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***Rostyslav KOSTIUK*[1], *Yuriy HORAK*[2], *Mykola OBUSHAK*[2], *Iryna SOBECHKO*[1]**

THERMODYNAMIC PARAMETERS OF SOLUBILITY OF 1-R-2-METHYL-5-PHENYL-PYRROLE-3-CARBOXYLIC ACIDS IN ACETONITRILE

[1]*Lviv Polytechnic National University,*
St. George's Square 3/4, 79013 Lviv, Ukraine
e-mail: rostyslav.r.kostiuk@lpnu.ua

[2]*Ivan Franko National University of Lviv,*
Kyryla i Mefodiya St., 6, 79005 Lviv, Ukraine

The 1-R-2-methyl-5-phenyl-pyrrole-3-carboxylic acids were synthesised by the Paal-Knorr reaction. The enthalpy and entropy of dissolution of acids in acetonitrile were calculated from the experimentally determined temperature dependence of solubility. Taking into consideration the enthalpy and entropy of melting reduced to 298.15 K, the enthalpies and entropies of mixing of the studied pyrrole acids with acetonitrile were calculated. The nature of the interaction between the solvent and the dissolved substances was determined.

Keywords: polysubstituted pyrroles; Paal-Knorr reaction; pyrrole-3-carboxylic acids; enthalpy of dissolution; enthalpy of mixing; enthalpy of melting; acetonitrile.

Introduction

The chemistry of heterocycles is an important branch of organic chemistry that encompasses a wide range of pharmacologically active compounds that can be obtained by synthesis or isolated from natural sources. Among these compounds, pyrrole derivatives with substituents of various types are of particular interest, as they exhibit a wide range of biological activity [1–3]. Such compounds are used as modifying additives in the production of cosmetics, polymers, and in the synthesis of substances with antioxidant properties [4]. In view of the above range of applications of compounds with a pyrrole fragment, the development of novel synthetic methods is one of the priorities of modern organic and pharmaceutical chemistry.

The pyrrole ring is an important structural element that is largely present in naturally occurring products and biomolecular structures such as chlorophyll, haemoglobin, myoglobin, cytochromes, vitamin B12, bilirubin, and biliverdin [5].

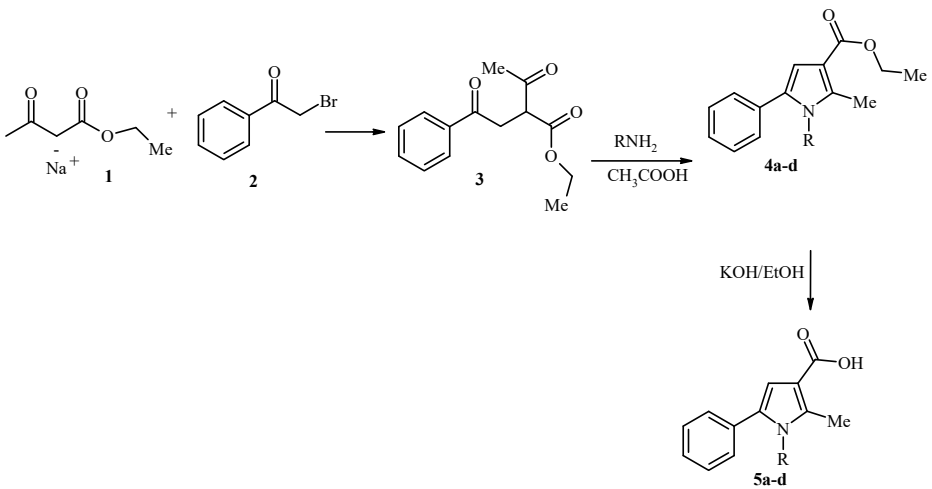
Its significance in biochemistry is explained by its flat, electron-saturated ring structure, which easily enters into electrophilic reactions and is capable of interacting with biomolecules through hydrogen bonds and π-π stacking interactions [6]. Due to these features, the pyrrole subunit contributed to the biological activity in

pharmacologically important compounds, including antifungal, antimicrobial, and anti-inflammatory [7].

