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Thermodynamic properties of methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in organic solutions

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The enthalpy and the entropy of dissolution of methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in 2-propanol, ethyl acetate, acetonitrile, 2-propanone and benzene were determined from the temperature dependence of its solubility.The enthalpies and the entropies of mixing at 298 K were calculated taking into account the enthalpy of melting of the compound, determined via differential thermal analysis.The influence of the solvent on the solubility of the compound and on the corresponding enthalpy and entropy of mixing values was shown.

Introduction

Intensive development of the synthesis of heterocyclic compounds is due to their usein food, agriculture and pharmaceutical industries.

In particular, their usein the pharmaceutical industry is associated with a wide range of biological activity [1,2].

It is known that the main basic requirement in pharmaceutical chemistry is the use of super pure substances at each stage of the synthesis [3]. Usually, the main methods of purifying of the substances are sublimation, distillation and recrystallization. In practice, recrystallization using so-called "classical" solvents is mostly applied for the purification of solids.

Therefore, the study of the solubility and thermodynamic parameters that accompany the process of solvent interaction with the dissolved substance is important for the optimization of the processes of extraction and purification of organic compounds[4].

Experimental part

Methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Fig. 1) was selected for the study. This is the representative of the BiginelliDihydropyrimidines, which has a wide range of biological activities[5-7].

The synthesis of methyl ester of methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate was performed according to the following method:0.05 mol of aromatic aldehyde,0.05 mol of urea, 0.075 mol of methyl acetate of acetone, 20 ml of ethanol and 4 drops of concentrated hydrochloric acid were placed in the reaction flask. The mixture was boiled for 3 hours, then cooled to 273 K and leaved for crystallization.The resulting precipitate was filtered and recrystallized from ethanol twice.The characteristics of the synthesized substance coincided with the values given in [8,9].

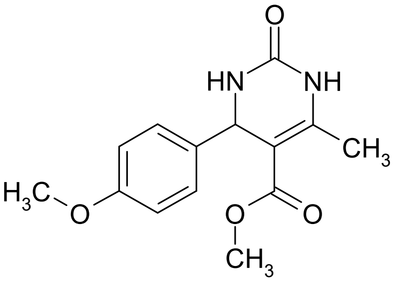

Figure 1. The structural formula of methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Purity of the substancewas 99% of its weight. It was determined chromatographically using the Agilent 1100 HPLC with a diode matrix and mass selective detector on a Zorbax SB-C18 (4.6 mm × 15 mm) column, employing eluent A acetonitrile–water with 0.1% TFA (95:5).

The range of the widely used organic solvents with different polarity was selected for solubility study, namely acetonitrile (I),ethylacetate (II), 2-propanol (III), 2-propanone (IV) and benzene (V).

Before using the solvents were purified by fractional distillation followed by their identification according to the refractive index (n_D^{20}) and the boiling temperature (T_b) (Table 1) [10]; the content of the main component, which was within 99 % by weight for the used solventswas determined by the gas-liquid chromatography using the "LHM-8D" chromatograph with a thermal conductivity detector. The columns of the chromatograph with a length of 2 m and diameter of 0.4 cm were filled with the Chromator N-AW solid phase with particle size of 0.20–0.25 mm, containing 10% polyethylene glycol adipate and 1% orthophosphoric acid. The carrier gas was helium. The temperatures of the columns and vaporizer were 423K and 493K, respectively. The current of the Katharometer Bridge was 120 mA.

Table 1. Physico-chemical characteristics of solvents

Solution	n_D^{20}		T_b, °C	
	lit. [5]	det.	lit. [5]	det.
I	1.3442	1.3444	81.6	81.4
II	1.3724	1.3722	77.1	76.8
III	1.3776	1.3776	82.2	81.9
IV	1.3591	1.3592	56.2	55.9
V	1.3724	1.3723	77.1	76.9

The saturation of solutions was carried out in a sealed glass container equipped with a teflon stirrer, a thermometer and a sampling pipe. The temperature of the water in the thermostat was maintained with an accuracy of ± 0.1 K.The speed of the stirrer was 30–40 rpm. To confirm the achievement of equilibrium, the experiments were conducted both in the mode of temperature increase and decrease.

