.387(2)	1.385(4)	1.388(5)	1.385(2)
N(3)-C(4)	1.368(2)	1.357(4)	1.364(6)	1.365(2)
C(4)-C(5)	1.508(2)	1.495(4)	1.505(6)	1.498(2)
C(2)-C(8)	1.336(2)	1.335(4)	1.329(6)	1.344(2)
C(5)-C(6)	1.344(2)	1.339(4)	1.327(6)	1.340(2)
C(8)-P(1)	1.794(2)	1.753(3)	1.771(4)	1.750(2)
P(1)-X(1)[a]	1.9678(6)	n/a	n/a	1.477(1)
C(7)-O(5)	1.216(2)	1.217(4)	1.232(6)	1.214(2)
O(4)-C(4)	1.206(2)	1.221(3)	1.215(5)	1.219(2)
O(5)···S(1)	2.871(2)	2.769(2)	2.823	2.803(1)
O(1)···S(1)	n/a	n/a	n/a	2.989(2)
N(3)···S	3.165(2)	n/a	n/a	n/a

[a]X is sulfur in *E,Z*-**5a** and oxygen in *Z*, *Z*-**2a**.

distance (3.242 Å) in the *Z*, *Z*-**5a** isomer, the DFT calculations exhibit the torsion angle S(2)P(1)C(8)C(2) of 10.4°. In order to estimate the role of H-bonding and O···S and S···S intramolecular contacts in the stabilization of the particular isomer, we have preformed the analysis of electron density distribution function ($\rho(\mathbf{r})$) within the PBE1PBE/6-311G* energy calculation for *E*, *Z*-**5a** and *Z*, *Z*-**5a** isomers according to Bader's "atoms in molecules" theory.[15] According to topological analysis of $\rho(\mathbf{r})$, all mentioned intramolecular contacts in *E*, *Z* and *Z*, *Z* isomers of **5a** correspond to bonding interatomic interactions of an intermediate type with $\rho(\mathbf{r})$ values in critical point (3,-1) varying in the range of 0.09–0.13 eÅ^{-3}. The energies of the contacts estimated using the correlation scheme of Espinosa et al.[16] are slightly different and vary in the range of 2.5–5.5 kcal/mol. It should be noted that H···S and O···S interactions in *E*, *Z*-**5a** are characterized by high energy values of 5.5 and 4.2 kcal/mol, while the corresponding values for S···S and O···S contacts, which may be realized in *Z*, *Z*-**5a**, are 2.5 and 3.9 kcal/mol. Thus, we can conclude that the prevalence of the *E*, *Z*-**5a** isomer in the crystal is the consequence of a higher energy of the H-bonding in comparison with S···S intermolecular contact. At the same time, estimated energies clearly show that disruption of P═S···H─N interaction will in turn lead to almost equal energies of the *E*,*Z* and *Z*,*Z* isomers.

To investigate the behavior of compounds **5a–c** in solution, their ^{31}P and ^{1}H NMR spectra were recorded from the moment of dissolving the

compound in $CDCl_3$ and DMSO-d_6/CCl_4(1:1) mixture until the process reached equilibrium. In contrast to the phosphorylated analogs *E*, *Z*-**2a–c**, for which in nonpolar solvents the equilibrium is fully shifted to the *E*, *Z*-isomer while retaining the strong intramolecular H-bond,[10] mono- and dithiosubstituted derivatives **5a**,**b** form a mixture of *E*, *Z* and *Z*, *Z* isomers immediately after dissolving in $CDCl_3$ ($\sim$ 2 min). At that moment, we observed two singlet signals in the ^{31}P NMR spectra with one of them substantially dominating as well as two sets of corresponding signals in the ^{1}H and ^{13}C NMR spectra. In both cases, the signal at low field dominating in the ^{31}P NMR spectrum immediately after dissolving the compound was assigned to the corresponding *E*, *Z*-isomer. The ratio *E*, *Z*:*Z*, *Z* 2 min after dissolving was 92:8 (**5a**) and 88:12 (**5b**) and reached equilibrium at 70:30 and 60:40 for **5a** and **5b**, respectively (Table II). The time required to reach the equilibrium in $CDCl_3$ was approximately 48 h.