As is known, solvents play a key role in the processes of compound synthesis and purification [8]. The choice of solvent for synthesis and recrystallization is primarily based on its chemical inertness toward the components involved in these processes. Particular attention is paid to the purity of pharmaceutical components, as it directly determines the quality of the final product. In this context, the thermodynamic parameters of the interaction between the solvent and the solute become crucial for calculating energy balances during synthesis, purification, and further processing. The aim of this study was to determine the thermodynamic parameters of solubility of 1-R-2-methyl-5-phenyl-pyrrole-3-carboxylic acids in acetonitrile.

Materials and research methods

The choice of substituents for the synthesis of 1-R-2-methyl-5-phenyl-pyrrole-3-carboxylic acids (Fig. 1) was based on the expected biological activity they can exhibit towards living organisms. The synthesis was carried out in two stages.



5: R = $CH_3(CH_2)_3$– (**a**), cyclohexyl (**b**), 4-$CH_3C_6H_4$ (**c**), Furfuryl (**d**).

Fig 1. Reactions scheme of two-step synthesis of the 1-R-2-methyl-5-phenyl-pyrrole-3-carboxylic acids.

First, to a suspension of finely divided sodium metal (0.03 mol) in 40 mL of toluene, 0.044 mol of ethyl acetoacetate was gradually added under cooling and vigorous stirring. The resulting mixture was stirred at room temperature for three days. After cooling to 10ºC, 0.03 mol of phenacyl bromide **2** was added and the reaction was stirred for 1 hour at 10ºC and then for 24 hours at room temperature. The reaction mixture was filtered to remove sodium bromide, toluene was evaporated under reduced pressure (30 mm Hg), and the residue was distilled under vacuum (Bp 178–180ºC/ 2 mm Hg). Ethyl 2-acetyl-4-oxo-4-phenylbutanoate **3** was obtained. Yield 6.35 g (86%).

In the second stage, 5.00 g (0.02 mol) of the obtained compound **3** in 30 mL of glacial acetic acid was reacted with 0.02 mol of the corresponding amine. The mixture

was refluxed for 2.5 hours. After cooling, it was diluted with 100 mL of water, and the viscous oils were extracted with dichloromethane, washed with water, dried over sodium sulfate for 2 hours, and the solvent was removed. To the crude ester, a solution of 2.24 g (0.04 mol) of KOH in 20 mL of ethanol was added. The mixture was heated for 15 min, cooled, diluted with 50 mL of water, and acidified with diluted HCl (1:1). The resulting acids **5a–d** were recrystallized from ethanol.

The structural formulas of the obtained compounds as a result of synthesis according to the proposed scheme are shown in Figure 2.

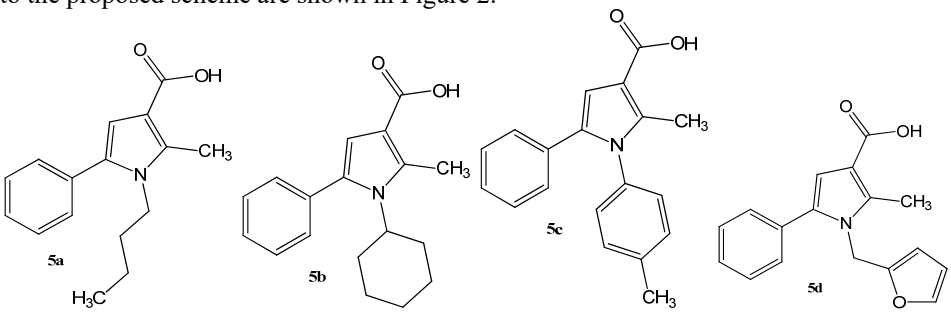


Fig. 2. 1-R-2-methyl-5-phenyl-pyrrole-3-carboxylic acids **5a-d**.

