Reaction between β-phenyl-α-alanine and 4-hydroxy-4-methylpent-2-ynenitrile: a spectroscopic and quantum chemical study*

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The sequence of isomeric transformations of intermediate adducts formed upon nucleophilic addition of β-phenyl-α-alanine to 4-hydroxy-4-methylpent-2-ynenitrile affording a neutral or two alternative zwitterionic forms (with protonated imino or amino groups) of the product was studied quantum chemically by the B3LYP/6-31G(d,p) method and by UV spectroscopy. In the isolated state, the equilibrium is completely shifted toward the neutral form. Taking into account the polyhydrate environment increases the portion of the zwitterionic form bearing a protonated imino group of the dihydrofuran cycle. Protonation of the amino group of amino acid is thermodynamically unfavorable.

Key words: quantum chemical calculations, density functional theory (DFT), B3LYP functional, UV spectroscopy, IR spectroscopy, NMR spectroscopy, β-phenyl-α-alanine, 4-hydroxy-4-methylpent-2-ynenitrile, *Z*-adduct, isomerism, zwitterionic state.

Amino acids represent the main type of building blocks for the synthesis of proteins, enzymes, hormones, and many other biologically important compounds.[1] Artificially synthesized amino acids modified with various pharmacophores are widely used for targeted synthesis of compounds with specified biological activity.[2—5] They are employed in the design of biological nanomaterials in tissue engineering and act as drug transport markers in living organisms.[6,7] Advances in biochemistry stimulate interest in the synthesis of artificial amino acids.[2] Their application to peptide synthesis allows one to control the activity of biologically important peptides.[4] Recently, the demand for new peptide structures for the design of novel drugs is rapidly growing.[3,8]

We have shown in our recent studies that acetylene hydroxynitriles chemo- and regiospecifically react with aliphatic amino acids[9,10] (glycine; β-alanine; γ-aminobutyric and ε-aminocaproic acids; D,L-valine; D,L-leucine; L-methionine), 2-aminobenzoic acid,[11] and D,L-tryptophan[12] under mild conditions with the formation of artificial amino acids bearing an iminodihydrofuran substituent. In the solid state, the compounds synthesized exist as unusual zwitterions with protonated imino group in the dihydrofuran ring instead of the expected protonated amino group of the acid.

In this work, taking the reaction of β-phenyl-α-alanine (**1**) with 4-hydroxy-4-methylpent-2-ynenitrile (**2**) as an example, we studied the effect of specific features of intermediate stages on the formation of the dihydrofuran ring and evaluated the probability of stabilization of the final product **3** in the neutral or zwitterionic form by quantum chemistry methods and NMR, IR, and UV spectroscopies.

Experiments showed that the reaction between compounds **1** and **2** proceeds in a weakly acidic medium (25% aqueous NaOH, pH ≈ 9) chemo- and regiospecifically and results in amino acid containing the iminodihydrofuran substituent in the amino group (**3**) (yield is 82%). We believe[13] that the primarily formed *Z*-adduct **A** undergoes isomeric transformations into the intermediates **B**—**D**. Subsequent intramolecular cyclization of the intermediate **D** leads to the neutral (**E**) or zwitterionic (**F** or **G**) forms of amino acid **3** (Scheme 1).

The ^{1}H NMR spectrum (CD_3OD) of the synthesized amino acid **3** exhibits a signal of olefinic proton at δ_H 4.74. Protons of CH and CH_2 groups give three doublets of doublets of the three-spin system ABX at δ_H 3.96, δ_H 3.33, and δ_H 2.96. The phenyl ring protons produce a multiplet in the region δ_H 7.19—7.16. The ^{13}C NMR spectrum also confirms the structure of amino acid **3**. Three close signals of C atoms in the COO^-, HN—C=CH, and $C{=}N^+H_2$ groups were assigned using the 2D HMBC (^{1}H—^{13}C) technique. The 2D NMR spectrum of amino acid **3** exhibits

