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ТЕРМОДИНАМІЧНІ ВЛАСТИВОСТІ РОЗЧИНІВ МЕТИЛ 6-МЕТИЛ-2-ОКСО-4-ФЕНІЛ- 1,2,3,4-ТЕТРАГІДРОПІРИМІДИН-5-КАРБОКСИЛАТУ В ОРГАНІЧНИХ РОЗЧИННИКАХ

За температурною залежністю розчинності метилового естеру 6-метил-2-оксо-4-арил-1,2,3,4-тетрагідропіримідин-5-карбонової кислоти в ізопропанолі, етилацетаті та бензолі розраховано ентальпію та ентропію його розчинення. З врахуванням ентальпії плавлення, визначеної за даними диференційно-термічного аналізу та перерахованої на 298К, розраховано ентальпії та ентропії змішування за 298 К. Показано вплив розчинника на розчинність та величини ентальпії і ентропії змішування за 298 К.

Ключові слова: ентальпія розчинення; ентальпія змішування; ентальпія плавлення; ентропія розчинення; ентропія змішування; ентропія плавлення; метиловий естер 6-метил-2-оксо-4-арил-1,2,3,4-тетрагідропіримідин-5-карбонової кислоти.

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THERMODYNAMIC PROPERTIES OF THE SOLUBILITY OF METHYL 6-METHYL-2-OXO-4-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE

From the temperature dependence of the solubility of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate in isopropanol, ethyl acetate and acetonitrile dissolution enthalpies and entropies were determined. Enthalpies and entropies of mixing at 298K were calculated using enthalpies of fusion determined by differential-thermal-analysis and adjusted to 298K. The influence of solvent on the solubility and magnitude of the enthalpy and entropy of mixing at 298K was shown.

Key words: dissolution; mixing; fusion; enthalpy; entropy; methyl 6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahidropirymidyn-5-carboxylate.

Problem setting and analysis of publications. Intensive development of the synthesis of heterocyclic compounds is caused by a wide range of their use in food, agriculture and pharmaceutical industries. In particular, their use in the pharmaceutical industry is caused by the wide spectrum of biological activity [1]. It is known [2] that in pharmaceutical chemistry one of the basic requirements is the use of pure substances at each stage of the synthesis. Typically, the main methods of substances cleaning are sublimation, distillation and recrystallization. In practice, recrystallization using the so-called "classic" solvents is common for the cleaning of solid substances is used mostly. Therefore, the study of solubility

and thermodynamic parameters accompanying interactions of solvent with solute is important to optimize the processes extraction and purification of organic compounds.

Aim of the work. To determine thermodynamic solubility characteristics of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahidropirymidyn-5-carboxylate experimentally, to establish the nature of it's interactions with acetonitrile, ethyl acetate and propan-2-ol.

Experimental results and discussion. Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahidropirymidyn-5-carboxylate (Fig. 1) which is the simplest representative of Bidzhenelli's dyhidropirymidynes and is characterized by a wide range of biological activity [3], solubility in acetonitrile, ethyl acetate and 2-propanol was chosen as object of current research.

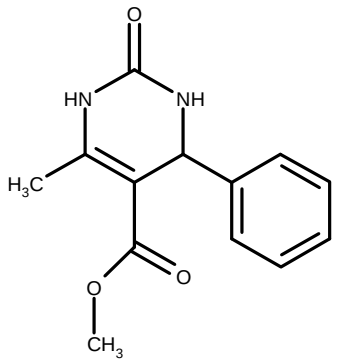

Fig. 1. The structural formula of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahidropirymidyn-5-carboxylate

Synthesis of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahidropirymidyn-5-carboxylate was conducted in the reaction flask with a capacity of 100 ml by mixing of 5.3 g (0.05 mol) of benzaldehyde, 3.0 g (0.05 mol) of urea, 8.70 g (0.075 mol) of ethyl methyl acetoacetic acid, 20 ml of ethanol and 4 drops of concentrated hydrochloric acid. The reaction mixture was heated for 3 hours, then cooled to 273K and left for crystallization. The formed precipitate (9.36 g) was filtered and recrystallized twice from ethanol. Output was 83 %. melting temperature *Tm* = 487K.

Identification of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahidropirymidyn-5-carboxylate was performed from the results of NMR spectroscopy. NMR spectra were recorded on a Varian 400 instrument (400 MHz), the solvent DMSO-d6. Chemical shifts (δ, ppm) are stated relatively to the signal of DMSO (2.50 ppm): 1H δ: 2.25 (s, 3H, CH3), 3.53 (s, 3H, CH3), 5.14 (s, 1H, CH), 7.20-7.35 (m, 5H, Ph), 7.75 (s, 1H, NH), 9.22 (s, 1H, NH).

