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SOLUBILITY STUDY OF 3-(1-(4-METHYLPHENYL)-5-PHENYLPYRROL-2-YL)PROPANOIC ACID IN ORGANIC SOLVENTS

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Abstract

In this study solubility temperature dependence of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid in the temperature range of 271.0–318.2 K using the gravimetric method at atmospheric pressure was experimentally determined for the first time in eight organic solvents, namely methyl acetate, ethyl acetate, acetone, acetonitrile, n-propanol, isopropanol, n-butanol, isobutanol. The primary results of experimental studies of the solubility temperature dependence for each of the studied solution systems were used to calculate the standard molar enthalpy and entropy of dissolution according to the Van't-Hoff equation. The enthalpy and entropy of fusion at the melting point were determined using the results of differential thermal analysis. The equations for the recalculation of the enthalpy and entropy of fusion to a temperature of 298.15 K are presented. Using the calculated values of enthalpy and entropy of fusion to 298.15 K, the thermodynamic parameters of the process of mixing the studied acid with organic solvents were calculated. The nature of intermolecular interactions between the solvent and the dissolved substance was analysed using thermodynamic parameters of mixing. The present study contains fundamental thermodynamic values that are of practical importance for the optimisation of processes of synthesis, processing and purification of the investigated N-substituted derivative of 3-(5-phenylpyrrol-2-yl)propanoic acid.

Keywords: solubility; enthalpy of dissolution; enthalpy of fusion; enthalpy of mixing; pyrrole derivatives; N-substituted 3-(5-phenylpyrrol-2-yl)propanoic acids.

ДОСЛІДЖЕННЯ РОЗЧИННОСТІ 3-(1-(4-МЕТИЛФЕНІЛ)-5-ФЕНІЛПІРОЛ-2-ІЛ)ПРОПАНОВОЇ КИСЛОТИ В ОРГАНІЧНИХ РОЗЧИННИКАХ

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Анотація

У роботі вперше проведене експериментальне дослідження температурної залежності розчинності 3-(1-(4-метилфеніл)-5-фенілпірол-2-іл)пропанової кислоти в інтервалі температур 271.0–318.2 К із використанням гравіметричного методу за атмосферного тиску в восьми органічних розчинниках, а саме: метилацетат; етилацетат; ацетон; ацетонітрил; н-пропанол; ізопропанол; н-бутанол; ізобутанол. Отримані первинні результати експериментальних досліджень температурної залежності розчинності для кожної з досліджуваних систем розчинів були використані для розрахунку стандартних молярних ентальпій та ентропій розчинення за рівнянням Вант-Гоффа. Ентальпію та ентропію плавлення за температури плавлення визначали з використанням результатів диференційно-термічного аналізу. Представлено рівняння перерахунку ентальпії та ентропії плавлення до температури 298.15 К. З використанням перерахованих величин ентальпії та ентропії плавлення до 298.15 К розраховано термодинамічні параметри процесу змішування досліджуваної кислоти з органічними розчинниками. За термодинамічними параметрами змішування проаналізований характер міжмолекулярних взаємодій між розчинником і розчиненою речовиною. Дане дослідження містить фундаментальні термодинамічні величини, що мають практичне значення для оптимізації процесів синтезу, переробки та очищення досліджуваного N-заміщеного похідного 3-(5-фенілпірол-2-іл)пропанової кислоти.

Ключові слова: розчинність; ентальпія розчинення; ентальпія плавлення; ентальпія змішування; похідні піролу; N-заміщені 3-(5-фенілпірол-2-іл)пропанові кислоти.

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Introduction

One of the priority areas of the chemical and pharmaceutical industries is the synthesis of organic substances with a heterocyclic fragment [1]. Particular attention is given to substances that contain nitrogen heteroatom in their structure. Thus, pyrrole and its polysubstituted derivatives are involved in biological processes and are quite common in nature [2; 3]. Compounds of this class are mostly found in the structures of cytochrome, hemoglobin, chlorophyll, vitamin B_{12}, etc. [4; 5]. Compounds with a pyrrole fragment possess biological activity and exhibit antitumor, antifungal, antiplasmodial, antioxidant, and anti-inflammatory effects [6–10]. A significant part of drugs contains at least one nitrogen-containing heterocycle [11], which confirms the prospect of their use as main or intermediate components in the creation of new drugs with predetermined pharmacophore properties. Such a variety of biological activities is explained by the possibility of combining substituents in the cycle through the interaction of pyrrole with electrophiles due to the presence of an aromatic structure in the pyrrole molecule [12]. Compounds of this class are also widely used in the chemical industry in the production of corrosion inhibitors, dyes, catalysts, plant protection products, and conductive materials for accumulators [13–16]. This, in turn, encourages the scientific community to look for new ways of synthesizing substances with a pyrrole fragment.

The vast majority of processes in the chemical and pharmaceutical industries involve solvents. Solvents are mostly used as reaction media in the synthesis of substances, as well as in their purification and recycling processes. Higher purity requirements are imposed on the components of drugs, as particular purity will directly affect the final quality of drugs. One of the most common purification methods is recrystallization from solution, the efficiency of which is directly influenced by the solubility temperature dependence of the compound [17; 18]. Also, thermodynamic parameters of solvent-solute interaction are necessary for technological calculations of energy balances of synthesis processes.

Thus, in [19] the biological activity of compounds with aryl-pyrrole fragments was analysed, which revealed a wide range of potential activity. In particular, 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid is predicted to have an effect on hypertension, multiple sclerosis, systemic lupus erythematosus, allergic rhinitis, colitis. However, the complete absence of their thermodynamic parameters motivated us to determine them experimentally.

Therefore, the aim of this work is to experimentally determine the solubility temperature dependence and calculate the thermodynamic parameters of the dissolution process of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid in organic solvents.

