DOI: 10.6060/tcct.20165912.5458

Для цитирования:
Иванов Е.В., Краснов А.В., Петровская С.Г. Некоторые термодинамические характеристики «тиомебикара» (2,4,6,8-тетраметилдитиогликольурила). *Изв. вузов. Химия и хим. технология*. 2016. Т. 59. Вып. 12. С. 40–44.

For citation:
Ivanov E.V., Krasnov A.V., Petrovskaya S.G. Some thermodynamic characteristics of «thiomebicar» (2,4,6,8-tetramethyldithioglycoluril). *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol*. 2016. V. 59. N 12. P. 40–44.

УДК 547.495.3+544-971

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НЕКОТОРЫЕ ТЕРМОДИНАМИЧЕСКИЕ ХАРАКТЕРИСТИКИ «ТИОМЕБИКАРА» (2,4,6,8-ТЕТРАМЕТИЛДИТИОГЛИКОЛЬУРИЛА)

Методами дифференциальной сканирующей калориметрии и масс-спектрометрии (в сочетании с эффузионным методом Кнудсена) определены энтальпийные характеристики процессов плавления и сублимации перспективного биоактивного препарата «тиомебикар» (2,4,6,8-тетраметилдитиогликольурил). Проведен сравнительный анализ полученных данных с таковыми для известного лекарственного средства «мебикар» (2,4,6,8-тетраметилгликольурил) – карбонильного аналога с выраженным транквилизирующим действием.

Ключевые слова: 2,4,6,8-тетраметилдитиогликольурил, температура плавления, теплота плавления, стандартная энтальпия сублимации

UDC 547.496.3+544-971

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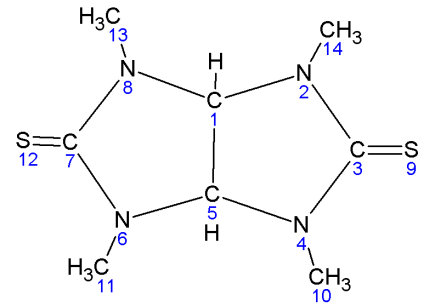
SOME THERMODYNAMIC CHARACTERISTICS OF «THIOMEBICAR» (2,4,6,8-TETRAMETHYLDITHIOGLYCOLURIL)

Using the differential scanning calorimetry and mass spectrometry (in combination with a Knudsen effusion method), the enthalpies of fusion and sublimation for the promising bioactive preparation «thiomebicar» (2,4,6,8-tetramethyldithioglycoluril) have been estimated. A comparative analysis of the obtained data with those for the well-known pharmatseutical «mebicar» (2,4,6,8-tetramethylglycoluril), being a full carbonyl-substituted analogue possessing the pronounced tranquilizing effect, has been carried.

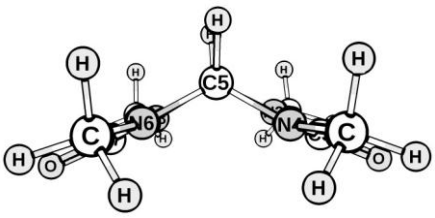
Key words: 2,4,6,8-tetramethyldithioglycoluril, melting point, fusion heat, sublimation standard enthalpy

INTRODUCTION

The heterocyclic molecules of a general formula $(CH)_2[(NR)_2CX]_2$ where R ≡ H or Alk and X ≡ O or S, consisting of two close-to-planar five-membered rings and HC−CH-bridging (glyoxalic) moiety, are known as *N*-alkyl-substituted glycoluril or thioglycoluril derivatives [1-3]. Among them, *N*-tetra-substituted compounds are considered to be the most active [4, 5]. They have found plenty of useful applications including the design and preparation of pharmaceuticals. Let us say, the commercial drug *mebicar* (*adaptol*) based on 2,4,6,8-tetramethylglycoluril is well-known daytime tranquilizer [6, 7]. The properties of *N*-tetramethylated dithioglycoluril or *thiomebicar* (see in Figs. 1*a*,*b*) are still poorly studied although this compound seems not less interesting with scientific and applied viewpoints.



a



b

Fig. 1. Molecular structures of the thiomebicar (a) and mebicar (b): a projection, being parallel to the bicycle plane)

Рис. 1. Структуры молекул тиомебикара (a) и мебикара (b): вид проекции, параллельной плоскости бицикла)

There are evidences that the substitution of carbonyl oxygen by sulphur in bioactive compounds leads often to increasing their activity (e.g., pharmaceutical *piracetam* is less psychotropically active than its thioanalog [8]). In accordance with the data derived using the program of "Prediction of Activity Spectra for Substances" (PASS) [9], the probability to detect the pharmacological activity for thiomebicar is also very high: P_a = 0.80 − 0.95. Meanwhile, the lack of reliable data on its thermodynamic properties in both the crystalline and dissolved state does not allow identifying the interaction-related peculiarities of pharmacophore centers (hydrophobic and donor-accepting groups) of a molecule in question.