1-Butyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid 5a. Mp 163ºC. ^{1}H NMR spectra (500 MHz, DMSO-d_6), δ, ppm: 11.70 (br.s, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.40–7.29 (m, 3H), 6.36 (s, 1H), 3.89 (t, J = 7.7 Hz, 2H), 2.54 (s, 3H), 1.41 (quint, J = 7.5 Hz, 2H), 1.08 (sext, J = 7.0 Hz, 2H), 0.70 (t, J = 7.4 Hz, 3H). ^{13}C NMR spectra (126 MHz, DMSO-d_6), δ, ppm: 166.16, 135.97, 132.79, 132.75, 128.85, 128.58, 127.38, 111.81, 109.64, 43.24, 32.03, 19.11, 13.27, 11.21. MS (m/z, ES-API): 258 (M^++1).

1-Cyclohexyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid 5b. Mp 227ºC. ^{1}H NMR spectra (500 MHz, DMSO-d_6), δ, ppm: 11.66 (br.s, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 7.0 Hz, 2H), 6.27 (s, 1H), 3.98 (tt, J = 12.7, 3.6 Hz, 1H), 2.66 (s, 3H), 2.03–1.46 (m, 8H), 1.16–1.08 (m, 2H). ^{13}C NMR spectra (126 MHz, DMSO-d_6), δ, ppm: 166.23, 135.47, 133.49, 133.26, 129.61, 128.36, 127.61, 112.37, 110.13, 57.02, 31.69, 25.91, 24.73, 12.80. MS (m/z, ES-API): 284 (M^++1).

2-Methyl-5-phenyl-1-(4-tolyl)-1*H*-pyrrole-3-carboxylic acid 5c. Mp 229ºC. ^{1}H NMR spectra (500 MHz, DMSO-d_6), δ, ppm: 11.93 (br.s, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 2H), 7.14–7.08 (m, 3H), 7.05 (d, *J* = 6.7 Hz, 2H), 6.65 (s, 1H), 2.33 (s, 3H), 2.28 (s, 3H). ^{13}C NMR spectra (126 MHz, DMSO-d_6), δ, ppm: 166.07, 137.90, 137.45, 135.07, 133.12, 132.12, 129.83, 128.19, 128.14, 127.65, 126.47, 112.70, 109.88, 20.65, 12.15. MS (m/z, ES-API): 292 (M^++1).

1-(Furan-2-ylmethyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid 5d. Mp 193ºC. ^{1}H NMR spectra (500 MHz, DMSO-d_6), δ, ppm: 11.81 (br.s, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.46–7.32 (m, 5H), 6.42 (s, 1H), 6.37 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.02 (d, *J* = 2.7 Hz, 1H), 5.12 (s, 2H), 2.53 (s, 3H). ^{13}C NMR spectra (126 MHz, DMSO-d_6), δ, ppm: 166.05, 150.31, 142.89, 136.70, 133.25, 132.22, 128.86, 128.63, 127.56, 112.32, 110.61, 109.74, 107.71, 41.06, 11.22. MS (m/z, ES-API): 282 (M^++1).

To study the solubility of pyrrole carboxylic acid derivatives, acetonitrile was chosen as a aprotic polar solvent (ε = 36), which ensures the effective dissolution of compounds with carboxylic, ketone, and amino groups [9]. Its low viscosity contributes to the rapid

achievement of equilibrium between the phases, and its chemical inertness guarantees the preservation of the structure of the substance under study during the experiment [10]. In addition, acetonitrile is highly miscible with water and organic solvents, which allows the polarity of the medium to be varied to simulate biologically relevant conditions [11]. Its high volatility (T_{boil} = 81.6 °C) simplifies the subsequent isolation and purification of products. The combination of these properties makes acetonitrile suitable for studying the physicochemical parameters of pyrrole derivatives solubility.

The solvent used for the study was manufactured by Merck (CAS 75-05-8). The solvent had a purity of ≥ 99.9% and was intended for chromatographic studies. The solvent was identified by its refractive index, which coincided with the literature data and the data indicated on the quality certificate of the substance, so it was used without preliminary purification.

The temperature dependence of the solubility of the studied acids was determined by the gravimetric method [8, 12–16].

