J Incl Phenom Macrocycl Chem (2007) 57:415–417
DOI 10.1007/s10847-006-9227-6

ORIGINAL ARTICLE

Molecular complexes of 4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-a]isoindol-4-ones with β-cyclodextrin

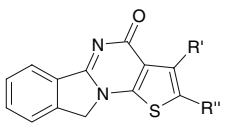
Sergii Rudiuk · Zoia Voitenko · Sergii Riabov · Alexander Roshal

Received: 15 May 2006 / Accepted: 20 October 2006 / Published online: 19 January 2007

Abstract The solubilization of 4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-a]isoindol-4-ones by β-cyclodextrin by two routes—solvatofluorochromic and extraction methods was studied. The solvatofluorochromic investigations showed that the changes occurred in the medium's polarity do not influence onto the fluorescent characteristics of these compounds. However, using extraction method their solubilization by β-cyclodextrin was observed.

Keywords β-Cyclodextrin · Condensed isoindoles · Molecular complexes

The cyclodextrins are widely used in pharmaceutics because of their biocompatibility, nontoxity and their capability to form the inclusion complexes with many organic compounds and drugs [1–5]. Condensed isoindoles have a number of interesting and promising properties both in chemical and biological [6–8] aspects. Thus, it is of a great interest to solubilize them in the water. We have synthesized a range of derivatives of the 4,10-dihydrothieno [3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-ones (**1**). The NMR-characteristics of these compounds are summarized in Table 1. We investigated their solubilization in the water by β-cyclodextrin applying both solvatofluorochromic and extraction methods.



1

1a	R'-R'' = $(CH_2)_4$	
1b	R' = H;	R'' = Ph
1c	R' = 4-C_6H_4Br;	R'' = Me
1d	R' = 4-C_6H_4Me;	R'' = H
1e	R' = 2,4-$C_6H_3Me_2$;	R'' = H
1f	R' = Me;	R'' = COOEt
1g	R' = Me;	R'' = Me
1h	R' = H;	R'' = Et
1i	R' = Ph;	R'' = H

First, we estimated qualitatively if a solubilization took place—dropping of the compound **1** to the water results to the formation of turbid solution. Then, after adding to the solution obtained a drop of β-cyclodextrin solution, it became transparent. So, it could be attributed that the solubilization of 4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-ones **1** happens.

These compounds absorb in the visible spectral region and demonstrate fluorescence at 440 nm. Changes of absorption and fluorescence in the presence of β-cyclodextrin we took as a criterion of molecular complexes formation. The optical densities and intensities of fluorescence of 4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-ones in the water in β-cyclodextrin presence and without it were compared. However, we didn't observe any sufficient changes of spectral properties for above compounds when β-cyclodextrin was

S. Rudiuk
Laboratoire des IMRCP, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse, France

Z. Voitenko
Taras Shevchenko Kiev National University, Volodymirskaya str. 64, Kiev 01017, Ukraine

S. Riabov (✉)
Institute of Macromolecular Chemistry, NAS of Ukraine, Kharkovskoe shosse 48, Kiev 02160, Ukraine
e-mail: jotas@mail.vtv.kiev.ua

A. Roshal
Institute of Chemistry of Kharkiv National University, 4 pl. Svobody, Kharkiv 61077, Ukraine

Table 1 The data of NMR-spectra of 4,10-dihydrothieno[3′,2′:5,6]pyrimido [2,1-a]isoindol-4-ones (**1**)

