Chem. Anal. (Warsaw), **51**, 653 (2006) **REVIEW**

Iodimetric Titration of Sulfur Compounds in Alkaline Medium

by Witold Ciesielski* and Robert Zakrzewski

Department of Instrumental Analysis, University of Łódź, ul. Pomorska 163, 90-236 Łódź, Poland

Keywords: Iodimetric titration; Potentiometry; Coulometry; Thiols; Determination

The possibilities of application of iodine as a titrant in determination of sulfur compounds have been presented. The influence of the reaction medium, the nature of compounds, and the thiol–thione tautomerism on the reaction stoichiometry of sulfur compounds with iodine has been discussed. The conditions of volumetric titration with visual and potentiometric end-point detection and coulometric titration with biamperometric end-point detection have been described. The advantages of the applied analytical techniques in the determination of selected sulfur compounds in farmaceutical preparations have been presented.

Przedstawiono możliwości zastosowania jodu jako titrantu do oznaczania związków siarki. Omówiono wpływ środowiska reakcji, budowy cząsteczki związku oraz tautomerii tiol–tion na stechiometrię reakcji związku siarki z jodem. Opisano warunki zastosowania miareczkowania objętościowego z wizualną i potencjometryczną detekcją punktu końcowego, a także miareczkowania kulometrycznego z biamperometryczną detekcją punktu końcowego. Przedstawiono zalety stosowanych technik analitycznych do oznaczania wybranych związków siarki w preparatach farmaceutycznych.

* Corresponding author. E-mail: ciesielski@uni.lodz.pl; Fax: +48 42 635 58 08

Iodine is one of the most popular reagents in a chemical analysis. In iodometry, it is used as a titrant in a direct titration, as well as in the indirect titration, which is based on the reaction between strong oxidizing agents and a large excess of iodide ions to produce iodine in the amount equivalent to the analyte. Iodine is subsequently titrated with a standard solution of a reducing agent [1].

Conditions in the solution play an important role during iodimetric reaction. To perform fast and complete reaction of the oxidants of relatively low reduction potential (*e.g.* sodium thiosulfate, hydrogen sulfide), acidic solution of iodine must be used. However, to oxidize weak reducing agents (arsenic(III) or antimonium(III) ions) with iodine, either neutral or alkaline medium is required.

Normal redox potential of the reversible I_2/I^- couple is 0.535 V. This value is independent of the solution pH up to pH 9. At higher pH, iodine reacts with hydroxide ions to produce iodide and iodate(I) ions.

Volatility of iodine significantly hinders iodimetric titration. However, loss of iodine decreases considerably when titration is performed swiftly, at low temperature, and in a conical flask with a glass stopper. Another way to prevent evaporation of iodine is to add potassium iodide to the iodine solution. In the presence of potassium iodide solubility of iodine in water increases due to the formation triiodide ions. Equilibrium of this reaction is favourably shifted to the right. Finally, triiodide ions instead of iodine become the reactive species.

The equation below describes oxidation of iodide ions by atmospheric oxygen in acidic solution:

$$4I^- + O_2 + 4H^+ \rightarrow 2I_2 + 2H_2O \quad (1)$$

It is recommended to perform titration in a shadowed place. Also the solution ought to be stored in dark-glass bottles. The reason for this action is to eliminate side reaction catalyzed by strong light and certain ions, for instance copper(II). Another factor that influences oxidation is pH of the reaction media. According to the general rule, reaction rate increases at lower pH. Therefore, reaction between iodide ions and oxygen is negligible in neutral conditions while in alkaline media is completely hindered.

To overcome the above obstacles, it is suggested to apply standard solution of potassium iodate(V) with a slight excess of potassium iodide as a titrant. Under strong acidic conditions, the below reaction proceeds [2]:

$$IO_3^- + 5I^- + 6H^+ \rightarrow 3I_2 + 3H_2O \quad (2)$$

in which iodine acts as an actual agent. The obvious advantage of this method is that the quantity of iodine in the titration is known and one uses standardized strong acidic solution.

There are numerous end-point detection techniques in iodimetric titration. It is observed that even a small drop of 0.05 mol L^{-1} iodine solution added to 100 mL of water causes the colour changes into pale-yellow. If more iodine solution is added, the mixture becomes brown. If some organic solvents, for example chloroform or carbon tetrachloride, are a part of a reaction medium, purple colour is obtained. Application of colloidal adsorbate-type indicators strengthens the titration sensitivity. The most widely used indicator of this type is starch. The presence of iodide ions enables formation of blue iodine-starch complex. This colour is a result of adsorption of triiodide ions onto colloidal macromolecules of starch. Starch is a very popular indicator in iodometry since it provides evident colour change. However, sensitivity of this colour reaction decreases at high temperature, in the presence of organic solvent, and at low pH due to hydrolysis of starch. Starch is insoluble in cold water, so only fresh solutions should be used. It is suggested to apply starch solution just before the end-point as the obtained suspension is unstable and also due to solubility of starch--iodine complex in water. There is a risk of positive errors in determinations when diluted solutions are used. To improve performance of starch in the solution, sodium starch glycollate is used instead. Then, in the presence of relatively high concentration of iodine, green coloured mixture turns to blue when end-point is reached.

Colloidally dispersed compounds, like xanthone, flavone, thioflavone and α-pyrone derivatives, inorganic salts of lanthanide basic acetates, coumarin, and acetylcoumarin form a blue complex with iodine [3]. Then, methylene blue and variamine blue can be applied as end-point indicators redox agents. There is a wide range of end--point detection methods in iodimetric titration based on potentiometric, amperometric, biamperometric, or spectrophotometric (detection of triiodide or starch-iodine is performed at 350 and 520 nm, respectively) techniques. Also coulometric titration with iodine is widely used and conditions for generating iodine have been described [4].

Thiols are one of the most important compounds used in various areas of industry and technology, *e.g.* as corrosion inhibitors. Some of them are employed for the drug preparation, photographic emulsions and developers, and lithographic plate materials. Thiols also find various applications in medicine. Thioamides (thiouracils and methylthioimidazole) have potential application in hyperthyroidism (Grave's disease) [5, 6, 7]. 6-Mercaptopurine (purinethiol) [5] and 2-thioguanine [8] belong to cytotoxic antimetabolites, which are used to treat leukemia and Crohn's disease. Thiopental is an ultrashort-acting intravenous anaesthetic [9] frequently used in the treatment of intensive care patients suffering from severe head injuries and in the treatment of intracranial hypertension [10].

STOICHIOMETRY OF IODIMETRIC TITRATION IN ACIDIC AND NEUTRAL MEDIA

In this study, a number of electrons transferred in a single reaction (z) was used as an indication of reaction ratio for iodine and thiols.

Titration of thiols with iodine in acidic or neutral medium proceeds according to the following stoichiometry:

$$2RSH + I_2 \leftrightarrows RS\text{-}SR + 2HI \quad (3)$$

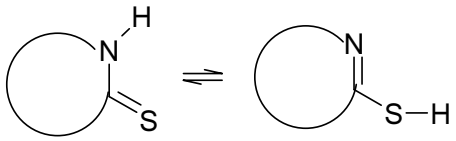
Satisfactory results of the determination were obtained in volumetric titration of 2-mercaptopyridine (within pH range 6.0–7.5) [11], 2-mercaptopyridine N-oxide (within pH range 5.0–8.0) [11], 2-mercaptopyrimidine (within pH range 6.5–7.0) [12], 2-mercapto-4-methylpyrimidine (within pH range 2.5–6.5) [12], 4,6-dimethyl--2-mercaptopyrimidine (within pH range 2.0–8.0) [12], and 2-thiocytosine (within pH range 6.5–8.0) [13] using iodine solution as a titrant in acidic and neutral media. Iodimetric titration of 2-mercaptobenzimidazole (within pH range 6.8–7.1) [14] and thioglycolic acid (in hydrochloric acid solution 1:3) [15] with starch as an end-point indicator have been also reported. However, the reaction rate between thiol and iodine is rather low and thus the procedure had to be modified and applied as an „indirect method". The sample was titrated with iodine till the suspension turned blue and the consumed volume of titrant was measured. Then, a small excess of iodine was added and immediately back-titrated with sodium thiosulfate solution. In the proposed method, pH has to be carefully controlled. Determination of 2-mercaptobenzothiazole using iodine as a titrant has been also performed [16]. However, the reaction rate was slow again and titration was conducted in non-aqueous medium.