As mentioned above, the *E*, *Z*-isomers of phosphorylated **2a–c** are stabilized in solution by the intramolecular H-bond. Therefore, the difference in behavior in solution for phosphorylated **2a–c** and thiphophorylated **5a**,**b** thiazolidinones is obviously connected with the difference in strength of the PO$\cdots$H and PS$\cdots$H intramolecular H-bonds (the latter is usually weaker[14]) in the case of **5a** and with the absence of such a H-bond in the thiazolidinone **5b** with dithiophosphoryl moiety.

In the DMSO-d_6/CCl_4 mixture, the ratio *E*, *Z*:*Z*, *Z* was 70:30 (**5a**) and 60:40 (**5b**) in 2 min after dissolving the compound and the equilibrium was fully shifted to the *Z*, *Z*-isomer within 6 h (Table II). It should be noted that in the ^{1}H NMR spectra both in the $CDCl_3$ and the DMSO-d_6/CCl_4mixture, the position of the C^{8}H doublet signal is shifted downfield for *E*, *Z*-**5a**,**b** as compared to the signal for the *Z*, *Z*-isomer. As for C^{6}H, the signals for both isomers **5a**,**b** appear very close in $CDCl_3$ solution, while in DMSO-d_6/CCl_4 solution the chemical shift to the lower field corresponds to C^{6}H in *E*, *Z*-**5a**,**b**.

At the same time, phosphonium-substituted thiazolidinone **5c** showed a singlet in the ^{31}P NMR spectrum and one set of signals in the ^{1}H and ^{13}C NMR spectra in both $CDCl_3$ and DMSO solutions. During the time of observation (2 min to 30 days) no changes were noted in the NMR spectra; therefore one may conclude that **5c** exists both in the solid state and in solution as the *Z*,*Z*-isomer.

Most probably in the case of **5a**,**b**, the *E*,*Z* $\rightarrow$ *Z*,*Z* transformation proceeds via imine–enamine mechanism similar to that of the phosphorylated analogs **2**. This is confirmed by the fact that the intensities of the ^{1}H NMR signals for C^{8}H and NH of the *E*, *Z*- and *Z*, *Z*-isomers

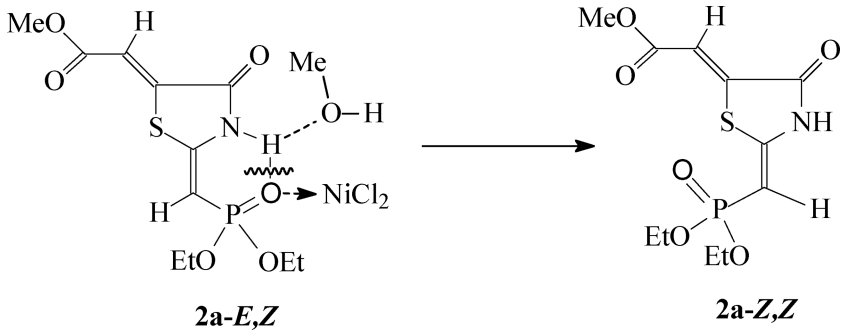
TABLE II ^{31}P Shifts and Selected ^{1}H NMR Parameters for Phosphorylated Thiazolidinones 5a–c in Different Solvents

	Solvent	*E*,*Z*:*Z*,*Z* ratio at the equilibrium	Isomer	δ_P	$\delta(C^8H)$, $^2J_{PH}$	$\delta(C^6H)$	δ(NH)	$\delta(OCH_3)$
5a	$CDCl_3$	70/30	*E*,*Z*	31.0	5.35/11.6	6.81	11.79	3.83
			Z,*Z*	30.9	5.11/12.4	6.80	11.61	3.70
	DMSO-d_6/CCl_4(1:1)	7/93	*E*,*Z*	31.3	6.26/12.0	6.66	11.85	3.8
			Z,*Z*	31.1	5.96/11.6	6.53	11.58	3.77
5b	$CDCl_3$	60/40	*E*,*Z*	87.7	5.77/4.2[a]	6.78	9.68	3.84
			Z,*Z*	87.1	5.27/4.2[a]	6.76	8.98	3.83
	DMSO-d_6/CCl_4(1:1)	0/100	*Z*,*Z*	89.0	5.22/5.6[a]	6.54	12.04 (br)	3.90
5c	$CDCl_3$	0/100	*Z*,*Z*	14.6	7.58/10.8	6.79	14.07	3.71
	DMSO-d_6/CCl_4(1:1)	0/100	*Z*,*Z*	17.0	7.18/10.8	6.64	14.2	3.72

[a] $^3J_{PH}$.

correspond to the isomer ratio estimated from the ^{31}P NMR spectrum, but do not correspond to the intensity of the signals of the other protons for the same isomer due to the fast prototropic exchange on the NMR time scale between the two isomers of the heterocyclic amine **5** via the corresponding imine.

