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QUANTUM-CHEMICAL INVESTIGATION OF THE MECHANISM OF *trans-cis* PHOTOISOMERIZATION OF 4-[2-(2-CHLOROPHENYL)VINYL]-6,6-DIMETHYL-2-OXO-1,2,5,6-TETRAHYDROPYRIDINE-3-CARBONITRILE

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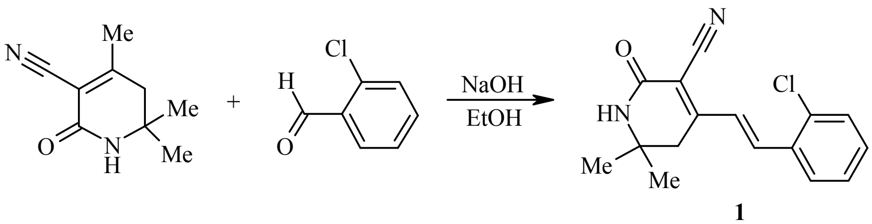
A quantum-chemical investigation has been carried out by the semiempirical AM1 method of the trans-cis photoisomerization mechanism of 4-[2-(2-chlorophenyl)vinyl]-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile. It was shown that the isomerization process proceeds in the excited singlet state S_1 by rotation of the 2-chlorophenyl substituent around the C(2)–C(3) bond. Electronic absorption spectra of the isomers were calculated by the INDO/S method Transitions caused by exitation of an electron from HOMO to LUMO were characterized by the greatest intensity.

Keywords: 4-[2-(2-chlorophenyl)vinyl]-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile, *trans-cis* photoisomerization, semiempirical method AM1, INDO/S, MOPAC2009.

Biological activity, inherent in many organic compounds, is usually linked with only one of the isomeric forms of a substance. Consequently a study of the stereoisomerization mechanism of synthesized compounds is of interest not only from a theoretical point of view, but has an important practical significance.

In continuation of our earlier investigations on the synthesis of biologically active compounds of the δ-lactam class we have obtained 4-[2-(2-chlorophenyl)vinyl]-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (**1**) by the condensation of 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile with 2-chlorobenzaldehyde in ethanol in the presence of catalytic quantities of NaOH.



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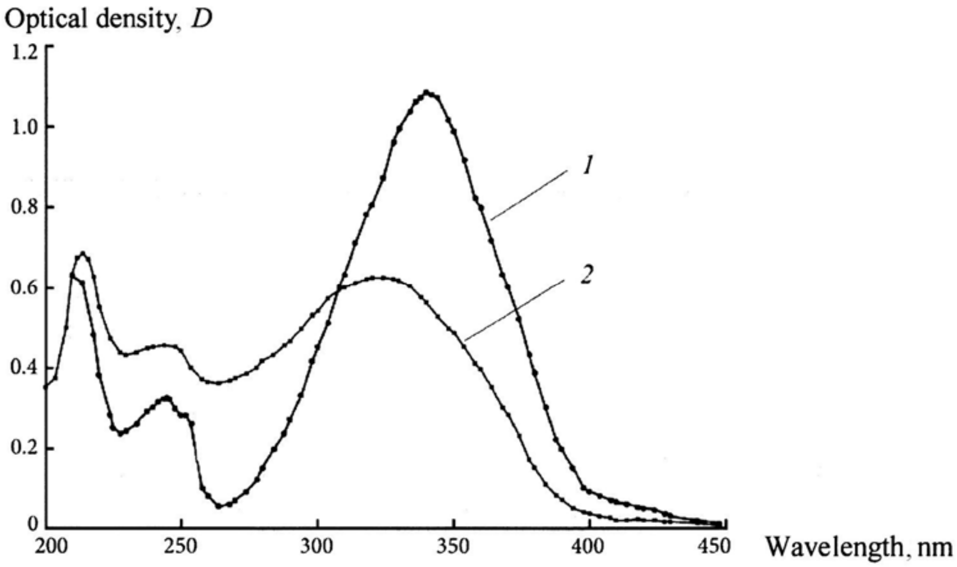

Fig. 1. Absorption spectrum of compound **1** in ethanol at 20°C before (*1*) and after (*2*) irradiating with daylight for 1 h.