Coulometric titration belongs to the most precise analytical methods. In order to fully utilize its advantages, it is necessary to have a properly designed electrolytical cell to guarantee 100% electrolysis efficiency and ensure sufficiently fast titration reaction rate, as well as to apply suitable end-point detection system [17].

Thioglycolic acid [18–21], 2-mercaptobenzothiazole [22], cysteine, 2-thiouracil, 6-mercaptopurine and 2-thioguanine [23], 2-mercaptoethanol, 1-mercaptoheptan, 4-methylbenzenethiol, and 2-mercaptobenzoic acid [21] were titrated coulometrically with the generated iodine. The possibilities of biamperometric [19–21, 24], potentiometric [21] and photometric [20] end-point detection in coulometric titrations have been studied. Further research has shown the improvement of results when special design of electrolysis cell (*e.g.* with integrated injection valve [20]) and non-aqueous media [21, 25] were applied. In order to overcome the problem of the low rate of iodimetric titration, discontinuous generation of iodine (especially close to the end--point of titration) has been proposed. Another solution to this problem was to gene-

rate 90% of the reagent followed by the addition of the analyte and further titration with either continuous or discontinuous generation of the titrant [21].

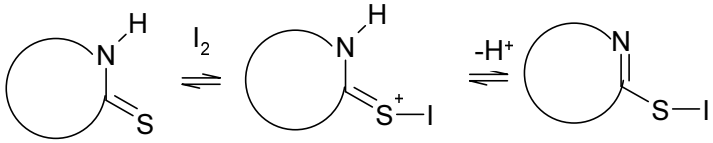
A neutral molecule of mercaptopyridine and mercaptopyrimidine can be converted into two different forms depending on pH value:



(4)

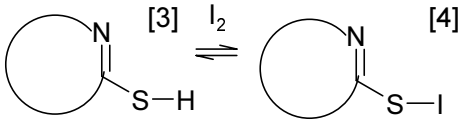
[1] [2]

Both forms can participate in the oxidation reaction [26, 27]:



(5)

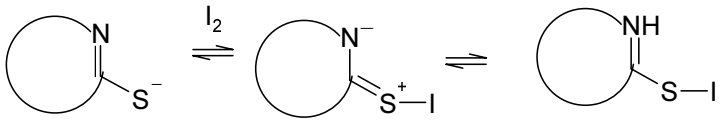
[1] [3] [4]



(6)

[2] [4]

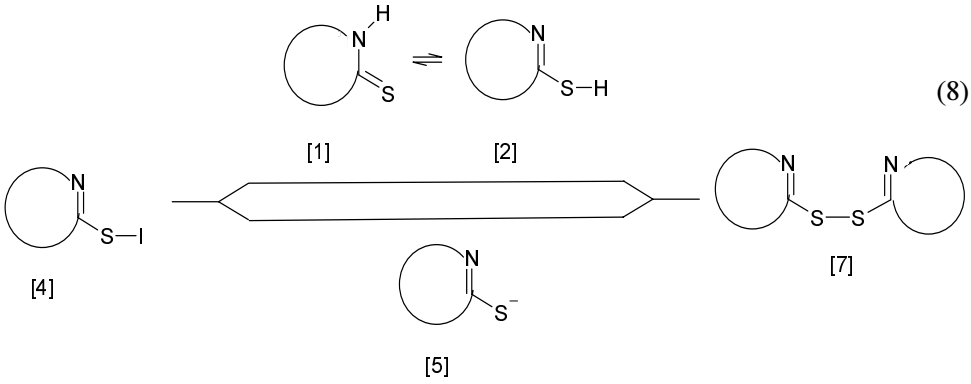
Mercaptopyridines and mercaptopyridine anions can react with iodine according to the equation:



(7)

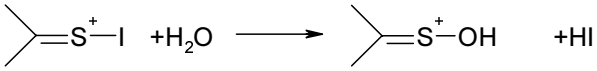
[5] [6] [4]

In equations (5)–(7), the same intermediate is created, which can participate in the next step:



(8)

The presence of heteroatom in the aromatic ring induces an increase of the mobility of delocalized electrons. Specifically, the presence of nitrogen atom in the aromatic ring delocalize π-electrons and increases activation energy. For this reason, 2-mercaptopyrimidine reacts with iodine in acidic medium in a narrower pH range than 2-mercaptopyridine. The pH ranges corresponding to 2-mercaptopyridine and 2-mercaptopyrimidine are 6.0–7.5 and 6.5–7.0, respectively [11, 12]. Tautomeric thione/thiol equilibrium of 2-mercaptopyridine is shifted towards the thione form. 2-Mercaptopyridine N-oxide exists only in the thiol form and it reacts stoichiometrically with iodine in either acidic or neutral medium, thus in a wider pH range. Accordingly, the thiol/thione transition hampers reaction (4). The pH ranges, where reaction (3) runs stoichiometrically, are 6.5–7.0 and 5.0–8.0 for 2-mercaptopyridine and 2-mercaptopyridine N-oxide, respectively [11]. The presence of –OH or –COOH group in 2-mercaptopirydine ring decreases the rate of reaction with iodine in acidic and neutral media. This is the reason why 2-mercaptonicotinic acid and 2-mercapto-3-pyridinol can not be determined in these media using iodine as a titrant. The group that makes thiomolecule more alkaline, makes the removal of hydrogen atom from nitrogen atom more difficult, which decreases the rate of reaction (5). Then, the following reaction may proceed:



(9)

It was also observed that at pH 7 4,6-dimethyl-2-mercaptonicotine nitrile reacts stoichiometrically with iodine according to equation (3). Methyl groups activate the mercaptopyrimidine ring as indicate higher pK_B values (protonation of the neutral molecule) of 2-mercapto-4-methylpyrimidine and 4,6-dimethyl-2-mercaptopyrimidine: 2.2 and 2.80, respectively, compared to 1.35 for 2-mercaptopyrimidine. Basic properties of 2-mercaptopyrimidine increase proportionally to the number of methyl

groups in the molecule. The presence of methyl groups in 2-mercaptopyrimidine molecule increases the pH range within which, in iodimetric determination, the number of electrons (z) transferred in a single reaction equals 1. The optimum pH ranges are 6.5–7.0 and 6.5–8.0 for 2-mercaptopyrimidine and 2-thiocytosine, respectively [12, 13]. Higher pK_B value of 2-thiocytosine (3.3) in comparison to pK_B of 2-mercaptopyrimidine (1.35) confirms that amino group activates the ring. Therefore, it is easier to oxidise 2-thiocytosine than 2-mercaptopyrimidine with iodine in acidic and neutral media.

The best results of coulometric titration of 6-mercaptopurine were obtained at pH 7 using biamperometric end-point detection system [24]. Titration conditions mentioned above were applied also in the determination of 2-thiouracil and 2-thioguanine. Direct titration was, however, unsuccessful since the iodimetric reaction ratio was too low. Indirect titration led to better results; back-titration with sodium arsenate(III) solution. Thioglycolic acid [15], 2-thioguanine [24] and 2-thiouracil [19, 24] were determined coulometrically employing the indirect procedure. An excess of iodine was generated, afterwards the thiol solution was added. After a particular time period, an excess of standard thiosulfate or sodium arsenate(III) solution was added and then back-titrated with the generated iodine.

In many cases iodimetric titration in either acidic or neutral media can not be performed due to non-stoichiometric formation of disulfide, too low rate of reaction (3), and its reversibility leading to the equilibrium state.

STOICHIOMETRY OF IODIMETRIC TITRATION IN ALKALINE MEDIUM

To avoid the above difficulties, titration was conducted in alkaline medium. It has been observed that stoichiometry of the reaction between thiol and iodine in alkaline medium is different that that observed in acidic and neutral media.

