# STRUCTURE OF CHEMICAL COMPOUNDS, METHODS OF ANALYSIS AND PROCESS CONTROL

## METHODS FOR THE SYNTHESIS AND ANALYSIS OF DIMETHYL SULFOXIDE (A REVIEW)

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Dimexide (dimethyl sulfoxide, DMSO) is a preparation widely used in medicine for the treatment of rheumatic disorders [1, 2]. The experimental and clinical investigations showed that DMSO is capable of inhibiting inflammation processes of various genesis, resembling in this respect nonsteroidal antiinflammatory agents [3]. DMSO is a low-toxicity compound: LD50 varies from 16.5 to 24 g/kg for white mice and from 19.7 to 28.3 g/kg for rats.

Mildly binding to proteins in both blood and tissues, DMSO is partly reduced to dimethyl sulfide and oxidized to dimethyl sulfone and sulfates. DMSO is rapidly eliminated in the unchanged form with expired air and with urine [4]. Upon local application, DMSO penetrates into a joint cavity and delivers other drugs to the same target [5]. The absence of accumulation effects, low toxicity, and broad pharmacological spectrum make DMSO a promising compound for clinical use.

### 1. SYNTHESIS OF DIMETHYL SULFOXIDE

Dimethyl sulfoxide was originally synthesized by A. M. Zaitsev at the Kazan State University in 1867. Zaitsev obtained DMSO upon slowly adding dimethyl sulfide to concentrated nitric acid. The oxidation of dimethyl sulfide is an exothermal process proceeding by the following scheme:

$$2H_3CSCH_3 + O_2 \rightarrow 2H_3CSOCH_3 + 66.52 \text{ kcal.}$$

The role of oxidizers can be performed by concentrated nitric acid, by oxygen mixed with nitrogen oxides, by hydrogen peroxide, etc. [6].

Processes developed in other countries for the synthesis of DMSO usually employed nitrogen oxides. However, these pathways are poorly applicable because nitrogen oxides are highly toxic and inflammable. In 1959, an accident during DMSO synthesis led to an explosion destroying a plant of the Stepan Chemical Co. in the USA [6]. Among the other methods developed for DMSO synthesis, we would like to mention the process of Bennett et al. [6] based on bubbling gaseous chlorine through an aqueous solution of dimethyl sulfide [6].

In the USSR, the commercial production of DMSO was developed at the Khimreaktivkomplekt experimental chemical plant (Staraya Kupavna) using a technology based on the oxidation of dimethyl sulfide with hydrogen peroxide. In 1968, B. D. Bogomolov and G. F. Proshkin suggested a method for obtaining the initial dimethyl sulfide from hydrolytic lignin, and in 1971, V. G. Vedernikov established optimum conditions for the oxidation of dimethyl sulfide to DMSO [6].

A method for the synthesis of the medicinal preparation dimexide was proposed in 1965 by Prof. N. M. Turkevich (Head of the Department of Pharmaceutical Chemistry at the Lvov Medical Institute). According to this, DMSO (technical grade) is oxidized by a mixture of oxygen with nitrogen(IV) oxide, after which the oxidation product is distilled in vacuum and the fraction boiling at 68 – 69°C is collected [7].

### 2. PURIFICATION OF DIMETHYL SULFOXIDE

When dimexide is synthesized by the method of dimethyl sulfide oxidation, the final product may contain residual dimethyl sulfide possessing an unpleasant odor and producing skin irritation, as well as admixtures of dimethyl sulfone and dimethyl sulfate. The latter two impurities are more toxic than DMSO: $LD_{50}$ = 12,0 and 0.45 g/kg, respectively.

In 1965, V. G. Vedernikov and V. F. Maksimov suggested three methods for the purification of dimethyl sulfoxide from undesirable impurities: (i) DMSO distillation with benzene additives; (ii) DMSO treatment with aluminum oxide followed by distillation; (iii) DMSO fractionation by

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freezing [7]. Later (in 1973), the same researchers suggested to purify DMSO by mixing with alkali metal sulfides, followed by extraction with water and distillation, whereby the impurities pass to the sulfide layer [8].

In 1971, Turkevich with coworkers suggested to obtain a pharmacopoeial DMSO preparation by purifying the technical product on heating to 100°C with potassium hydroxide followed by distillation. This treatment virtually completely removed the admixtures of dimethyl sulfide, dimethyl sulfone, and dimethyl sulfate [9].

## 3. PHYSICAL AND CHEMICAL PROPERTIES

Pure DMSO is a transparent, colorless and odorless hygroscopic liquid; m.p., 18.45°C (readily overcooled); b.p., 189°C (with decomp.), density at 25°C, 1.0960; refractive index, 1.4795; molecular dipole moment, $13.03 \times 10^{-30}$ C · m; dynamic viscosity at 20°C, 2.473 kPa · sec; surface tension at 20°C, $42.9 \cdot 10^{-3}$ N/m; dielectric permittivity at 20°C, 48.9; standard enthalpy of evaporation, 57.28 kJ/mole [10]. DMSO is readily miscible in all proportions with water, ethyl alcohol, ether, aldehydes, ketones, and esters.