The acids were dissolved in sealed glass round-bottomed vessels equipped with a Teflon stirrer, thermometer and sampling hole, which were placed in a thermostat with temperature control with an accuracy of ±0.1 K. The stirrer rotation was 30–40 rpm. The saturation of the solutions was carried out for 48 hours without stirring and 2 hours with constant stirring. were performed by changing the temperature regime, that is after raising the temperature, it was reduced and vice versa. In this way, the results were obtained that minimised the influence of external factors. The absence of a hysteresis loop on the solubility temperature dependence curve confirms the achievement of a state close to equilibrium.

Samples of the solutions were taken in series of three samples, transferred to pre-weighed sealed bullion bottles with subsequent solvent removal in an oven at a temperature of 363-373 K. After solvent removal, sealed, cooled in a desiccator, and weighed. The weighing was carried out at a room temperature of 296 ± 2 K using pre-calibrated and verified balances, with a weighing accuracy of ±0.0002 grams.

Research results and discussion

Table 1 shows the results of the acid dissolution experiments, including the mass of solvent (m_1), mass of solute (m_2), mole fraction of solubility (X_2) and temperature (T) at which the solubility was determined. The linear equations obtained by the least squares method are presented in the form of the Van Hoff equation. (1)

$$lnX_2 = -\Delta_{sol}H/RT + \Delta_{sol}S/R \quad (1)$$

where $\Delta_{sol}H$ and $\Delta_{sol}S$ are the enthalpies and entropies of solubility. Hereinafter, the errors of all values are given for a significance level of 0.95.

Table 1

Temperature dependence of solubility of pyrrole carboxylic acid derivatives in acetonitrile*

T. K	m_1. g	m_2. g	$X_2 \cdot 10^3$	T. K	m_1. g	m_2. g	$X_2 \cdot 10^3$	T. K	m_1. g	m_2. g	$X_2 \cdot 10^3$
1-Butyl-2-methyl-5-phenyl-1H-pyrrole-3-carboxylic acid											
273.15	1.3153	0.0157	1.90	279.25	1.3803	0.0203	2.34	286.35	0.7544	0.0147	3.10
273.15	0.9530	0.0114	1.91	279.25	1.4721	0.0217	2.34	286.55	1.4963	0.0292	3.10
273.15	1.7104	0.0206	1.92	279.25	1.6578	0.0246	2.36	286.55	1.3310	0.0260	3.11
274.95	0.6868	0.0085	1.97	284.05	1.7840	0.0316	2.82	287.05	1.7601	0.0343	3.10
274.95	1.5754	0.0199	2.01	284.95	0.6883	0.0123	2.84	287.05	0.9745	0.0190	3.10
274.95	1.7458	0.0221	2.01	284.05	1.6147	0.0290	2.85	287.05	1.4710	0.0288	3.11
277.15	1.5227	0.0210	2.20	284.05	1.2715	0.0228	2.85	288.45	1.7118	0.0346	3.21

277.15	1.3690	0.0192	2.23	284.95	1.5700	0.0286	2.89	288.45	1.4121	0.0286	3.22

Продовження табл. 1

T. K	m_1. g	m_2. g	$X_2 \cdot 10^3$	T. K	m_1. g	m_2. g	$X_2 \cdot 10^3$	T. K	m_1. g	m_2. g	$X_2 \cdot 10^3$
277.15	1.5114	0.0212	2.23	284.95	1.4729	0.0269	2.90	288.45	1.6459	0.0334	3.23
277.95	1.1202	0.0161	2.29	286.35	0.5741	0.0111	3.06	292.05	1.5818	0.0375	3.76
277.95	1.1241	0.0162	2.29	286.55	1.3535	0.0263	3.09	292.05	1.5123	0.0362	3.80
277.95	1.2977	0.0189	2.31	286.35	0.8884	0.0173	3.10	292.05	1.3281	0.0319	3.82
$\ln X_2=(4.17\pm0.24)-(2853\pm68)\cdot 1/T$											