TABLE 1. Characteristics of the *trans* and *cis* Isomers of Compound **1** in the S_0, S_1, and T_1 Electronic States, Calculated by the AM1 Method

Calculated characteristics	Electronic state	Isomer	
		trans	*cis*
Heat of formation, kcal/mol	S_0	37.4	38.5
	S_1	121.3	117.7
	T_1	71.5	70.0
Dihedral angle H(1)–C(1)–C(2)–H(2), deg	S_0	179.8	-2.2
	S_1	90.6	89.8
	T_1	96.6	96.2
Dihedral angle C(1)–C(2)–C(3)–C(4), deg	S_0	52.0	134.5
	S_1	1.7	179.0
	T_1	0.2	179.6
Bond length C(1)–C(2), Å	S_0	1.342	1.339
	S_1	1.381	1.386
	T_1	1.437	1.440
Bond order C(1)–C(2)	S_0	1.855	1.882
	S_1	1.100	1.091
	T_1	1.056	1.053
Bond length C(2)–C(3), Å	S_0	1.457	1.456
	S_1	1.438	1.440
	T_1	1.402	1.402
Bond order C(2)–C(3)	S_0	1.011	1.011
	S_1	1.364	1.359
	T_1	1.426	1.424

According to the data of ^1H NMR spectroscopy the synthesized compound **1** has the *trans* configuration relative to the exocyclic double bond [1]. The results of biological testing showed that compound **1** displays high cytotoxicity *in vitro* in relation to multilayer cancer cells HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) (LC_{50} 2-3 μg/ml) [1].

In the present work we have established that on irradiating an alcoholic solution of *trans* alkene **1** ($0.34 \cdot 10^{-4}$ M) with daylight, changes were observed in the UV absorption spectrum characteristic for the photoinduced *trans-cis* isomerization process. These were a reduction in the intensity of the long-wave band accompanied by a small hypsochromic shift (from 340 to 320 nm) and some increase in the intensity of the absorption in the high frequency, so-called cissoid, region of the spectrum (Fig. 1) [2]. Photostationary equilibrium was established after approximately 1 h. It was established on the basis of results of HPLC analysis that the photostationary mixture contains 91% *cis* isomer and 9% *trans* isomer.

In the ^1H NMR spectrum of product **1** dissolved in DMSO-d_6, after irradiation with daylight, a reduction was observed in the intensity of two doublets at 7.30 and 7.66 ppm (J = 16.0 Hz), characteristic of *trans*-disposed protons –CH=CH–, and the appearance of two new doublets at 6.71 and 7.14 ppm (J = 12.2 Hz), characteristic of –CH=CH– protons in a *cis* position. Moreover the sets of signals in the ^{13}C NMR spectrum were doubled, as were the signals of the protons of the phenyl and tetrahydropyridine rings of compound **1**.

To clarify the molecular mechanism of the compound **1** photoisomerization we have carried out a quantum-chemical study using the semiempirical AM1 method [3]. The obtained structure, electronic, and energy characteristics of the compound in the ground and two lowest excited states are given in Table 1 and in Figs. 2, 3.