It is interesting to note that we failed to isolate the individual *Z*, *Z*-**2** isomers by recrystallization from alcohol, in which the equilibrium is shifted to the corresponding *Z*, *Z*-isomer due to the rupture of the intramolecular P=O···H–N bond and formation of intermolecular H-bonds with the solvent. However, the addition of one molar equivalent of $NiCl_2$ to the MeOH solution of compound *E*, *Z*-**2a** bearing a diethoxyphosphoryl group resulted in crystallization of the less favorable *Z*, *Z*-**2a** isomer (the difference in energy between the two isomers for compound **2a** is 8.3 kcal/mol[10]) (Scheme 4). In the ^{31}P NMR spectrum of the reaction mixture (before crystallization), a broad singlet at 25.3 ppm was observed. The downfield shift of the signal in comparison to those of *E*, *Z*-**2a** and *Z*, *Z*-**2a** observed in the same solvent (20.2 and 19.2 ppm, respectively) confirmed the formation of an intermediate nickel complex, which is stable only in solution.



2a-*E,Z* **2a-*Z,Z***

SCHEME 4

The structure of *Z*, *Z*-**2a** was unambiguously confirmed by single crystal X-ray analysis (Figure 4) and coincided well with the calculated one (see ref. [10]). In this case the presence of nickel ions either favored a fast rupture of the intramolecular H-bond due to complexation with the phosphoryl moiety or further formation of a complex with participation of P=O and ester C=O groups as coordination sites. Both factors should stabilize the *Z*, *Z*-**2a** isomer crystallized from solution and give the possibility of the realization of the thermodynamically unfavorable process.

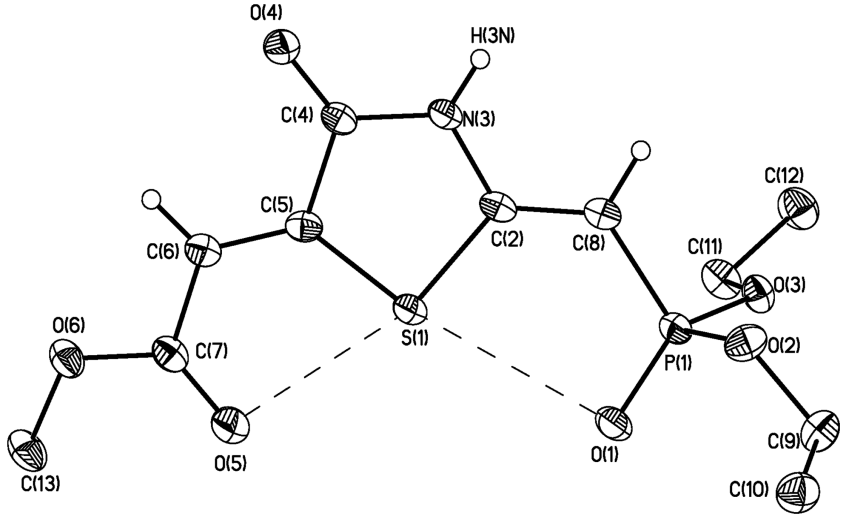


FIGURE 4 View of *Z*, *Z*-**2a** in the crystal; thermal ellipsoids are drawn at 50% probability level.

At the same time, we cannot exclude that crystallization of the *Z*, *Z*-**2a** isomer may be solely due to kinetics of crystal growth in the presence of cations. Indeed, it is known that some substances can serve as nucleation inhibitors and thus prevent crystal growth of a particular polymorph or isomer at the stage of nucleation and hence assist in the formation of the less thermodynamically stable crystal.[17] In order to investigate the role of nickel ions, we are going to perform additional experiments with other compounds **2** and other metal ions, as well as to check the formation of any coordination bonds between nickel and the ligand by spectroscopic techniques.