This work is a continuation of the experimental studies of the thermodynamic properties of solutions carried out at Lviv Polytechnic National University [20–23].

Experimental

The synthesis of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid was carried out according to the following reaction scheme (Fig. 1):

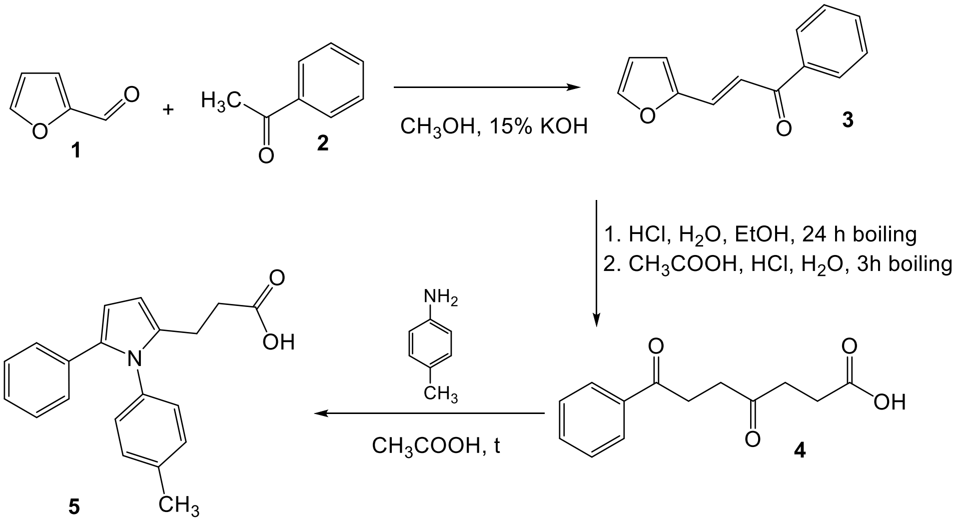

Fig. 1. Synthesis of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid

Furfurylidene acetophenone ***(3).*** To the reaction mixture of furfural **1** (80 g), acetophenone **2** (100 g) and methanol (200 mL) under vigorous stirring was added 0.05 mol of 15 % KOH solution. The temperature of the reaction mixture was maintained in the range of 20–25°C. After stirring for 3 hours, the reaction mixture was neutralized with acetic acid, diluted with water (400 mL) extracted with dichloromethane, washed with water. The organic layer was separated and dried with sodium sulfate. After distillation of the solvent, the residue was distilled in vacuum to obtain furfurylidene acetophenone (**3**). Yield 111.7 g (68 %). B.p. 150 °C/2 mm Hg.

4,7-Dioxo-7-phenylheptanoic acid ***(4).*** A mixture of furfurylidene acetophenone **3** (0.2 mol), ethanol (300 mL), conc. HCl (90 mL) and water (15 mL) were refluxed for 24 hours. The alcohol was distilled off and a black viscous mass was obtained, to which 200 mL of conc. HCl, 200 mL of glacial acetic acid, 400 mL of water was added and heated under reflux for the next 3 hours. After cooling, the formed light yellow crystalline precipitate of 4,7-dioxo-7-phenylheptanoic acid (**4**) was decanted from the residual resin, filtered, washed three times with water and recrystallized from ethanol. Yield 19.2 g (41 %). M.p. 110–112°C.

3-(1-(4-Methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid ***(5).*** A mixture of 4,7-dioxo-7-phenylheptanoic acid **4** (5.85 g, 0.025 mol), 4-toluidine (2.67 g, 0.025 mol) and glacial acetic acid (50 mL) was heated under reflux for 6 hours. After cooling, the reaction mixture was transferred to a flask with 100 mL of cold water and stirred. After 20 min, the formed acid precipitate (**5**) was filtered off, washed with water and recrystallized from a mixture of ethanol/dimethylformamide solvents. Yield 5.6 g (73 %), M.p. 154.8°C.

To study the solubility and enthalpies of phase transitions, a sample after three times recrystallization from an ethanol /dimethylformamide mixture was used.

The structure of compound (**5**) was confirmed by NMR and IR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 170 Avance 500 spectrometer (500 and 126 MHz, respectively) in DMSO-d_6 solutions. The IR spectra was obtained on a Shimadzu IRSpirit-T instrument. Mass spectral analyses were performed using an Agilent 1100 series LC/MSD with API-ES/APCI mode (200 eV) instrument.

3-(1-(4-Methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid. IR (ATR, cm^{-1}): ν 3025, 2902, 2638, 1686, 1602, 1553, 1498, 1438, 1410, 1345, 1314, 1272, 1235, 1212, 1174, 1108, 1052, 1024, 973, 950, 934, 920, 817, 794, 659, 530, 503, 470. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 12.13 (s, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.12 (t, J = 7.4 Hz, 2H), 7.05–7.01 (m, 3H), 6.98 (d, 7.6 Hz, 2H), 6.28 (d, J = 3.6 Hz, 1H), 6.02 (d, J = 3.6 Hz, 1H), 2.57 (t, J = 7.6 Hz, 2H), 2.40 (t, J = 7.6 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 174.0, 137.6, 136.4, 135.1, 133.8, 133.4, 130.1, 128.6, 128.4, 127.5, 126.1, 109.0, 106.6, 33.1, 22.6, 21.1. MS (m/z): 306 (M^{+}+1).

The degree of purity of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid is indirectly confirmed by the constant value of the melting point and the enthalpy of fusion and vaporization.

To study the solubility temperature dependence of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid, a number of “classical” organic solvents with a low boiling point and different polarity produced by Merck were chosen: methyl acetate (CAS 79-20-9, EC Number 201-185-2), ethyl acetate (CAS 141-78-6, EC Number 205-500-4), acetone (CAS 67-64-1, EC Number 200-662-2), acetonitrile (CAS 75-05-8, EC Number 200-835-2), n-propanol (CAS 71-23-8, EC Number 200-746-9), isopropanol (CAS 67-63-0, EC Number 200-661-7), n-butanol (CAS 71-36-3, EC Number 200-751-6) and isobutanol (CAS 78-83-1, EC Number 201-148-0).