1-Cyclohexyl-2-methyl-5-phenyl-1H-pyrrole-3-carboxylic acid											
281.05	1.5741	0.0043	0.39	296.55	1.7743	0.0083	0.67	305.95	1.8549	0.0123	0.96
281.05	1.3127	0.0036	0.39	296.55	1.1469	0.0054	0.68	313.55	1.9400	0.0152	1.13
281.05	1.7037	0.0047	0.40	299.05	1.5191	0.0076	0.72	313.55	1.7540	0.0138	1.14
286.65	2.0450	0.0068	0.48	299.05	1.0765	0.0054	0.73	313.55	1.6515	0.0132	1.15
286.65	1.8149	0.0061	0.48	299.05	1.6583	0.0084	0.73	317.45	1.8039	0.0158	1.27
286.65	2.2132	0.0075	0.49	301.35	2.0065	0.0114	0.82	317.45	2.2785	0.0205	1.30
290.15	1.6120	0.0060	0.54	301.35	1.7039	0.0098	0.83	317.45	2.0902	0.0189	1.31
290.15	1.3793	0.0052	0.54	301.35	2.2079	0.0128	0.84	319.25	1.9762	0.0189	1.38
290.15	1.0355	0.0040	0.55	305.95	2.3023	0.0148	0.93	319.25	1.2232	0.0118	1.39
296.55	1.3483	0.0062	0.67	305.95	2.5883	0.0167	0.93	319.25	1.8835	0.0183	1.41
$\ln X_2=(2.62\pm0.19)-(2942\pm56)\cdot 1/T$											

2-Methyl-5-phenyl-1-(4-tolyl)–1H-pyrrole-3-carboxylic acid											
295.15	2.1462	0.0083	0.54	300.15	1.2635	0.0061	0.67	313.15	2.1291	0.0153	1.01
295.15	1.2048	0.0047	0.54	303.15	1.2613	0.0064	0.71	313.15	1.2691	0.0091	1.01
295.15	1.2957	0.0051	0.55	303.15	1.6258	0.0083	0.72	315.15	1.2897	0.0099	1.08
296.85	1.9417	0.0078	0.57	303.15	1.5078	0.0078	0.72	315.15	1.4467	0.0111	1.08
296.85	1.3036	0.0053	0.57	308.15	2.0448	0.0120	0.83	315.15	2.0452	0.0158	1.08
296.85	1.4763	0.0061	0.58	308.15	2.0888	0.0123	0.83	316.35	1.2050	0.0094	1.10
299.85	2.0629	0.0094	0.64	308.15	0.7700	0.0047	0.85	316.35	0.8150	0.0064	1.11
299.85	1.4025	0.0064	0.64	312.15	1.7655	0.0120	0.96	316.15	1.8855	0.0150	1.12
299.85	1.0992	0.0051	0.65	312.15	1.1283	0.0078	0.97	316.35	2.0990	0.0168	1.12
300.15	2.0884	0.0099	0.66	312.15	1.0818	0.0076	0.99	316.15	1.5617	0.0126	1.14
300.15	1.3025	0.0062	0.67	313.15	1.4529	0.0104	1.01	316.15	1.9443	0.0157	1.14
$\ln X_2=(3.24\pm0.19)-(3176\pm60)\cdot 1/T$											

1-(Furan-2-ylmethyl)-2-methyl-5-phenyl-1H-pyrrole-3-carboxylic acid											
275.75	1.7339	0.0058	0.49	286.65	1.7634	0.0088	0.73	303.95	1.1358	0.0099	1.26
275.75	2.1195	0.0072	0.50	286.65	1.4230	0.0071	0.73	304.35	1.6016	0.0147	1.33
275.75	1.4414	0.0049	0.50	288.85	1.4858	0.0080	0.79	304.35	1.7598	0.0163	1.35
284.25	1.4136	0.0062	0.64	288.85	0.7940	0.0045	0.82	304.35	1.3644	0.0128	1.37
284.25	1.5056	0.0066	0.64	288.85	1.5874	0.0090	0.82	306.65	2.2896	0.0234	1.49
284.25	2.0819	0.0092	0.64	293.85	1.4609	0.0090	0.90	306.65	1.9790	0.0202	1.49
290.65	1.4179	0.0064	0.65	293.85	1.4568	0.0090	0.90	306.65	1.2269	0.0126	1.50
290.65	1.3691	0.0062	0.66	293.85	1.5551	0.0098	0.92	313.15	1.6634	0.0212	1.85
290.65	1.2582	0.0057	0.66	294.95	1.4403	0.0097	0.98	313.15	1.6262	0.0209	1.87
285.45	1.6993	0.0080	0.69	294.95	1.7412	0.0118	0.98	313.15	1.3066	0.0169	1.88
285.45	1.4968	0.0071	0.69	294.95	1.8699	0.0127	0.99	317.15	1.7252	0.0257	2.17
285.45	1.5491	0.0075	0.70	303.95	1.8983	0.0164	1.26	317.15	1.9901	0.0299	2.18
286.65	1.9205	0.0096	0.73	303.95	1.7706	0.0153	1.26	317.15	1.3478	0.0203	2.19
$\ln X_2=(3.71\pm0.30)-(3136\pm88)\cdot 1/T$											