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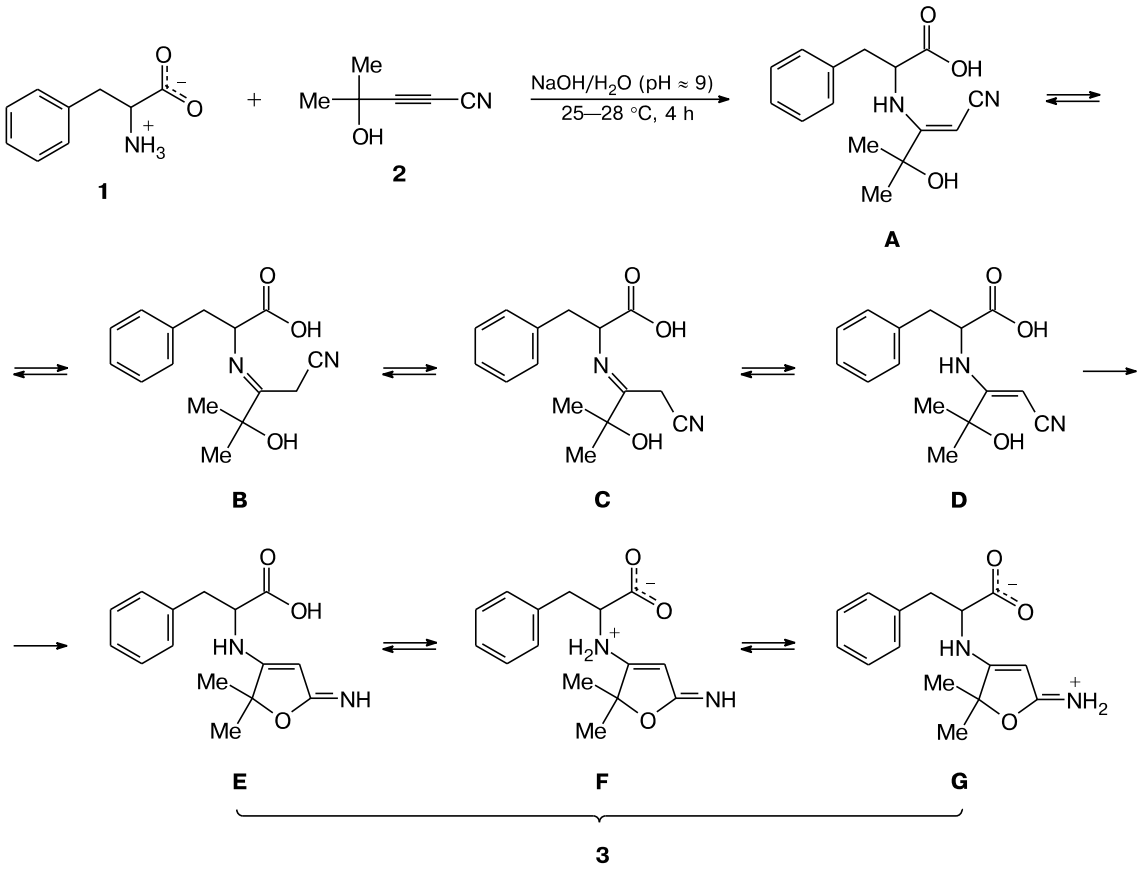
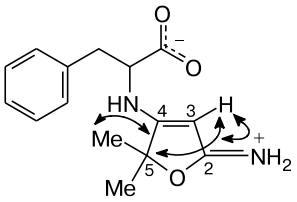
Scheme 1



cross-peaks between signals of the olefinic atom H(3) and the C(2) and C(5) atoms of the iminodihydrofuran ring, as well as between signals of methyl protons and the C(4) atom of the iminodihydrofuran ring:



The reaction between compounds **1** and **2** in the presence of NaOH (initial concentrations of **1** in the reaction mixture were $1.6 \cdot 10^{-1}$ and $1.8—2.0 \cdot 10^{-4}$ mol L^{-1}) was studied by UV spectroscopy. The UV spectrum of aqueous solution of compound **1** exhibits a strong absorption band at 205 nm and weak absorption in the region 240—270 nm with pronounced vibrational structure (Fig. 1, *a*). The spectrum of compound **2** demonstrates weak bands in the region 210—260 nm with maxima at 212, 224, 234, and 256 nm (Fig. 1, *b*). Amino acid **3** (form **G**) is characterized (see Fig. 1) by a maximum at 271 nm (H_2O, $\lambda_{max} = 271$ nm (lg ε 4.38)). The UV spectrum of a sample taken from a 1 : 1 : 0.25 reaction mixture (**1** : **2** : NaOH, c_1 =