The absence of a hysteresis loop on the curve of the temperature dependence of solubility confirms the achievement of a state close to equilibrium.

Samples of solutions were selected in series of 2–3 specimens and transferred to the pre-weighed (with a precision of ± 0.0002 g) boxes. After weighing, the boxes were opened, and dried to a constant mass in the thermo cabinets at a temperature of 343K. The mass of the dry residue of the ester was determined and its mole fraction in the saturated solution was calculated.

The masses of the solvent (m_1), the masses of the dissolved substance (m_2),the solubility of the substance (in mole fractions, x_2), and the temperature (T) at which the dissolution was carried out are presented in Table 2. The equation of the temperature dependence of solubility can be presented as follows:

$$\ln x_2 = A - B/T \quad (1)$$

The coefficients A and B of the equation (1) and their sample variances calculated using the least squares method are also presented in the same table.

Results and discussion

Table 2. Temperature dependence of the solubility of methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in organic solvents

T,K	m_1, g	m_2, g	$x_2 \cdot 10^3$
Acetonitrile			
295.2	1.5723	0.0114	1.07
295.2	1.8764	0.0140	1.10
295.2	1.9832	0.0164	1.22
300.2	1.6617	0.0154	1.38
300.2	1.6336	0.0153	1.39
300.2	1.7632	0.0162	1.36
303.7	1.6926	0.0191	1.67
303.7	1.6359	0.0181	1.64
303.7	1.7609	0.0195	1.64
309.5	1.5291	0.0234	2.26
309.5	1.7101	0.0261	2.26
309.5	1.6687	0.0252	2.24
314.7	1.5698	0.0280	2.64
314.7	1.6658	0.0304	2.70
314.7	1.6287	0.0294	2.67
320.2	1.5120	0.0335	3.28
320.2	1.5217	0.0338	3.29
320.2	1.5775	0.0335	3.14
323.7	1.4939	0.0365	3.62
323.7	1.6218	0.0382	3.49
323.7	1.5573	0.0364	3.46
328.7	1.6159	0.0475	4.35
328.7	1.5963	0.0451	4.18
328.7	1.3892	0.0383	4.07
334.2	1.6183	0.0572	5.22
334.2	1.6834	0.0606	5.32
334.2	1.6744	0.0598	5.27

337.2	1.5626	0.0614	5.80
337.2	1.6785	0.0683	6.01
337.2	1.6783	0.0656	5.77
342.2	1.7857	0.0860	7.10
342.2	1.5729	0.0756	7.09
342.2	1.5106	0.0728	7.11
ln x_2= (6.37±0.30)–(3878±94)*1/T			
Ethylacetate			
302.6	3.4529	0.0236	2.17
302.6	3.8074	0.0267	2.23
303.5	1.7220	0.0119	2.19
303.5	1.7424	0.0122	2.22
303.5	1.7393	0.0123	2.25
308.5	3.3687	0.0265	2.50
308.5	3.1185	0.0244	2.48
308.5	3.1907	0.0248	2.47
313.5	3.2680	0.0293	2.85
313.5	3.5851	0.0316	2.80
313.5	3.3439	0.0302	2.87
314.5	2.0381	0.0194	3.02
314.5	1.8883	0.0176	2.96
316.5	1.8105	0.0173	3.04
316.5	1.8676	0.0187	3.18
316.5	1.9944	0.0201	3.20
318.0	2.0773	0.0211	3.23
318.0	2.2959	0.0240	3.32
318.0	2.5392	0.0258	3.23
322.8	1.7371	0.0210	3.84
322.8	1.7721	0.0217	3.89
322.8	1.7894	0.0219	3.89
323.1	3.2297	0.0361	3.55
323.1	3.3728	0.0381	3.58
323.1	3.5401	0.0400	3.59
327.0	1.7094	0.0217	4.03
327.0	1.8875	0.0241	4.05
328.0	3.4119	0.0451	4.19
328.0	3.2501	0.0427	4.17
328.0	3.2969	0.0442	4.25
330.5	1.5642	0.0223	4.53
330.5	1.8414	0.0259	4.47
330.5	1.7962	0.0250	4.42
332.5	3.1418	0.0492	4.96
332.5	3.1601	0.0497	4.99
332.5	3.9031	0.0608	4.94
337.5	3.1071	0.0561	5.72
337.5	3.1251	0.0566	5.74
337.5	3.1293	0.0564	5.72
lnx_2= (3.00±0.33)-(2774±105)*1/T			
2-propanol			
288.1	4.8235	0.0101	0.45
288.1	3.2550	0.0064	0.43
288.1	3.6815	0.0069	0.41
293.6	2.4539	0.0067	0.59
293.6	2.2948	0.0065	0.62
293.6	2.3102	0.0064	0.60
298.3	2.2597	0.0080	0.77
298.3	2.2333	0.0086	0.84
298.3	2.3634	0.0082	0.75
300.5	2.3768	0.0095	0.86
300.5	2.3772	0.0096	0.87
300.5	2.4225	0.0096	0.86
304.5	2.5489	0.0128	1.09
304.5	2.5386	0.0114	0.98
304.5	2.5273	0.0123	1.06