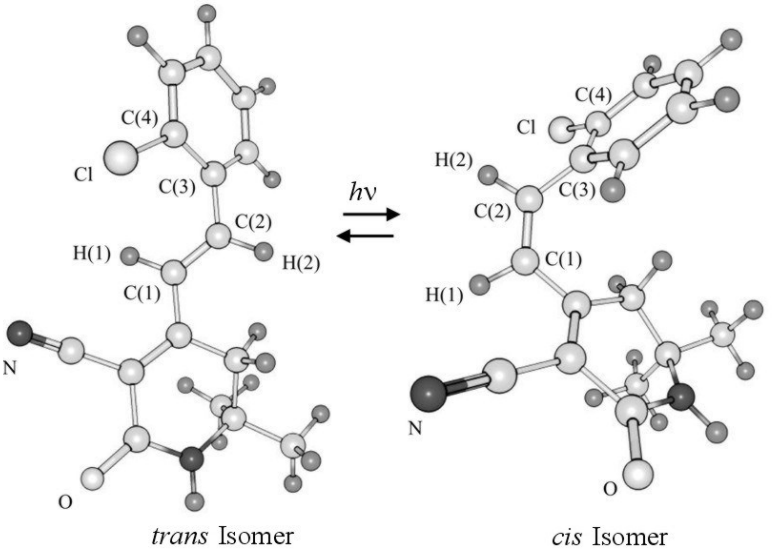

Fig. 2. Optimum geometry of *trans* and *cis* isomers of compound **1** in the ground electronic state S_0, calculated by the AM1 method.

According to the calculations the dihedral angle H(1)–C(1)–C(2)–H(2), characterizing the isomeric form of the compound, for the *trans* isomer in the ground state is equal to 179.8°, and for the *cis* isomer it is -2.2°. According to the formation heat values, the *trans* form is the energetically more preferred structure than the *cis* isomer. However in solution, as we see, the *cis* form predominates significantly. Such photoinduced formation of the thermodynamically less stable form of any compound from the more stable form is called an "optical pump" [4]. Comparison of the calculated values of the C(1)–C(2) bond order indicates that the double bond of the *cis* isomer is more stable than in the case of the *trans* configuration. The order of the C(2)–C(3) bond between the central bridge and the aryl substituent for both isomers is the same and is equal to 1.011.

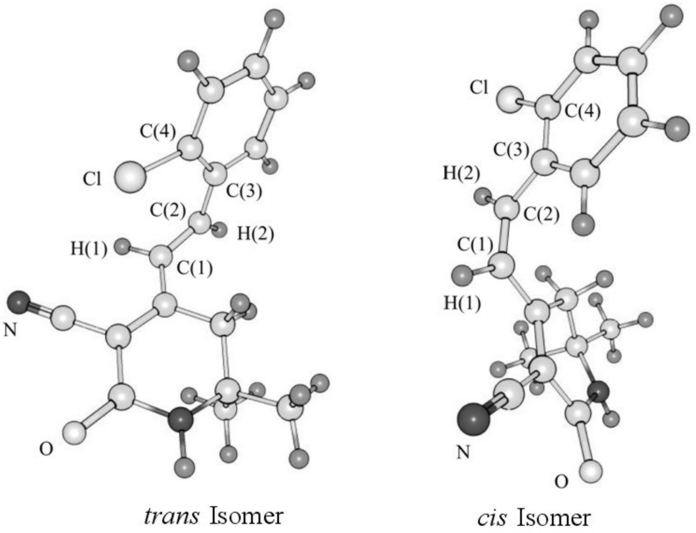

Fig. 3. Geometry of *trans* and *cis* isomers of molecule **1** in the S_1 state calculated by the AM1 method.