* The numerical values of columns 5-8 and 9-12 are a continuation of columns 1–4.

Thermodynamic solubility functions, such as $\Delta_{sol}H$ and $\Delta_{sol}S$, take into account the transition of solid carboxylic acids into the liquid phase of the solution and the process

of its formation. In this case, to calculate the change in the mixing entropy (Δ_{mix}S) and the mixing enthalpy ($\Delta_{mix}H$), which characterise the behaviour and interaction of the components in solution, it is necessary to calculate the values of the fusion entropy ($\Delta_{fus}S$) and the fusion enthalpy ($\Delta_{fus}H$) for the type of compound under study, bringing them to the average temperature of the experiment, or to the generally accepted 298 K. For this purpose, the general equations for calculating the thermodynamic parameters of the dissolution of a crystalline substance can be used: $\Delta_{sol}S = \Delta_{fus}S + \Delta_{mix}S$ and $\Delta_{sol}H = \Delta_{fus}H + \Delta_{mix}H$.

The results of the calculation of ΔmixH and ΔmixS, as well as the mole fractions of solubility are shown in Table 2

Table 2

Thermodynamic parameters of the process of dissolution of 1-R-2-methyl-5-phenyl-pyrrole-3-carboxylic acids in acetonitrile at 298.15K

№	Substance name	$X_2 \cdot 10^3$	$\Delta_{sol}H^o$	$\Delta_{mix}H^o$	$\Delta_{sol}S^o$,	$\Delta_{mix}S^o$
			kJ/mol		J/mol·K	
1	1-Butyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid	4.52	23.72±0.57	–2.6±2.7	34.7±2.0	–21.8±6.2
2	1-Cyclohexyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid	0.71	24.46±0.56	–5.9±3.2	21.8±1.6	–31.6±6.6
3	2-Methyl-5-phenyl-1-(4-tolyl)-1*H*-pyrrole-3-carboxylic acid	0.60	26.41±0.50	–4.9±3.3	26.9±1.6	–27.84±6.8
4	1-(Furan-2-ylmethyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid	0.60	26.07±0.73	–3.3±3.1	30.8±2.5	–26.7±6.9

It was not possible to determine the enthalpies ($\Delta_{fus}H$) and entropies ($\Delta_{fus}S$) of fusion for the substances under study by experimental methods, since the results of the studies conducted using the Q-1500 D derivatograph showed that these substances decompose during the melting process. Therefore, to calculate $\Delta_{fus}H$, we chose the analytical method published in [18–20]. According to them, the specific value of the entropy of fusion ($\Delta_{fus}S_{Tfus}$) is a constant value for each class of organic compounds. Thus, for example, for substances with imidazole, pyrrole, pyrazole fragments, the value of $\Delta_{fus}S_{Tfus}$=0.460± 0.032 J/(g·K), for arylfuran $\Delta_{fus}S_{Tfus}$=0.323±0.027 J/(g·K).