To summarize the results, we can conclude that although stabilization of a particular isomer of 2-(phosphorus substituted)methylidenethiazolidine-4-one is dictated by the particular intramolecular interaction in a solid state, the specific conditions, i.e., specific salvation, can facilitate the formation of the thermodynamically less favorable isomer.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with a Bruker AMX-400 spectrometer using the signals of the solvent as internal standard (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P) as external standard. The ^{13}C NMR spectra were recorded using the JMODECHO mode, the signals for the

C atom bearing odd and even numbers of protons have the opposite polarities. IR spectra were recorded in KBr pellets with a Magna-IR750 Fourier spectrometer (Nicolet), resolution 2 cm^{-1}, 128 scans. The assignment of the absorption bands in the IR spectra was made according to the literature.[18,19] Melting points are uncorrected.

The thioacetamides **4b**,**c** were obtained by the standard procedure[20] described earlier.

2-(Diphenylthiophosphoryl)ethanethioamide (4a)

Compound **4a** was obtained following the general procedure for the transformation of a cyano group to the corresponding thioamide reported by us previously.[20] A mixture of diphenylthiophosphorylacetonitrile (1.28 g, 5 mmol) and diisopropyldithiophosphoric acid (1.07 g, 5 mmol) in 2 mL of MeOH was kept at approximately 20°C for 7 days. Then Et_2O was added to the reaction mixture, and the precipitate was filtered off and recrystallized from ethyl acetate to yield **4a** (0.89 g, 61%) as a light-yellow solid. Mp 203–204°C. ^{31}P NMR (DMSO-d_6): $\delta =$ 41.7 ppm. ^1H NMR (DMSO-d_6): $\delta = 4.14$ (d, $^2J_{PH} = 14.2$ Hz, 2H, CH_2P), 7.46–7.97 (m, 10H, C_6H_5P), 8.95 (s, 1H, NH_2), 9.48 (s, 1H, NH_2). IR (KBr, ν/cm^{-1}): 491, 565, 612 (P=S), 690, 735, 984, 1100, 1433 (N–C=S + CH_2), 1628, 3141 (NH_2), 3263, 3311. Found: C 57.68; H 4.71; N 4.76. Calcd. for $C_{14}H_{14}NPS_2$: C 57.71, H 4.84; N 4.81%.

(E)-2-[(Diphenylthiophosphoryl)methylene]-(Z)-5-(methoxycarbonyl-methylene)-thiazolidin-4-one (5a)

Dimethylacetylendicarboxilate (0.38 g, 2.7 mmol) was added to a suspension of 2-(diphenylthiphosphoryl)ethanethioamide**4a** (0.8 g, 2.7 mmol) in $CHCl_3$ (10 mL), and the mixture was stirred overnight at room temperature. Over this time, a clear orange solution was formed. It was refluxed for 8 h. The solvent was evaporated in vacuo, and the residue was recrystallized from EtOAc to afford the thiazolidin-4-one *E*, *Z*-**5a** as light-yellow crystalline solid. Yield 0.3 g (80%); mp 153–154°C. IR (KBr, ν/cm^{-1}): 694 (P=S), 1203, 1217 (ν_{as} CNC), 1310 (ν_s CNC), 1604 (C=C), 1684 (C^7=O), 1724, 1734 (C^4=O), 3071 (br, NH). Found: C 56.99; H 3.91; N 3.54. Calcd. for $C_{19}H_{16}NO_3PS_2$: C 56.85, H 4.02; N 3.49%.^{13}C NMR ($CDCl_3$, 100.61 MHz): *E*, *Z*-**5a**: $\delta = 52.4$ (s, OCH_3), 89.3 (d, $^1J_{PC} =$ 89.1 Hz, C^8), 114.4 (s, C^6), 128.8 (d, $^3J_{PC} = 13.0$ Hz, C-*m* of C_6H_5P), 130.8 (d, $^2J_{PC} = 11.0$ Hz, C-*o* of C_6H_5P), 131.75 (s, C-*p* of C_6H_5P), 131.76 (s, C-*p* of C_6H_5P), 133.5 (d, $^1J_{PC} = 89.0$ Hz, C-*i* of C_6H_5P), 140.3 (s, C^5), 150.2 (s, C^2), 164.3 (s, C^7), 166.6 (s, C^4); *Z*, *Z*-**5a**: $\delta = 53.7$ (s, OCH_3),

84.2 (d, $^1J_{PC}$ = 91.5 Hz, C^8), 114.4 (s, C^6), 128.5 (d, $^3J_{PC}$ = 12.6 Hz, C-*m* of C_6H_5P), 130.7 (d, $^3J_{PC}$ = 10.2 Hz, C-*o* of C_6H_5P), 131.5 (s, C-*p* of C_6H_5P), 134.1 (d, $^1J_{PC}$ = 85.8 Hz, C-*i* of C_6H_5P), 140.3 (s, C^5), 152.4 (s, C^2), 166.6 (s, C^7), 172.6 (s, C^4).