The temperature dependence of the solubility was determined by the gravimetric method in a three-necked flask equipped with a stirrer, thermometer and sampling pipe. The dissolution temperature was maintained using a water thermostat with an accuracy of ±0.1 K. The stirrer speed was 40–50 rpm. The saturation of the solutions, after establishing the set temperature, was carried out for 120 min with stirring followed by 60 min of keeping without stirring.

Solution samples (1.4–2.0) g were taken in series of three samples, transferred to pre-weighed glass vials, which were hermetically sealed and re-weighed. The solvent was removed to a constant mass of dry residue in the thermostat at a temperature of 353–373 K. The weighing of the glass vials to determine the mass of the solution and dry residue was carried out on an analytical balance VLR–200 (accuracy ±0.0002 g). To confirm the establishment of equilibrium, the experiments were carried out in both temperature increasing and decreasing modes. The absence of a hysteresis loop on the solubility temperature dependence curve confirms the achievement of a state close to equilibrium.

The thermodynamic parameters of the melting process of the studied acid were determined on a derivatograph Q–1500 D of the Paulik-Paulik-Erdey system in a dynamic mode at a heating rate of 5 K/min in an air atmosphere [16].

The calculation of the enthalpy of fusion ($\Delta_{fus}H^o$) was performed according to (Eq. 1), taking into account the loss of part of the heat due to the vaporization of the sample:

$$K \cdot S = Q_{fus} + Q_{vap} = m_0 \cdot \Delta_{fus}H^o + \\ + \Delta m_{vap} \cdot \Delta_{vap}H^o \qquad (1)$$

where Q_{fus} and Q_{vap} are the amount of heat absorbed during the fusion and vaporization of the sample, respectively, J; $\Delta_{fus}H^o$ and $\Delta_{vap}H^o$ are specific enthalpies of fusion and vaporisation of the sample, respectively, J/g; m_0 is the mass of the sample corresponding to the temperature of its fusion beginning T_{fus}, g; Δm_{vap} is a loss of sample mass (vapour mass) over the period taken into account when determining the peak area S (K·s) on the differential thermal analysis curve, g; K is the heat transfer coefficient of the derivatograph, J/(K·s).

The value of $\Delta_{vap}H^o$ was calculated from the temperature dependence of the vaporization rate of the sample in the temperature range where the acid sample was in a liquid aggregate state before the degradation process began. To determine the vaporization rate, the integral curve of the sample mass loss was differentiated every 30 seconds. The temperature dependence of the vaporization rate of a substance was approximated by the linear form of the Arrhenius equation ($\ln v = A - B/T$, where $B = E_{act}/R$). At the same time, the values of the enthalpy of vaporization and the activation energy (E_{act}) were considered equal, since vapor condensation in the presence of the liquid phase is practically an activation-free process (Eq. 2):

$$\Delta_{vap}H^o = E_{act} + RT_{fus} \qquad (2)$$

Results and discussion

The results of the experimental study of the dissolution of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid are given in Table 1, namely: m_1 is mass of solvent; m_2 is mass of dissolved acid; x_2 is mole fraction of solubility, T is temperature at which solubility is determined; linear equations determined as a result of processing the experimental values by the least squares method are given in the form of the Schrader's equation (Eq. 3).

$$\ln X_2 = -\frac{\Delta_{sol}H^o}{RT} + \frac{\Delta_{sol}S^o}{R} \qquad (3)$$

where $\Delta_{sol}H^o$ and $\Delta_{sol}S$ are enthalpy and entropy of dissolution. Hereinafter, the errors of all values are given for a significance level of 0.95.

Table 1

Solubility temperature dependence of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid in organic solvents

T, K	m_1, g	m_2, g	$x_2\cdot10^3$	T, K	m_1, g	m_2, g	$x_2\cdot10^3$	T, K	m_1, g	m_2, g	$x_2\cdot10^3$
1	2	3	4	5	6	7	8	9	10	11	12
Methyl acetate											
293.4	1.9664	0.0289	3.55	303.1	1.6092	0.0348	5.22	307.9	1.5720	0.0437	6.70
293.4	1.5983	0.0236	3.57	303.1	1.4765	0.0324	5.30	310.1	1.6142	0.0500	7.46
293.4	1.5988	0.0233	3.53	303.5	1.4882	0.0334	5.42	310.1	1.5297	0.0474	7.47
298.0	1.5791	0.0272	4.16	303.5	1.8875	0.0413	5.29	310.1	1.5213	0.0470	7.44
298.0	1.3771	0.0240	4.21	303.5	1.3459	0.0306	5.49	312.4	1.3826	0.0489	8.51
298.0	1.6768	0.0300	4.32	306.2	1.9680	0.0521	6.38	312.4	1.5736	0.0547	8.37
299.5	1.6136	0.0318	4.76	306.2	1.4641	0.0389	6.41	312.4	1.4924	0.0513	8.28
299.5	1.5747	0.0311	4.77	306.2	1.0758	0.0286	6.41	316.0	1.4410	0.0590	9.84
299.5	1.5008	0.0300	4.83	307.9	1.5645	0.0434	6.69	316.0	1.5655	0.0644	9.88
303.1	1.3979	0.0304	5.26	307.9	1.4468	0.0402	6.70	316.0	1.4743	0.0604	9.85
$\ln x_2 = (8.74\pm0.45)-(4227\pm137)\cdot1/T$; $R^2 = 0.9926$											
Ethyl acetate											
294.4	1.4668	0.0290	5.67	300.5	1.4786	0.0386	7.48	308.0	1.4365	0.0501	9.97
294.4	1.5396	0.0305	5.69	300.5	1.2908	0.0336	7.46	310.0	1.4593	0.0566	11.06
294.4	1.4353	0.0285	5.69	303.6	1.3692	0.0408	8.53	310.0	1.5061	0.0579	10.97
294.6	1.7189	0.0355	5.93	303.6	1.5736	0.0462	8.40	310.0	1.3985	0.0539	10.99
294.6	1.4292	0.0298	5.98	303.6	1.3578	0.0396	8.35	311.9	1.3235	0.0550	11.85
294.6	1.4559	0.0294	5.80	306.2	1.4024	0.0467	9.52	311.9	1.2891	0.0535	11.84
297.1	1.4757	0.0335	6.50	306.2	1.5475	0.0518	9.56	311.9	1.2424	0.0521	11.95
297.1	1.5893	0.0349	6.29	306.2	1.4100	0.0472	9.57	314.5	1.3132	0.0604	13.09
297.1	1.3983	0.0314	6.43	308.0	1.4433	0.0498	9.86	314.5	1.5162	0.0697	13.08
300.5	1.7119	0.0459	7.67	308.0	1.4300	0.0494	9.87	314.5	1.3931	0.0639	13.06
$\ln x_2 = (7.63\pm0.27)-(3765\pm81)\cdot1/T$; $R^2 = 0.9974$											
Acetone											
271.0	1.2406	0.0669	10.16	277.3	1.3384	0.0926	12.99	283.0	0.5780	0.0495	16.04