Iodimetric determination of sulfur compound proceeds at various reaction stages and depends on the type of compound and the concentration of NaOH solution (for details see Tab. 1). Thiol (thiocarbonyl) group is oxidized to either sulfi (equation 10) or sulfo group (equation 11), or to sulfate ion (equation 12):

$$R\text{–}S^- + 2I_2 + 4OH^- \rightarrow R\text{–}SO_2^- + 4I^- + 2H_2O \qquad z = 4 \qquad (10)$$

$$R\text{–}S^- + 3I_2 + 6OH^- \rightarrow R\text{–}SO_3^- + 6I^- + 3H_2O \qquad z = 6 \qquad (11)$$

$$R\text{–}S^- + 4I_2 + 10OH^- \rightarrow R\text{–}O^- + 8I^- + 5H_2O + SO_4^{2-} \qquad z = 8 \qquad (12)$$

Table 1. Conditions of iodimetric determination of sulfur compounds with potentiometric end-point detection in alkaline medium

Compound	Concentration of NaOH, mol L^{-1}	Determination range, μmol	z^*	Ref.
S^{2-} (sulfide)	5	8–86	8	[28]
$S_2O_3^{2-}$ (thiosulfate)	3	7–222	8	[28
SO_3^{2-} (sulfite)	4	94–750	2	[28]
$S_4O_6^{2-}$ (tetrathionate)	5	10–800	14	[56]
Thioglycolic acid	1	30–600	6	[36]
3-Mercaptopropionic acid	7	20–250	4	[36]
D-Penicillamine	5	50–200	4	[36]
Mercaptosuccinic acid	1	100–500	4	[36]
N-Methylthiourea	2	100–1000	8	[36]
N-Phenylthiourea	2	20–1000	8	[36]
N,N'-Dimethylthiourea	0.1	25–125	8	[36]
Dithiobiurea	2	5–125	16	[36]
Dithiooxamide	5	15–300	12	[36]
Ethionamide	5	25–500	8	[36]
Nicotinaldehyde thiosemicarbazone	5	46–230	8	[47]
2-Mercaptopyridine	2	100–500	4	[61]
2-Mercapto-3-pyridinol	5	10–500	4	[11]
2-Mercaptonicotinic acid	0.5	50–250	4	[11]
4,6-Dimethyl-2-mercaptonicotine nitrile	0.1	50–500	4	[49]
2-Mercaptopyrimidine	0.5	100–500	4	[61]
2-Mercapto-4-Methylpyrimidine	0.5	50–250	4	[12]
4,6-Dimethyl-2-mercaptopyrimidine	0.5	50–500	4	[12]
2-Thiocytosine	3	10–250	4	[13]
Ethyl 4-amino-2-mercaptopyrimidine-5-carboxylate	0.5	25–500	6	[49]
4,5-Diamino-2,6-dimercaptopyrimidine	3	20–250	16	[12]
2-Thiouracil	4 6	100–500 1000	4	[38]

(Continuation on the next page)

Table 1 (Continuation)

Compound	Concentration of NaOH, mol L^{-1}	Determination range, μmol	z*	Ref.
6-Methyl-2-thiouracil	2	100–500	4	[37]
6-Benzyl-2-thiouracil	3	100–500	4	[37]
6-Propyl-2-thiouracil	2	125–500	4	[57]
6-Amino-2-thiouracil	5	30–700	6	[38]
5-Carbethoxy-2-thiouracil	2	60–500	4	[38]
5-Methyl-2-thiouracil	1 2 3	100–200 200–300 300–500	4	[38]
2-Thioorotic acid	2	20–1000	4	[12]
2-Thiobarbituric acid	3	10–350	6	[48]
2-Mercapto-4(3*H*)-quinazolinone	3	50–500	4	[60]
2-Mercapto-1-methylimidazole	2	87	4	[58]
	1	10–500		[59]
Carbimazole	1	30–500	4	[39]
2-Mercaptobenzimidazole	1	25–1000	4	[40]
2-Mercapto-5-methoxybenzimidazole	1	10–1000	4	[40]
2-Mercapto-5-nitrobenzimidazole	1	10–1000	4	[40]
2-Mercaptobenzothiazole	0.1	25–1000	4	[40]
6-Ethoxy-2-mercaptobenzothiazole	1	10–1000	4	[40]
2-Mercaptobenzoxazole	1	20–1000	8	[**]
1*H*-1,2,4-triazole-3-thiol	2	20–2000	4	[41]
3-Amino-1*H*-1,2,4-triazole-5-thiol	5	50–500	4	[41]
3-Phenyl-1*H*-1,2,4-triazole-5-thiol	0.5	25–1000	4	[41]
4-Methyl-5-(trifluoromethyl)- 4*H*-1,2,4-triazole-3-thiol	1	25–500	4	[41]
1-Phenyl-1*H*-tetrazole-5-thiol	0.1	125–500	6	[41]
1-(4-Hydroxyphenyl)-1*H*-tetrazol-5-thiol	1	50–1000	6	[41]
Sodium (5-mercapto-1*H*-tetrazol-1-yl)acetate	1	10–1000	4	[41]
5-Phenyl-1,3,4-oxadiazole-2-thiol	1	25–500	8	[44]

(Continuation on the next page)

Table 1 (Continuation)

Compound	Concentration of NaOH, mol L^{-1}	Determination range, μmol	z*	Ref.
4,4-Dimethyloxazolidine-2-thione	4	50–1000	6	[43]
2-Mercapto-5-methyl-1,3,4-thiadiazole	1	50–1000	4	[**]
5-Amino-2-mercapto-1,3,4-thiadiazole	0.1	100–200	8	[**]
2,5-Dimercapto-1,3,4-thiadiazole	0.1	25–125	8	[42]
2-Mercaptothiazoline	0.1	10–500	4	[42]
2-Mercapto-4-methyl-5-thiazoleacetic acid	0.5	10–1000	4	[42]
6-Mercaptopurine	2	270–700 50–500	4	[35] [**]
2-Thioguanine	2	10–250	4	[45]
2-Amino-6-hydroxy-8-mercaptopurine	0.5	125–1000	8	[**]
2,8-Dimercapto-6-hydroxypurine	7	100–500	8	[43]
4-Hydroxy-2-mercaptopteridine	0.5	125–1000	4	[49]

* z – number of electrons transferred in a single reaction.
** Results not published.

Iodimetric reaction consists of two steps. In the first step either $R–SO_2^-$ or $R–SO_3^-$ is formed. Total oxidation of a thiol to sulfate ion proceeds in the next step. Stoichiometry of the particular step depends on the NaOH concentration and the nature of compounds.

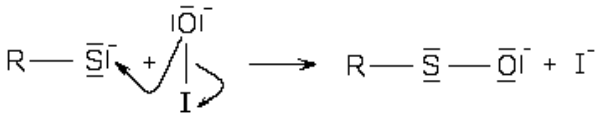
It is known that iodine disproportionates quickly in alkaline medium to produce iodide and iodate(I) ions, the latter being virtual oxidizing agent:

$$I_2 + 2OH^- \rightarrow I^- + IO^- + H_2O \tag{13}$$

Titration in alkaline medium is possible only when the reaction of iodate(I) ion with a thiol is faster than disproportionation of iodate(I) ion [28, 29]:

$$3IO^- \rightarrow IO_3^- + 2I^- \tag{14}$$

In alkaline medium, thiols dissociate to give an anion which can react with iodate(I) according to the following equation:



(15)

Two ions: iodate(I) and thiolate take part into the above reaction. To provide satisfactory rate of this process, it is needed to reduce electron density at the sulfur atom in thiolate anion. The lower charge density at the sulfur atom, the lower concentration of NaOH is needed for quantitative determination.

The samples of thiols (thiourea and tetramethylthiourea [30], thiopental [31, 32], 1,3-diethyl-2-thiobarbituric acid [33], 6-methyl- and 6-propyl-2-thiouracil [34], 6-mercaptopurine [35]) were dissolved in NaOH solution and iodine solution was added. In the presence of excess of iodine in the reaction solution and applying long reaction time thiols were completely oxidized to sulfate ions. The number of electrons transferred in a single reaction is z = 8. After some time, the solution was acidified. The excess of iodine was back-titrated applying visual end-point detection.

Reaction yields were 86% for 6-methyl-2-thiouracil (3.5-hour reaction time, 0.1 mol L^{-1} NaOH solution), 95% and 98% for 6-mercaptopurine (15-minute and 2-hour reaction time, respectively, 2 mol L^{-1} NaOH solution), and 97% for thiopental (15-minute reaction time, 20% NaOH solution). The results of iodimetric determination of thiopental were identical to those obtained in argentometric titration [34].

Performance of the method was checked at different temperature conditions for 6-methyl- and 6-propyl-2-thiouracil [34] and thiopental [32]. For 6-methyl-2-thiouracil, iodimetric reaction yield in 0.1 mol L^{-1} NaOH solution was 76% at 20°C and 100% at 90–100°C, respectively. When 0.05 mol L^{-1} NaOH solution was used, the yields were 66% and 97% for 20°C and 90–100°C, respectively. Reaction yield was unsatisfactory for 0.25 mol L^{-1} NaOH solution and at 20°C. Obviously, temperature is a key factor in back titration of thiouracils with iodine in alkaline medium. Complete iodimetric titration in alkaline medium requires 40 min. In case of thiopental, the solution was incubated in a boiling water bath [32] to complete the reaction in 3.33 mol L^{-1} NaOH solution. Complete iodimetric titration of thiopental lasted for 15 min.

