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Basicity, Quaternization and Hydrolysis of 2*H*- and 4*H*-1,3-Benzothiazine Isomers [1]

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Summary. The basicities of 2*H*- and 4*H*-1,3-benzothiazines (**1**, **2**) were measured spectrophotometrically in buffer solutions. The rates of quaternization with methyl iodide were monitored in sealed ampoules by an oscillometric method. The stabilities were determined by measurement of the rate of acidic hydrolysis via changes in the uv/vis spectra. As a cyclic Schiff base, 4-aryl-2*H*-1,3-benzothiazine (**2**) is the stronger base, and reacts about ten times faster with methyl iodide; its stability is greater than that of 2-aryl-4*H*-1,3-benzothiazine (**1**). On the basis of these results and by means of the different water-solubilities of the hydrochlorides the isomers formed during the synthesis can be separated and purified.

Keywords. 1,3-Benzothiazines; Basicity; Rate of hydrolysis; Quaternization.

Basizität, Quaternisierung und Hydrolyse von isomeren 2*H*- und 4*H*-Benzothiazinen

Zusammenfassung. Die Basizität und die Geschwindigkeit der Hydrolyse von 2*H*- und 4-*H*-Benzothiazinen (**1**, **2**) in saurer Lösung wurde UV/VIS spektroskopisch gemessen. Die Reaktionsgeschwindigkeit der Quarternisierung mit Methyljodid wurde oszillometrisch in geschlossenen Ampullen bestimmt. 4-Aryl-2*H*-1,3-benzothiazin (**2**) ist als zyklische Schiffsche Base die stärkere Base, deren Reaktionsgeschwindigkeit mit Methyljodid ungefähr zehnmal größer ist als die des 2-Aryl-4*H*-1,3-benzothiazin (**1**); **2** ist auch stabiler. Aufgrund dieser Ergebnisse und der unterschiedlichen Wasserlöslichkeit ihrer Hydrochloride konnten die während der Synthese nebeneinander entstehenden Isomeren getrennt werden.

Introduction

Following earlier systematic studies [2] on 1,3-benzothiazine derivatives, determination of the basicities and stabilities of the hydrochlorides of 2-aryl-4*H*- and 4-aryl-2*H*-1,3-benzothiazines were of interest for practical reasons. In the course of the synthesis of these compounds the two isomeric heterocycles are formed together, and their separation was possible earlier only by means of preparative TLC [3]. We use these compounds as starting materials, and therefore an effective preparative separation method had to be devised that was suitable for larger quantities. Furthermore, we wanted to demonstrate by physicochemical methods that the 4-aryl-2*H*-1,3-benzothiazines, as cyclic Schiff bases, are stronger bases than the 2-aryl-4*H*-1,3-benzothiazines, which are cyclic thioacid imides. We also set out to

confirm the observation [4, 5] that in acidic solution the 4*H*-1,3-benzothiazines are hydrolysed faster than the 2*H*-1,3-benzothiazine isomers, by determining the rate constants of the hydrolysis of these compounds.

Results and Discussion

Basicity

These investigations were carried out with the isomers 6,7-dimethoxy-2-phenyl-4*H*-(**1**) and 6,7-dimethoxy-4-phenyl-2*H*-1,3-benzothiazine (**2**).

The basicities of compounds **1** and **2** can be measured spectrophotometrically, since the basic functional group is a part of the chromophore, and thus the uv/vis spectra of the bases are significantly different from those of the conjugate acids. In the spectrum of the hydrochloride of the base, a bathochromic shift is observed:

$$\lambda_{max}(\mathbf{1}) = 245\,\text{nm} \rightarrow \lambda_{max}(\mathbf{1} \cdot \text{HCl}) = 275\,\text{nm},$$

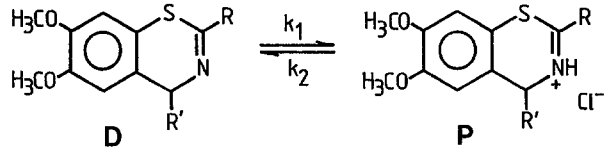
$$\lambda_{max}(\mathbf{2}) = 365\,\text{nm} \rightarrow \lambda_{max}(\mathbf{2} \cdot \text{HCl}) = 426\,\text{nm}.$$

Through measurement of the absorbance in buffers at various *pH*, the concentrations of the two forms (see formula scheme) can be determined and the basicity can be computed [5],

$$pK_A = pH + \log\frac{\mathbf{P}}{\mathbf{D}},$$

$$pK_B = 14 - pK_A,$$

where **P** and **D** are the concentrations of the protonated and deprotonated bases.