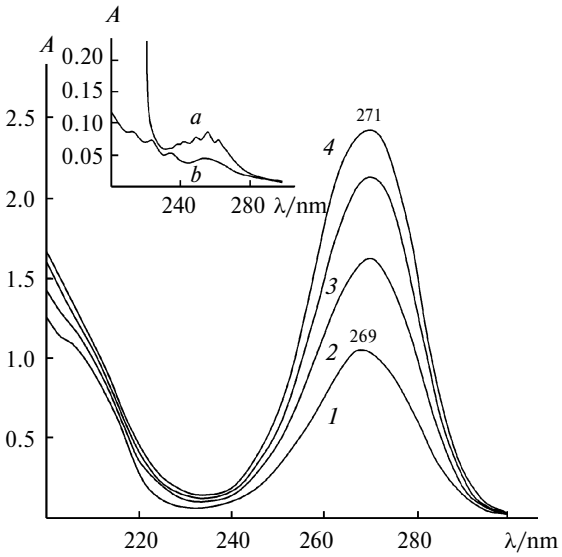


Fig. 1. Absorption spectra of aqueous solution of the reaction mixture of β-phenyl-α-alanine (**1**), 4-hydroxy-4-methylpent-2-ynenitrile (**2**), and NaOH, 1 : 1 : 0.25 ($c_1 = 1.6 \cdot 10^{-1}$ mol L^{-1}, d = = 0.1 cm, 23—25 °C). The spectra were recorded after 15 min (*1*), 50 min (*2*), 1.5 h (*3*), and 3.5 h (*4*). Inset: UV spectra of compound **1** ($c_1 = 2.2 \cdot 10^{-4}$ mol L^{-1}, d = 1 cm, 23—25 °C) (*a*) and compound **2** ($c_2 = 2.4 \cdot 10^{-4}$ mol L^{-1}, d = 1 cm, 23—25 °C) (*b*).

$= 1.6 \cdot 10^{-1}$ mol L^{-1}) shows two absorption bands at 205 and 269 nm (see Fig. 1).

An analysis of the results obtained shows that within 3.5 h the long-wavelength band is shifted to 271 nm and its intensity simultaneously increases by 2.5 times, while the strong absorption at 205 nm disappears. We believe that the band at 271 nm corresponds to absorption of the final product **3** (form **G**).

The UV spectra of the samples of the reaction mixture with the same composition 1 : 1 : 0.25 but another initial concentration of compound **1** ($c_1 = 1.8$—$2.0 \cdot 10^{-4}$ mol L^{-1}) also exhibit a new absorption band at 236 nm, while the absorption band at 271 nm manifests itself as a shoulder (Fig. 2).

Within 10.5 h, the intensities of the bands in the region 240—280 nm increase, the vibrational structure simultaneously becomes less pronounced, a clearly seen absorption maximum appears at 271 nm, and the intensity of the band at 236 nm decreases (see Fig. 2). The observed intersection point of the absorption bands at 224 nm (see Fig. 2) may indicate the presence of two equilibrium systems of intermediates, **A** → **B** or **C** → **D**, in the reaction mixture. The band at 236 nm probably corresponds to absorption of these intermediates while the band at 271 nm corresponds to the final product **3** (form **G**).