No.	Chemical shifts, p.m.								
	Aromatic protons of isoindole fragment				CH_2 of isoindole	Protons of R′ and R″			
1a	8.44 d. 1H (CHarom)	8.14 t. 1H (CHarom)	8.03 d. 1H (CHarom)	7.99 t. 1H (CHarom)	5.78 s. 2H CH_2	3.23 m. 2H CH_2	3.08 m. 2H CH_2	2.13 m. 4H $2CH_2$	
1b	8.49 d. 1H (CHarom)	8.18 t. 1H (CHarom)	8.08 d. 1H (CHarom)	8.02 m. 1H + 2H(R) (CHarom)	5.90 m. 2H CH_2	7.86 m. 2H CHarom	7.63 m. 2H CHarom		
1c	8.39 d. 1H (CHarom)	8.17 t. 1H (CHarom)	8.06 d. 1H (CHarom)	8.00 t. 1H (CHarom)	5.86 s. 2H CH_2	7.78 d. 2H 2CHarom	7.35 d. 2H 2CHarom	2.64 s. 3H CH_3	
1d	8.48 d. 1H (CHarom)	8.18 t. 1H (CHarom)	8.07 d. 1H (CHarom)	7.99 t. 1H (CHarom)	5.89 s. 2H CH_2	7.51 d. 2H 2CHarom	7.42 d. 2H 2CHarom	7.51 s. 1H CHarom	2.58 s. 3H CH_3
1e	8.45 d. 1H (CHarom)	8.19 t. 1H (CHarom)	8.08 d. 1H (CHarom)	7.99 t. 1H (CHarom)	5.91 s. 2H CH_2	7.52 s. 1H CHarom	7.25 m. 3H 3CHarom	2.50 s. 3H CH_3	2.28 s. 3H CH_3
1f	8.50 d. 1H (CHarom)	8.22 t. 1H (CHarom)	8.08 d. 1H (CHarom)	8.03 t. 1H (CHarom)	5.86 s. 2H CH_2	4.71 q. 2H OCH_2	3.17 s. 3H CH_3	1.65 t. 3H CH_3	
1g	8.44 d. 1H (CHarom)	8.14 t. 1H (CHarom)	8.03 d. 1H (CHarom)	7.99 t. 1H (CHarom)	5.77 s. 2H CH_2	2.71 s. 3H CH_3	2.69 s. 3H CH_3		
1h	8.47 d. 1H (CHarom)	8.16 t. 1H (CHarom)	8.05 d. 1H (CHarom)	8.00 t. 1H (CHarom)	5.83 s. 2HO CH_2	3.20 q. 2H CH_2	1.61 t. 3H CH_3		
1i	8.39 d. 1H (CHarom)	8.15 t. 1H (CHarom)	8.04 d. 1H (CHarom)	7.95 t. 1H (CHarom)	5.87 s. 2H CH_2	7.59 m. 6H 6CHarom			

added. For example, the fluorescence curves for 2-phenyl-4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-one (**1b**) are shown in Fig. 1.

The solvatofluorochromic investigations revealed that the changes occurred in the medium's polarity do not influence onto the absorption and emission characteristics of 4,10-dihydrothieno-[3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-ones **1**, e.g. on shifting of the absorption and fluorescence band or its intensity. That fact permitted to conclude that transfer of **1** in less polar cyclodextrin cavity does not influence on their spectral properties.

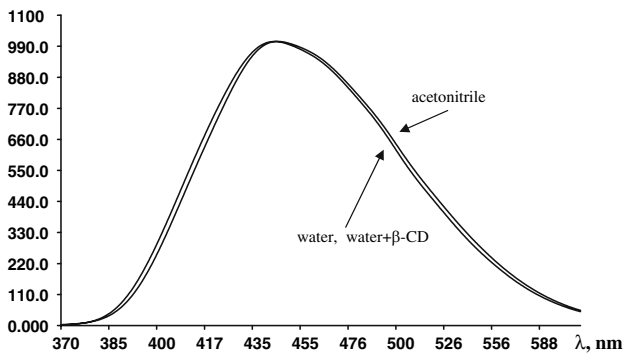


Fig. 1 The fluorescence spectra of 2-phenyl-4,10-dihydrothieno[3′,2′:5,6] pyrimido[2,1-*a*]isoindol-4-one **1b** in acetonitrile and water correspondingly, with *β*-cyclodextrin and without it

Thus, it was impossible to observe directly the solubilization of compounds **1a–i** with *β*-cyclodextrin by the spectral methods. That is why, we decided to use indirect method for investigation of this process.

Compounds were dissolved in dichloromethane, and the solutions obtained were extracted in the same conditions by distilled water and *β*-cyclodextrin water solution. The fluorescence of the cyclodextrin-containing water extract appears to be three times (approximately) more intensive compared with water. The spectral effect obtained for compound **1a** is shown in Fig. 2.

The results obtained permit to demonstrate the better extraction of compounds investigated to water medium in the presence of *β*-cyclodextrin. This phenomenon can be interpreted by incapsulation of 4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-a]isoindol-4-ones into cyclodextrin cavity.