Continuation of Table 1

1	2	3	4	5	6	7	8	9	10	11	12
271.0	1.4308	0.0774	10.19	277.3	1.2808	0.0886	12.98	289.5	1.2934	0.1515	21.79
271.0	1.2503	0.0682	10.26	278.0	1.2960	0.0933	13.50	289.5	1.2529	0.1509	22.39
274.0	1.3626	0.0835	11.52	278.0	1.2988	0.0935	13.50	289.5	1.2237	0.1464	22.25
274.0	1.3477	0.0826	11.52	278.0	1.3376	0.0960	13.46	298.0	1.2334	0.1793	26.90
274.0	1.2545	0.0769	11.52	282.0	1.3256	0.1115	15.74	298.0	1.2847	0.1862	26.82
274.5	1.0280	0.0637	11.64	282.0	1.3095	0.1104	15.78	298.0	1.1222	0.1618	26.69
274.5	1.0593	0.0655	11.62	282.0	1.2975	0.1097	15.83	303.0	1.3430	0.2479	33.91
274.5	1.2965	0.0802	11.62	283.0	1.3870	0.1184	15.97	303.0	1.2187	0.2246	33.87
277.3	1.3811	0.0955	12.98	283.0	0.7781	0.0666	16.01	303.0	1.1083	0.2033	33.71
$\ln x_2 = (6.67\pm0.32)-(3048\pm89)\cdot 1/T$; $R^2 = 0.9950$											
Acetonitrile											
294.1	1.3032	0.0094	0.96	302.9	1.3628	0.0152	1.49	312.0	1.2651	0.0225	2.39
294.1	1.3108	0.0097	0.99	302.9	1.2493	0.0138	1.48	313.1	1.2034	0.0225	2.50
294.1	1.3023	0.0096	0.99	304.4	1.2912	0.0156	1.62	313.1	1.3222	0.0245	2.48
298.5	1.3001	0.0117	1.20	304.4	1.3613	0.0164	1.61	313.1	1.2581	0.0238	2.53
298.5	1.3202	0.0118	1.20	304.4	1.2964	0.0156	1.62	316.8	1.2131	0.0254	2.80
298.5	1.3169	0.0118	1.20	309.1	1.1884	0.0165	1.86	316.8	1.2827	0.0267	2.79
300.0	1.2467	0.0120	1.29	309.1	1.3228	0.0183	1.85	316.8	1.2319	0.0255	2.77
300.0	1.3565	0.0131	1.29	309.1	1.2862	0.0179	1.87	317.5	1.0562	0.0228	2.89
300.0	1.2785	0.0124	1.30	312.0	1.1968	0.0204	2.28	317.5	1.2793	0.0280	2.93
302.9	1.2534	0.0141	1.51	312.0	1.3463	0.0240	2.39	317.5	1.2076	0.0260	2.88
$\ln x_2 = (7.89\pm0.46)-(4360\pm143)\cdot 1/T$; $R^2 = 0.9927$											
n-Propanol											
286.2	1.4356	0.0146	2.00	294.5	1.3900	0.0261	3.68	303.4	1.2356	0.0422	6.67
286.2	1.3799	0.0140	1.99	294.5	1.2217	0.0234	3.75	305.0	1.3212	0.0535	7.91
286.2	1.2780	0.0130	2.00	297.1	1.3588	0.0314	4.53	305.0	1.2718	0.0516	7.92
288.5	1.3930	0.0168	2.36	297.1	1.3987	0.0327	4.57	305.0	1.2252	0.0496	7.90
288.5	1.3487	0.0162	2.36	297.1	1.2553	0.0292	4.55	308.2	1.2450	0.0583	9.13
288.5	1.2921	0.0156	2.37	300.6	1.1939	0.0341	5.59	308.2	1.3330	0.0652	9.53
291.5	3.4872	0.0530	2.98	300.6	1.3665	0.0387	5.54	308.2	1.3104	0.0615	9.15
291.5	2.8754	0.0438	2.99	300.6	1.1989	0.0339	5.53	314.1	1.1965	0.0877	14.22
291.5	3.0728	0.0465	2.97	303.4	1.1109	0.0377	6.64	314.1	1.3133	0.0967	14.29
294.5	1.3681	0.0263	3.77	303.4	1.3800	0.0468	6.63	314.1	1.2505	0.0922	14.30
$\ln x_2 = (15.65\pm0.32)-(6260\pm98)\cdot 1/T$; $R^2 = 0.9985$											
Isopropanol											
292.0	1.2592	0.0159	2.48	299.1	1.4142	0.0318	4.40	308.0	1.3202	0.0563	8.32
292.0	1.3611	0.0178	2.57	299.1	1.4055	0.0316	4.40	308.4	1.2922	0.0524	7.91
292.0	1.3074	0.0164	2.46	301.5	1.4484	0.0375	5.07	308.4	1.2264	0.0496	7.89
295.5	1.4793	0.0227	3.01	301.5	1.3605	0.0356	5.12	308.4	1.2407	0.0504	7.93
295.5	1.2662	0.0197	3.05	301.5	1.2217	0.0318	5.10	313.0	1.3544	0.0718	10.32
295.5	1.2665	0.0197	3.05	302.9	1.8076	0.0514	5.57	313.0	1.2807	0.0683	10.38
298.6	1.4270	0.0295	4.05	302.9	1.5178	0.0434	5.59	313.0	1.2381	0.0663	10.42
298.6	1.3308	0.0265	3.91	302.9	1.4588	0.0421	5.64	318.2	1.3063	0.0969	14.39
298.6	1.2826	0.0264	4.04	308.0	1.4822	0.0631	8.30	318.2	1.3395	0.0992	14.37
299.1	1.6508	0.0372	4.42	308.0	1.2928	0.0554	8.37	318.2	1.1983	0.0888	14.37
$\ln x_2 = (15.61\pm0.62)-(6304\pm187)\cdot 1/T$; $R^2 = 0.9938$											
n-Butanol											
290.2	1.3799	0.0160	2.80	299.5	1.4002	0.0307	5.30	305.0	1.2821	0.0358	6.74
290.2	1.3892	0.0162	2.83	299.5	1.2706	0.0278	5.28	307.0	1.3887	0.0450	7.81
290.2	1.2215	0.0145	2.87	301.5	1.4351	0.0327	5.50	307.0	1.3893	0.0448	7.77
293.1	1.5607	0.0215	3.33	301.5	1.3773	0.0313	5.48	307.0	1.2544	0.0404	7.76
293.1	1.3932	0.0191	3.32	301.5	1.2917	0.0293	5.48	309.8	1.3359	0.0495	8.92
293.1	1.2339	0.0170	3.33	303.0	1.7663	0.0425	5.80	309.8	1.3766	0.0525	9.18
296.8	1.3702	0.0230	4.06	303.0	1.4710	0.0339	5.56	309.8	1.1614	0.0440	9.11
296.8	1.3547	0.0238	4.24	303.0	1.3159	0.0306	5.61	313.5	1.3684	0.0637	11.17
296.8	1.2848	0.0226	4.26	305.0	1.4283	0.0396	6.68	313.5	1.4221	0.0667	11.26
299.5	1.3511	0.0286	5.11	305.0	1.3802	0.0383	6.69	313.5	1.2164	0.0570	11.25
$\ln x_2 = (12.58\pm0.56)-(5357\pm169)\cdot 1/T$; $R^2 = 0.9932$											
Isobutanol											
291.0	1.3770	0.0132	2.33	300.5	1.3563	0.0247	4.40	307.0	1.4059	0.0366	6.28
291.0	1.3379	0.0130	2.36	300.5	1.4005	0.0252	4.34	307.0	1.2903	0.0336	6.29
291.0	1.3058	0.0125	2.32	300.5	1.4339	0.0262	4.41	307.0	1.2299	0.0320	6.27