The pronounced polarization (high dipole moment) allows the DMSO molecule to form associates and adducts with various organic and inorganic compounds. For this reason, DMSO readily solvates organic and inorganic salts (cations) and acids, serving as a good aprotic coordinating solvent for such compounds. The solubilities of its salts are, for example, as follows (25°C; g/100 g): $(CH_3COO)_2Hg$, 100; $SnCl_2 \cdot H_2O$, 40; $ZnCl_2$, 30; $FeCl_3 \cdot 6H_2O$, 30; NaI, 30; $NaNO_2$, 20 [10]. Due to its high penetrating ability, together with good solvating properties, DMSO molecules readily enter cells, providing for the transport of drugs. Competing with water for hydrogen bonds, DMSO is capable of displacing water and binding to proteins, changing their configurations and properties [11].

As for the chemical properties, DMSO can produce both oxidizing and reducing effects. In particular, DMSO oxidizes thiols to disulfides, and some sulfides – to sulfoxides. In the presence of catalysts (strong acids and their pyridinium salts, oxygen, halogens), DMSO oxidizes primary alcohols and their tosylates, as well as primary alkyl bromides and iodides, to aldehydes. Secondary alcohols are oxidized by DMSO to ketones, and ketones and ketene imides are oxidized to α-hydroxycarboxylic acids and their amides, respectively; oxiranes are oxidized (in the presence of boron trifluoride ester) to α-hydroxyketones. DMSO interacts with methyl iodide to form trimethylsulfoxonium iodide $(CH_3)_3S^+(O) \cdot I^-$, and reacts with NaH and KH with the formation of methyl sulfinylcarbion salts $CH_3S(O)CH_2M^+$ (M = Na, K). Reacting with 1,3-diene, DMSO serves as a soft dienophilic agent.

DMSO can be oxidized to dimethyl sulfone. This reaction is accelerated in the presence of electrophilic agents (nitric and hydrochloric acids, etc.); DMSO oxidation in the presence of halogen acid anhydrides may acquire the character of an explosion [10, 12]. At temperatures above 150°C, DMSO exhibits slow disproportionation to dimethyl sulfide and dimethyl sulfone by the scheme:

$$2(CH_3)_2SO \rightarrow (CH_3)_2S + (CH_3)_2SO_2.$$

## 4. IDENTIFICATION OF DIMETHYL SULFOXIDE

A method for DMSO identification based on the oxidizing properties of this compound was originally proposed by Turkevich et al. [13]. According to this method, DMSO is used to oxidize benzyl alcohol to benzaldehyde, after which the latter is reduced by silver in ammonium solution [1, 14]. Note that, under the same conditions, benzyl alcohol is not oxidized by oxygen from air. This method is simple and convenient for DMSO identification in medicinal forms, but possesses low sensitivity. According to the United States Pharmacopoeia (USP-XXIII), the identity of DMSO preparations is established by reaction with hydroiodic acid. The precipitate obtained in this reaction is dried and dissolved in water to yield a solution of red color [15].

In the presence of concentrated hydrochloric acid, DMSO oxidizes the product of condensation of tryptophan with glyoxylic acid with the formation of a violet dye ($\lambda_{max}$ = 540 nm). Another spectrophotometric method suggested for DMSO identification involves the treatment of DMSO solution in a glacial acetic acid – acetylchloride mixture with a sodium nitrite solution, which leads to the development of a pink color ($\lambda_{max}$ = 545 nm) [16]. Unfortunately, both these reactions employ poorly available reagents that are difficult to handle, which hinders use of this method in pharmaceutical analysis. The normative documentations in Russia (Pharmacopoeial Clause 42–2980 – 98) and the USA [15] also recommend identifying DMSO by its IR absorption spectrum measured in the $4000 – 600\ cm^{-1}$ wavenumber range.

The most widely used method for DMSO identification in medicinal preparations is gas chromatography (GC). An advantage of this technique is the possibility of simultaneously determining the content of impurities [15].

## 5. QUANTITATIVE ANALYSIS FOR DIMETHYL SULFOXIDE

The numerous methods available for the quantitative determination of DMSO and accompanying impurities can be divided into three main groups: titrimetric, optical, and chromatographic.

*5.1. Titrimetric Methods*

Titrimetric methods for the quantitative determination of DMSO in preparations are based on the redox properties of this compound.