The purity of the substance was determined by the chromatographic method with using Agilent 1100 HPLC, equipped with diode matrix and mass selective detector on the column Zorbax SB-C18, 4.6 mm × 15 mm, eluent A acetonitrile-water with 0,1 % TFA (95: 5) and is 100.0 %.

Large-tonnage organic solvents which differ in polarity were selected for solubility studies: acetonitrile, ethyl acetate and propan-2-ol. Before using solvents were purified by fractional distillation followed by their identification by refraction index (n_D^{20}) and boiling temperature (T_{boil}); content of main component (expressed as % wt.) was determined using gas-liquid chromatography. (Table 1).

Table 1

Physical and chemical properties solvent

Solvent	*M* g/mol	n_D^{20}		T_{boil}, K		Content of main component, %
		lit.	determ.	lit.	determ.	
Acetonitrile	41,053	1,3442 [4]	1,3444	81,6 [4]	81,4	99,9
Ethyl acetate	88,106	1,3724 [4]	1,3722	77,1 [4]	76,8	99,9
Propan-2-ol	60,096	1,3776 [4]	1,3776	82,2 [4]	81,9	99,9

Saturation of solution of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahidropirymidyn-5-carboxylate was carried out in a sealed glass vessel equipped with a teflon stirrer, thermometer and pipe for sampling in two stages. During the first phase substance was kept in a solvent at room temperature for two days without mixing. At the beginning the second phase mixing was turned on (rotation speed of the mixer - 60-70 rev/min) for 90 minutes at a temperature of experiment. The temperature was maintained within ±0,1 K. Experiments were conducted both in a mode of raising and lowering of the temperature to prove the establishment of equilibrium. The absence of hysteresis loop on the curve of the temperature dependence of the solubility confirms achievement of a state close to equilibrium.

Solutions were sampled by the series of 2-3 samples and transferred to cups weighted with precision ±0,0002 g. After weighing the cups were opened, dried to constant weight at 343K. the mass of dry ester residue was determined and its mole fraction in a saturated solution was calculated. Table 2 shows the mass of solvent (m1) and solute (m2), the solubility of the substance expressed in mole fractions (x2) and temperature of the experiments (T).

Table 2

The temperature dependence of the solubility of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate in organic solvents