305.9	2.3978	0.0124	1.12
305.9	2.3844	0.0119	1.08
305.9	2.5098	0.0125	1.08
308.6	2.3675	0.0134	1.22
308.6	2.4467	0.0145	1.29
308.6	2.4759	0.0137	1.20
310.0	2.3843	0.0148	1.34
310.0	2.3666	0.0143	1.31
315.6	2.4651	0.0204	1.80
315.6	2.4283	0.0196	1.75
315.6	2.4715	0.0207	1.81
316.5	2.3308	0.0193	1.79
316.5	2.4282	0.0187	1.67
316.5	2.4724	0.0211	1.85
319.2	2.3468	0.0232	2.15
319.2	2.3899	0.0248	2.25
319.2	2.5210	0.0218	1.87
324.0	2.4705	0.0287	2.52
324.0	2.4238	0.0265	2.37
324.0	2.4765	0.0260	2.27
326.5	2.3044	0.0292	2.74
326.5	2.3629	0.0313	2.87
326.5	2.3082	0.0294	2.76
$\ln x_2 = (7.81 \pm 0.34) - (4473 \pm 106) * 1/T$			
2-propanone			
292.0	2.5863	0.0320	2.59
292.0	2.8693	0.0356	2.60
292.0	3.0272	0.0367	2.54
294.5	1.7105	0.0233	2.85
294.5	1.7887	0.0250	2.93
294.5	2.0628	0.0288	2.93
300.1	2.1850	0.0361	3.46
300.1	2.2032	0.0368	3.50
300.1	2.5885	0.0433	3.50
302.9	1.2480	0.0229	3.84
302.9	1.6770	0.0308	3.84
302.9	2.6811	0.0491	3.84
303.2	2.1286	0.0390	3.83
303.2	2.3435	0.0420	3.75
303.2	2.3641	0.0432	3.83
307.5	1.9363	0.0392	4.23
307.5	1.5232	0.0307	4.22
307.5	2.4256	0.0491	4.23
308.1	2.1184	0.0456	4.50
308.1	2.2592	0.0474	4.39
308.1	2.3153	0.0494	4.46
313.5	1.5207	0.0376	5.17
313.5	1.4366	0.0348	5.06
313.5	1.9630	0.0483	5.14
313.7	2.3768	0.0591	5.20
313.7	2.4292	0.0608	5.23
313.7	2.2969	0.0580	5.28
317.2	2.4467	0.0651	5.56
317.2	2.6655	0.0712	5.58
317.2	2.8333	0.0757	5.58
319.4	2.3614	0.0690	6.10
319.4	2.2488	0.0648	6.02
319.4	2.3722	0.0681	5.99
321.9	2.2318	0.0691	6.47
321.9	2.0859	0.0669	6.69
321.9	1.9420	0.0616	6.62
323.0	1.8674	0.0605	6.76
323.0	2.4881	0.0837	7.02
323.0	3.0350	0.1026	7.05

