Thermal analysis of 2-amino-3-chloro-1,4-naphthoquinones

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Abstract : Based on a complex thermal analysis, the thermal stability of 2-amino acid-3-chloro-1,4-naphthoquinones was investigated, and thermodynamic properties of melting of the foregoing compounds were identified. It has been determined that an increase in the hydrocarbon chain length of an amino acid substituent gives rise to the increasing thermal stability of compounds, their temperatures as well the enthalpy of fusion. The results of the performed analysis can be used to create highly efficient processes of obtaining and purifying 2-amino acid-3-chloro-1,4-naphthoquinones and their modifications.
Keywords : thermogravimetric and differential thermal analyses, 1,4-naphthoquinones, amino acids.

Introduction

Naphthoquinones are highly reactive organic compounds due to two carbonyl groups in their structure which can accept or donate electrons. This ensures a peculiar reactional capability of naphthoquinones, giving them special characteristics. That is why these compounds feature a wide spectrum of biological action and application [1,2,3,4]. According to the *in vitro* results, some synthetic naphthoquinones exhibited a radical scavenging activity (RSA) against 1,1-diphenyl-2-picrylhydrazyl (DPPH) [5].

Among the number of synthetic 1,4-naphthoquinone derivatives, aminonaphthoquinones occupy a special place. According to the results of *in vitro* and *in vivo* studies, they are of less toxicity compared with the other 1,4-naphthoquinones derivatives [6,7]. Amino derivatives of 1,4-naphthoquinone can be used for the synthesis of a large number of organic compounds with bactericidal, fungicidal [8,9], antioxidant properties [10] with low toxicity [5,6].

At present kinetic and thermodynamic properties of 1,4-naphthoquinone derivatives are almost not investigated. Most known schemes and methods for the calculation of the thermodynamic properties of organic compounds are also unsuitable for this class of substances [11,12,13]. Therefore, it is critical to do a comprehensive thermal study on the properties of some 1,4-naphthoquinone derivatives, as it may enable a creation of a reliable database of fundamental thermodynamic and kinetic properties for not enough explored, but practically important classes of compounds. Additionally, these data can be used to create highly efficient processes of synthesis, purification and modification of new bioactive and practically useful compounds.

Experimental

Chemicals and methods

All chemicals used in this study were purchased from Aldrich. IR spectra were recorded with the spectrophotometer Specord M-80 in KBr tablets. NMR spectra were recorded on the spectrometer Varian VXR-300 and ^{1}H chemical shifts measured in relation with the TMS internal standard in δ ppm. The thin layer chromatography (TCL) was performed on Silufol UV-254 and visualized under UV or with iodine vapor. The elemental analysis of compounds was conducted in a standard laboratory setting designed for a microanalysis.

The RSA evaluation was conducted on the spectrophotometer Specord M-40. Methanol solutions of the test compounds (10^{-4}M concentration) were mixed with a methanol solution of DFPH (10^{-4}M concentration) at a ratio of 1:3. A decrease in absorption at 517 nm of DPPH was measured after a 30-minute storage in a dark place. The actual decrease in absorption induced by the test compounds **4a-d** was calculated by subtracting that of control. A methanol solution of ascorbic acid (10^{-4} M concentration) was used as a standard. The percentage inhibition was also calculated. All the tests and analyses were performed in triplicates and averaged [14].

Thermographic investigations were done on a – 1500 D derivatograph of system F. Paulik, J. Paulik and L. Erdey, connected to an IBM-compatible PC. The samples were analyzed in a dynamic mode at the heating rate of 276.15K/min under the atmosphere of air. Al_2O_3 was used as a standard.

Synthesis

The interaction of 2,3-dichloro-1,4-naphthoquinone **1** (0.022 mol) with the amino acids **2a-d** (0.022 mol) was performed in a dimethylsulfoxide/water system (5:1) [15] at 343.1 K temperature for 1 hour. The yield of 1,4-naphthoquinone amino acid derivatives **4a-d** was 57-65%. The obtained products were triply recrystallized from ethanol.

57% (4a); 60% (4b); 64% (4c); 65% (4d).

R= -CH$_2$- (2a; 4a), -CH$_2$-CH$_2$- (2b; 4b), -CH$_2$-CH$_2$-CH$_2$- (2c; 4c), -CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$- (2d; 4d).