Table 1, ending

1	2	3	4	5	6	7	8	9	10	11	12
293.5	1.3621	0.0145	2.58	301.6	1.4605	0.0272	4.50	307.9	1.3455	0.0362	6.49
293.5	1.3267	0.0148	2.70	301.6	1.3505	0.0251	4.49	307.9	1.3750	0.0368	6.46
293.5	1.2630	0.0139	2.67	301.6	1.2340	0.0229	4.48	307.9	1.1772	0.0315	6.46
298.8	1.4362	0.0213	3.58	303.0	1.3752	0.0258	4.54	312.2	1.0190	0.0359	8.47
298.8	1.3538	0.0200	3.57	303.0	1.4333	0.0270	4.55	312.2	1.3006	0.0455	8.41
298.8	1.2111	0.0176	3.52	303.0	1.1601	0.0219	4.56	312.2	1.3139	0.0456	8.36
299.1	1.3546	0.0198	3.54	305.2	1.4714	0.0334	5.47	313.0	1.2130	0.0443	8.79
299.1	1.3898	0.0203	3.53	305.2	1.3448	0.0306	5.49	313.0	1.4043	0.0510	8.73
299.1	1.2184	0.0189	3.76	305.2	1.2666	0.0288	5.49	313.0	1.2588	0.0458	8.75
$\ln x_2 = (13.45\pm0.48)-(5688\pm150)\cdot 1/T$; $R^2 = 0.9922$											

The thermodynamic solubility parameters $\Delta_{sol}H^o$ and $\Delta_{sol}S^o$, given in Table 3, characterize, in addition to the process of solution formation, the phase transition of solid 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid into the liquid phase of the solution. Therefore, to calculate the change in enthalpy ($\Delta_{mix}H^o$) and entropy ($\Delta_{mix}S^o$) of mixing (solvation), which characterize the interaction of components in solution, it is necessary to take into account the value of the enthalpy ($\Delta_{fus}H^o$) and entropy ($\Delta_{fus}S^o$) of fusion of the acid under study (Eqs. 4–5).

$$\Delta_{sol}H^o = \Delta_{fus}H^o + \Delta_{mix}H^o \qquad (4)$$

$$\Delta_{sol}S^o = \Delta_{fus}S^o + \Delta_{mix}S^o \qquad (5)$$

The values of $\Delta_{fus}H^o$ and $\Delta_{vap}H^o$ (Table 2) were determined by the results of differential thermal and thermogravimetric analysis methods using equations (1) and (2). This table also shows the temperature interval (T_1–T_2), in which $\Delta_{vap}H^o$ was calculated and the total mass loss of the sample at the given temperature interval (ΣΔm).