T, К	m_1, г	m_2, г	$x_2 \cdot 10^3$	*T*, К	m_1, г	m_2, г	$x_2 \cdot 10^2$	*T*, К	m_1, г	m_2, г	$x_2 \cdot 10^2$
acetonitrile											
293,5	1,5360	0,0079	0,86	314,6	1,6864	0,0194	1,91	327,8	1,4746	0,0255	2,87
293,5	1,7045	0,0089	0,87	318,5	1,4160	0,0178	2,09	327,8	1,544	0,0264	2,84
299,2	1,5275	0,0097	1,06	318,5	1,6556	0,0203	0,04	327,8	1,7016	0,0285	2,78
299,2	1,5578	0,0099	1,06	318,5	1,7071	0,0210	2,05	328,0	1,3112	0,0222	2,81
299,2	1,8031	0,0116	1,08	319,5	1,5168	0,0203	2,23	328,0	1,6228	0,0289	2,96
304,0	1,6047	0,0117	1,21	319,5	1,5992	0,0211	2,20	331,2	1,3286	0,0283	3,54
304,0	1,6893	0,0122	1,21	319,5	1,6333	0,0224	2,28	331,2	1,4347	0,0304	3,53
309,0	1,5071	0,0131	1,45	323,1	1,4995	0,0226	2,51	331,2	1,4464	0,0298	3,42
309,0	1,7056	0,0147	1,44	323,1	1,5553	0,0230	2,46	336,5	1,3443	0,0349	4,31
314,6	1,4488	0,0165	1,89	323,1	1,6825	0,0249	2,47	336,5	1,5314	0,0393	4,26
314,6	1,4510	0,0167	1,92	323,5	1,3954	0,0206	2,46	336,5	1,6233	0,0421	4,31
314,6	1,5196	0,0171	1,87	323,5	1,4162	0,0212	2,49				
314,6	1,6668	0,0190	1,90	323,5	1,6030	0,0232	2,41				
ethyl acetate											
287,4	1,8880	0,0059	1,13	297,0	2,2603	0,0096	1,53	318,5	1,9247	0,0150	2,78
287,4	1,9373	0,0061	1,13	299,7	1,8957	0,0087	1,65	318,5	1,6604	0,0128	2,76
287,4	2,1058	0,0065	1,10	299,7	2,0251	0,0094	1,66	318,5	1,6084	0,0126	2,81
293,1	1,7869	0,0068	1,37	299,7	1,8796	0,0091	1,73	322,5	1,7528	0,0162	3,30
293,1	1,7935	0,0069	1,37	300,5	1,8458	0,0085	1,65	322,5	1,8757	0,0174	3,31
293,1	1,5755	0,0060	1,36	300,5	1,7961	0,0083	1,66	322,5	1,8084	0,0167	3,29
294,5	1,6400	0,0064	1,39	300,5	1,9838	0,0095	1,72	328,8	1,7557	0,0201	4,09
294,5	1,6019	0,0062	1,39	304,0	1,7614	0,0090	1,84	328,8	1,8986	0,0210	3,94
295,7	1,4007	0,0056	1,43	304,0	1,9394	0,0101	1,86	328,8	1,7600	0,0199	4,03
295,7	1,4763	0,0059	1,43	304,0	1,8286	0,0094	1,85	331,8	1,9000	0,0228	4,28
295,7	1,8191	0,0072	1,43	310,0	1,4350	0,0091	2,28	331,8	1,8428	0,0224	4,33
297,0	1,4321	0,0063	1,57	310,0	1,7691	0,0108	2,19	331,8	1,5117	0,0182	4,29
297,0	1,9290	0,0080	1,49	310,0	1,8278	0,0112	2,19				
propan-2-ol											
292,6	2,1700	0,0088	0,99	307,5	1,3341	0,0096	1,75	317,5	2,2567	0,0257	2,77
292,6	2,5383	0,0105	1,01	307,5	1,4760	0,0111	1,84	320,1	1,7614	0,0204	2,83
294,1	1,4629	0,0058	0,97	307,5	1,9124	0,0146	1,87	320,1	1,8890	0,0220	2,83
294,1	1,9529	0,0083	1,04	309,5	1,5166	0,0117	1,89	320,1	2,0295	0,0238	2,86
296,6	1,6948	0,0083	1,19	309,5	1,5506	0,0117	1,85	323,1	1,4550	0,0189	3,16
296,6	1,7320	0,0083	1,17	309,5	1,7660	0,0140	1,93	323,1	1,5817	0,0211	3,25
297,5	1,2247	0,0056	1,13	314,6	1,4373	0,0150	2,54	328,0	1,4300	0,0213	3,63
297,5	1,3242	0,0061	1,12	314,6	1,5369	0,0155	2,46	328,0	1,4524	0,0217	3,64
300,2	1,6773	0,0097	1,41	314,6	1,5803	0,0160	2,46	328,0	1,6942	0,0253	3,63
300,2	1,8344	0,0104	1,39	315,5	1,2674	0,0124	2,38	332,0	1,0485	0,0187	4,34
303,0	1,3242	0,0079	1,45	315,5	1,4518	0,0144	2,41	332,0	1,3238	0,0232	4,27
303,0	1,5829	0,0093	1,43	315,5	1,6808	0,0166	2,41	332,0	1,4282	0,0250	4,27
303,0	1,7672	0,0104	1,43	316,1	3,3074	0,0363	2,67	332,4	1,2404	0,0236	4,62
304,6	1,5102	0,0099	1,60	316,1	3,3883	0,0373	2,68	332,4	1,4066	0,0275	4,76
304,6	1,6059	0,0111	1,68	317,5	1,9170	0,0215	2,73	332,4	1,5183	0,0292	4,67
304,6	1,6338	0,0109	1,63	317,5	2,2547	0,0254	2,75				

Values obtained from the temperature dependences were approximated by a linear equation: $lnx_2 = -\Delta_{sol}H/RT + \Delta_{sol}S/R$, where: $\Delta_{sol}H$ - dissolution enthalpy of solid compounds studied; $\Delta_{sol}S$ - entropy change during dissolution of solid compounds studied and are shown in Table 3. Error for all values is calculated with significance level of 0.95 hereinafter.

Table 3

Thermodynamic solubility parameters of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate in organic solvents at 298K.