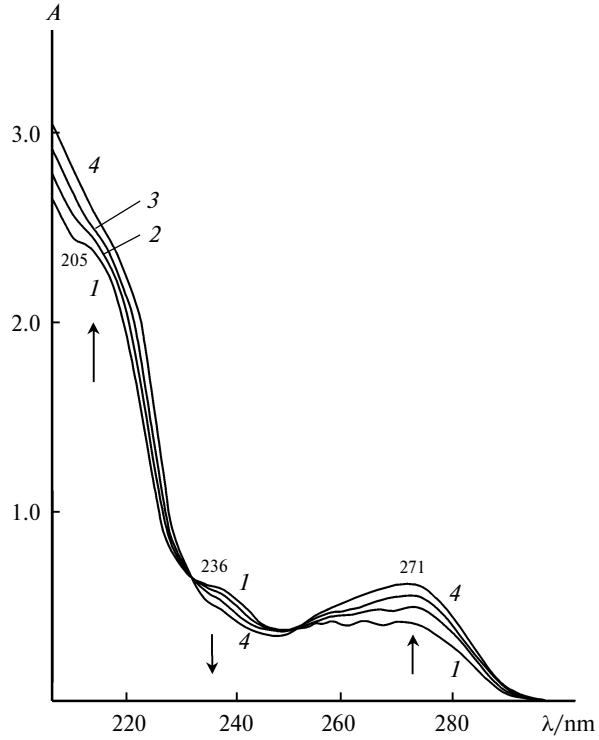


Fig. 2. Absorption spectra of aqueous solution of the reaction mixture of β-phenyl-α-alanine (**1**), 4-hydroxy-4-methylpent-2-ynenitrile (**2**), and NaOH, 1 : 1 : 0.25 ($c_1 = 1.8 \cdot 10^{-4}$ mol L^{-1}, $d = 1$ cm, 23—25 °C). The spectra were recorded after 5 min (*1*), 2.5 h (*2*), 6.5 h (*3*), and 10.5 h (*4*).

The IR spectrum of amino acid **G** exhibits a number of absorption bands in the region 3500—2600 cm^{-1} with maxima at 3407, 3223, 3085, 3060, 3029, 2981, 2933, and 2873 cm^{-1} corresponding to NH, $=^+NH_2$, C=CH, and CH groups.[14,15] A broad absorption band at 1680 cm^{-1} corresponds to the carboxylate anion, the frequency 1619 cm^{-1} corresponds to C=C stretching vibrations, and the frequency 1572 cm^{-1} corresponds to bending vibrations of $=^+NH_2$ group.[14,15]

It should be noted that the NMR and IR spectra of compound **3** (form **G**) are similar to those of the modified amino acid, *viz.*, 2-[(5-iminio-2,2-dimethyl-2,5-dihydro-3-furanyl)amino]acetate (obtained by the reaction of glycine with compound **2**) whose zwitterionic structure was confirmed by X-ray analysis.[9]

The potential energy surface of intramolecular transformations of intermediate **A** (see Scheme 1) was analysed by the B3LYP/6-31G(d,p) quantum chemistry method. A scheme of intramolecular transformations of the *Z*-adduct of the amino acid **A** is shown in Fig. 3.

The first step, namely, the antarasurface 1,3-prototropic shift (in the isolated state of adduct **A**) characterized by a high activation barrier (70.47 kcal mol^{-1}, **TS1**), leads to a thermodynamically almost equiprobable intermediate **B** (see Fig. 3). Probably, in a real system, water molecules present in the reaction mixture promote the transition **A** → **B**. Calculations with taking into account the H_2O molecule as mediator of the 1,3-prototropic shift predict a decrease in the barrier height (48.23 kcal mol^{-1}) by nearly 1.5 times. Free rotation of cyanomethyl group (E_a = 2.55 kcal mol^{-1}) in the intermediate **B** initiates an exothermic transition **B** → **C** which leads to stabilization of the molecular system (its energy decreases by 2.32 kcal mol^{-1}, see Fig. 3). The step **C** → **D** represents a kind of inverted tautomeric transition **A** → **B** and is characterized by a close activation barrier value, *viz.*, 73.95 kcal mol^{-1} for the gas phase and 50.66 kcal mol^{-1} with participation of the mediator molecule.

In the stage **D** → **E**, intramolecular nucleophilic addition of hydroxyl group to the nitrile group results in the formation of the iminodihydrofuran ring. In the gas phase, this stage corresponds to the most pronounced stabilization of the molecular system (see Fig. 3).