Since the investigated substances belong to compounds with an arylpyrrole fragment, and the literature contains publications that investigate compounds with these fragments, namely: 3-(1,5-diphenylpyrrole-2-yl)-propanoic acid $\Delta_{fus}H_{442.4} = 43.6$ ±1.2kJ/mol, $\Delta_{fus}S_{442.4}$ =0.3383 J/g·K [19]; 3-(5-phenylpyrrole-2-yl)-propanoic acid $\Delta_{fus}H_{416.5}$ = 28.71±0.78 kJ/mol, $\Delta_{fus}S_{416.5}$ =0.3203 J/g·K[20]; 3-(1-(pyridin-3-yl)-5-phenylpyrrole-2-yl)propanoic acid $\Delta_{fus}H_{438.4} = 36.5$± 1.3kJ/mol, $\Delta_{fus}S_{438.4}$ =0.2848 J/g·K[20]; 3-(1-(4-methylphenyl)-5-phenylpyrrole-2-yl)propanoic acid $\Delta_{fus}H_{427.9} = 36.61$ ±0.88, $\Delta_{fus}S_{427.9}$ =0.2802 J/g·K[20], the calculated average specific value of $\Delta_{fus}S$ from the above values is 0.3059±0.0041 J/(g·K).

Taking into account the molecular weight of the studied substances, the molar value of the entropy of melting was calculated, Equation 2.

$$\Delta_{fus}S=(0.3059\pm0.0041)\cdot M, \text{ (J/(mol·K)} \quad (2)$$

Using the known ratio of equation (3), the values of the melting enthalpies of the studied compounds were calculated according to equation 4. The results are shown in Table 3.

$$\Delta_{fus}S_{Tfus}=\Delta_{fus}H_{Tfus}/T_{fus} \quad (3)$$

$$\Delta_{fus}H_{Tfus}=(\Delta_{fus}S)\cdot T_{fus}\ (\text{kJ/mol}) \quad (4)$$

The values of enthalpy and entropy of fusion were converted to 298.15 K using the equation given in [18].

The results of the conversion of thermodynamic parameters to the generally accepted temperature of 298.15 K are given in Table 3.

Table 3

Recalculation of the thermodynamic parameters for the dissolution of acids 5a–d in acetonitrile at 298.15K

№	Substance name	T_{boil}, K	$\Delta_{fus}H^o_{Tfus}$ kJ/mol	$\Delta_{fus}S^o_{Tfus}$ J/mol·K	$\Delta_{fus}H^o_{298}$	$\Delta_{fus}S^o_{298}$
1	1-Butyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid	436.35	34.3±2.4	78.7±5.5	26.3±2.6	56.5±5.9
2	1-Cyclohexyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid	500.75	43.4±3.0	86.7±6.0	30.4±3.2	53.4±6.4
3	2-Methyl-5-phenyl-1-(4-tolyl)-1*H*-pyrrole-3-carboxylic acid	502.25	44.7±3.1	89.1±6.2	31.3±3.3	54.7±6.6
4	1-(Furan-2-ylmethyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid	466.65	40.2±2.8	86.0±6.0	29.4±3.0	57.5±6.4

The obtained values of enthalpies and entropies of melting ($\Delta_{fus}H^o_{298}$ and $\Delta_{fus}S^o_{298}$) indicate that all the studied carboxylic acids are characterised by pronounced intermolecular interactions in the solid state. Also, relatively high values of these parameters indicate the formation of a stable crystal framework, the destruction of which requires significant thermal energy, i.e. the structure of substances is ordered.

A comparative analysis of the standard values ($\Delta_{fus}H^o_{298}$ and $\Delta_{fus}S^o_{298}$) shows that all the studied acids retain the thermodynamic features characteristic of compounds with branched aromatic and aliphatic fragments. The values of the mixing enthalpies ($\Delta_{mix}H$) of the studied substances in acetonitrile are similar within the calculated error of the calculation method, since the same type of interaction between the functional groups of the studied acids and the solvent is observed.

Recalculation of the thermodynamic functions to a standard temperature makes it possible to compare the thermal effects for the synthesised 1-R-2-methyl-5-phenylpyrrole-3-carboxylic acids to determine the degree of stability of the solid state for each of them.