Table 2

Thermodynamic parameters of fusion and vaporization processes of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid

Sample number	T_1-T_2, K	$\sum\Delta m\cdot10^3$, g	A	-B, K	$\Delta_{vap}H$, kJ/mol	m_0, g	Δm_{vap}, g	S, K·s	q_{vap}, J	$K\cdot10^3$, J/K·s	$\Delta_{fus}H$, kJ/mol
T_{fus} = 427.9±1.5 K											
1	450.7–463.0	0.005	25.08	12427	106.9	0.0612	0.43	1930.9	0.1525	3.888	36.67
2	514.3–581.9	5.950	14.32	12591	108.2	0.0740	0.17	2266.0	0.0618	4.001	36.95
3	524.2–594.0	20.600	14.77	12414	106.8	0.1026	0.36	350.1	0.1248	35.090	36.21
Mean value: 107.3 ± 1.8											Mean value: 36.61 ± 0.88

The value of entropy of fusion ($\Delta_{fus}S^o$) was calculated according to the known equation (Eq. 6).

$$\Delta_{fus}S^o = \frac{\Delta_{fus}H^o}{T_{fus}} \qquad (6)$$

In order to summarize the results of experimental studies of solubility carried out at the temperature intervals given in Table 1, which cover the generally accepted temperature of 298.15 K, it was decided to calculate the values of $\Delta_{mix}H^o$ and $\Delta_{mix}S^o$ at this temperature.

To recalculate $\Delta_{fus}H^o$ and $\Delta_{fus}S^o$ to 298.15 K or any other temperature, the Kirchhoff equation is used, in which the value of the change in heat capacity during the melting process for the substance under study is unknown. Since the experimental determination requires additional research using expensive equipment, analytical methods for calculating the change in heat capacity during the melting process are mostly used [22; 24]. Thus, according to the method given in [24], to calculate the change in heat capacity, it is necessary to use the group contributions determined at a temperature of 298.15 K for the solid and liquid aggregate state, in [22] the value of the change in heat capacity is determined during the melting process as a constant value. Therefore, to calculate $\Delta_{fus}H^o$ and $\Delta_{fus}S^o$ to 298.15 K, we used equations (7) and (8) given in [22].

$$\Delta_{fus}H^o_{298} = \Delta_{fus}H^o_{T_{fus}}\left[1 + \frac{298.15 - T_{fus}}{1.35\cdot T_{fus}}\right] \qquad (7)$$

$$\Delta_{fus}S^o_{298} = \Delta_{fus}S^o_{T_{fus}}\left[1 + 0.74\cdot\ln\frac{298.15}{T_{fus}}\right] \qquad (8)$$

Recalculated by equations (7) and (8) values of $\Delta_{fus}H^o_{298}$ and $\Delta_{fus}S^o_{298}$ were 28.4±1.0 kJ/mol and 60.5±1.8 J/(mol·K), respectively. The values of $\Delta_{mix}H^o_{298}$ and $\Delta_{mix}S^o_{298}$ were calculated using equations (4) and (5) and are presented in Table 3. This table also shows the value of the mole fraction of the dissolved acid at 298.15 K.

Table 3

Thermodynamic parameters of dissolution of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid in organic solvents at 298.15 K

Solvent	$x_2 \cdot 10^3$	$\Delta_{sol}H^o_{298}$, kJ/mol	$\Delta_{sol}S^o_{298}$, J/(mol·K)	$\Delta_{mix}H^o_{298}$ kJ/mol	$\Delta_{mix}S^o_{298}$, J/(mol·K)
1	2	3	4	5	6
Methyl acetate	4.31	35.10±1.10	72.6±3.7	6.7±1.5	12.1±4.1
Ethyl acetate	6.77	31.30±0.67	63.4±2.2	2.9±1.2	2.9±2.8
Acetone	28.20	25.34±0.74	55.4±2.7	-3.1±1.2	-5.1±3.2
Acetonitrile	1.18	36.20±1.80	65.6±5.8	7.8±2.1	5.1±6.1
n-Propanol	2.45	52.00±1.00	129.9±2.7	23.6±1.4	69.4±3.2
Isopropanol	3.87	52.40±1.50	129.7±5.1	24.0±1.8	69.2±5.4
n-Butanol	4.53	44.50±1.40	104.6±4.7	16.1±1.7	44.1±5.0
Isobutanol	3.56	42.30±1.20	111.8±4.0	13.9±1.6	51.3±4.4

The values of $\Delta_{mix}H^o_{298}$ and $\Delta_{mix}S^o_{298}$ (Table 3) are positive in all the studied systems, since the destruction of primary bonds in solvents and the acid under study consumes more energy than is released during the formation of new bonds, except for acetone. In acetone, the values of the thermodynamic mixing parameters are slightly less than zero, which indicates the formation of stronger new bonds than in the initial molecules due to the relative "compactness" of the acetone molecule.

At the same time, the highest values of the enthalpy of mixing are observed when the investigated acid dissolves in alcohols, particularly in propanol isomers, which belong to lower alcohols. It is due to the energy consumption during the breaking of hydrogen bonds between hydroxyl groups of alcohol molecules. The values of these energies are much higher than the energy of intermolecular interactions between dissimilar molecules in the resulting solution. Regarding the values of $\Delta_{mix}H^o_{298}$ of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid in butanols, these values are somewhat lower compared to propanols, which is due to the nature of higher alcohols, since an increase in the length of the hydrocarbon radical causes a decrease in polarity, which directly affects the value of $\Delta_{mix}H^o_{298}$.