According to the calculations, on transition to the excited state S_1 the thermodynamically more stable structure becomes the *cis* isomer (Table 1, Fig. 3). The small lengthening of the C(1)–C(2) bond (by 0.039 and 0.047 Å in the *trans* and *cis* isomers respectively) is accompanied by a significant reduction (from 1.855 to 1.100 for the *trans* form and from 1.882 to 1.091 for the *cis* isomer) in bond order, which indicates conversion of the multiple bond into a single bond, and consequently to the possibility of rotation around it. For many compounds, as for example for the stilbene molecule, it is considered that the process of photochemical *trans-cis* isomerization occurs as a result of such rotation of the structure fragments around the weakened central C=C bond [5]. From our data it follows that such a mechanism of isomerization is impossible for compound **1** due to the peculiarities ot the structure of the isomers in state S_1. As is evident from Fig. 3, the structures of the *trans* and *cis* isomers are close. The values of dihedral angles H(1)–C(1)–C(2)–H(2) practically coincide (90.6° and 89.8° for the *trans* and *cis* forms, respectively). The main difference is in the 2-chlorophenyl substituent orientation. In the *trans* isomer the dihedral angle C(1)–C(2)–C(3)–C(4) is equal to 1.7°, but in the *cis* isomer it amounts to 179.0° (Table 1). Consequently, mutual *trans-cis* isomerization must proceed by rotation of the 2-chlorophenyl ring around the C(2)–C(3) bond. A search for the transition state of such a process was carried out by the intrinsic reaction coordinate method for which the torsion angle C(1)–C(2)–C(3)–C(4) was taken. A heat of formation of 127.6 kcal/mol corresponds to the transition state of the system with reaction coordinate equal to 80.1°. Based on the data of Table 1 it follows that the energy of activation for the *trans* → *cis* transition was 6.3 kcal/mol, but the energy of activation for the reverse *cis* → *trans* transition was significantly higher and equal to 9.9 kcal/mol.

This indicates that the photoactivation of the *trans* isomer with subsequent conversion into the *cis* form is energetically a more favorable process than the reverse conversion and will lead in the photostationary state to a predominance of the *cis* isomer in solution. The difference found in the values of the activation energy **,**must lead to the absorption maximum shift of the spectrum to the side of higher frequencies, which was also observed in the experimental UV spectra. Calculations of the direct deactivation of the S_1 state show that the *trans* and *cis* isomers are converted into the corresponding isomers of the ground state of the molecule.

It has been established for many chemical compounds that *trans-cis* isomerization proceeds with involvement of the triplet states [6-8]. As the calculations showed, significant changes in the spatial structure of the isomers of compound **1** do not occur upon intercombinational transition to this state. It is seen from Table 1 that both dihedral angles H(1)–C(1)–C(2)–H(2) and C(1)–C(2)–C(3)–C(4) are close to their values in the S_1 state. Redistribution of electron density in the molecule caused by the transition leads to a small weakening of the central C(1)–C(2) bond and an increase in the C(2)–C(3) bond order in both isomeric forms to a value of approximately 1.425, which must significantly hinder the rotation of the phenyl ring around this bond. The deactivation of the T_1 state, unlike the excited S_1 state, leads both for the *trans* and for the *cis* isomer only to the *trans* isomer of the ground state.

The obtained data therefore point in favor of a singlet mechanism for the *trans-cis* photoisomerization of compound **1**.

The electronic absorption spectra of both isomeric forms were calculated by the semiempirical INDO/S method [9], using the geometry of the ground state optimized by AM1 method. The obtained values for the energies of transitions and oscillator strengths are given in Table 2. Analysis showed that transitions caused by exitation of an electron from the highest occupied molecular orbital to the lowest vacant molecular orbital ($\pi \rightarrow \pi^*$) were characterized by the greatest intensity. For the *trans* isomer the highest value of oscillator strength (0.867) corresponds to the transition energy with wavelength 327.7 nm. This value is in good agreement with the maximum of the absorption band (λ = 340 nm) of the experimental spectrum. In the case of the *cis* isomer the found value of the oscillator strength (0.446) is approximately one half, but the energy of the electronic transition at 315.2 nm is close to the maximum position (λ = 320 nm) of the experimental spectrum of the equilibrium mixture in which the *cis* isomer predominates significantly (Fig. 1).