Seen in this light, we consider it would be interesting to assess the influence of C=O → C=S substitution on some thermodynamic characteristics (such as the molar enthalpies of sublimation, $\Delta_{sub}H_n^0$, and fusion, $\Delta_{fus}H_n^0$, as well as melting point, $t_{m.p.}$) of *N*-tetramethylglycoluril, based on the previously derived data for mebicar [10]. Immediately prior to discussing the obtained results, it should be noted also that there are several names for the title compound. Its agreed-upon (in the literature) name is 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dithione or tetramethylated bicyclic *bis*ureas (*bis*-tioureas) of the octane series (see Figs. 1*a*,*b*), while the IUPAC naming is 1,3,4,6-tetramethyl-tetrahydro-imidazo[4,5-d]imidazole-2,5(1*H*,3*H*)-dithione [2, 3, 11]. Hence, further for simplicity, we will stick with a trivial (commercial) name of each of the compounds being compared.

EXPERIMENTAL

The tiomebicar or mebicar-S_2 sample ($C_8H_{14}N_4S_2$; molar mass: 230.3589 g·mol^{-1}) was synthesized in the Laboratory of nitrogen-containing compounds of N.D. Zelinsky Institute of Organic Chemistry of the RAS (Moscow) according to the

procedure [2]: by way of reaction of mebicar with a Lawesson's reagent under the influence of heating and stirring. The product yield was not less than 70%. The synthesized sample was recrystallized from absolute ethanol (Fluka puriss, mass fraction purity > 0.998) with further drying for 24 h under reduced (down to ~ 10 Pa) pressure at t = 70 °C to constant mass. The sample purity, being checked using a HPLC method, was 99.5 mol %, with the residual water content (according to a Karl-Fischer titration method) about of 0.007 wt. %. Additionally, the ^{1}H NMR spectrum of thiomebicar was measured for the first time on a Bruker AM 300 MHz (as well as 75 MHz) spectrometer in DMSO-d_6 at T = 300 K. Being derived by such way, the chemical shifts (δ/ppm) were: 3.23 (s, 12 H, 4 Me), 5.69 (s, 2 H, CH−CH) {as well as 33.96 (Me), 77.80 (CH−CH), 181.99 (C=S), respectively}.

The determination of sublimation enthalpy was carried out by a Knudsen's effusion method with mass-spectrometric control of vapor phase. Magnetic mass spectrometer MI 1201 ("SELMI", Ukraine) adapted for effusion experiments in the temperature range from 273 K to 1500 K was used for this purpose. A detailed description of the apparatus as well as experimental procedure has been reported previously [12]. Here we will only note that the resolution of the instrument allowed the determination of the mass number for ions with an accuracy of ±2 amu within a range of (2 to 850) amu at accelerating voltage of 5 kV. Herewith a sample of (50 to 100) mg was evaporated from a molybdenum cylindrical effusion cell with the ratio of "vaporization surface square to effusion orifice square" being equal to ~1000. Choosing the optimal temperature range for mass-spectroscopic measurements was performed proceeding from thermal analysis of the thiomebicar specimen by means of a multipurpose differential scanning calorimeter DSC 204 F1 "Phoenix" (Netzsch-Gerätebau GmbH, Germany). Data on $\Delta_{fus}H_n^0$ and $t_{m.p.}$ derived from heating curves in the melting region were estimated (for both the title compound and mebicar) with the expanded uncertainty of ±0.5 kJ·mol^{-1} and ±0.5ºC, respectively (at a 95% level of confidence).