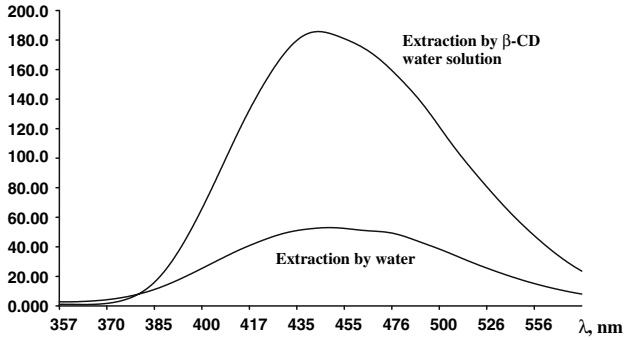


Fig. 2 Comparison of the fluorescence spectra for the substance **1a** extracted by water and β-cyclodextrin water solution

Experimental part

The NMR-spectra were carried out using Bruker-400 in TFA with TMS as a standard. The absorption spectra were recorded on the spectrophotometer Hitachi U3210, and the fluorescence spectra on the spectrofluorimeter F4010.

Solvatofluorochromic investigation of 4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-ones (1) solubilization by β-cyclodextrin

Before providing experiments 4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-ones **1a–i** were recrystallized two times from DMF. Several small crystals of compounds **1** were dissolved in acetone. One drop of this solution was added to the distilled water and some other solvents—DMFA, methanol, DMSO. Both absorption and fluorescence spectra of the solution obtained were monitored. Separately, β-cyclodextrin water solution was prepared. Then, a drop of this solution was added to the water solution of 4,10-dihydrothieno [3′,2′:5,6] pyrimido[2,1-*a*]isoindol-4-ones **1**, and absorption and fluorescence spectra were monitored again.

The extraction method for investigation of 4,10-dihydrothieno[3′,2′:5,6] pyrimido[2,1-*a*]isoindol-4-ones 1 solubilization by β-cyclodextrin

The concentrated solution of 4,10-dihydrothieno[3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-ones **1** in dichloromethane was prepared. Two test tubes were taken, filled with 2 ml of distilled water and with 2 ml of β-cyclodextrin water solution, respectively. To each test tube 10 ml of compound **1a** dissolved in dichloromethane was added. After 5 min of stirring at room temperature, aliquation proceeded for 15 min and finally, fluorescence spectra of both aqueous phases separated were accomplished.

Acknowledgement This work is supported by the STCU (Science and Technology Center in Ukraine), Project No. 3643.

References:

1. Inoue, Y., Rekharsky,M.V.: Proceedings of the 12th International Cyclodextrin Symposium – Montpellier, France, 16–19 May 2004, pp. 263–266
2. Gazpio, C., Zomoza, A., Gonzalez-Gaitano, G., Isasi, J.R., Martinez-Oharriz, C., Velaz, I.: Proceedings of the12th International Cyclodextrin Symposium – Montpellier, France, 16–19 May 2004, pp. 271–274
3. Jordheim, L.P., Degobert, G., Fessi, H., Simon, P., Peyrottes, S., Perigaud, C., Dumontet, C.: Proceedings of the 12th International Cyclodextrin Symposium – Montpellier, France,16–19 May 2004, pp. 291–294
4. Szejtli, J.: Cyclodextrin Technology, Kluwer. Academic Press, Dordrecht p. 321 (1988)
5. (a) Szejtli, J.: Introduction and general overview of cyclodextrin chemistry. Chem. Rev. **98**(5), 1743–1754 (1998); (b) Hedges, A.R.: Industrial applications of cyclodextrins. Chem. Rev. **98**(5), 2035–2044 (1998)
6. Houlihan, W.J., Sandoz A.G.: Patent 3509147 US, C07D51/48, No.591694, 1970
7. Voitenko, Z.V., Doct. of Sci. Thesis, Taras Shevchenko Kiev National University, 2006
8. Voitenko, Z.V., Pocholenko, O.A., Chkarov, O.O., Shishkin, O.V., Shishkina, S.V., Dall'Ava, A., Vedrenne, M., Sanchez, M., Wolf, J-G.: Structure of the cycloaddition products of pyrido[2,1-a]isoindole with maleimide derivatives: x-ray diffraction analysis and ^{1}H NMR variable-temperature spectra. Eur. J. Org. Chem. **2001**(7), 1401–1405 (2001)