The use of DMSO in the synthesis provides a transition of amino acids into a anionic form that allows nucleophilic substitution reactions to occur [15]. Due to its basic properties, DMSO **3** along with strong mineral acids forms salts and acts, therefore, as an acceptor of HCl in this synthesis. Upon further heating this salt **5** decomposes to thioether, water and chlorine.

Quantum chemical calculations of the Fukui function[17] (using Schrödinger programme) suggest that the electrophilicity of a carbon atom in C^3 position of the compounds **4a-d** is sufficiently low (**4a** - 0.037; **4b** - 0.039; **4c** - 0.040; **4d** - 0.050), which prevents reactions in the presence of a chlorine atom near the quinone cycle to occur.

The compounds **4a-d** were characterized by elemental analysis, IR, NMR spectrometry, whose results are shown in Table 1 below, in order to confirm their identity and purity.

Table 1 Spectral data and elemental analysis of compounds 4 a-d.

Comp.	Formula	IR (KBr), ν (cm^{-1})	^{1}H NMR ((CD$_3$)$_2$SO), δ ppm	Elemental analysis	
				Calcd.	Found
4a	C$_{12}$H$_8$NO$_4$	3344 (OH), 1720 (C=O of COOH); 1672 (C=O); 1592, 1564 (C=C); 1520 (NH); 1248, 1108 ((-CH$_2$-)$_n$); 680 (C-Cl)	12.90 (1H, s., COOH); 8.10–8.06 (2H, d., CH, Ar); 7.82–7.74 (2H, m., CH, Ar); 6.44 (1H, s., NH), 4.37–4.32 (2H, d., α-CH$_2$)	C, 54.26 H, 3.04 Cl, 13.35 N, 5.27	C, 54.22 H, 3.09 Cl, 13.29 N, 5.31
4b	C$_{13}$H$_{10}$NO$_4$	3336 (OH), 1728 (C=O of COOH); 1680 (C=O); 1600, 1568 (C=C); 1512 (NH); 1340, 1288, 1140 ((-CH$_2$-)$_n$); 680 (C-Cl)	12.42 (1H, s., COOH); 8.10–8.05 (2H, d., CH, Ar); 7.81–7.76 (2H, m., CH, Ar), 6.96 (1H, s., NH), 3.65–3.59 (2H, qu., β-CH$_2$), 2.34–2.31 (2H, t., α-CH$_2$)	C, 55.83 H, 3.60 Cl, 12.68 N, 5.01	C, 55.78 H, 3.59 Cl, 12.69 N, 5.05
4c	C$_{14}$H$_{12}$NO$_4$	3324 (OH), 1712 (C=O of COOH); 1680 (C=O); 1600, 1552 (C=C); 1504 (NH); 1344, 1296, 1200 ((-CH$_2$-)$_n$); 680 (C-Cl)	12.12 (1H, s., COOH); 8.11–8.07 (2H, d., CH, Ar); 7.82–7.74 (2H, m., CH, Ar), 7.01 (1H, s., NH), 3.74–3.70 (2H, qu., γ-CH$_2$), 2.39–2.33 (2H, t., α-CH$_2$), 2.21–2.15 (2H, m., β-CH$_2$)	C, 57.25 H, 4.12 Cl, 12.07 N, 4.77	C, 57.28 H, 4.19 Cl, 12.09 N, 4.70
4d	C$_{16}$H$_{16}$NO$_4$	3288 (OH), 1712 (C=O of COOH); 1680 (C=O); 1600, 1553 (C=C); 1518 (NH); 1338, 1296, 1200, 1145 ((-CH$_2$-)$_n$); 680 (C-Cl)	12.00 (1H, s., COOH); 8.10–8.05 (2H, d., CH, Ar); 7.82–7.75 (2H, m., CH, Ar), 7.21 (1H, s., NH), 3.21–3.16 (2H, qu., ε-CH$_2$), 2.19–2.14 (2H, t., α-CH$_2$), 1.90–1.83 (2H, m., δ-CH$_2$), 1.41–1.32 (2H, m., β-CH$_2$), 1.26–1.21 (2H, m., γ-CH$_2$)	C, 59.00 H, 5.01 Cl, 11.02 N, 4.35	C, 59.30 H, 4.19 Cl, 11.10 N, 4.42

Results and Discussion

The results of comprehensive thermal analysis show that thermolysis of the samples of the compounds **4b-d** proceeds via a similar mechanism, as the thermogravimetric (TG), differential thermal analysis (DTA) and thermogravimetric (DTG) curves resemble each other in their shapes.