The values of the enthalpy of mixing of the acid under study are also influenced by the values of the acceptor A_N and donor D_N numbers, dielectric constant ε and dipole moment μ of the organic solvents used. Table 4 shows the quantitative data on the physical characteristics of the selected organic solvents.

Table 4

Physical characteristics of selected organic solvents [25]

Solvent	A_N	D_N	ε	μ, D
Methyl acetate	10.7	16.5	6.70	1.69
Ethyl acetate	9.3	17.1	6.40	1.88
Acetone	12.5	17.0	21.40	2.69
Acetonitrile	18.9	14.1	38.80	3.44
n-Propanol	37.3	19.8	21.80	1.65
Isopropanol	33.5	21.1	19.92	1.59
n-Butanol	36.8	19.5	17.80	1.75
Isobutanol	–	37.0	16.68	1.79

In all solvents, except for acetone and acetonitrile, there is a directly proportional relationship between the values of their physical characteristics and the enthalpies of mixing of the acid under study in the following order: ethyl acetate, methyl acetate, isobutanol, n-butanol, isopropanol and n-propanol. The deviation of the dependence when using acetone and acetonitrile can be considered in terms of the presence of functional groups that provide the possibility of forming an intermolecular hydrogen bond. Acetone demonstrates high solubility of the acid, as the nature of acetone allows it to interact effectively with both polar and non-polar groups in the acid. As for the interactions of the solute with acetonitrile, the energy properties of the molecules of which are provided by dipole-dipole and dispersion interactions, cause a different type of interaction when mixing the components, in comparison with substances containing carbonyl and hydroxyl groups.

At the same time, the calculated value of the n-octanol-water distribution constant logP = 5.07±0.37 indicates a strong lipophilic nature of the compound, which indicates high membrane penetration, but also poor water solubility, bioaccumulation and extensive metabolism.

Conclusions

As a result of the experimental studies, the thermodynamic properties of solutions of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid in methyl acetate, ethyl acetate, acetone, acetonitrile, n-propanol, isopropanol, n-butanol and isobutanol were determined for the first time. According to the results of differential thermal analysis, the enthalpy and entropy of fusion at the melting point were determined, which were reduced to the standard temperature of 298.15 K. Using the calculated thermodynamic parameters of the mixing process of 3-(1-(4-methylphenyl)-5-phenylpyrrol-2-yl)propanoic acid for the systems of the studied solvents, the nature of the interaction between the solvent and the dissolved substance was determined. The obtained experimental values will make it possible to optimize the processes that will take place with the participation of the studied systems.

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References

[1] Vitaku, E., Smith, D. T., Njardarson, J. T. (2014). Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.*, *57*(24), 10257–10274. https://doi.org/10.1021/jm501100b

[2] Battersby A. R. (2000). Tetrapyrroles: the pigments of life. *Nat. Prod. Rep.*, *17*(6), 507–526. https://doi.org/10.1039/b002635m

[3] Bharathi, H. G., Raj, A. G., Baladhandapani Aruchamy, Pandurangan Nanjan, Drago, C., & Ramani, P. (2023). Pyrrole: A Decisive Scaffold for the Development of Therapeutic Agents and Structure-Activity Relationship. *Chem Med Chem.*, *19*(1). https://doi.org/10.1002/cmdc.202300447

[4] Sowmya, P. V., Boja Poojary, K. V., Vishwanatha, U., Shetty, P. (2017). Fluorinated pyrrole incorporated 2-thiazolyl hydrazone motifs: a new class of antimicrobial and antituberculosis agents. *Arch. Pharmacal Res.* https://doi.org/10.1007/s12272-017-0967-1

[5] Brothers, P. J., Senge, M. O. (2022). *An introduction to porphyrins for the Twenty-First Century*. Fundamentals of Porphyrin Chemistry. Wiley Online Library. https://doi.org/10.1002/9781119129301.ch1

[6] Masci, D., Hind, C., Islam, M. K., Toscani, A., Clifford, M., Coluccia, A., Conforti, I., Touitou, M., Memdouh, S., Wei, X., La Regina, G., Silvestri, R., Sutton, J. M., Castagnolo, D. (2019). Switching on the Activity of 1,5-Diaryl-Pyrrole Derivatives against Drug-Resistant ESKAPE Bacteria: Structure-Activity Relationships and Mode of Action Studies. European *J. Med. Chem.*, *178*(1), 500–514. https://doi.org/10.1016/j.ejmech.2019.05.087

[7] Battilocchio, C., Poce, G., Alfonso, S., Porretta, G. C., Consalvi, S., Sautebin, L., Pace, S., Rossi, A., Ghelardini, C., Di Cesare Mannelli, L., Schenone, S., Giordani, A., Di Francesco, L., Patrignani, P., Biava, M. (2013). A class of pyrrole derivatives endowed with analgesic/anti-inflammatory activity. *Bioorg. Med. Chem.*, *21*(13), 3695–3701. https://doi.org/10.1016/j.bmc.2013.04.031

[8] Li Petri, G., Spanò, V., Spatola, R., Holl, R., Raimondi, M.V., Barraja, P., Montalbano, A. (2020). Bioactive Pyrrole-Based Compounds with Target Selectivity. European *J. Med. Chem.*, *208*, 112783. https://doi.org/10.1016/j.ejmech.2020.112783

[9] Rita C. C. Carvalho, Martins W. A., Silva T. P., Kaiser C. R., Bastos M. M., Luiz C. S. Pinheiro, Krettli A. U., Núbia Boechat. (2016). New pentasubstituted pyrrole hybrid atorvastatin–quinoline derivatives with antiplasmodial activity. *Bioorg. Med. Chem. Lett.*, *26*(8), 1881–1884. https://doi.org/10.1016/j.bmcl.2016.03.027