The results obtained are important for future thermodynamic modelling and prediction of solubility in polar aprotic solvents such as acetonitrile, selection of recrystallisation and purification conditions.

Conclusion

New compounds – N-substituted 2-methyl-5-phenylpyrrole-3-carboxylic acids – were obtained by the Paal-Knorr reaction. The thermodynamic properties of solutions of these compounds in acetonitrile were characterized for the first time in the course of

experimental studies. The enthalpies and entropies of dissolution and mixing of the solute in the solvent were calculated.

The obtained experimental data can be used to optimise technological processes involving the studied systems.

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РЕЗЮМЕ

***Ростислав КОСТЮК*[1], *Юрій ГОРАК*[2], *Микола ОБУШАК*[2], *Ірина СОБЕЧКО*[1]**

ТЕРМОДИНАМІЧНІ ПАРАМЕТРИ РОЗЧИННОСТІ 1-R-2-МЕТИЛ-5-ФЕНІЛПІРОЛ-3-КАРБОНОВИХ КИСЛОТ У АЦЕТОНІТРИЛІ

[1]*Національний університет "Львівська політехніка",*
кафедра фізичної, аналітичної та загальної хімії
пл. Св. Юра, 3/4, 79013 Львів, Україна
e-mail: rostyslav.r.kostiuk@lpnu.ua

[2]*Львівський національний університет імені Івана Франка,*
вул. Кирила і Мефодія, 6, 79005 Львів, Україна

Галузь органічної хімії, що займається синтезом та виділенням з природних джерел різних фармакологічно активних сполук зараз активно розвивається. Одна з основних причин – активний пошук речовин, що можуть мати широкий спектр біологічної активності та знаходити застосування у різних видах промисловості.

Одним із таких гетероциклів виступає пірол та його похідні з замісниками різного типу. Такі речовини можуть застосовуватись як основні або проміжні компоненти для виробництва лікарських засобів, що проявляють протизапальну, антибактеріальну дії. Тому розробка новітніх методів синтезу є одним із пріоритетів сучасної органічної та фармацевтичної хімії, але без надійних термодинамічних даних їх синтез, використання, очищення та транспортування ускладнюється. Значущість піролу у біохімії пояснюється плоскою, електронно-насиченою кільцевою структурою, яка легко вступає в електрофільні реакції та здатна до взаємодії з біомолекулами через водневі зв'язки й π–π стекінгові взаємодії

Реакцією Пааля-Кнорра синтезовано 1-R-2-метил-5-фенілпірол-3-карбонові кислоти, а саме 1-бутил-2-метил-5-феніл-1H-пірол-3-карбонову кислоту, 2-метил-5-феніл-1-циклогексил-1H-пірол-3-карбонову кислоту, 2-метил-1-(4-толіл)-5-феніл-1H-пірол-3-карбонову кислоту та 2-метил-5-феніл-1-(фуран-2-ілметил)-1H-пірол-3-карбонову кислоту. Вибір замісників для кожної сполуки підбирався на основі

біологічної активності. Для кожної із них було експериментально визначено температурну залежність розчинності і на основі цих даних розраховано ентальпії та ентропії розчинення у ацетонітрилі. Експериментальне визначення ентальпій та ентропій плавлення виявилось неможливим через розклад самих сполук у процесі плавлення. Визначення велось розрахунково, опираючись на літературні дані авторів, що використовували у своїх дослідження речовини з вищими температурами плавлення, проте з подібними фрагментами сполук, що було синтезовано для даного дослідження. Отримані літературні значення усереднювались та перераховувались для нашого типу сполук за аналітичними методами. Отримані дані приводились до стандартних умов.

Порівняльний аналіз стандартних значень ентальпії та ентропії плавлення регламентує, що всі синтезовані кислоти зберігають термодинамічні властивості, які є характерними для такого типу сполук. Значення ентальпії змішування є подібні в межах розрахункової похибки.

Ключові слова: полізаміщені піроли; реакція Пааля-Кнорра; пірол-3-карбонові кислоти; ентальпія розчинення; ентальпія змішування; ентальпія плавлення; ацетонітрил.

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