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Cetylpyridinium tetrachlorozincate as standard for tenside titration

Analytical methods with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in respect to environmental and economical concern, part 19[3]

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Received December 1, 2003, accepted December 9, 2003

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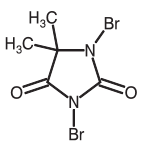
Pharmazie 59: 615–617 (2004)

The determination of the cationic active disinfectants benzalkonium chloride, benzethonium chloride, cetrimide, and cetylpyridinium chloride according to PH. EUR. 2002 resp. supplement 4.3/2003 can be improved using the DBH-method. By application of column extraction the iodide determination can be performed in the organic layer by visual indication. However, titration in aqueous solution with sodium dodecyl sulphate as titrant and methyl orange resp. bromophenol blue as indicator can be performed more simple. Cetylpyridinium tetrachlorozincate is recommended as a standard for tenside titration.

1. Introduction

PH. EUR. 2002 and supplement 4.3/2003 determine the content of the cationic active disinfectants benzalkonium chloride, benzethonium chloride, cetrimide, and cetylpyridinium chloride using the ICl-method (Andrews 1903; Hartke et al. 1993; Hilp and Senjuk 2001). An excess of potassium iodide is added to the aqueous solution of the sample to be analysed. Iodide and the quaternary ammonium cation form an ion pair, which is extracted with chloroform resp. with methylene chloride (benzethonium chloride). By this indirect method the content of the quaternary ammonium salt results from the difference of a blank value and the concentration of the remaining iodide in the aqueous solution. The applied ICl-method for the iodide determination requires also environmentally hazardous chloroform and a high concentration of hydrochloric acid. Furthermore, using this two phase titration, the recognition of the end point is complicated and tedious due to very slow decolorization of the chloroform phase (Hartke et. al. 1997; Hilp and Senjuk 2001).
Therefore, it was interesting, if the determination of quaternary ammonium salts according to PH. EUR. 2002 and supplement 4.3/2003 can be improved using 1,3-dibromo-5,5-dimethylhydantoin (DBH-method; Hilp and Senjuk 2001)



DBH [77-48-5]

2. Investigations and results

2.1. Determination of cationic active quats using DBH

The DBH-method can improve the iodide determination. Nevertheless, such a modified method of PH. EUR. 2002 and suppl.4.3/2003 due to extraction by shaking and bad phase separation is time consuming and difficult to perform (Hartke 1993). Therefore, after separation of the two phases Beckett and Stenlake (1968) recommend to filtrate the chloroform layer over a loosely-packed plug of cotton wool to absorb entrained aqueous liquid. After washing with chloroform the cotton wool has to be taken into the titration solution to obtain the exact content of iodide concentration in the aqueous phase.
The method can be simplified and the iodide concentration can be determined in the organic phase, using the column extraction with Extrelut® (Kunugi and Tabei 1991), a kieselgur of suitable grain size from the company Merck KGaA. Except for cetrimide all environmentally hazardous chlorinated hydrocarbons recommended by the PH. EUR. 2002 and supplement 4.3/2003 could be replaced by ethyl acetate resp. ethyl acetate-cyclohexane. As cetrimide iodide (Beckett and Woodward 1963) is practically insoluble in ethyl acetate, the column extraction can only be performed with methylene chloride or nitromethane or nitroethane. Cetylpyridinium iodide (Macovski 1936; Knight and Shaw 1938) dissolves with solvatochromism resulting in a yellow colour in ethyl acetate resp. in chlorinated hydrocarbons. Thus, the endpoint of the titration according to the DBH-methods using sodium thiosulphate cannot be recognised by decolorisation of the organic layer. By addition of sodium dodecyl sulphate resp. sodium tetraphenylborate a white precipitate of cetylpyridinium dodecyl sulphate (Chernova et al. 1995) resp. cetylpyridinium tetraphenylborate (Bloom and Ross 1977) is formed, so that a fine suspension is obtained by stirring, which allows to titrate from pink to white.