Considering the isolated system, transition of intermediate **E** to the zwitterionic states **F** and **G** upon protonation of amino group of the amino acid or imino group of the iminodihydrofuran ring is thermodynamically unfavorable. A shift of the equilibrium toward the zwitterionic structures **F** and **G** can be due to their interaction with the polyhydrate environment or to the packing effect (solid phase). Based on the dipole moment values of the structures **E**, **F**, and **G** (Table 1), the reactive field of the solvent can significantly change the relative stabilities of the neutral and zwitterionic isomers.

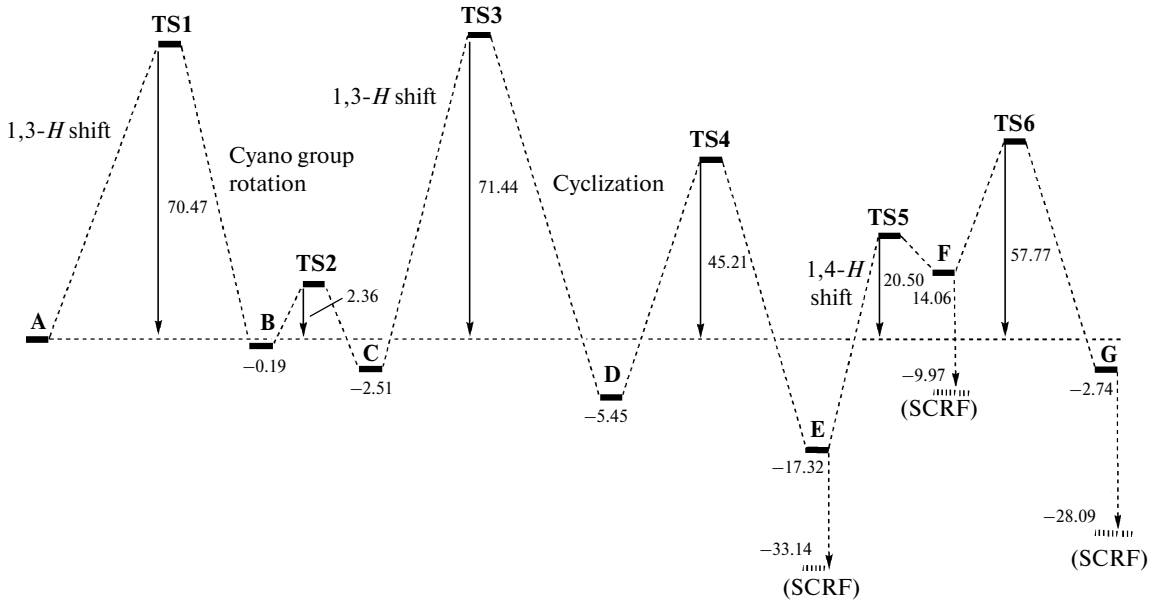


Fig. 3. Scheme of intramolecular transformations of intermediate **A** (see Scheme 1). Shown are the relative energies (in kcal mol^{-1}) of isomers **E**, **F**, and **G** calculated with inclusion of the solvent field (procedure SCRF=IPCM, $\varepsilon = 80$).

The effect of the inner-sphere solvation environment was taken into account within the framework of the self-consistent reactive field (SCRF) model and using the "supermolecule" model in which the solvation environment was simulated by four water molecules. In the former case, significant stabilization of the isomers **E**, **F**, and **G** was attained (their energies decreased by 15.82, 24.03, and 25.35 kcal mol^{-1}, respectively; see Fig. 3). The relative stabilities of the neutral and ionic isomers equalize, although the neutral form **E** remains the most stable. The energy gap between the isomers **E** and **G** narrows substantially from 14.58 to 5.05 kcal mol^{-1} (see Fig. 3).

Table 1. The lowest or imaginary harmonic frequencies (ω) and the dipole moments (μ) of the structures obtained from B3LYP/6-31G(d,p) calculations

Structure	ω/cm^{-1}	μ/D	Structure	ω/cm^{-1}	μ/D
A	9	4.88	**TS5**	i208	7.83
TS1	i856	3.29	**F**	24	9.19
B	16	2.98	**TS6**	i1763	9.88
TS2	i55	2.89	**G**	22	11.29
C	21	3.06	**E**·4H$_2$O	14	8.67
TS3	i849	2.91	**F**·4H$_2$O	13	10.01
D	19	6.73	**G**·4H$_2$O	19	3.42
TS4	i1941	6.95	Dimer **E**	4	7.11
E	23	4.64	Dimer **G**	8	15.16

Note. The total energies of structures **A**, **E**·4H$_2$O, **F**·4H$_2$O, **G**·4H$_2$O, and the dimers **E** and **G** calculated with inclusion of zero-point vibrational energies are respectively equal to −917.92910, −1223.81640, −1223.79258, −1223.83723, −1834.95286, and −1834.94418 a.u.

