J. Chem. Thermodynamics 78 (2014) 152–158

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

Effect of the structure, solid state and lipophilicity on the solubility of novel bicyclic derivatives

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ARTICLE INFO

Article history:
Received 16 April 2014
Received in revised form 9 June 2014
Accepted 12 June 2014
Available online 30 June 2014

Keywords:
Novel bicyclic derivatives
Solubility
Lipophilicity
Descriptors

ABSTRACT

Novel bicyclic derivatives have been synthesized. The solubility of drug-like substances in phosphate buffer pH 7.4 has been measured within the range of ($9.02 \cdot 10^{-5}$ to $1.05 \cdot 10^{-4}$) mol/l. The relationship between the chemical nature and the structure of the aryl substituents and the solubility parameter was investigated. The fusion temperatures, enthalpies and entropies have been determined experimentally. The influence of thermophysical characteristics and lipophilicity on the solubility was studied using regression analysis. The calculations by the solubility/lipophilicity equation showed an overall improvement of the predictions equal to 0.5 log units. It was concluded that the solvation has a considerable influence on the solubility of the compounds under consideration. It was also determined that the alkyl- and halogen-derivatives solubility values correlate with HYBOT descriptors characterizing the (donor + acceptor) properties of the substances. The thermodynamic parameters of the solubility process were calculated using the temperature dependences. The study also revealed that the solubility of the bicyclic compounds is characterized by high endothermicity of the processes and negative entropies.

1. Introduction

Solubility is an important molecular property, which plays a large role in the behavior of compounds and is of interest in diverse areas of physical, pharmaceutical, material and environmental research. It is well known that solubility limitations are determined, on the one hand, by the physicochemical properties of the solid state and, on the other hand, by the compound solvation characteristics. The results of the numerous investigations [1] show that the growth of the molecule size and polarizability, the increase in the lipophilicity and the extension of the energy interval between the highest occupied molecular orbital and the lowest unoccupied one reduce the solubility. Besides, the ability to form hydrogen bonds also has a great influence on the compound solubility in polar solvents. One of the ways to regulate the solubility of the compounds is a structural modification of the molecule.

The literature data indicate the efficiency of bicyclic heterocyclic derivatives in treatment of different medical problems, such as cancer [2], influenza [3], fungal infections [4] and neurodegenerative diseases [5]. It is demonstrated [6], that a substituted tert-amino group in the structure of the bicyclic compound affects physicochemical properties including an aqueous solubility. The authors [7] synthesized bicyclic thiazines capable of inhibiting nitric oxide synthase and investigated the influence of their structure on the radioprotective biological activity. To increase the bioavailability the authors suggested synthesizing a more lipophilic analogue by 'inserting' a parent structure into a bicyclo[3.3.1]nonane core. The introduction of the aryl fragment into the bicyclic structure creates an optimal hydrophilicity/lipophilicity balance which is supposed to enhance the efficiency of the pharmacological action of these compounds [8]. In addition, the different chemical nature of the substituents introduced into the benzene ring – alkyl, carbonyl, and halogen derivatives are widely used in pharmaceutics and make it possible to predict new specific properties of the synthesized substances.

The present study is a continuation of our investigations into novel bicyclic compounds [9]. The goal of the investigation is to determine the regularities in the influence of the molecular structure, solid state, lipophilicity and (donor + acceptor) properties of the investigated drug-like bicyclic derivatives on their solubility in the phosphate buffer solution pH 7.4, modeling the blood system medium.

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http://dx.doi.org/10.1016/j.jct.2014.06.014
0021-9614/

2. Experimental section

2.1. Materials

The eleven novel bicyclic heterocycle derivatives [3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine were synthesized as indicated in scheme 1.

A solution of sodium bicarbonate (1.85 g, 22 mmol) in the minimal amount of water was added dropwise to a stirred solution of 3,4-dichlorophenylisothiocyanate (2.04 g, 10 mmol) and (3-bromomethyl)piperidine hydrobromide (2.56 g, 10 mmol) in 30 ml of methanol. When the formation of the precipitate was over, it was filtered and recrystallized from dioxane to yield 2.1 g (70%) of the obtained compound as a white solid. ^{1}H NMR spectra of compounds were recorded on a Bruker CXP-200 instrument (Germany) in $CDCl_3$. Chemical shifts δ are referenced to Me_4Si. Elemental analysis of the compounds obtained was performed on CHN analyzer Carbo Erba (Czech Republic). The origin, purification method, purity, and method of purity determination of all samples are presented in table 1.