(E)-2-[(Diethoxythiophosphoryl)thio]methylene-(Z)-5-(methoxycarbonyl-methylene)thiazolidin-4-one (5b)

Compound **5b** was prepared using the procedure described for **5a**, except that 0.292 g (2.7 mmol) of *S*-(2-amino-2-thioxoethyl) *O*,*O*-diethyl phosphodithioate **4b** was used instead of thioamide **4a**, and the reaction was performed at room temperature over 6 h. Thiazolidinone *E*, *Z*-**5b** was obtained in 57% yield after purification by column chromatography (acetone-hexane 2:3); mp 120–121°C. IR (KBr, ν/cm^{-1}): 656 (P=S), 1606 (C=C), 1698 (C^7=O and C^4=O), 3138 (br, NH). ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 15.8 (d, $^3J_{PC}$ = 8.4 Hz, $\underline{C}H_3CH_2O$), 52.4 (s, OCH_3), 64.6 (d, $^2J_{PC}$ = 5.0 Hz, OCH_2), 91.5 (d, $^2J_{PC}$ = 7.6 Hz, C^8), 113.9 (s, C^6), 142.8 (s, C^5), 143.2 (d, $^3J_{PC}$ = 10.8 Hz, C^2), 166.6 (s, C^7), 166.7 (s, C^4). Found: C 35.84; H 4.41; N 3.75. Calcd. for $C_{11}H_{16}NO_5PS_3$: C 35.76, H 4.36; N 3.79%.

(Z)-2-[(Triphenylphosphonio)methylene]-(Z)-5-(methoxycarbonylmethylene)-thiazolidin-4-one Chloride (5c)

A suspension of 2.7 g (7.26 mmol) of triphenylphosphonium salt **4c** and 1.03 g (7.26 mmol) of DMAD in 15 mL of MeOH was stirred over 12 h at ambient temperature. Diethyl ether (15 mL) was added to the reaction mixture, and the obtained precipitate was filtered and air-dried to give 3.18 g (81%) of **5c**·MeOH, mp 179–180°C. Found: C 60.78; H 4.67; N 2.74. Calcd. for $C_{26}H_{25}ClNO_4PS$: C 60.76, H 4.90; N 2.72%. After drying in vacuo, *Z*, *Z*-**5c** was isolated in 75% yield; mp 252–254°C. IR (KBr, ν/cm^{-1}): 1106, 1177, 1194 (ν_{as} CNC), 1329 (ν_s CNC), 1438, 1568, 1585 (C=C), 1692 (C^7=O), 1716 (C^4=O), 2987 (br, NH). ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ = 52.4 (s, OCH_3), 75.8 (d, $^1J_{PC}$ = 110.8 Hz, C^8), 116.5 (s, C^6), 119.5 (d, $^1J_{PC}$ = 92.3 Hz, C-*i* of C_6H_5P), 130.4 (d, $^3J_{PC}$ = 13.2 Hz, C-*m* of C_6H_5P), 133.6 (d, $^2J_{PC}$ = 11.0 Hz, C-*o* of C_6H_5P), 135.5 (s, C-*p* of C_6H_5P), 140.5 (s, C^5), 160.2 (d, $^2J_{PC}$ = 9.7 Hz, C^2), 163.2 (s, C^7), 166.2 (s, C^4). Found: C 62.18; H 4.51; N 3.01. Calcd. for $C_{25}H_{21}ClNO_3PS$: C 62.30, H 4.39; N 2.91%.