TABLE 2. Calculated Spectral Characteristics for *trans* and *cis* Isomers of Compound **1**

trans Isoner		*cis* Isomer	
Energy, nm	Oscillator strength	Energy, nm	Oscillator strength
337.7	0.009	342.7	0.007
327.7	0.867	315.2	0.446
283.9	0.006	283.3	0.004
257.4	0.115	250.1	0.133
250.1	0.030	241.0	0.184
229.0	0.031	240.5	0.124
226.4	0.081	225.9	0.019
226.1	0.148	222.7	0.170
223.4	0.085	217.7	0.059
220.6	0.010	216.3	0.044

The investigation carried out enables the special features of the electronic mechanism to be revealed for the photoinduced process of *trans-cis* isomerization, and to give an interpretation of the experimentally observed UV absorption spectrum of 4-[2-(2-chlorophenyl)vinyl]-6,6-dimethyl-2-oxo-1,2,5,6-tetrahydro-pyridine-3-carbonitrile.

EXPERIMENTAL

The UV spectra of compound **1** were recorded in ethanol on a Unicam SP 1800 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were obtained on a Varian 400 MR (400 and 100 MHz respectively) in DMSO-d_6, internal standard was TMS. HPLC analysis was carried out under reversed phase chromatography conditions. Measurements were carried out on a Varian ProStar chromatograph, on an Alltech column packed with Apollo C18 sorbent 4.6×150 mm. Mobile phase: acetonitrile–0.1% phosphoric acid in water (pH 2.3). Linear gradient (15 min) from 40 to 100% acetonitrile, then 5 min in isocratic mode (100% acetonitrile). Consumption of mobile phase was 1 ml/min.

Compound *trans*-1. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (6H, s, $(CH_3)_2$); 2.87 (2H, s, 5-CH_2); 7.30 (2H, d, *J* = 16.0, –CH=); 7.66 (2H, d, *J* = 16.0, -CH=); 7.46, 7.47, 7.57, and 7.89 (4H, all m, H Ar); 8.10 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 28.2 ($(CH_3)_2$); 36.7 (C-5); 50.7 (C-6); 106.6 (C-3); 114.7 (C≡N); 127.1 and 135.9 (–CH=CH-); 128.0 (C-5'); 128.1 (C-6'); 130.2 (C-3'); 131.7 (C-4'); 132.7 (C-1'); 133.6 (C-2'); 158.6 (C-4); 160.3 (C-2).

Compound *cis*-1. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.06 (6H, s, $(CH_3)_2$); 2.28 (2H, s, 5-CH_2); 6.71 (2H, d, *J* = 12.2, –CH=); 7.14 (2H, d, *J* = 12.2, –CH=); 7.31, 7.34, 7.41, and 7.54 (4H, all m, H Ar); 8.20 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm; 28.1 ($(CH_3)_2$); 40.3 (C-5); 50.7 (C-6); 108.2 (C-3); 114.4 (C≡N); 127.2 and 159.8 (–CH=CH–); 127.2 (C-4'); 129.5 (C-6'); 130.6 (C-5'); 131.0 (C-3'); 132.3 (C-1'); 134.2 (C-2'); 159.8 (C-4); 160.6 (C-2).

Quantum-chemical calculations were carried out by the AM1 semiempirical method using the MOPAC2009 program [10] with full optimization of all geometric parameters of both the ground and two lowest excited states of the isomers. Calculations of the excited states were carried out using the key word OPEN(2,2). Refinement of the transition state, localized by the intrinsic reaction coordinate method, was carried out by minimizing the gradient norm (NLLSQ).

The spectroscopic parameters of the *trans* and *cis* isomers of compound **1**, enabling interpretation and indexation of the electronic absorption spectra, were calculated by the INDO/S-CI [9] with the ArgusLab 4.0.1 program [11]. Calculations of the configuration interaction included once-excited configurations, designed from the 10 highest occupied and 10 virtual molecular orbitals. Calculation of the effect of the medium (ethanol) was carried out by introducing appropriate values of the dielectric constant (24.55), refractive index (1.361), and mass density (0.798). Figures 1-3 were obtained using the programs JPlot [12] and ChemCraft [13].

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