The influence of NaOH concentration on the course of reaction between thiols and iodine

In many cases concentration of NaOH solution greatly affected the course of oxidation reaction. It was necessary to find an appropriate concentration of NaOH that allows iodimetric reaction to proceed stoichiometrically. These optimum conditions for particular compounds are given in Table 1. They correspond to the numbers of electrons transferred in a single reaction z = 4, z = 6, or z = 8.

At significantly lower concentrations of NaOH than these given in Table 1 the reaction did not proceed stoichiometrically according to equations (10), (11), or (12) (depending on the nature of a compound). In case of 3-mercaptopropionic acid, mercaptosuccinic acid, N-methylthiourea, N-phenylthiourea, [36], 3-hydroxy-2-mercapto-

pyridine, 2-mercaptonicotinic acid [11], 2-thiouracil [38] and its derivatives: 6-benzyl- [37], 6-amino- [38], 5-carbethoxy- [38] and carbimazole [39], 2-mercaptobenzimidazole and its derivatives: 5-methoxy- and 5-nitro-, 6-ethoxy-2-mercaptobenzothiazole [40], 1*H*-1,2,4-triazole-3-thiol, 3-phenyl-1*H*-1,2,4-triazole-5-thiol, 4-methyl-5-trifluoromethyl-1,2,4-triazolin-3-thione, 1-(4-hydroxyphenyl)-1*H*-tetrazole-5-thiol, 5-thiol--sodium(5-mercapto-1*H*-tetrazol-1-yl)acetate [41], 2-mercapto-4-methyl-5-thiazoleacetic acid [42], 2-amino-6-hydroxy-8-mercaptopurine [*], and 2,8-dimercapto-6--hydroxypurine [43], higher concentration of NaOH did not result in further oxidation of these compounds and the changes in the consumption of iodine in iodimetric reaction were small. In the single reaction of N'N-dimethylthiourea, thioglycolic acid, D-penicillamine [36] and 3-amino-1*H*-1,2,4-triazole-5-thiol [41] the number of electrons transferred decreased with an increase of NaOH concentration. For compounds listed in Table 1 and not mentioned above, higher concentration of NaOH may be followed by an increase in the number of electrons transferred in a single reaction, which means further oxidation of the product of reaction (10) or (11).

High concentration of iodide ions guaranteed 100% current efficiency in case of titration with iodine in alkaline medium [17]. It was necessary to find the appropriate concentration of NaOH solution that allows iodimetric reaction to proceed stoichiometrically in coulometric titration. These most advantageous conditions for particular compounds are given in Table 2. The corresponding numbers of electrons transferred in single reactions are z = 4, z = 6, or z = 8. Optimum concentration of NaOH solution depends on the thiol concentration iodimetrically titrated in alkaline medium. Generally, the lower concentration of thiol was titrated, the lower concentration of NaOH solution was applied in coulometric titration compared to the concentration used in volumetric titration.

Table 2. Conditions of iodimetric determination of sulfur compounds with coulometric end-point detection in alkaline medium

Compound	Concentration of KI, mol L^{-1}	Concentration of NaOH, mol L^{-1}	Determination range, μmol	Ref.
2-Mercaptonicotinic acid	0.5	0.1	0.04–8	[11]
2-Mercaptopyrimidine	1	0.5	0.1–4	[12]
6-Methyl-2-thiouracil	1	1	0.2–20	[17]
6-Benzyl-2-thiouracil	0.5	0.1	0.1–5	[61]
6-Propyl-2-thiouracil	1	0.5	0.5–5	[57]

(Continuation on the next page)

* Results not published yet.

Table 2 (Continuation)

Compound	Concentration of KI, mol L^{-1}	Concentration of NaOH, mol L^{-1}	Determination range, μmol	Ref.
2-Thioorotic acid	1	0.1	0.1–5	[12]
2-Thiobarbituric acid	1	3	0.1–20	[48]
2-Mercapto-4(3*H*)-quinazolinone	1	0.5	0.2–2	[13]
2-Mercapto-1-methylimidazole	1	0.1	0.02–4	[17]
Carbimazole	1	0.05	0.5–20	[39]
2-Mercaptobenzimidazole	1	1	1.0–10	[40]
2-Mercaptobenzothiazole	1	0.1	0.25–40	[40]
5-Phenyl-1,3,4-oxadiazole-2-thiol	1	2	0.5–5	[44]
6-Mercaptopurine	1	0.1	0.02–20	[17]
2-Thioguanine	1	0.25	0.03–25	[45]
2-Mercaptothiazoline	1	0.1	0.2–10	[42]
2,5-Dimercapto-1,3,4-thiadiazole	1	0.05	0.1–5	[42]
2-Mercapto-4-methyl-5-thiazoleacetic acid	1	0.1	0.1–10	[42]
Ketotifen	1	2	0.25–2	[55]
Vitamin B_1 (thiamine)	0.26	0.013	9–27	[51]

The influence of the nature of thio-compound on the course of reaction with iodine

It is advantageous if tautomeric thione-thiol equilibrium is shifted towards the thiol form. There was no possibility to determine 1,3-diethyl-2-thiobarbituric acid and 2-mercapto-3-methylbenzothiazole since the thione/thiol transition was prevented, whereas potentiometric titration of 2-thiobarbituric acid and 2-mercaptobenzothiazole were performed successfully [40, 48]. Carbamizole, which exists only in the thione form, undergoes hydrolysis and decarboxylation in alkaline medium. 2-Mercapto-1--methylimidazole, the product of these reactions, reacts easily with iodine in alkaline medium [39, 58, 59].

Disturbance of aromaticity in the pyrimidyl ring impedes oxidation reaction with iodine in alkaline medium. Such phenomenon is observed in thiopental molecule. Potentiometric titration of thiopental was conducted in strongly alkaline solution. The increase of NaOH concentration in the solution did not cause the increase of the

number of electrons transferred in a single reaction (z = 7.43) [48]. Titration results were reproducible. Reaction rate for thiopental was smaller that that for 2-thiobarbituric acid. It is possible to determine thiopental by iodometric titration only if the excess of iodine is added to the alkalized thiopental solution, then acidified after some time, and back-titrated with thiosulfate solution [31, 32]. According to the procedure, oxidation reaction is relatively fast and thiolate groups are transformed to sulfate ions. The number of electrons transferred in a single reaction equals to z = 8.

Similar disturbance of aromaticity appears in the molecule of 4,4-dimethyloxalidine-2-thione [43]. To determine this compound, more concentrated NaOH solution (4 mol L^{-1}) is needed compared to 1 or 2 mol L^{-1} NaOH solution used in the determination of 1-methyl-2-mercaptoimidazole [58, 59]. Moreover, oxidation mechanism is different.

Mercaptopyridine series [11]. Carboxylic group lowers electron density at sulfur atom in pyridine ring. Therefore, determination of 2-mercaptonicotinic acid in alkaline medium requires lower concentration of NaOH solution (0.5 mol L^{-1}) than that used in the determination of 2-mercaptopyridine (2 mol L^{-1} NaOH solution). Introduction of nitrile group into pyridine ring increases the rate of oxidation reaction. 4,6-Dimethyl-2-mercaptonicotine nitrile was titrated in 0.1 mol L^{-1} NaOH solution. Hydroxyl group increases electron density at sulfur atom in pyridine ring. Therefore, 2-mercapto-2-pyridinol was determined using more concentrated NaOH solution concentration (5 mol L^{-1}) compared that used in the determination of 2-mercaptopyridine.

Mercaptopyrimidine series [12, 13]. Substitution at position 4 in mercaptopyrimidine ring makes the rate of iodimetric reaction in alkaline medium decrease in the following order: –H (0.5 mol L^{-1} NaOH solution), $-NH_2$ (3 mol L^{-1} NaOH solution), –OH (4 mol L^{-1} NaOH solution), –SH (requires indirect determination). Methyl groups have no influence on the course of oxidation with iodine in alkaline medium. 0.5 mol L^{-1} NaOH solution was used for determination of 2-mercaptopyrimidine and its 4-methyl- and 4,6-dimethyl- derivatives.