(Z)-2-[(Diethoxyphosphoryl)methylene]-(Z)-5-(methoxycarbonylmethylene)-thiazolidin-4-one(Z,Z-2a)

$NiCl_2$ hexahydrate (119 mg, 0.5 mmol) was added to a solution of (E)-2-[(diethoxyphosphoryl)methylene]-(*Z*)-5-(methoxycarbonylmethylene)thiazolidin-4-one *E*, *Z*-**2a** (160 mg, 0.5 mmol) obtained as described previously[10] in MeOH (3 mL). Yellowish crystals, which precipitated from the yellow-green solution over time (14 days), were filtered and air-dried to give 104 mg (65%) of Z,Z-2a. Mp 95–96 °C. Found: C 41.18; H 4.99; N 4.03. Calcd. for $C_{11}H_{16}NO_6PS$: C 41.12, H 5.02; N 4.36%.

X-Ray Crystallography

X-ray diffraction experiments were carried out with a Bruker SMART 1000 CCD area detector, using graphite monochromic Mo-Kα radiation (λl = 0.71073 Å, ω-scans) at 110 K. The low temperature of the crystals was maintained with a Cryostream (Oxford Cryosystems) open-flow N_2 gas cryostat. Reflection intensities were integrated using SAINT software[21] and absorption correction was applied semi-empirically using SADABS program.[22] The structures were solved by direct method and refined by the full-matrix least-squares method against F^2 in anisotropic approximation for no-hydrogen atoms. NH hydrogen atoms were located from the Fourier density synthesis and refined in isotropic approximation. Analysis of Fourier density synthesis has revealed that half of the methanol molecule in *E*, *Z*-**5c** is disordered over two positions with equal occupancies (0.25). The hydrogen atom of the OH group for one-quarter of the methanol molecule was not located. The positions of all other hydrogen atoms were calculated geometrically. Crystal data and structure refinement parameters for *E*, *Z*-isomers of **5a–c** and *Z*, *Z*-**2a** are presented in Table III. All calculations were performed using the SHELXTL software.[23]

Theoretical Calculations

Geometry optimization was carried out using the PBE/TZ2p basis set implemented in the Priroda program package.[24] Electron density function of E,Z- and Z,Z-isomers of **5a** were calculated within PBE1PBE1/6-311G* single point calculation using Gaussian 98.[25] The topological analysis of the $\rho(\mathbf{r})$ was performed using the MORPHY98 program package.[26] The energy of interactions (Econt) was estimated from the values of potential energy density, v(r), using the correlation scheme Econt = 0.5 v(r) in accordance with the literature.[16]

TABLE III Crystallographic Data for *E,Z*-5a, *E,Z*-5b, *E,Z*-5c, and *Z,Z*-2a

	***E,Z*-5a**	***E,Z*-5b**	***E,Z*-5c**	***Z,Z*-2a**
CCDC[a]	669810	669808	669809	669811
Formula	$C_{19}H_{16}NO_3PS_2$	$C_{11}H_{16}NO_5PS_3$	$C_{25}H_{21}ClNO_3PS \cdot 0.5\ CH_3OH$	$C_{11}H_{16}NO_6PS$
Formula weight	401.42	369.40	497.93	321.28
T (K)	120	120	120	120
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	P-1	$P2_1/c$
Z (Z′)	4(1)	4(1)	2(1)	4(1)
a (Å)	9.7626(6)	7.0220(9)	11.150(2)	16.279(8)
b (Å)	7.7805(5)	27.940(4)	11.180(2)	9.237(4)
c (Å)	24.3248(15)	8.6975(10)	12.720(3)	9.690(4)
α(°)	90.00	90.00	90.30(3)	90.00
β(°)	92.167(2)	105.744(3)	113.60(3)	101.232(6)
γ(°)	90.00	90.00	116.60(3)	90.00
V (Å^3)	1846.3(2)	1642.4(3)	1265.9(4)	1429.2(11)
d_{calc} (g·cm^{-3})	1.444	1.494	1.306	1.493
μ(ñm^{-1})	3.94	5.66	3.26	3.62
F(000)	832	768	518	672
$2\theta_{max}$ (°)	57	60	50	57
Reflections measured	10389	15934	4665	6729
Independent reflections	4794	4765	4348	3510
Observed reflections [$I > 2\sigma(I)$]	4017	2560	2969	3043
Number of parameters	299	193	306	245
R_1	0.0416	0.0595	0.0630	0.0348
wR_2	0.0941	0.1368	0.1625	0.0806
GOF	1.082	1.024	1.049	0.987
$\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-3})	0.405/–0.279	0.667/–0.403	0.691/–0.539	0.362/–0.279

[a]The crystallographic data have been deposited with the Cambridge Crystallographic Data Center. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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