[10] Zhan, X., Lan, L., Zhang, Y., Chen, J., Zhao, K., Wang, S., Xin, Y., Mao, Z. (2016). Synthesis and Cytotoxicity Evaluation of New 3-substituted 4-(4-methyloxy phenyl)-1*H*-Pyrrole Derivatives. *Bull. Korean Chem. Soc.*, *37*(2), 200–206. https://doi.org/10.1002/bkcs.10653

[11] Kerru, N., Gummidi, L., Maddila, S., Gangu, K. K. Jonnalagadda, S. B. (2020). A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules*, *25*(8), 1909. https://doi.org/10.3390/molecules25081909

[12] Ivan, B.-C., Barbuceanu, S.-F., Hotnog, C. M., Anghel, A. I., Ancuceanu, R.V., Mihaila, M.A., Brasoveanu, L.I., Shova, S., Draghici, C., Olaru, O. T., Nitulescu, G. M., Dinu, M., Dumitrascu, F. (2022). New Pyrrole Derivatives as Promising Biological Agents: Design, Synthesis, Characterization, In Silico, and Cytotoxicity Evaluation. *Int. J. Mol. Sci.*, *23*(16), 8854. https://doi.org/10.3390/ijms23168854

[13] Rebbah, B., El Haib, A., Lahmady, S., Forsal, I., Gouygou, M., Mallet-ladeira, S., Medaghri-alaoui, A., Rakib, E.M., Hannioui, A. (2024). Synthesis, Characterization, and Inhibition Effects of a Novel Eugenol Derivative Bearing Pyrrole Functionalities on the Corrosion of Mild Steel in a HCl Acid Solution. *RSC Advances.*, *14*(20), 14152–14160. https://doi.org/10.1039/d4ra01337a

[14] Amin, A., Qadir, T., Sharma, P. K., Jeelani, I., Abe, H. (2022). A Review on The Medicinal And Industrial Applications of N-Containing Heterocycles. *Open Med. Chem. J.*, *16*(1). https://doi.org/10.2174/18741045-v16-e2209010

[15] Chandima, B., Ruwan, G., Gamage, P. L., Miller, J. T., Kularatne, R. N., Biewer, M. C., Stefan, M. C. (2020). Pyrrole-Containing Semiconducting Materials: Synthesis and Applications in Organic Photovoltaics and Organic Field-Effect Transistors. *ACS Appl. Mater. Interfaces.*, *12*(29), 32209–32232. https://doi.org/10.1021/acsami.0c07161

[16] Filipa, A., A.V. M. (2014). Experimental and high level ab initio enthalpies of formation of di- tri- tetra- and pentamethyl-substituted pyrroles. J. *Chem. Thermodyn.*, *75*, 1–7. https://doi.org/10.1016/j.jct.2014.04.003

[17] Du, C. (2022). The solubility of ethyl candesartan in mono solvents and investigation of intermolecular interactions. *Liquids*, *2*(4), 404–412. https://doi.org/10.3390/liquids2040023

[18] Liu, Y., Guo, H. (2021). Solubility determination and crystallization thermodynamics of an intermediate in different organic solvents. *J. Mol. Liq.*, *339*, 116821. https://doi.org/10.1016/j.molliq.2021.116821

[19] Sitar, A., Shevchenko, D., Matiichuk, V.V., Skrypska, O., Lesyuk, O., Khomyak, S., Lytvyn, R., Sobechko, I.,

Horak, Yu. (2024). Synthesis of 3-(1R-5-phenyl-1-N-pyrrol-2-yl)propanoic acids and prediction of their biological activity. *Visnyk of the Lviv University. Series Chemistry*, *65*(1), 223–230. https://doi.org/10.30970/vch.6501.223 (in Ukrainian)

[20] Sobechko, I., Chetverzhuk, Y., Horak, Y., Serheyev, V., Kochubei, V., Velychkivska, N. (2017). Thermodynamic properties of 2-cyano-3-[5-(phenyl)-2-furyl]-2-propenamide and 2-cyano-3-[5-(4-methylphenyl)-2-furyl]-2-propenamide solutions in organic solvents. *Chem. Chem. Technol., 11*(2), 131–137. https://doi.org/10.23939/chcht11.02.131

[21] Sobechko, I., Dibrivnyi, V., Horak, Y., Velychkivska, N., Kochubei, V., Obushak, M. (2017). Thermodynamic properties of solubility of 2-methyl-5-arylfuran-3-carboxylic acids in organic solvents. *Chem. Chem. Technol., 11*(4), 397–404. https://doi.org/10.23939/chcht11.04.397

[22] Sobechko, I., Horak, Y., Dibrivnyi, V., Obushak, M., Goshko, L. (2019). Thermodynamic Properties of 2-Methyl-5-arylfuran-3 Carboxylic Acids Chlorine Derivatives in Organic Solvents. *Chem. Chem. Technol.*, *13*(3), 280–287. https://doi.org/10.23939/chcht13.03.280

[23] Klachko, O., Matiychuk, V., Sobechko, I., Serheyev, V., Tishchenko, N. (2020). Thermodynamic Properties of 6-Methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid Esters. *Chem. Chem. Technol.*, *14*(3), 277–283. https://doi.org/10.23939/chcht14.03.277

[24] Acree, W., Chickos, J. S. (2016). Phase Transition Enthalpy Measurements of Organic and Organometallic Compounds. Sublimation, Vaporization and Fusion Enthalpies From 1880 to 2015. Part 1. C1– C10. *J. Phys. Chem. Ref. Data*, *45*(3), 033101. https://doi.org/10.1063/1.4948363

[25] Gutmann Acceptor and Donor number https://www.stenutz.eu/chem/solv21.php