Calculations using the "supermolecule" model led to inverted order of the thermodynamic stability of hydrated molecular systems **E**·4H$_2$O, **F**·4H$_2$O, and **G**·4H$_2$O (see Note to Table 1). The system with the zwitterionic form **G** (Fig. 4) appeared to be the most stable. The molecular systems with the neutral (**E**) and zwitterionic (**F**) isomers are 10.35 and 27.39 kcal mol^{-1} less stable, respectively. In addition, the system **F**·4H$_2$O readily goes to the state **E**·4H$_2$O (activation barrier is at most 4 kcal mol^{-1}).

To evaluate the stabilizing effect of the packing of the amino acid isomers, we obtained the structural and energy characteristics of the dimer with the optimal topology ("head-to-tail" motif). According to calculations, in the isolated state, the dimer **E** (Fig. 5) is 5.26 kcal mol^{-1} more stable than dimer **G** (see Note to Table 1). Owing to steric hindrances due to the interaction of bulky substituents, the dimers formed by the zwitterionic isomers **F** can not be stabilized. Taking account of the effect of the inner-sphere solvation environment within the framework of the SCRF model led to inverted order of the relative stabilities of the dimers **E** and **G**, namely, the dimer **G** appeared to be 17.04 kcal mol^{-1} more stable than dimer **E**.

The results obtained suggest that the formation and accumulation of the zwitterionic form with the protonated amino group of the amino acid **F** in the polyhydrate state and in the crystal is unlikely. In a polar solvent, the neutral (**E**) and zwitterionic (**G**) isomers of the amino acid can form and accumulate, probably, with the equilibrium shifted toward the isomer **G**. In the solid phase, the isomers are packed as the zwitterionic structures **G**.