D **P**

1: $R = Ph, R' = H$

2: $R = H, R' = Ph$

$$K_A = [H^+] \cdot \frac{k_2}{k_1}$$

The pK_A and pK_B values computed [7] are as follows:

1: $pK_B = 10.82$, $pK_A = 3.18$, $\log \varepsilon_P = 4.38$, $\log \varepsilon_D = 3.68$,

2: $pK_B = 9.36$, $pK_A = 4.64$, $\log \varepsilon_P = 4.10$, $\log \varepsilon_D = 3.47$.

From these pK_A values, it can be concluded that the investigated benzothiazine derivatives are weak bases, and that 6,7-dimethoxy-4-phenyl-2*H*-1,3-benzothiazine (**2**), a Schiff base derivative, is a significantly stronger base than 6,7-dimethoxy-2-phenyl-4*H*-1,3-benzothiazine (**1**).

Rate of Quaternization

Since important data about the stereoelectronic and stereochemical properties of nitrogen-containing compounds can be obtained through their quaternization, the rates of quaternization were determined. The obtained data and the computed activation parameters are shown in Table 1.

Table 1. Kinetic parameters of quaternization of **1** and **2** with methyl iodide

Compound	k_1/T (10^{-5} s^{-1}/K)	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (J/K mol)	$\Delta G^{\neq}_{298\,K}$ (kJ/mol)
1	2.36/331 3.24/337 9.04/347 17.07/352	89.47	−45.9	103.1
2	6.81/315 10.67/321 16.58/326 22.29/331	62.75	−106.7	94.5

It can be seen from the tabulated data that the stronger base reacts about ten times faster than the weaker one, i.e. the free energy of activation is smaller for compound **2** than for compound **1**. It should be mentioned that the activation entropy of compound **1** is about twice that of **2**. This means that in the activation complex of compound **2** the newly-formed bond between the nitrogen and the methyl group is stronger than that in compound **1**, which is in accordance with the difference between the basicities of the two compounds.

Acidic Hydrolysis

It seemed worthwhile to measure the acidic hydrolysis of the compounds, in order to obtain data on their stabilities and hence to develop a method for their separation. Therefore, the first step of the hydrolysis was measured, i.e. the water addition, which is the slowest step. On water addition, the C=N bond is transformed into a C—N bond and thus the conjugation is broken; this can be followed by means of uv/vis spectrophotometry. Through the use of hydrochloric acid in a 1 000-fold excess, pseudo-first-order kinetics can be found. The kinetic data and activation parameters are given in Table 2.

The stability of isomer **2** is considerably greater than that of isomer **1**. Though the activation entropy of **2** is about half that of **1** as in the case of quaternization, its activation free energy is higher than that of **1**. This compensation is explained by the activation enthalpy, since the double bond of the cyclic thioacid imide is less stable than that of the cyclic Schiff base.

As this effect is predominant, the reaction cannot be carried out under the same conditions for the two isomers. Therefore, at low temperature the hydrolysis of the 2*H* isomer (**2**) cannot be measured, and nor can that of the 4*H* isomer (**1**) at high temperature, since the rate is then too low or too high, respectively.

Table 2. Kinetic parameters of acidic hydrolysis of **1** and **2**

Compound	k_1/T ($10^{-6}\,s^{-1}/K$)	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (J/K mol)	$\Delta G^{\neq}_{298\,K}$ (kJ/mol)
1	16.7/343 34.0/353 66.5/363	68.6	−118.4	103.8
2	1.63/373 2.25/383 3.07/393	35.4	−243.5	107.9

The excellent water-solubility of the hydrochloride of compound **2**, compared with the practically water-insolubility of the salt of isomer **1**, could be utilized to separate the isomers. This was also possible in the case of other aryl substituents in a preparative way. Moreover, the different hydrolysis rates permitted the removal of a small amount of the hydrochloride of **1**, present in an aqueous solution of the hydrochloride of **2**, through heating of the solution, and thus isomer **2** could readily be obtained [2].

Experimental

The syntheses of compounds **1** and **2** have been described elsewhere [4].

The basicity measurements were made in methanol on a SPECORD UV/VIS spectrophotometer, using buffer solutions in the $pH = 2$–7 region. The evaluation was at 275 nm for compound **1** and at 426 nm for compound **2**. The molar absorptivities of forms **D** and **P**, the concentrations and the base ionization constants were computed with the simplex method [7] using a Commodore 128 personal computer.

The rates of quaternization of compounds **1** and **2** were measured by using a methyl iodide excess in acetonitrile. The reactions were carried out till 50% conversion and thus the evaluation could be performed with good approximation for a pseudo-first-order reaction. The formation of the quaternary salts was monitored via an oscillometric method.

The acidic hydrolysis was carried out in sealed ampoules in a thermostat at different temperatures, with a precision of ± 0.2°C, and evaluations were made on a SPECORD UV/VIS spectrophotometer at 377 and 430 nm for compound **1** and at 340 and 430 nm for compound **2**.

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