The thermogram for one of the series of compounds under investigation – the sample 6-[(3-dichloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl) amino]hexanoic acid **4d** – is depicted in Figure 1.

The endothermic effect on the DTA curve within a temperature range of 383.5 - 445.2 K with the maximum at 398.2 K is not followed by the mass loss and corresponds to the melting process of the sample.

The intensive mass loss of the sample at the temperature above 475.7 K, followed by an extreme point that is apparent on the DTG curve with the maximum at 497.0 K and the exothermic effect on the DTA curve with the maximum at 499.3 K, demonstrates that thermo-oxidative and destructive processes occur in the compound **4d**.
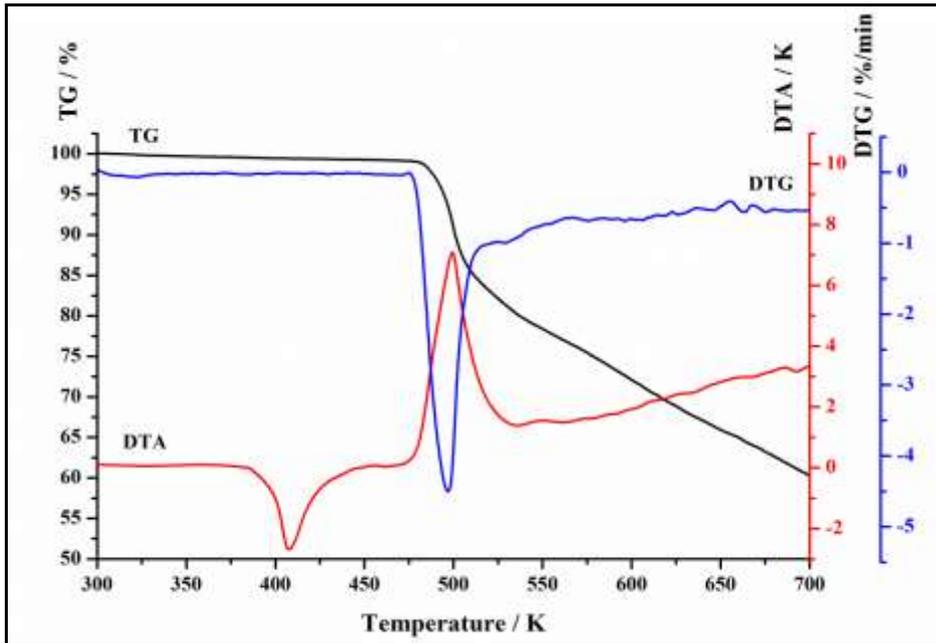
Fig. 1.Thermogram of the sample 4d.

Results of thermogravimetric analysis

Figures 2 and 3 show the comparison of the TG and DTA curves for the investigated samples in the temperature range of 300 – 700 K.
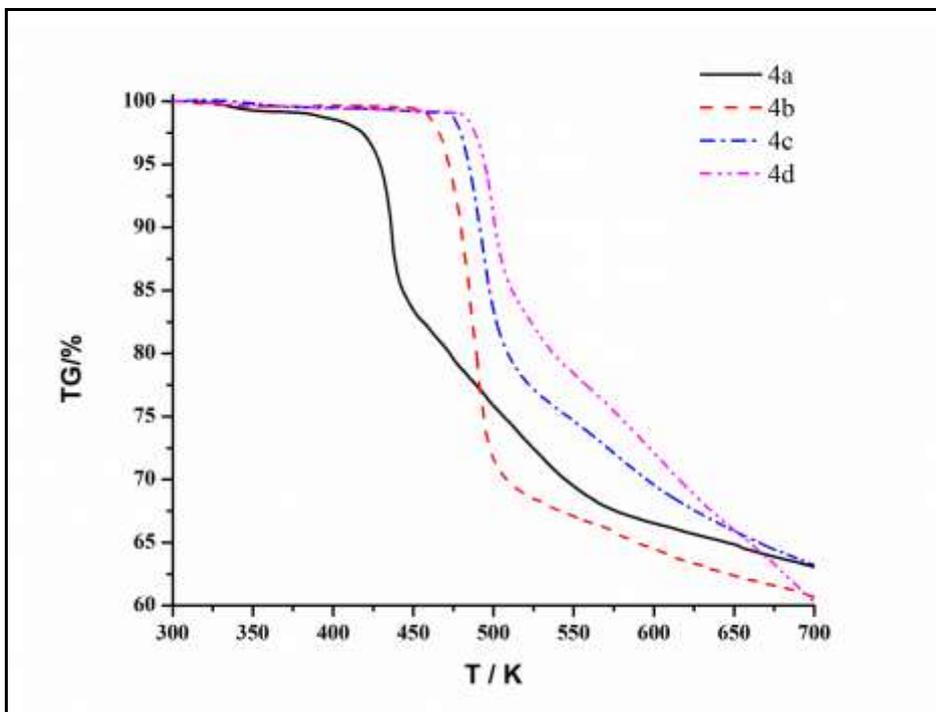