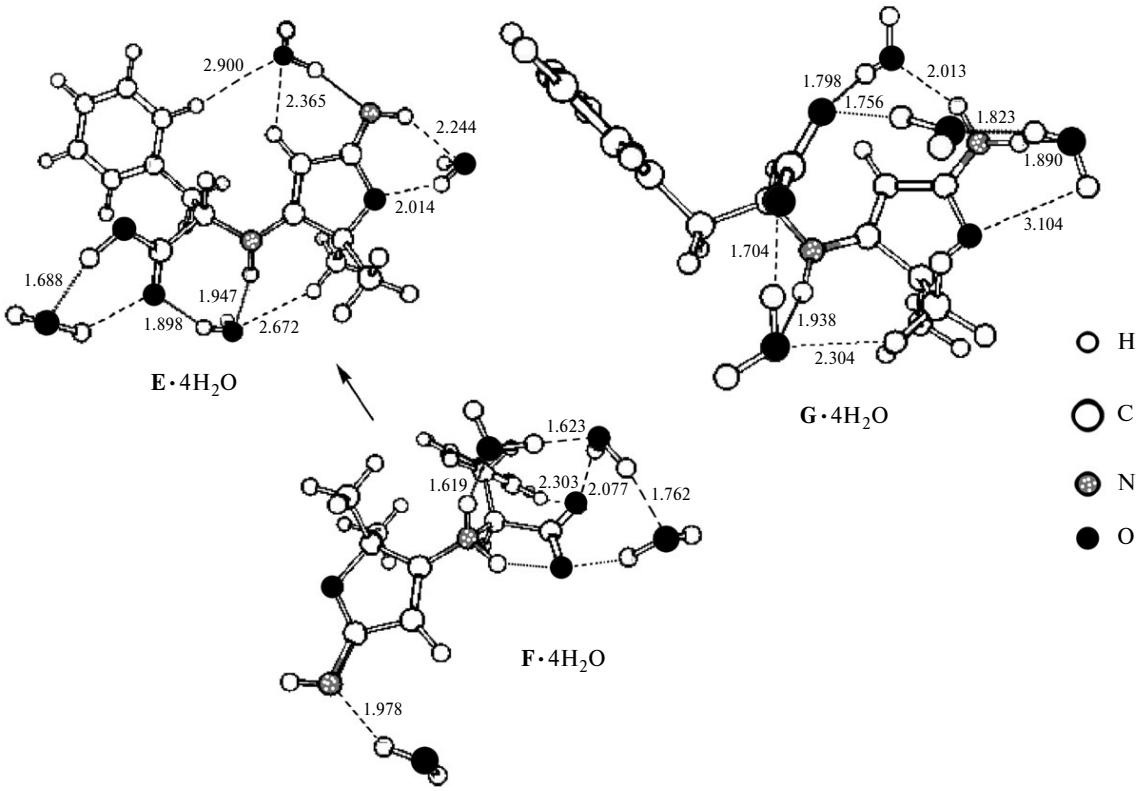


Fig. 4. Molecular structures of polyhydrated isomers **E**, **F**, and **G** (distances are given in Ångstrøms).

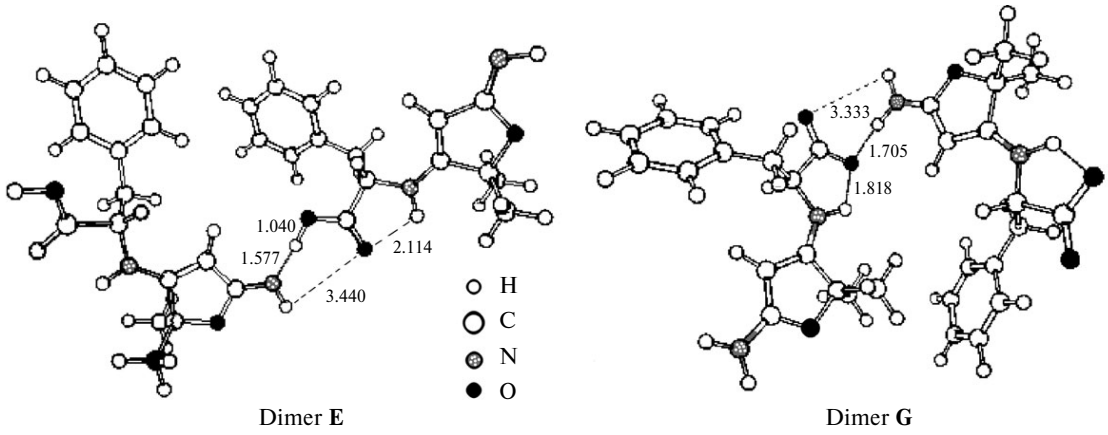


Fig. 5. Molecular structures of dimers **E** and **G** (distances are given in Ångstrøms).

Experimental

Quantum chemical calculations were carried out with the GAUSSIAN-98 program[16] in the 6-31G(d,p) basis set. Calculations of the molecular structures and studies of the gradient channels connecting them were performed within the density functional theory (DFT) with the B3LYP three-parameter functional.[17,18] Full geometry optimization of the molecular systems was performed until a gradient value of 10^{-5} a.u. Bohr^{-1}. In the studies of flat regions of the potential energy surfaces, the gradient value was 10^{-6} a.u. Bohr^{-1}. Stationary points were identified by analyzing the Hesse matrix. The search for and location of transition states was carried out by the synchronous transit method QST.[19] Vibrational frequencies at the saddle points were analyzed and the correspondence between the critical points and the gradient line connecting them was proved by the intrinsic reaction coordinate (IRC) method.