324.5	2.5791	0.0913	7.38
324.5	2.4054	0.0846	7.34
324.5	2.5456	0.0897	7.35
$\ln x_2 = (4.00\pm0.18)-(2904\pm)*1/T$			
Benzene			
289.6	2.4786	0.0008	0.091
289.6	2.6762	0.0009	0.095
289.6	2.8471	0.0010	0.099
296.5	2.7515	0.0014	0.14
296.5	2.8234	0.0013	0.13
296.5	2.7963	0.0013	0.13
297.5	2.6792	0.0013	0.14
297.5	2.8786	0.0015	0.15
297.5	2.7224	0.0014	0.15
302.0	2.7644	0.0017	0.17
302.0	2.7498	0.0016	0.16
302.0	2.7571	0.0017	0.17
303.5	2.4365	0.0017	0.20
303.5	2.7143	0.0019	0.20
303.5	2.7748	0.0020	0.20
308.0	2.7373	0.0023	0.24
308.0	2.7681	0.0025	0.25
308.0	2.6976	0.0024	0.25
308.4	2.7423	0.0024	0.24
308.4	2.8253	0.0025	0.25
308.4	2.8591	0.0024	0.24
313.2	2.6504	0.0030	0.32
313.2	2.8526	0.0032	0.32
313.2	1.9127	0.0022	0.33
318.3	2.8097	0.0037	0.37
318.3	2.7499	0.0039	0.40
318.3	2.7667	0.0039	0.40
320.6	2.5814	0.0040	0.43
320.6	2.7403	0.0042	0.43
320.6	2.8416	0.0043	0.43
323.5	2.7511	0.0049	0.50
323.5	2.8875	0.0052	0.51
323.5	2.6973	0.0047	0.49
$\ln x_2 = (6.63\pm0.32)-(4606\pm98)*1/T$			

Standard enthalpy ($\Delta_{sol}H^o$) and entropy ($\Delta_{sol}S^o$) changes of dissolution were calculated using the following equations:

$$\Delta_{sol}H^o = R\cdot B \qquad (2a)$$

$$\text{and}\Delta_{sol}S^o = R\cdot A. \qquad (2b)$$

were R is universal gas constant; A and B – constants of the equation (1). The values of $\Delta_{sol}H^o$ and $\Delta_{sol}S^o$are presented in Table 3 under the numbers. For acetonitrile – I. ethylacetate – II. 2-propanol – III. 2-propanon – IV and benzene – V. correspondingly.

Table 3. Thermodynamic parameters of solubility of methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1.2.3.4-tetrahydropyrimidine-5-carboxylate in organic solvents at 298K

Solution	$\Delta_{sol}H^o_{298}$	$\Delta_{mix}H^o_{298}$	$\Delta_{sol}S^o_{298}$	$\Delta_{mix}S^o_{298}$
	$kJ\cdot mol^{-1}$		$J\cdot mol^{-1}\cdot K^{-1}$	
I	32.24±0.78	3.3±1.0	53.0±2.5	–2.3±2.9
II	23.07±0.87	–5.8±1.1	24.9±2.7	-30.4±3.1
III	37.19±0.88	8.3±1.1	64.9±2.8	9.6±3.1
IV	24.14±0.45	–4.8±1.0	33.3±1.5	-22.0±2.1
V	38.29±0.81	9.4±1.1	55.1±2.7	–0.2±3.1