Thiouracil series [37, 38, 48, 60]. Charge distribution corresponding to π-electrons is uniform. There is an excess of electrons on heteroatoms and electron deficiency at carbon atoms at positions 2, 4, and 6. Introduction of methyl and hydroxyl groups at position 6 of thiouracil molecule increases oxidation reaction rate. Then, 2 mol L^{-1}, 3 mol L^{-1}, and 4 mol L^{-1} NaOH solutions are needed for determination of 6-methyl-2-thiouracil, 2-thiobarbituric acid and 2-thiouracil, respectively. Amino group has an opposite effect on the reaction rate. Then, more concentrated NaOH solution (5 mol L^{-1}) has to be used for determination of 6-amino-2-thiouracil. Noteworthy, hydroxyl and amino groups affect the oxidation mechanism with iodine in alkaline

medium. The number of electrons transferred in a single reaction changes from z = 4 for 2-thiouracil to z = 6 for 6-amino-2-thiouracil and 2-thiobarbituric acid.

The presence of electrophilic substituent in position 5 of 2-thiouracil molecule decreases an excess of electrons on carbon atom in this position. Nevertheless, determination of 5-methyl-2-thiouracil was possible after selection of the appropriate NaOH solution concentration for each concentration of the studied compound. Electron--donor substituents prevent stoichiometric reaction with iodine in alkaline medium from proceeding enough quickly. Determination of 5,6-diamino-2-thiouracil and 6-amino-5-nitroso-2-thiouracil was not possible since the number of electrons transferred in the reaction is greater than 8 within the studied range of NaOH concentration. In contrast, determination of 5-carbethoxy-2-thiouracil (4 mol L^{-1} NaOH solution) with iodine in alkaline was performed successfully.

The presence of condensed phenyl ring in 2-mercapto-4(3*H*)-quinazolinone molecule decreases electron density compared to 2-thiouracil. Also lower concentration of NaOH solution (3 mol L^{-1}) was used to determine 2-mercapto-4(3*H*)-quinazolinone [60] (4 mol L^{-1} in case of 2-thiouracil) [38].

Triazolethiol series [41]. It has been found that for potentiometric determination of 1*H*-1,2,4-triazole-3-thiol with iodine higher concentration of NaOH solution (2 mol L^{-1}) is needed than in case of 1*H*-1,2,4-triazole-3-thiol substituted with phenyl (0.5 mol L^{-1} NaOH solution), trifluoromethyl and methyl groups (1 mol L^{-1} NaOH solution). The explanation is that acceptor groups lowers electron density at sulfur atom in thiolate group. Determination of 3-amino-1*H*-1,2,4-triazole-5-thiol requires higher concentration of NaOH solution (5 mol L^{-1}) than that used during titration of 1*H*-1,2,4,-triazole-3-thiol. In this case, introduction of a strong donor group (amino or hydrazine) into position 5 causes a significant disturbance of aromaticity in 1, 2, 4 - triazol ring. It was not possible to determine appropriate conditions for determination of 4-amino-5-hydrazine-1*H*-1,2,4-triazole-3-thiol with iodine in alkaline medium [49].

If nitrogen atom in 3-phenyl-1,2,4-triazole-5-thiol molecule is replaced with oxygen atom (5-phenyl-1,3,4-oxadiazol-2-thiol), electron density at sulfur atom in thiolate group decreases. Moreover, the stoichiometry of the oxidation reaction becomes different: 3-phenyl-1,2,4-triazole-5-thiol was titrated in 0.5 mol L^{-1} NaOH solution and the number of electrons transferred in a single reaction was 4; also 5-phenyl--1,3,4-oxadiazol-2-thiol was titrated in 1 mol L^{-1} NaOH solution and the corresponding number of electrons transferred in a single reaction z = 8. Further oxidation of 3-phenyl-1,2,4-triazole-5-thiol (beyond the step of z = 4) is difficult since its sulfi derivatives are stabilized *via* intermolecular hydrogen bond [44].

Tetrazolethiol series [41]. Hydrogen atom at position 1 in either triazole or tetrazole ring exhibits acidic properties and undergoes dissociation in alkaline medium. In the resulting anion, electron density at sulfur atom in thiolate group increases. If the formation of the above anion is prevented, then NaOH solution of lower concentration is applied as a reaction medium for iodimetric determination. All studied 1*H*-triazoles were substituted with particular groups at position 1 position and the used concentrations of NaOH solutions were lower than that used in case of 1*H*-1,2,4-triazoles-3-thiol.

An introduction of an aromatic substituent at position 1 in tetrazolethiol ring changes stoichiometry of iodimetric reaction. The reason is higher stability of aromatic derivatives of tetrazolethiol than of aliphatic ones. The number of electrons transferred per one mol of 1-phenyl-1*H*-tetrazole-5-thiol and 1-(4-hydroxyphenyl)-1*H*--tetrazole-5-thiol is 6. Moreover, determination of these two compounds requires lower concentration of NaOH solution (0.1 and 1 mol L^{-1}, respectively) than that used in the determination of sodium (5-mercapto-1*H*-tetrazol-1-yl) acetate (2 mol L^{-1}). Aromatic groups lower electron density at sulfur atom in thiolate group due to stronger electron delocalization.

Hydroxyl group is a donor group and slightly increases electron density at sulfur atom in thiolate group in phenyl ring; thus, it makes oxidation difficult. Determination of 1-(4-hydroxyphenyl)-1*H*-tetrazole-5-thiol requires higher concentration of NaOH solution than that used in the determination of 1-phenyl-1*H*-tetrazole-5-thiol.

Benzimidazolethiol and benzothiazolethiol series [40]. The presence of condensed ring in benzazols decreases basic properties of nitrogen atom in a pyrrole ring and increases reactivity of thiolate group. The studied series of benzimidazolethiols and benzothiazolethiols require lower concentration of NaOH solution (1 and 0.1 mol L^{-1}, respectively) than that used in case of 2-mercapto-1-methylimidazole (1 or 2 mol L^{-1}) [58, 59]. 2-Benzimidazolethiol was also successfully determined with iodine in the pH range 10–12. Under such pH conditions, the number of electrons transferred in a single reaction is z = 4. Methoxy- and nitro- groups substituted at position 5 in benzimidazolethiol molecule do not have any impact on the rate of oxidation reaction with iodine in alkaline medium. In the molecule of 2-benzothiazolethiol the second nitrogen atom is replaced with sulfur. Thus, electron density at sulfur atom in thiolate group is decreased compared to 2-benzimidazolethiol, which undergoes oxidation in more alkaline medium than 2-benzothiazolethiol does.

It has been observed that the mechanism of oxidation reaction (with iodine in alkaline medium) change if nitrogen heteroatom in either 2-benzimidazolethiol or 3-phenyl-1,2,4-oxadiazole-2-thiol is replaced with oxygen atom [40, 41, 44]. Then, also the number of electrons transferred in a single reaction increases from z = 4 to z = 8.

Mercaptopurine and mercaptopteridine series [35, 43, 45]. Purine is a condensed-ring molecule consisting of pyrimidine and imidazole rings. Pteridine is also a condensed-ring molecule which contains pyrimidine and pyrazine rings. There is a deficiency of π-electrons in pyrimidine ring of purine and in pteridine molecule. Pteridines are stronger bases than purine since pteridine anion is better stabilized by mezomeric effect than the purine one. Negative charge in imidazole ring in purine anion increases electron density in pyrimidine ring compared to pteridine anion. Then, oxidation of mercaptopurine proceeds in more alkaline medium (2 mol L^{-1} NaOH solution) than the reaction of mercaptopteridine with iodine (0.5 mol L^{-1} NaOH solution).

Though electrophilic substituent in position 2 of 6-mercaptopurine increases electron deficiency due to the inductive effect, determination of 2-thioguanine and 6-mercaptopurine were conducted in 2 mol L^{-1} NaOH solution [35, 45].

Mercaptothiadiazole series [42, 43]. Determination of 2-mercapto-4-methyl--5-thiazoleacetic acid is conducted in a lower concentration of NaOH solution (0.1 mol L^{-1}) [42] compared to 2-mercapto-1-methylimidazole (1 or 2 mol L^{-1} NaOH solution) [58, 59]. This is due to the fact that the excess of π-electrons at C–2 position in imidazole molecule is smaller compared to this excess at C–2 position in thiadiazole ring [46]. Additionally, the presence of electrophilic substituent at position 5 of mercaptothiadiazole increases this deficiency *via* the inductive effect.