RESULTS AND DISCUSSION

The thermal measurements showed that the fusion of thiomebicar sample occurs in a very narrow temperature range, being (236.9 to 243.4) ºC without the decomposition process, at $t_{m.p.}$ = 240.15 ºC. By processing (integrating) of DSC melting curve, the value of $\Delta_{fus}H_n^0$ = 23.6 kJ·mol^{-1} for thiomebicar has been derived. In the case of mebicar, the considered quantities were estimated to be 228.15 ºC and 19.1 kJ·mol^{-1}, respectively. That is, on going from *N*-tetraalkyl-substituted glycoluril to its thioanalog, there is a tendency to increase in heat of fusion (by ~4.5 kJ·mol^{-1}) at insignificantly growing temperature of the given process. This fact may be connected with a greater thermal stability of the crystal structure of the latter, probably, due to the formation of stronger bonds in the molecular packing. It is worth noticing that the C−H···O(S)-contacts play a great role in the formation of both crystal kinds [4, 11]. According to the inferences presented in [13], in spite of the common view that S···H bonds are weaker than O···H bonds, the total interaction energies are likely the same in the region of carbonyl and thyonil groups. The point is that, in contrast to ureas, the thiourea's C−N bond is enhanced, while the polarity of C−S bond increases. However, in the case of comparison of bicyclic *bi*-*s*ureas with *bis*thioureas the configuration factor is crucial. Due to rigidity of the heterocyclic core and annelated *cis*-fusion of five-membered rings, the mebicar and thiomebicar molecules adopt a conformation of a "half-open book" [4, 10, 14] (Fig. 1*b*). One can assume that the structure packing of thiomebicar is more "suited" for intermolecular contacts including H-bonding.

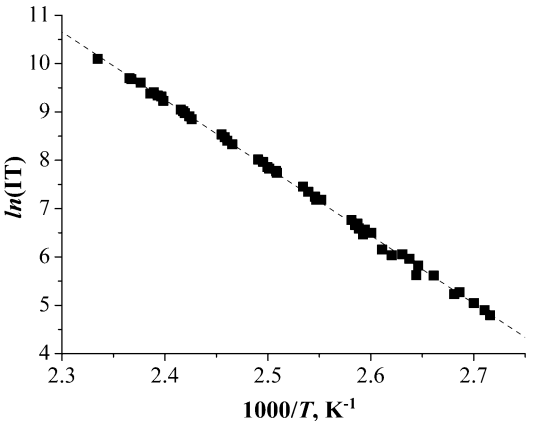


Fig. 2. The *ln* (IT) against *1/T* for thiomebicar
Рис. 2. Зависимость *ln* (IT) от *1/T* для тиомебикара

From this viewpoint, the $\Delta_{sub}H_n^0$ quantity is more sensitive to the energy state of heterocyclic structures being compared. As follows from Fig. 2, the *ln*(IT) − 1/*T* function (where I is the measured ion currents for each species and *T* is temperature of the Knudsen cell) for thioglycoluril is quite well approximated by straight line. The ionic fragments were found to have the temperature coefficients of sublimation being identical with parent ion. No hysteresis in the ion intensity for trends of increasing and decreasing temperature was observed. This circumstance

proves that thermodynamic equilibrium was established in the effusion cell.

The $\Delta_{sub}H_n^0(T)$ values were derived from the linear slope: $B = \Delta_{sub}H_n^0(T)/R$ (see Fig. 2). The analysis carried out using the modified Kirchhoff's equation [12] showed that the value of $\Delta_{sub}H_n^0(298.15\ K) = (116.3 \pm 2.1)\ kJ \cdot mol^{-1}$ for the title compound virtually (within an error limit) does not differ from the mean-weighted value of sublimation enthalpy in the temperature range studied. Previously [10], the value of $\Delta_{sub}H_n^0(298.15\ K) = (108.6 \pm 2.8)\ kJ \cdot mol^{-1}$ for mebicar was derived in the same way. The data obtained are confirmed that the C=O → C=S substitution in the molecules of *N*-tetramethylglycoluril leads to strengthening of its crystalline structure. Herewith, despite the slight difference in $\Delta_{sub}H_n^0$ (being by 7% only), there is a phenomenally sharp decrease (almost four orders of magnitude!) in solubility of a heterocycle in water on going from mebicar to thiomebicar. Suffice it to say that if the solubility of the former attains *ca*. 5 mol·(kg solvent)$^{-1}$, the latter is virtually insoluble in aqueous media. Such an unusual situation did not observe previously at studying the dissolution of open-chain or monocyclic urea derivatives and their thioanalogues. This circumstance requires further investigation.

Acknowledgements

We are grateful to Prof. A.N. Kravchenko and Dr. V.V. Baranov (N.D. Zelinsky Institute of Organic Chemistry of the RAS, Moscow) for assistance in synthesis, purifying and identifying of the thiomebicar sample.

All mass-spectroscopic experiments in the given work were supported by the grant from the Ministry of Education and Science of Russian Federation.

The heats of fusion (melting points) were measured using the equipment of the "The Upper-Volga Regional Centre of Physicochemical Researches" (located at the G.A. Krestov Institute of Solution Chemistry of the RAS, Ivanovo, Russia).

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Поступила в редакцию 13.07.2016
Принята к опубликованию 28.10.2016

Received 13.07.2016
Accepted 28.10.2016