The calculated thermodynamic parameters of dissolution $\Delta_{sol}H^o$and$\Delta_{sol}S^o$characterize both the process of formation of a solution from liquid components (mixing, which is characterized by the enthalpy$\Delta_{mix}H^o$ and entropy $\Delta_{mix}S^o$ of mixing)and the phase transition of the crystalline substance to the liquid phase of the solution (melting, which is characterized by the enthalpy $\Delta_{fus}H^o$ and entropy $\Delta_{fus}S^o$ of fusion)that is:

$$\Delta_{sol}H^o = \Delta_{mix}H^o + \Delta_{fus}H^o$$

$$\Delta_{sol}S^o = \Delta_{mix}S^o + \Delta_{fus}S^o.$$

The enthalpy of fusion of ester at its temperature of fusion ($\Delta_{fus}H^o_{473.5}$=39.90±0.65 kJ·mol^{-1}) was determined via differential thermal analysis using Q-1500 D Paulik-Paulik-Erdeyderivatograph as was described in [12].

The change in entropy at a temperature of fusion$\Delta_{fus}S^o_{473.5}$=84.3±1.4 J·mol^{-1}·K^{-1}).was calculated by equation (3):

$$\Delta_{fus}S_{T_{fus}} = {\Delta_{fus}H_{T_{fus}}} \Big/ {T_{fus}} \qquad (3)$$

The values obtained during experimental study belong to different temperatures:the values of$\Delta_{sol}H^o$ and $\Delta_{sol}S^o$were calculated in the temperature rangegiven in Table 2.the value of$\Delta_{fus}H^o$was defined at the temperatureoffusion of the substance.Therefore, togeneralize the obtained results and to calculate $\Delta_{mix}H^o$ and $\Delta_{mix}S^o$ at a temperature of 298 K the values of $\Delta_{fus}H^o$ and $\Delta_{fus}S^o$ were converted to a temperature of 298 K. using the following approximate equations taken from Ref.[11]:

$$\Delta_{fus}H_T = \Delta_{fus}H_{T_{fus}} + \Delta_{fus}Cp(T - T_{fus}) = = \Delta_{fus}H_{T_{fus}}\left[1 + \frac{T - T_{fus}}{1,35 \cdot T_{fus}}\right] \qquad (4)$$

$$\Delta_{fus}S_T = \Delta_{fus}S_{T_{fus}} + \Delta_{fus}Cp \ln\frac{T}{T_{fus}} = = \Delta_{fus}S_{T_{fus}}\left[1 + \frac{1}{1,35}\ln\frac{T}{T_{fus}}\right] \qquad (5)$$

$$\Delta_{fus}S_{T_{fus}} \Big/ \Delta_{fus}Cp_{T_{fus}} = \Delta_{fus}H_{T_{fus}} \Big/ T_{fus} \cdot \Delta_{fus}Cp_{T_{fus}} = =1,35 \pm 0,11 \qquad (6)$$

Where *Cp* is heat capacity of a substance.

We have to use these approximate equations because of the absence of experimental data on heat capacity of the ester under consideration.

The resulting values for the ester are: $\Delta_{fus}H^o_{298}$ = 28.90 ± 0.69kJ·mol^{-1}; $\Delta_{fus}S^o_{298}$ = 55.3 ± 1.5J·mol^{-1}·K^{-1}.

The value and the signof$\Delta_{mix}H^o$and$\Delta_{mix}S^o$.calculated on the basis of$\Delta_{fus}H^o_{298}$and$\Delta_{fus}S^o_{298}$.are determined by the difference in the energy of breaking of the intermolecular bonds in the individualsubstances and energy offormation of new bonds between the solute and the solvent. The positive values of the enthalpy of mixing of the investigated systems in the indicated range of concentrations and temperatures show that the energy of breaking of intermolecular bonds in the individual substances prevailsover the energy released as a result of the formation of new intermolecular bonds in solution.in contrast to the negative values.

Conclusions

The thermodynamic parameters of solubility of methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1.2.3.4-tetrahydropyrimidine-5-carboxylatein organic solvents of different polarity were determined. The obtained experimental and calculated data can be used to predict the reaction behavior of the substance in solution.as well as to optimize the processes of its purification and separation.

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