2.1.1. (4-Methyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**1**)

Anal. Calcd. for $C_{14}H_{18}N_2S$: C 68.25%, H 7.36%, N 11.37%. Found: C 68.33%, H 7.40%, N 11.32%.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.62 (*d*, *J* = 12.90 Hz, 1H, C(6)H_a), 1.73 to 2.18 (*m*, 3H, C(6)H_e, C(7)H_2), 2.48 (*c*, 3H, CH_3), 2.56 (*d*, *J* = 10.17 Hz, 1H, C(5)H), 2.93 (*dd*, *J* = 2.35, 12.05 Hz, 1H, C(4)H_a), 3.19 to 3.45 (*m*, 3H, C(4)H_e, C(8)H_a, C(9)H_a), 3.77 (*d*, *J* = 13.70 Hz, 1H, C(8)H_e), 4.32 (*d*, *J* = 13.30 Hz, 1H, C(9)H_e), 6.91 (*d*, *J* = 7.83 Hz, 2H, H_{ar}) 7.27 (*d*, *J* = 7.83 Hz, 2H, H_{ar}).

2.1.2. (3-Methyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**2**)

Anal. Calcd. for $C_{14}H_{18}N_2S$: C 68.25%, H 7.36%, N 11.37%. Found: C 68.39%, H 7.44%, N 11.26%.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.19 (1H, *m*, H_{ar}), 6.87 (1H, *d*, *J* = 7.6 Hz, H_{ar}), 6.66 (1H, *c*, H_{ar}), 6.63 (1H, *d*, *J* = 7.6 Hz, H_{ar}), 4.15 (1H, *d*, *J* = 12.2 Hz, C(9)H_e), 3.61 (1H, *dq*, *J* = 1.9, 13.7 Hz, C(8)H_e), 3.16 (3H, *m*, C(4)H_e, C(8)H_a, C(9)H_a), 2.79 (1H, *dd*, *J* = 2.7, 11.7 Hz, C(4)H_a), 2.43 (1H, *dd*, *J* = 2.7, 11.0 Hz, C(5)H), 2.33 (3H, *c*, CH_3), 1.74 (3H, *m*, C(6)H_e, C(7)H_2), 1.45 (1H, *m*, C(6)H_a).

2.1.3. (4-Ethyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**3**)

Anal. Calcd. for $C_{15}H_{20}N_2S$: C 69.19%, H 7.74%, N 10.76%. Found: C 69.03%, H 7.84%, N 10.84%.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.13 (2H, *d*, *J* = 8.3 Hz, H_{ar}), 6.78 (2H, *d*, *J* = 8.3 Hz, H_{ar}), 4.17 (1H, *d*, *J* = 13.0 Hz, C(9)H_e), 3.63 (1H, *dq*, *J* = 1.8, 13.6 Hz, C(8)H_e), 3.15 (3H, *m*, C(4)H_e, C(8)H_a, C(9)H_a), 2.76 (1H, *dd*, *J* = 2.7, 12.7 Hz, C(4)H_a), 2.68 (2H, *q*, *J* = 7.6, CH_2), 2.40 (1H, *dd*, *J* = 2.4, 10.8 Hz, C(5)H), 1.70 (3H, *m*, C(6)H_e, C(7)H_2), 1.47 (1H, *m*, C(6)H_a), 1.25 (3H, *t*, *J* = 7.6, CH_3).

2.1.4. (4-Isopropyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**4**)

Anal. Calcd. for $C_{16}H_{22}N_2S$: C 70.03%, H 8.08%, N 10.21%. Found: C 69.93%, H 8.18%, N 10.14%.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.27 (*c*, 3H, CH_3), 1.27 (*c*, 3H, CH_3), 1.39 to 1.57 (*m*, 1H, C(6)H_a), 1.62 to 2.00 (*m*, 3H, C(6)H_e, C(7)H_2), 2.44 (*d*, *J* = 8.38 Hz, 1H, C(5)H), 2.81 (*dd*, *J* = 2.83, 12.71 Hz, 1H, C(4)H_a), 2.91 (*m*, 1H, $CHMe_2$), 3.06 to 3.36 (*m*, 3H, C(4)H_e, C(8)H_a, C(9)H_a), 3.65 (*d*, *J* = 13.96 Hz, 1H, C(8)H_e), 4.20 (*d*, *J* = 13.96 Hz, 1H, C(9)H_e), 6.82 (*d*, *J* = 8.38 Hz, 2H, H_{ar}) 7.20 (*d*, *J* = 8.38 Hz, 2H, H_{ar}).