Thiourea and other aliphatic thiol series [36, 47, 56]. Determination of thiourea in alkaline medium was unsuccessful since there was no possibility to find an appropriate concentration of NaOH solution. Within the studied range, the number of electrons transferred in a single iodimetric reaction was around $z = 7$. Introduction of a substituent to nitrogen atom in thiourea molecule enables determination of N-methylthiourea and N-phenylthiourea in 2 mol L^{-1} NaOH solution. However, the mechanism is changed and the number of electrons transferred in a single reaction is then $z = 4$. Further introduction of methyl group into methylthiourea molecule allows one to use lower concentration of NaOH solution, namely 0.1 mol L^{-1}, for determination of N,N'-dimethylthiourea. After further introduction of methyl groups one obtains N,N,N',N'-tetramethylthiourea, which is, unfortunately, impossible to be determined using iodine since the number of electrons transferred in a single reaction is around $z = 7$.

Ethionamid requires high concentration of NaOH solution (5 mol L^{-1}) since the molecule dissociates in alkaline medium and the resulting ion is stabilized by mezomeric effects.

In thiocarboxylic acids series, elongation of aliphatic chain does not favour oxidiation with iodine. However, introduction of an additional carboxylic group into

a chain has the opposite effect. For thioglycolic acid, the mechanism of oxidation is changed since the number of electrons transferred in a single reaction is z = 6. Steric effect may cause that higher concentration of NaOH solution is needed for determination of D-penicillamine.

UNUSUAL POTENTIOMETRIC TITRATION CURVES

In some cases, the shape of potentiometric titration curve in strong alkaline medium is untypical. During iodimetric titration in alkaline medium using platinum wire indicator electrode a strong rise in the potential near the end-point has been observed (200–300 mV/0.1 mL of the titrant). A small amount of added iodine (oxidizer) caused a strong potential drop in the initial part of curve. Sometimes, only one drop of a titrant caused such phenomenon (*e.g.* 2-mercaptopyrimidine and its derivatives: 4-methyl- and 4,6-dimethyl- [12], 2-thiocytosine [13], N,N'-dimethylthiourea [36], 5-carbethoxy-2-thiouracil [38], 2-mercaptobenzothiazole [40], sodium (5-mercapto-1*H*-tetrazol-1-yl)acetate and 1-phenyl-1*H*-tetrazole-5-thiol [41], 2,5-dimercapto--1,3,4-thiadiazole and 2-mercapto-2-thiazoline [42], 2,8-dimercapto-6-hydroxypurine and 4,4-dimethyloxazolidine-2-thione [43], thiopental [48], 5-phenyl-1,3,4-oxadiazol--2-thiol [44], 2-thioguanine [49] as well as 6-mercaptopurine). An example of the influence of hydroxide ions on the shape of potentiometric curve is shown in Figure 1.

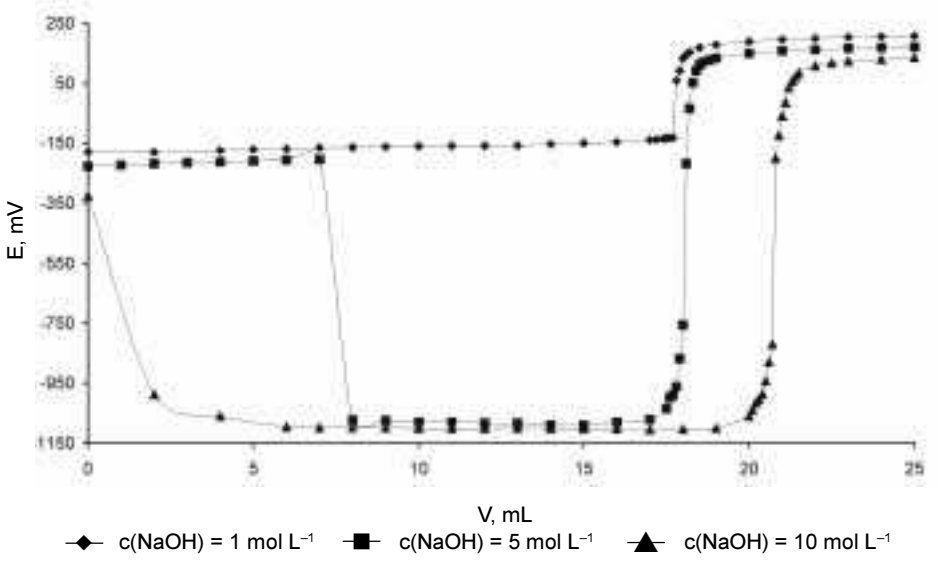


Figure 1. Potentiometric titration curves of 2-amino-6-hydroxy-8-mercaptopurine in variously concentrated NaOH solution; amount of analyte: 125 μmol, titrant concentration: 0.5 mol L^{-1} iodine; indicator electrode: platinum wire

The influence of the concentration of NaOH solution influenced the moment of appearance of potential drop [43]. For most of the thiols studied by us, when more concentrated NaOH solution was used, the smaller volume of iodine solution was sufficient to cause a potential drop.

It has been found that the shape of potentiometric titration curves depend on the amount of titrated compound. These shapes were typical and did not exhibit a potential drop when 4,4-dimethyloxazolidine-2-thione (within the range 50–200 μmol) was titrated in 4 mol L^{-1} NaOH solution. However, the potential drop appeared when larger amounts of the compound were determined. When 500 μmol of the compound were titrated, potential drop appeared only after adding almost whole amount of iodine participating in the reaction. When 1000 μmol of the thiol was determined, potential drop occurred at the beginning of titration. In this procedure a significant rise in the potential was observed close to the equivalence point (800–1000 mv/0.1 mL of the titrant). Such large increase of the potential does not occur in other potentiometric titrations.

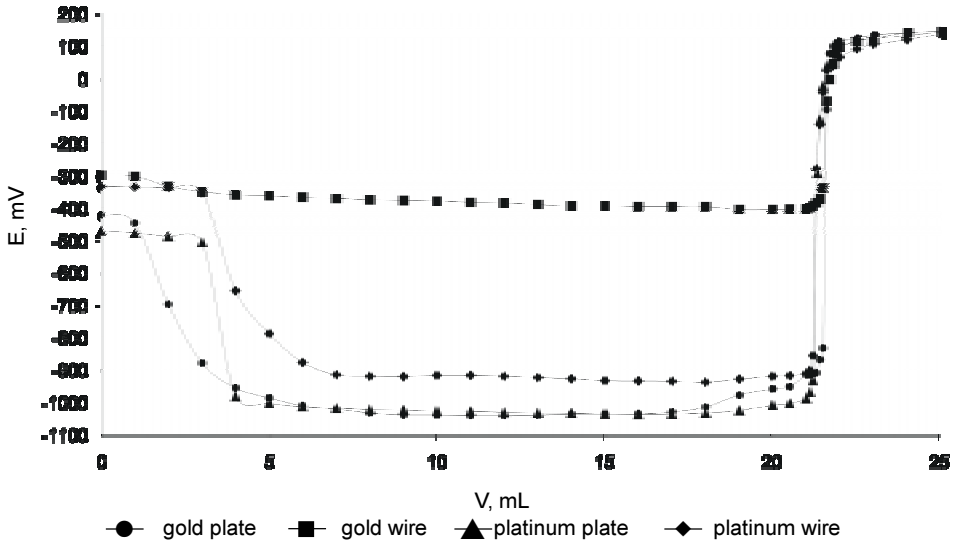


Figure 2. Potentiometric titration curves of 2-amino-6-hydroxy-8-mercaptopurine in 10 mol L^{-1} NaOH obtained using different indicator electrodes; amount of analyte: 125 μmol; titrant concentration: 0.5 mol L^{-1} iodine

Preparation procedures of the working electrodes have an influence on the shape of the obtained potentiometric curves. In our research we have investigated platinum and gold indicator electrodes (wire and plate). Using these electrodes, the potential drop always appeared in case of the studied sulfur compounds. Using a platinum

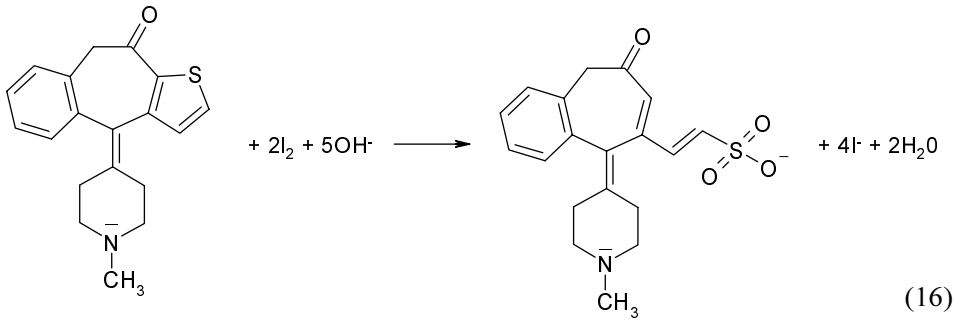
indicator electrode (wire and plate) and a gold plate electrode we have observed the potential drop in the initial part of the curves. Interestingly, when gold wire indicator electrode was used, potential drop did not appear. Metals used for the preparation of wire and plate electrodes have different structures as they were produced in a different way. In case of wire electrodes metal was drawn, whereas in case of plate electrodes metal was rolled. The influence of indicator electrode on the shape of potentiometric titration curve is exemplified in Figure 2.