Electronic absorption spectra were recorded on a Perkin–Elmer Lambda 35 spectrophotometer at 23—25 °C (H_2O, EtOH, $d = 0.1$ and 1 cm). IR spectra were measured on a Bruker Vertex-70 Fourier spectrometer (KBr pellets). ^{1}H and ^{13}C NMR spectra (400.13 and 100.62 MHz, respectively) were recorded on a Bruker DPX-400 instrument in CD_3OD with HMDS as internal

standard. To assign the NMR signals and to determine the structures of the compounds under study, heteronuclear 2D NMR spectroscopy HMBC ($^1H—^{13}C$) was used. Elemental analysis was done with a Flash 1112 Series EA analyzer. The course of reaction was monitored by TLC on Al_2O_3 with chloroform—benzene—ethanol (20 : 4 : 1) mixture as eluent. β-Phenyl-α-alanine was purchased from Merck, 4-hydroxy-4-methyl-2-pentynenitrile was obtained following a known procedure.[20]

Reaction of β-phenyl-α-alanine with 4-hydroxy-4-methylpent-2-ynenitrile. β-Phenyl-α-alanine (**1**) (0.0825 g, 0.5 mmol) in water (2.5 mL) was heated to 40—45 °C with stirring until complete dissolution. The solution was cooled to 25 °C and 1% aqueous NaOH solution (0.5 mL) and 4-hydroxy-4-methyl-2-pentynenitrile (**2**) (0.0556 g, 0.51 mmol) was added successively. The reaction mixture was stirred for 4 h at 25—28 °C. Water was removed *in vacuo*, the residue was dissolved in ethanol and passed through a Schott funnel filled with Al_2O_3 (layer 2—3 cm thick). Ethanol was removed *in vacuo*. Light-yellow crystals of 2-[(5-iminio-2,2-dimethyl-2,5-dihydro-3-furanyl)amino]-3-phenylpropanoate (**3**) were obtained (0.112 g). Yield 82%, m.p. 190—192 °C (with decomp.). Found (%): C, 65.40; H, 6.73; N, 10.38. $C_{15}H_{18}N_2O_3$. Calculated (%): C, 65.69; H, 6.57; N, 10.20. UV spectrum (C_2H_5OH), λ_{max}/nm (log ε): 274 (4.37); (H_2O): 271 nm (4.38). IR spectrum (KBr), ν/cm^{-1}: 3407, 3223 (NH, $=^+NH_2$); 3085, 3060, 3029 (=C—H); 2981, 2933, 2873 (CH); 1680 (C=O); 1619 (C=C); 1572 (δ $^+NH_2$). ^1H NMR spectrum (δ, *J*/Hz): 1.56, 1.40 (both s, 6 H, Me); 3.96, 3.33, 2.96 (all dd, 3 H, CH_2C^*H, ABX, $^2J_{AB} = 13.9$, $^3J_{AX} = 4.4$, $^3J_{BX} = 9.8$); 4.74 (s, 1 H, H(3)); 7.19—7.16 (m, 5 H, Ph). ^{13}C NMR spectrum (δ): 25.2, 24.6 (Me); 39.5 ($\underline{C}H_2C^*H$); 64.4 ($CH_2\underline{C}^*H$); 76.7 (C(3)); 92.3 (C(5)); 127.7 (*p*-Ph); 130.4, 129.4 (*o*,*m*-Ph); 139.2 (*i*-Ph); 176.0 ($C=^+NH_2$); 177.5 (HN—$\underline{C}$=CH); 178.3 (COO^-).

Preparation of solutions for recording UV spectra. From the reaction mixture prepared as described above, with the initial concentration of β-phenyl-α-alanine (**1**) equal to $1.67 \cdot 10^{-1}$ mol L^{-1}, samples (0.01 mL) were taken and diluted with water (1.5 mL, $c_1 = 1.10 \cdot 10^{-3}$ mol L^{-1}, $d = 0.1$ cm).

β-Phenyl-α-alanine (**1**) (0.0165 g, 0.1 mmol) in water (1.0 mL) was heated to 40—45 °C and stirred until complete dissolution. The solution was cooled to 25 °C and 1% aqueous NaOH (0.09 mL) and 4-hydroxy-4-methylpent-2-ynenitrile (**2**) (0.0127 g, 0.116 mmol) was successively added with stirring. The reaction mixture (0.02 mL) thus obtained was diluted with water (9 mL, $c_1 = 1.8 \cdot 10^{-4}$ mol L^{-1}, $d = 1$ cm), stirred, and poured into a cell (23—25 °C).

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