2.2. Determination of cationic active quats according to JAP 2001 in aqueous medium using sodium tetraphenylborate as standard solution and methyl orange as indicator

JAP 2001 determines benzalkonium chloride and benzethonium chloride in acidic aqueous solution in a pH-

range of 2.6–3.4 using sodium tetraphenylborate (Kalignost®) as standard solution and methyl orange as indicator. By formation of an ion pair the titration solution becomes yellow. Corresponding to the pH-range of 2.6–3.4 methyl orange changes to red not until the quaternary ammonium cation has been precipitated quantitatively as tetraphenylborate. According to our investigations this one-phase titration can also be applied for the determination of cetrimide und cetylpyridinium chloride. The method of JAP 2001 using visual indication is simpler to perform than the determinations of the PH. EUR. 2002 and supplement 4.3/2003 also with the improvement by application of DBH and column extraction with Extrelut®.

2.3. Determination of cationic active quats in aqueous medium using sodiumdodecyl sulphate standard solution and methyl orange or bromophenol blue as indicator

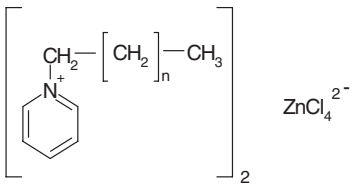
However, the standard solution sodium tetraphenylborate is not stable concerning the titre. JAP 2001 and USP 2000 demand to prepare the standard solution before use. Furthermore, the gravimetric standardisation of the sodium tetraphenylborate solution with potassium hydrogen phthalate according to both pharmacopoeias is time consuming.

In the literature a sodium dodecyl sulphate standard solution is described (Schulz 1996). By addition of a formaldehyde solution the standard solution shall be stable for about 3 months. For the preparation of the solution a specially purified product with a determined content of 99.2% (Merck) has to be applied. The titre of the standard solution is obtained by an exact weight of the sodium dodecyl sulphate, because no primary standard is known.

Moreover, we find, that after a short time glass burettes flow out poorly using a solution of sodium tetraphenylborate. This is not the case, when sodium dodecyl sulphate is applied.

Benzalkonium chloride, benzethonium chloride, cetrimide and cetylpyridinium chloride of PHARM. EUR. 2002 and supplement 4.3/2003 can be determined with exact relative standard deviation with methyl orange or with bromophenol blue or a mixture of both as indicators. The indicator change is well to recognise.

2.4. Standard for titration of anionic active tensides



Cetylpyridinium tetrachlorozincate

A primary standard substance shall not be hygroscopic. This property have most of the quaternary ammonium salts. The substance must have a well-defined composition and has to be thermostable. The content may not change over a long time and has to be determined with a facile method.

A stabilisation can be obtained by variation of the anion. In the literature several cationic active substances with different anions are described (Gautier 1955). However, these substances are improper for our intended purpose. The exchange of the anions can be performed only over the silver salt, because the liberated base, obtained by means of applying a strong-base anion exchanger, readily decomposes.

A further possibility to stabilise a salt consists in the preparation of bases with complex anions such as triiodomercurate (HgI_3^-) and tetraiodomercurate (HgI_4^{2-}). These anions are inapplicable due to ecological concerns. Thus, we synthesised cetylpyridinium tetrachlorozincate by a simple reaction of cetylpyridinium chloride and zinc oxide in hydrochloric acidic, aqueous solution in nearly quantitative yield. This salt is not described in the literature as far as we know. The compound is not hygroscopic, can be recrystallized from ethanol and has a melting point of 92 °C. After storage at a temperature of 70 °C over a period of one week the salt was still analytically pure. The purity of the salt can be examined by an easily performed zinc determination.

3. Discussion

The determination of the four cationic active quats using sodium dodecylsulphate and methyl orange resp. bromophenol blue with visual indication is essentially simpler to perform than the assays of PH. EUR. 2002 resp. supplement 4.3/2003 and should replace the present prescription. A tenside selective electrode (Schulz 1996; Schulz and Gerhards 1996) allows also a potentiometric indication. However, it may come up for discussion, if the application of a relatively expensive and only one year maintainable[4] tenside selective electrode is reasonable for a monograph of a pharmacopoeia. A photometric indication for example using a phototrode[5] may be more appropriate than a tenside selective electrode.