It has been found that the shapes of the titration curves obtained at high concentrations of NaOH depend on the material of the indicator electrode, concentration of NaOH solution, and the amount of determined compounds. These phenomena are related to adsorption processes and charging of the electrical double layer at the phase boundary of the indicator electrode.

RING-OPENING REACTION BY IODINE IN ALKALINE MEDIUM

The compounds with a thiol group attached to heterocyclic ring and containing either nitrogen or oxygen heteroatom and sulfur heteroatom undergo cleavage of heterocyclic ring. This process for 2-mercaptothiazoline and 2,5-dimercapto-1,3,4--thiadiazole [42] in the presence of iodine in alkaline medium proceeds at high concentration of NaOH. The corresponding number of electrons transferred in a single reaction exceeds z = 8 per thiol group. The first step is oxidation of the thiol group. Reaction proceeds according to equation (12) in optimally concentrated NaOH solution. Under more alkaline conditions, further oxidation proceeds to give a RO^- derivative and sulfate ion. The total number of electrons transferred in a single reaction is z = 8 per one mercapto group (equation (12)). In the second step carbon-sulfur bond in heterocyclic ring is broken. This happens in iodimetric reaction of 2-mercaptothiazoline and 2,5-dimercapto-1,3,4-thiadiazole at higher concentration of NaOH. The number of electrons transferred in a single reaction increases then above 8 per one thiol group.

The ring-opening reaction of thiazole [50, 51] and penicillin [52–54] by hydroxide ions has been also reported. After the cleavage of heterocyclic system, sulfur atom might be subsequently oxidized either to disulfide [51] or sulfonate form [52–54]. Similar reaction mechanism might explain the behaviour of ketotifen during its iodimetric titration with iodine in alkaline medium [55]:



(16)

SIMULTANEOUS DETERMINATION OF THIO-COMPOUNDS BY IODIMETRIC METHOD; APPLICATIONS OF THE METHOD

The mixture of thiosulfate and tetrathionate was titrated with iodine in neutral medium (pH = 7) in the presence of starch as end-point indictor. Then, NaOH solution was added up to the concentration of 5 mol L^{-1} [56]. Under such conditions tetrathionate transforms into thiosulfate and sulfite ions within 1–10 min:

$$2S_4O_6^{2-} + 6OH^- \rightarrow 3S_2O_3^{2-} + 2SO_3^{2-} + 3H_2O \quad (17)$$

The resulting solution was titrated with iodine with potentiometric end-point detection. The amount of thiosulfate was estimated from the reaction in neutral medium (z = 1). The quantity of tetrationate was calculated from the reaction in alkaline medium (z = 14).

The above method was applied to the determination of several thyroid compounds [17, 36–39, 45, 57, 58, 59], anticancer compounds [17, 45], thiamine [51], and tableted antiasthmatic drug [55] applying potentiometric and coulometric titration. The results are shown in Table 3. It has been found that tablet excipients of all determined drugs do not interfere under the applied conditions of analysis.

Table 3. Results of iodimetric determination of sulfur compounds in drug samples

Name of the drug/ compound	Method	Declared content, mg	Found, mg	RSD	Ref.
Trecator/ ethionamide	Potentiometric titration	250	251 ± 0.7	0.3	[36]
Propycil 50/6-propyl-2-thiouracil	Potentiometric titration	50	49.8 ± 0.4	0.6	[57]
			49.4 ± 0.3	0.3	
	Coulometric titration		50.1 ± 0.03	0.1	
			49.8 ± 0.2	0.2	
Tyreostat II/6-propyl-2-thiouracil	Potentiometric titration	25	25.08 ± 0.16	0.6	[38]
Propyl-Thiouracil/ 6-propyl-2-thiouracil	Potentiometric titration	50	49.8 ± 0.4	0.8	[38]
Methylthiouracilum/ 6-metylo-2-tiouracyl	Potentiometric titration	100	100.6 ± 0.4	0.38	[37]
	Coulometric titration	100	99.7 ± 0.1	0.1	[17]
Basdene/6-benzyl-2-thiouracil	Potentiometric titration	25	24.9 ± 0.2	0.71	[37]
Metizol/2-mercapto-1-methylimidazole	Coulometric titration	5	5.08 ± 0.01	0.2	[17]
	Potentiometric titration		5.10		
Thyromazol/ 2-mercapto-1-methylimidazole	Potentiometric titration	5	4.96 ± 0.04	0.8	[59]
Carbimazole HENNING/carbimazole	Coulometric titration	5	5.020 ± 0.001	0.02	[39]
Mercaptopurinum/6-mercaptopurine	Coulometric titration	50	49.9 ± 0.1	0.2	[17]
Lanvis/2-thioguanine	Potentiometric titration	40	39.5 ± 0.1	0.15	[45]
	Coulometric titration		39.7 ± 0.2	0.4	
Thiamine hydrochloride	Coulometric titration	100 3	99.7 2.985		[51]
Ketotifen/ketotifen	Coulometric titration	1	1.003 ± 0.002	0.2	[55]
Pozitan/ketotifen			1.001 ± 0.007	0.7	
Zaditen/ketotifen			0.998 ± 0.002	0.2	

PROCEDURES

Potentiometric titration in alkaline medium

Volumetric titrations with potentiometric end-point detection were applied to determine large quantities of sulfur compounds. For potentiometric measurements

two- electrode circuit was utilized: it comprised a platinum indicator electrode and saturated calomel electrode as the reference electrode. Sometimes an Ag/AgCl reference electrode was applied [59]. The samples of studied compounds were dissolved in appropriately concentrated NaOH solution and titrated with iodine. 5 s waiting time was applied after each addition of iodine to let the potential response stabilize [11–13, 36–45, 48, 55–57, 59, 60]. The equivalence point of the reaction was determined either from the first derivative curve, or from the inflection point of potentiometrical curve. Close to the titration end-point, a small amount of iodine was introduced.

Coulometric titration in alkaline medium

Lower concentrations of compounds were determined by coulometric titration using biamperometric end-point detection [11, 12, 17, 39, 40, 42, 44, 45, 48, 49, 51, 55, 57, 61]. For coulometric measurements a Universal Coulometric Analyser was utilized. Electrolysis cell [62] was equipped with two platinum electrodes, each of 5 cm^2-in-area, plugged into a generating circuit, and a double electrode plugged into a biamperometric indicator circuit.

Two detection systems: potentiometric [18] and biamperometric [17] were utilized in coulometric titration with iodine in alkaline medium. Potentiometric end-point detection with platinum and saturated calomel electrodes was impossible owing to the slow response of the platinum indicator electrode at low concentrations of the investigated compound and the titrant. Thus, biamperometric indicator system was applied for coulometric titration in alkaline medium. The dependence of the current generated at the indicator electrode on the potential differences has confirmed that the iodate(I)/iodide system in alkaline medium is reversible like the iodine/iodide system in neutral medium. The measured biamperometric current increased significantly with an increase of potential differences of indicator electrodes up to 200 mV. Above this value, further increase of the current was only slight. The potential of 200 mV was chosen as an optimum voltage for biamperometric detection system. Sensitivity of biamperometric detection decreased with an increase of NaOH concentration in the reaction medium.

Indirect titration in alkaline medium

Thiopental [31, 32], 1,3-diethyl-2-thiobarbituric acid [33] and 6-propyl-2-thiouracil [34] were determined by indirect titration with iodine in alkaline medium. The required amount of thiol was dissolved in appropriately concentrated NaOH solution, and iodine solution was added. After some time, the solution was acidified. The excess of iodine was back-titrated applying either visual or potentiometric end-point detection.