Fig. 2. TG curves for the samples 4a-d.

The data of thermogravimetric analysis (Fig. 2) show that the compound **4d** has the highest thermal stability. The start of thermo-oxidative and destructive processes in this sample is shifted to the region of higher temperatures (475.7 K). The compound **4a** is characterized by the lowest thermal stability. The start of intensive mass loss of this compound is observed at the lowest temperatures (401.2 K). The enthalpy of fusion appears to be absent on the DTA curve for the sample **4a** (Fig. 3) compared to the samples **4b-d**. An exothermic effect that

is manifest in the region of 401.2 - 468.4 K is attributed to thermo-oxidative and destructive processes in this sample.

Based on the data of thermogravimetric analysis, it may be concluded that the thermal stability of samples **4a-d** increases with an increasing number of carbon atoms in the amino acid substituent. The thermal stability of the compounds increases as a distance of carboxyl group becomes longer, namely the influence of negative mesomeric effect in the aminno acid substituent reduces, leading to an increase in the electron density near the amino group and its nucleophilicity as well as ability to form a stronger bond with carbon of quinone cycle in the C^2 position.

According to the quantum chemical calculations of the Fukui function (using Schrödinger programme), the electrophilicity of a nitrogen atom in the amino acid substituent of the compounds **4a-d** changes as follows: **4a** – 0.276; **4b** – 0.281; **4c** – 0.284; **4d** – 0.290.

Due to their high thermal stability, the compounds **4a-d**have been used to inhibit free radical polymerization processes, caused by thermal and other factors. The results of RSA test show that RSA of compounds **4a-d** of interest varies from 71.3 - 84.9%. The RSA of a standard compound, an ascorbic acid, is equal to 79%.

A tiny amount (0.0165%) of the compound **4b**, 120 times smaller in comparison with the known modifier, a Zn-Si filler, is enough to add to the polyester composition for inhibition of curing an unsaturated polyester resin.

Results of differential thermal analysis

Not less important for this class of compounds are the results of differential thermal analysis, giving a possibility to find the temperature, enthalpies of fusion and indirectly prove the identity of compounds.

The enthalpies of fusion for the compounds **4b-d** were found by the area of extrema observed on the DTA curves at a temperature range of 384.1 - 475.2 K. The temperature at wich the DTA curve begins to deviate from the baseline corresponds to a melting point of the compounds. Consistency within the experimental error and melting points of the compounds taken at different stages of their recrystallization has additionally confirmed the identity of compounds.