4. Experimental

4.1. Materials

Benzalkonium chloride [8001-54-5], EGA-Chemie KG; benzethonium chloride [121-54-0], Medice; bromophenol blue [115-39-9] Reag. PH. EUR, Riedel-deHaën art. 32712; cetrimide [505-86-2], cetrimide 14, tetradecyltrimethylammonium bromide Riedel-deHaën art. 02883; cetylpyridinium chloride monohydrate [123-03-5] Merck art 2349; cyclohexane, Reag. PH. EUR. Merck art 159137; dichloromethane, methylene chloride [75-09-2], extra pure, DAB, NF, Merck Art. 106049; ethyl acetate, [141-78-6] extra pure, Riedel-deHaën Art. 27227; Extrelut®, refill pack for column fillings, Merck art.11738; formaldehyde solution [50-00-0], min. 36.5%, analytical reagent ACS, stabilized, Riedel-deHaën art. 33220; hexamethylenetetramine [100-97-0], for synthesis, Merck-Schuchardt art. 8.18712; methyl orange [547-58-0], Reag. PH. EUR. Merck art. 159275; nitromethane [75-52-5] for synthesis, Merck art. 820894; nitroethane [79-24-3], for synthesis, Merck art. 806843; sodium dodecyl sulphate for biochemistry and surfactant test $\geq$ 99.0, Merck art. 1.12533.0050; sodium edetate [6381-92-6] p.a. Titriplex® III solution for 1000 ml of 0.1 M, Merck art. 109992; xylenol orange tetrasodium salt [3618-43-7], metal indicator, ACS, Merck art. 108677; zinc oxide, [1314-13-2], extra pure, PH. EUR. Merck art. 108846; for other chemicals see Hilp and Senjuk (2001); SSS = 5-sulfosalicylic acid.

4.2. Solutions

Bromophenol blue 3 mM: 201 mg (0.3 mmol) of bromophenol blue are dissolved with water to 100 ml; 0.05 M DBH/0.5 M NaOH: 1.43 g (0.005 mol) of DBH are dissolved with stirring in 0.5 M NaOH to 100.0 ml; sodium dodecyl sulphate 0.02 M: 5.8137 g (20 mmol) of sodium dodecyl sulphate are dissolved with addition of 10 ml of 35% formaldehyde solution to 1000.0 ml; methyl orange 3 mM: 98.2 mg (0.3 mmol) methyl orange are dissolved with water to 100 ml. A solution of bromophenol blue and methyl orange is less stable than the separately prepared solution of the indicators; 0.2 M SSS/10 M Hac: 50.8 g (0.2 mol) of 5-sulfosalicylic acid dihydrate are dissolved in 580 ml of acetic acid and water to 1000.0 ml; 0.25 M $ZnCl_2$/0.5 M HCl: 2.035 g (25 mmol) of ZnO are dissolved in 100ml of 1 M HCl.

4.3. Assays

4.3.1. Determination using DBH-method and solid phase extraction (Extrelut®)

0.3 mmol of the quaternary ammonium salt are dissolved in 10 ml of water and 2.5 ml of 0.2 M KI are subsequently added. The solution is brought

on the polypropylene column, filled with Extrelut®, and soaked in for about 15 min. Precipitated iodide of the quaternary ammonium base is dissolved in the above mentioned solvent, and also taken to the column. The column is eluted completely with 100 ml of the organic solvent. The eluate (organic phase) is shaken with 10 ml of 0.05 M DBH/0.5 M NaOH for 5 min. After addition of 5 ml of 0.2 M SSS/10 M HAc and 5 min stirring 5.0 ml of 1 M KI is pipetted and titrated with 0.1 M $Na_2S_2O_3$ until decolorization of the solution.

Benzethonium chloride, $C_{27}H_{42}ClNO_2$, $M_r = 448.1$

Weight: 134.4 mg; eluent: ethyl acetate, $n = 7$; $\bar{x} = 98.6\%$; $s_{rel} = 0.63\%$

Cetrimide, $C_{17}H_{38}BrN$, $M_r = 336.4$

Weight: 98.46 mg; eluent: dichlormethane, $n = 7$; $\bar{x} = 99.6\%$; $s_{rel} = 0.96\%$

Cetylpyridinium chloride, $C_{21}H_{38}ClN \times H_2O$, $M_r = 358.0$

The addition of 5 ml of sodium dodecyl sulphate ($0.1 \text{ mol} \cdot l^{-1}$) is necessary before pipetting potassium iodide, because cetylpyridinium iodide dissolves in chloroform with a yellow colour. A fine suspension is formed. The end of the titration can be recognised by the change of the colour from pink to white.