CONCLUSION

Iodimetric titration in alkaline medium allows one to determine many more thiols than it is possible in either neutral or acidic media. Noteworthy, concentration of hydroxide ions influence titration to a great extent. Owing to a substantial increase (of what potential) recorded at the end-point, the obtained results are accurate and reproducible.

The proposed technique yields good results in case of determination of thiols in pharmaceutical preparations. The analytical procedures employed are easy to perform as they do not require separation of thiols from other non-interfering tablet excipients.

Anodically generated iodine in alkaline medium has proved to be the best oxidant in coulometric determination of thiols. The presented method enables one to determine more thiols compounds than titration with anodically generated chlorine [63] or bromine [64]. This is due to the fact that thiols react faster with iodate(I) than with chlorine and bromine. The applied reaction solutions containing potassium iodide and NaOH are stable – unlike acidic solutions, iodide present in alkaline ones does not undergo oxidation with oxygen. Coulometric method is partly automated and as an absolute method requires no standard solutions.

REFERENCES

1. Christian G.D., *Analytical Chemistry*, John Wiley and Son, New York 1994, p. 360.
2. Harris D.C., *Quantitative Chemical Analysis*, W.H. Freeman and Company, New York 2003, p. 362.
3. Bishop E., *Indicators*, Pergamon Press, Sydney 1972, p. 664.
4. Ramsay W.J., Farrington P.S. and Swift E. H., *Anal. Chem.*, **22**, 332 (1950).
5. Swonger A.K. and Matejski M. P., *Nursing Pharmacology. An Integrated Approach to Drug Theraphy and Nursing Parctise*, Scott, Foresman and Company, London 1988, p. 1166.
6. Jorgensen E.C., in: *Medicinal Chemistry,* [Burger, A., Ed.], Wiley-Interscience, New York 1970, Part 1, p. 853.
7. Mandel S.J. and Cooper D.S., *J. Clin. Endocrinol. Metabol*., **86**, 2354 (2001).
8. Haskell Ch.M. and Cline M.J., in: *Essential of Pharmacology. Introduction of the Principles of Drugs Action*, [Bevan J.A., Ed.], Harper and Row, New York 1976, p. 542.
9. Yamamoto L.G., Yim G.K. and Britten A.G., *Pediatr. Emerg. Care*, **6**, 200 (1990).
10. Schalen W., Messeter K. and Nordstrom C.H., *Acta Anaestesiol. Scand*., **36**, 36 (1992).
11. Ciesielski W. and Zakrzewski R., *Chem. Anal. (Warsaw)*, **44**, 1055 (1999).
12. Ciesielski W., Zakrzewski R., Krenc A. and Zielińska J., *Talanta*, **47**, 745 (1998).
13. Ciesielski W. and Zakrzewski R., *Chem. Anal. (Warsaw)*, **41**, 399 (1996).
14. Gottfrucht A., *Metal Finishing*, **67**, 50 (1969).
15. Weizhang L., *Huaxue Shijie*, **24**, 300 (1983); *Chem Abstr*., **100**, 91125s (1984).

16. Lorenz O. and Echte E., *Kautschuk und Gummi*, **6**, 300 (1956).
17. Ciesielski W., *Chem. Anal. (Warsaw)*, **36**, 555 (1991).
18. Oganesyan L.B. and Konkova N.F., *Zh. Anal. Khim*., **35**, 1995 (1980).
19. Pastor T.J., Vajgand V.J. and Antonijevic V.V., *Mikrochimica Acta*, 1983 (III), 203.
20. Ruettinger H.H. and de Spohn U., *Anal. Chim. Acta*, **202**, 75 (1987).
21. Pastor T.J. and Antonijevic V.V., *Anal. Chim. Acta*, **196**, 229 (1987).
22. Kucera Z., Karlik M. and Krofta J., *Collect. Czech. Chem. Commun*., **47**, 588 (1982).
23. Pastor T.J. and Barek J., *Mikrochim. Acta*, **1989**(I), 407.
24. Zima J., Rohlickova R. and Barek J., *Cesk. Farm*., **38**, 107 (1989).
25. Kostromin A.I., Badretolinova G.Z. and Abdullin I.F., *Zh. Anal. Khim.*, **38**, 872 (1983).
26. Kurzawa J. and Janowicz K., *Acta Chim. Hung.*, **125**, 147 (1988).
27. Kurzawa J., *Chem. Anal. (Warsaw)*, **32**, 875 (1987).
28. Norkus A.K. and Shimkyavichute G.S., *Zh. Anal. Khim*., **26**, 39 (1971).
29. Norkus P.K., *Zh. Anal. Khim*., **23**, 908 (1968).
30. Joshi M.K., *Anal. Chim. Acta*, **14**, 509 (1956).
31. Wojahn H., *Arch. Pharm*., **288**, 1 (1955).
32. Jančik F., Körbl J. and Hodonická J., *Českoslov. Farm*., **13**, 70 (1964).
33. Wojahn H., *Arch. Pharm*., **284**, 243 (1951).
34. Wojahn H. and Wempe E., *Arch. Pharm*., **285**, 280 (1952).
35. Jancik F., Budesinsky B. and Cinkova D., *Cesk. Farm*., **6**, 108 (1957).
36. Ciesielski W., Krenc A. and Żłobińska U., *Chem. Anal. (Warsaw)*, **50**, 397 (2005).
37. Ciesielski W. and Zakrzewski R., *Arch. Pharm*., **331**, 371 (1998).
38. Ciesielski W. and Zakrzewski R., *Chem. Anal. (Warsaw)*, **45**, 135 (2000).
39. Ciesielski W. and Krenc A., *Anal. Lett.*, **33**, 1545 (2000).
40. Ciesielski W., and Krenc A., *Chem. Anal. (Warsaw)*, **49**, 577 (2004).
41. Ciesielski W. and Krenc A., *Collect. Czech. Chem. Commun*., **67**, 1193 (2002).
42. Ciesielski W., Zakrzewski R. and Żłobińska U., *Asian J. Chem*., **18**, 1377 (2006).
43. Ciesielski W. and Krenc A., *Chem. Anal. (Warsaw)*, **48**, 939 (2003).
44. Ciesielski W. and Krenc A., *J. Anal. Chem*., **60**, 974 (2005).
45. Ciesielski W. and Krenc A., *Pharmazie*, **53**, 801 (1998).
46. Młochowski J., *Chemistry of Heterocyclic Compounds*, PWN, Warszawa 1994, (in Polish).
47. Budešinskij B. and Vachek J., *Českoslov. Farm*., **7**, 241 (1958).
48. Ciesielski W., Kowalska J. and Zakrzewski R., *Talanta*, **42**, 733 (1995).
49. Krenc A, Thesis, University of Łódź (Poland), Department of Instrumental Analysis, Łódź 2001.
50. Williams R.R. and Ruehle A.E., *J. Am. Chem. Soc*., **57**, 1856 (1935).
51. Kalinowski K. and Sykulska Z., *Acta Pol. Pharm.*, **16**, 111 (1959).
52. Merz K.W., Knieps H. and Lehmann H., *Pharmazie*, **20**, 764 (1965).
53. Glombitza K.W. and Pallenbach D., *Arch. Pharm*., **302**, 695 (1969).
54. Glombitza K.W. and Pallenbach D., *Arch. Pharm*., **302**, 985 (1969).
55. Ciesielski W., Zakrzewski R. and Żłobińska U., *Pharmazie*, **60**, 237 (2005).
56. Ciesielski W., Żłobińska U. and Krenc A., *Chem. Anal. (Warsaw)*, **46**, 397 (2001).
57. Ciesielski W. and Zakrzewski R., *Analyst*, **122**, 491 (1997).
58. Blazek J., Krecmar J. and Stejskal Z., *Cesk. Farm*., **6**, 441 (1957).
59. Aslanoglu M. and Peker N., *J. Pharm. Biomed. Anal*., **33**, 1143 (2003).
60. Ciesielski W., Zakrzewski R. and Kasprzak K., *Chem. Anal. (Warsaw)*, **41**, 1083 (1996).
61. Zakrzewski R., Thesis, University of Łódź (Poland), Department of Instrumental Analysis, Łódź 1997.

62. Jędrzejewski W. and Ciesielski W., *Chem. Anal. (Warsaw)*, **23**, 781 (1978).
63. Ciesielski W. and Skowron M., *Chem. Anal. (Warsaw)*, **49**, 619 (2004).
64. Bishop E., *Comprehensive Analytical Chemistry*, Vol. IID, Elsevier Scientific Publishing Company, Amsterdam 1975, p. 507.

Received March 2006
Accepted July 2006