Upon completion of heating, the samples of compounds were investigated with IR and NMR spectroscopy and the elemental analysis. The samples of specific absorption bands present in spectra indicated the constancy of their chemical composition and abscence of destructive processes when melted.
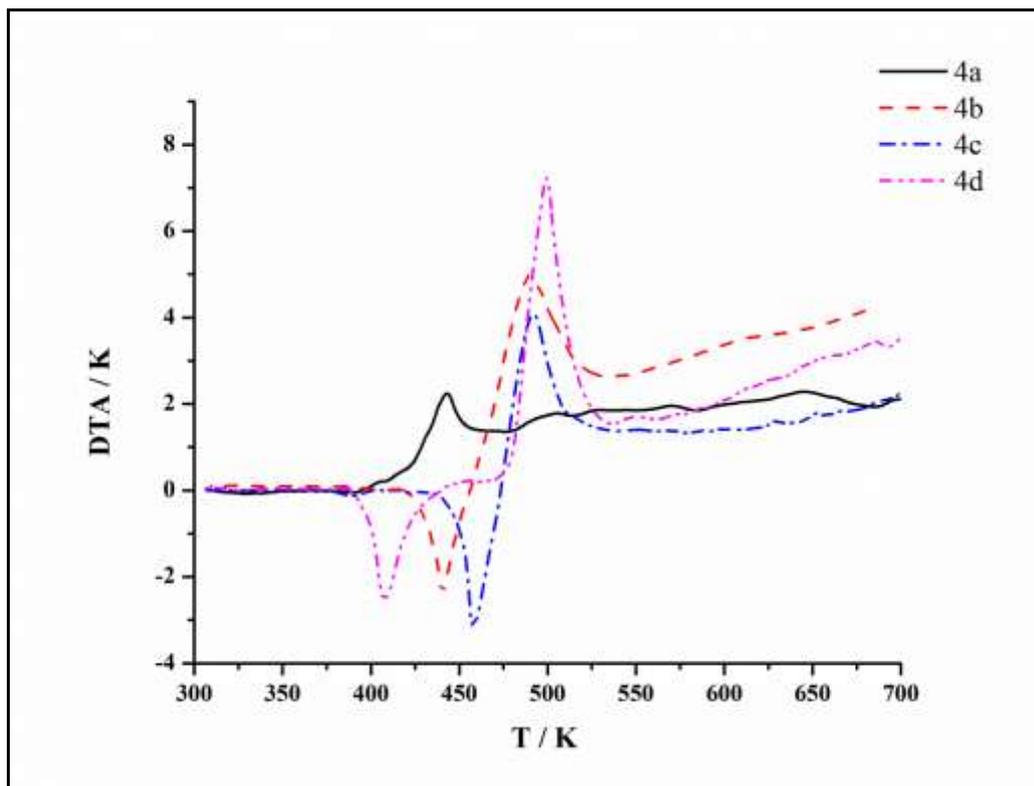
Fig. 3. DTA curves for the samples 4a-d.

The quantitative DTA method refers to the so called relative research methods, requiring a prior calibration of the device and determination of heat transfer constant by using the standard substances with their known enthalpies of fusion.

The derivatographpans were calibrated with the purified samples of reference material[18]. The temperature-dependent heat transfer coefficient was described by the equation:

$$K = 0.094 - 3.5 \cdot 10^{-4}T + 5.1 \cdot 10^{-7}T^2 \qquad (1)$$

The thermal effects of fusion of the substances were found by the equation:

$$\Delta_{fus}H \cdot m = K \cdot S, \qquad (2)$$

where: m is the sample mass (g), which represents the onset temperature of fusion T_{fus}; S means the area of peak (K·s), bounded by the DTA curve; K indicates the heat transfer coefficient (J/K·s), which defines the correspondence between the thermal effect of the process and the peak area of the DTA curve; $\Delta_{fus}H$ – the enthalpy of fusion of the sample (J/g).

The peak area bounded by the DTA curve was calculated using the equation:

$$S = \int_{t_1}^{t_2} \Delta T(t)\, dt \qquad (3)$$

where: t means time (s); ΔT is the difference of temperatures between the standard substance and the sample at a given time that was found by evaluating the ordinate length of the DTA curve with the ± 0.01 K accuracy.

The results of the enthalpies of fusion and changes in entropies of fusion obtained for the compounds are listed in Table 1. This table also shows heat transfer coefficients that refer to the compounds' melting points. The DTA data of the samples with their similar weights were used to determine the thermodynamic parameters for the melting of the substances. T_{fus} indicated the average melting point.

Table 2 : Results of measuring thermodynamic parameters for the melting of compounds 4b-d.