2.1.5. (4-Chloro-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**5**)

Anal. Calcd. for $C_{13}H_{15}ClN_2S$: C 58.53%, H 5.67%, N 10.50%. Found: C 58.53%, H 5.67%, N 10.50%.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.23 (4H, *m*, H_{ar}), 4.19 (1H, *d*, *J* = 12.8 Hz, C(9)H_e), 3.66 (1H, *dq*, *J* = 1.9, 13.6 Hz, C(8)H_e), 3.18 (3H, *m*, C(4)H_e, C(8)H_a, C(9)H_a), 2.72 (1H, *dd*, *J* = 2.8, 12.7 Hz, C(4)H_a), 2.42 (1H, *dd*, *J* = 2.3, 10.9 Hz, C(5)H), 1.73 (3H, *m*, C(6)H_e, C(7)H_2), 1.47 (1H, *m*, C(6)H_a).

2.1.6. (3,4-Dichloro-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**6**)

Anal. Calcd. for $C_{13}H_{14}Cl_2N_2S$: C 51.83%, H 4.68%, N 9.30%. Found: C 51.58%, H 4.84%, N 9.24%.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.38 (1H, *d*, *J* = 8.6 Hz, H_{ar}), 6.99 (1H, *d*, *J* = 2.3 Hz, H_{ar}), 6.73 (1H, *dd*, *J* = 2.3, 8.6 Hz, C(5)H), H_{ar}), 4.19 (1H, *d*, *J* = 12.2 Hz, C(9)H_e), 3.64 (1H, *dq*, *J* = 1.9, 13.7 Hz, C(8)H_e), 3.25 (3H, *m*, C(4)H_e, C(8)H_a, C(9)H_a), 2.84 (1H, *dd*, *J* = 2.8, 11.6 Hz, C(4)H_a), 2.51 (1H, *dd*, *J* = 2.8, 10.9 Hz, C(5)H), 1.77 (3H, *m*, C(6)H_e, C(7)H_2), 1.47 (1H, *m*, C(6)H_a).

2.1.7. (3-Chloro-4-methyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**7**)

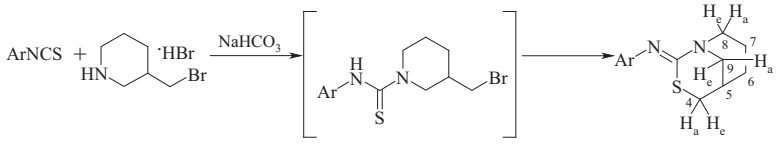
Anal. Calcd. for $C_{14}H_{17}ClN_2S$: C 59.88%, H 6.10%, N 12.62%. Found: C 59.62%, H 6.01%, N 12.77%.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.31 (1H, *d*, *J* = 8.1 Hz, H_{ar}), 7.27 (1H, *d*, *J* = 2.3 Hz, H_{ar}), 7.08 (1H, *dd*, *J* = 2.3, 8.1 Hz, H_{ar}), 4.18 (1H, *d*, *J* = 12.2 Hz, C(9)H_e), 3.63 (1H, *dq*, *J* = 2.0, 13.7 Hz, C(8)H_e), 3.18 (3H, *m*, C(4)H_e, C(8)H_a, C(9)H_a), 2.80 (1H, *dd*, *J* = 2.8, 11.7 Hz, C(4)H_a), 2.47 (1H, *dd*, *J* = 2.6, 10.8 Hz, C(5)H), 2.30 (3H, *c*, CH_3), 1.77 (3H, *m*, C(6)H_e, C(7)H_2), 1.46 (1H, *m*, C(6)H_a).

2.1.8. (4-Fluoro-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**8**)

Anal. Calcd. for $C_{13}H_{15}FN_2S$: C 62.37%, H 6.04%, N 7.59%. Found: C 62.44%, H 5.98%, N 8.06%.

^{1}H NMR (200 M Hz, $CDCl_3$, δ): 1.55 (*d*, *J* = 13.03 Hz, 1H, C(6)H_a), 1.63 to 2.15 (*m*, 3H, C(6)H_e, C(7)H_2), 2.53 (*d*, *J* = 11.17 Hz, 1H, C(5)H), 2.84 (*d*, *J* = 12.10 Hz, 1H, C(4)H_a), 3.01 to 3.39 (*m*, 3H, C(4)H_e, C(8)H_a, C(9)H_a), 3.65 (*d*, *J* = 13.96 Hz, 1H, C(8)H_e), 4.20 (*d*, *J* = 12.10 Hz, 1H, C(9)H_e), 6.95 (*d*, *J* = 8.38 Hz, 2H, H_{ar}) 7.58 (*d*, *J* = 8.38 Hz, 2H, H_{ar}).



SCHEME 1.