Weight: 107.4 mg, eluent: chloroform , $n = 2$, $\bar{x} = 99.8\%$

4.3.2. Determination according to JAP. XIII (2001)

Cetylpyridinium chloride, $C_{17}H_{38}BrN$, M_r =336.4

Weight: 144,5 mg,; $n = 7$; $\bar{x} = 99.5\%$; $s_{rel} = 0.08$

4.3.3. Determination in aqueous medium using sodium dodecyl sulphate as standard solution and methyl orange/bromophenol blue as indicator

About 0.2 mmol of the substance to analyse, accurately weighed, are dissolved in 50 ml of water. After addition of 0.5 ml of 0.1 M HCl to get a pH-value of about 2.7, 0.1 ml of 3 mM methyl orange and 0.1 ml of 3 mM bromophenol blue are added and titrated with 0.02 M sodium dodecyl sulphate until the green colour of the solution changes to red.

Benzalkonium chloride, $C_{20}H_{40}ClN$, $M_r = 354.0$

$n = 7$; $\bar{x} = 98.6\%$;; $s_{rel} = 0.21\%$ (a water content of 9.24% is taken into account)

Benzethonium chloride (3.75% loss of drying is taken into account)
$n = 7$; $\bar{x} = 99{,}0\%$; $s_{rel} = 0.25\%$

Cetrimide 14, tetradecyltrimethylammonim bromide,
$n = 7$; $\bar{x} = 99.5\%$;; $s_{rel} = 0.19\%$

Cetylpyridinium chloride monohydrate
$n = 7$; $\bar{x} = 99.7\%$;; $s_{rel} = 0.05\%$

4.3.4. Preparation of cetylpyridinium tetrachlorozincate as standard

8.95 g (25 nmol) of cetylpyridinium chloride monohydrate are dissolved in 400 ml of H_2O with warming. 100 ml of 0.25 M $ZnCl_2$/0.5 M HCl (see 4.2) are dropped to the warm solution. A clear solution has to be obtained. A precipitate should be dissolved by warming to get freely filtrable crystals, when cooling up slowly over night. 9.80 g (96%) of colourless needles are obtained, F 92 °C (ethanol), $C_{42}H_{76}Cl_4N_2Zn$, (816.3) calcd. C 61.80, H 9.38, Cl 17.37, N 3.43, Zn 8.01, found C 61.86, H 9.48, Cl 17.35, N 3.56, Zn 7.99 ($n = 5$, $s_{rel} = 0{,}11$); Tenside titration according 4.33 using sodium dodecyl sulphate as standard solution and methyl orange/bromophenol blue as indicator: $n = 7$; $\bar{x} = 99.6\%$;; $s_{rel} = 0.08\%$
Determination of zinc: About 163 mg (0.2 mmol) of cetylpyridinium tetrachlorozincate are dissolved in 50 ml of water. Add 0.1 ml of freshly prepared, aqueous 0.2% xylenol orange solution and 1 g of hexamethylenetetramine and titrate with 0.02 M sodium edetate until the violet-pink colour of the solution turns to light greyish blue. 1 ml of 0.02 M sodium edetate is equivalent to 1.3076 mg of Zn corresponding to 8.163 mg of $C_{42}H_{76}Cl_4N_2Zn$.

Acknowledgements: The authors acknowledge the former president of the University of Marburg Prof. Dr. Dr. h. c. W. Schaal and Mr. Th. Komm, international office of the Philipps-University, financing the stay of Mrs. Swetlana Zembatowa née Senjuk at Marburg and the companies Medice, Püttner GmbH & Co KG, Iserlohn and Novartis Pharma GmbH, Nuremberg for delivery of cationic active tensides.

[3] Cooperation between the Setchenov Academy of Moscow and the Philipps-University of Marburg; part 18; Hilp (2004)
[4] Metrohm Application Bulletin No.233/2 d p.4
[5] Mettler-Toledo GmbH Analytical, Sonnenbergstraße 74, CH-8603 Schwerzenbach

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