Sample	m, g	S, K·s	$\Delta_{fus}H$, J/g	$\Delta_{fus}H$, kJ/mol	$\Delta_{fus}S$, J/g·К	$\Delta_{fus}S$, J/mol·К
Compound **4b**M_r = 279.696 g/mol; T_{fus} = 421.1 ±1.5 K; K = 0,0371 J/K·s						
1	0.2020	446.5	82.01	22.81	0.195	54.17
2	0.2000	450.2	83.51	23.36	0.198	55.47
			Average value:	23.09 ± 0.28	0.197 ± 0.002	54.82 ± 0.65
Compound **4c**M_r = 293.723 g/mol; T_{fus} = 437.2 ± 1.3 K; K = 0.0385 J/K·s						
1	0.2002	631.6	121.46	35.68	0.278	81.61
2	0.2002	663.1	127.52	37.46	0.292	85.68
			Average value:	36.57 ± 0.89	0.285 ± 0.007	83.6 ± 2.0
Compound **4d**M_r = 307.752 g/mol; T_{fus} = 384.1 ± 0.6 K; K = 0.0348 J/K·s						
1	0.2000	588.2	102.35	31.50	0.267	82.01
2	0.2002	559.2	97.20	29.91	0.253	77.87
			Average value:	30.71 ± 0.80	0.260 ± 0.007	79.9 ± 2.1

        Based on the data given in Table 2, it can be argued that the nature of the amino acid substituent greatly affects physical and chemical properties of melting of the compounds 4b-d. Increasing number of carbon atoms in the amino acid substituents of the compounds 4b-c results in an increase in their temperatures and enthalpies of fusion. Caused by an increasing length of hydrocarbon chain of the amino acid substituent such a specific change of the thermodynamic parameters of the melting of the 4b-c compounds can be explained by an increasing strength of intermolecular hydrogen bonds involving carbonyl groups. IR spectra of the compounds 4a-d exhibit absorption bands in the region of 3288 to 3336 cm^{-1} that accord with the stretching vibrations of hydroxyl groups of carboxylic acids existing in dimeric form [19]. Moreover, within the region of 1712 - 1728 cm^{-1} in these spectra narrow absorption bands were revealed due to the stretching vibrations of carbonyl groups of acid dimers. As the distance of –COOH group in the amino acid substituents of the compounds 4b-c becomes longer, the electron density on the carbonyl oxygen increases, which causes the formation of much stronger intermolecular hydrogen bonds of the dimeric structure of compound 4c in comparison with that of compound 4b.

        Unlike the compound 4c,the compound 4d with a longer hydrocarbon chain is characterized by lower values of T_{fus} and $\Delta_{fus}H$. The quantum chemical calculations show that the compound 4d could form an internal molecular hydrogen bond in the presence of –COOH group and quinoide oxygenatom in position C^{1}position whose energy is 17.8 kcal/mol. Such a specific behavior of the aminohexanoic acid residue of the compound 4d decreases the strength of intermolecular interactions, causing a decrease in the enthalpy of fusion for the compound 4d compared to the compound 4c.

        It should be noted that the TGA/DTA results for the amino acid derivatives of 1,4-naphthoquinone correlate well with each other. The increase in the hydrocarbon chain of amino acid substituent of these compounds leads to a shift of extremas on DTA curves (compound **4b-c**). Furthermore, the temperature intervals of intensive mass loss (compound **4b-d**) were shifted towards higher temperatures, resulting thus in the increase of their thermal and heat stability.

Acknowledgements

Conclusions

This paper covers the synthesis of 2-amino acid-3-chloro-1,4-naphthoquinones **4a-d.** The methods of chemical and physical analyses used have proven identity of the compounds.

Based on the thermal studies, it has been found that the increase in the hydrocarbon chain length of amino acid substituent facilitates the increase of thermal stability and melting points of the examined compounds with the exception of the compound containing ε-amino acid residue. The latter has a lower melting point than other amino acid derivatives.

The experimentally obtained thermodynamic properties of fusion of amino acid substituted 1,4-naphthoquinone **4a-d** can be used to define the thermodynamic parameters of dissolving the compounds. The $\Delta_{fus}H$ and $\Delta_{fus}S$ values correspond to a phase transition of compounds to a solvent phase. These values can be used to determine the thermodynamic properties of mixing substances with different solvents. The enthalpies of mixing characterize the types of interactions, which occur between the components of the solution, and are necessary to optimize the synthesis and purification of compounds [20].

The experimentally obtained thermodynamic properties of fusion can be used for supplementing a database of thermodynamic properties for the derivatives of 1,4-naphthoquinone. In addition, with the experimental results of thermal stability of the compounds, it is possible to create highly efficient processes of obtaining and purifying 2-amino acid-3-chloro-1,4-naphthoquinones for their modifications when new compounds with a broad range of applications are subject to synthesis.

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