№	Solvent	$x_2 \cdot 10^3$	$\Delta_{sol}H^o$	$\Delta_{mix}H^o$	$\Delta_{sol}S^o$	$\Delta_{mix}S^o$
			kJ/mol		J/mol K	
1	Acetonitrile	0,990±0,097	30,1±1,1	7,1±2,2	43,4±3,3	1,3±4,9
2	Ethyl acetate	1,573±0,043	24,05±0,53	1,0±2,0	27,0±1,7	-15,1±4,3
3	Propan-2-ol	1,218±0,058	31,14±0,86	8,1±2,1	48,7±2,7	6,6±4,7

Thermodynamic parameters of solubility $\Delta_{sol}H$ and $\Delta_{sol}S$, are describing the formation of a solution and a phase transition of crystalline substances to the liquid phase in solution. Therefore, to determine the change in enthalpy ($\Delta_{mix}H$) and entropy (Δ_{mix}S), describing the interaction of components in the solution, the values of melting enthalpies ($\Delta_{fus}H$) and entropies ($\Delta_{fus}S$) of substances at 298K are required (equations 1, 2).

$$\Delta_{sol}H = \Delta_{fus}H + \Delta_{mix}H \quad (1)$$

$$\Delta_{sol}S = \Delta_{fus}S + \Delta_{mix}S \quad (2)$$

Melting enthalpies of substances were determined by differential thermal analysis (DTA) data obtained using derivatograph Q-1500 D of Paulik - Paulik – Erdey system. Samples were analyzed dynamically with the heating rate of 3 K/min in air atmosphere. The heats of melting of the substances were calculated using the equation (3) that takes into account the amount of heat absorbed by the sample during the evaporation process:

$$K \cdot S = Q_{fus} + Q_{vap} = m_o \cdot \Delta H_{fus} + \Delta m_{vap} \cdot \Delta H_{vap} \quad (3)$$

where Q_{fus} and Q_{vap} - the amounts of heat (J), which is absorbed by the melting or evaporation of the substances, respectively; m_o – sample mass (g) which corresponds to the temperature of the beginning of its melting T_{fus}; Δm_{vap} – sample weight loss (vapour mass, g) for the period taken into account to determine the peak area S (K·s) under the DTA curve; K = coefficient of heat transfer $K = 0{,}03668 - 1{,}13\ 10^{-4}T + 2{,}721\ 10^{-7}T^2$; $S^2 = 5{,}96\ 10^{-8}$[5] (J / K·s), $D_{fus}H$ and $D_{vap}H$ - specific enthalpies of melting and evaporation of the substance (J/g).

The results of fusion enthalpies of the compounds determination at the melting temperature obtained by DTA, are shown in table 4.

The entropy change at the melting point ($D_{fus}S_{Tfus}$) is calculated by equation 4 and is shown in table 4.

$$\Delta_{fus}S_{T_{fus}} = \Delta_{fus}H_{T_{fus}} \Big/ T_{fus} \quad (4)$$

Table 4

Enthalpy of fusion of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

m_o, g	Dm_{vap}, g	S, K·s	q_{vap}, J	$D_{fus}H_{Tfus}$, kJ/mol	$D_{fus}H_{298}$, kJ/mol	$D_{fus}S_{Tfus}$, J/mol K	$D_{fus}S_{298}$, J/mol K
T_{fus}= 487,7±1.0K; K = 0,04643 J/K·s							
0,1982	0,0013	566,3	0,5361	32,0		65,6	
0,2000	0,0014	583,6	0,6039	32,6		66,9	
Average value:				32,3 ± 1.8	23,0 ± 1.9	66,3 ± 3,7	42,1 ± 3,9

Experimental values were obtained at different temperatures, so the value $\Delta_{sol}H^o$ and $\Delta_{sol}S^o$ calculated in temperature ranges (Table. 2) $D_{fus}H^o$ value determined by the melting temperature of substances (tab. 4) so in order to generalize the results and the possibility of calculating the thermodynamic parameters

($\Delta_{mix}H^o$; $\Delta_{mix}S^o$) at 298K was necessary in terms $D_{fus}H^o$; $D_{fus}S^o$ to 298 K, this equation are used in [6]. The results of calculation are shown in Table 4.

$\Delta_{mix}H$ and $\Delta_{mix}S$ values calculated by equations 1 and 2 (Table. 3) are determined by the difference of energy of destruction of intermolecular bonds in the molecules of source components and the energy of formation of new bonds in solutions. Positive values of mixing enthalpies for all investigated systems indicate that the destruction of intermolecular bonds in individual substances require more energy than is released during the formation of new intermolecular bonds in the solutions.

Conclusion: As a result of investigations thermodynamic properties of solubility of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahidropirymidyn-5-carboxylate in organic solvents of different polarity were determined. The experimental and calculated data can be used to predict the reaction behavior of the substance in the solution, and to optimize purification and separation processes.

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