**5.1.1. DMSO oxidation techniques**. Methods based on the reducing properties of DMSO employ strong oxidizers capable of oxidizing DMSO to dimethyl sulfone. The equivalence factor in these reactions is 1/2. According to one of the first methods for DMSO determination by oxidation, pro-

posed in 1937 by Böhme [17], DMSO is oxidized with monoperphthalic acid by the scheme

$$CH_3SOCH_3 + RCOOOH \rightarrow CH_2SO_2CH_3 + RCOOH.$$

For this purpose, a sample of the DMSO-containing preparation is dissolved in acetic acid. To this solution is added (at a reduced temperature) a solution of monoperphthalic acid in diethyl ether. The reaction mixture is allowed to stand for 24 h, after which the excess of monoperphthalic acid is determined by iodometric titration. The determination is hindered by mercaptans and sulfides, which are also oxidized under these conditions.

Another method, which is most frequently proposed in the literature, employs the inverse dichromatometric determination of DMSO. It is recommended to perform the analysis by preliminarily boiling the sample with a solution of potassium dichromate in the presence of concentrated sulfuric acid, whereby DMSO is oxidized to dimethyl sulfone. The excess potassium dichromate is titrated either with a 0.1 M Fe(II) – ammonium sulfate solution (using N-phenylanthranilic acid as the indicator) [16, 18] or with a 0.1 M sodium thiosulfate solution [1, 16]. This method cannot be used for determining DMSO in multicomponent compositions (ointments, gels, creams) because of the high oxidizing activity of potassium dichromate.

In this respect, a more convenient method is offered by the reverse iodometric determination of DMSO in an aqueous solution at pH 4 in the presence of excess chloramine B in solution. The method is based on the ability of chloramine B to decompose in an acid medium with the evolution of gaseous chlorine, which oxidizes DMSO to dimethyl sulfone [19].

**5.1.2. DMSO reduction techniques**. According to the procedure proposed in [20], DMSO is reduced with tin(II) chloride in the presence of hydrochloric acid by the reaction

$$CH_3SOCH_3 + SnCl_2 + 2HCl \rightarrow CH_3SCH_3 + SnCl_4 + H_2O.$$

The analysis is carried out after boiling a weighed amount of the DMSO-containing preparation in a solution of tin(II) chloride and hydrochloric acid. The excess tin(II) chloride is titrated with a ferric ammonium alum solution until the appearance of a reddish-blue color (using potassium indigotrisulfonate as the indicator).

In 1951, Barnard and Hargrave [21] developed an indirect method for the determination of sulfoxides using a titanium(III) chloride solution. Titanium(III) ions reduce sulfoxides to sulfides by the reaction

$$CH_3SOCH_3 + 2Ti^{3+} + 2H^+ \rightarrow CH_3SCH_3 + 2Ti^{4+} + H_2O.$$

The sample to be analyzed (0.7 – 1.0 mg-eq.) is dissolved in acetic acid and the flask is filled with nitrogen, after which a 0.1 M titanium(III) solution is added and the reaction mixture is heated for 1 h at 80°C. Then a boiling solution of ferric ammonium alum is added, and the mixture is kept for 30 sec and rapidly cooled. Upon cooling, phosphoric acid and carbon tetrachloride are added and the mixture is vigorously shaken to transfer sulfide to the organic layer. The amount of iron(II) ions in the aqueous layer is determined by dichromatometric titration using diphenylamine sulfonate as the indicator.

In a modification of this method described in 1957 by Legault and Groves [22], DMSO is reduced by ferric ammonium alum and ammonium sulfate. Upon cooling the solution, phosphoric acid is added and the mixture is extracted with dimethyl sulfide, *n*-butanol, and carbon tetrachloride. Finally, the extract is titrated with potassium dichromate. In 1963, Ma [23] suggested a method for determining DMSO by reduction of a sample under the action of zinc and hydrochloric acid by the scheme

$$CH_3SIOCH_3 + Zn + 2HCl \rightarrow CH_3SCH_3 + ZnCl_2 + H_2O.$$

The process is conducted in a Jones microreducer. For this purpose, a solution of the sample in a 5% solution of hydrochloric acid in ethyl alcohol is passed through the reducer for 10 min, after which the sulfide contained in the eluate is determined by dichromatometric titration [23].

The most convenient method is based on the ability of DMSO to oxidize iodide ions to free iodine in glacial acetic acid in the presence of acetyl chloride (initiator). The resulting free iodine is determined by titration with sodium thiosulfate. This method is used for determining the DMSO content in 5% chondroxide ointment (Pharmacopoeial Clause 42-2424 – 94).

**5.1.3. Methods employing the protonophilic properties of DMSO.** In 1958, Wimer [24] pointed out that DMSO can be protonated at the oxygen atom and then titrated with an 0.1 M perchloric acid solution by the scheme

$$(CH_3)_2SO + HClO_4 \rightarrow [(CH_3)_2SOH]^+ClO_4^-.$$

The final point of titration is established potentiometrically. The proposed method is specific for sulfoxides in the presence of all sulfur-containing functional groups because the mercapto group exhibits only acidic properties, while sulfide and sulfo groups do not possess basic properties in acetic anhydride [16, 25].

A common disadvantage of all titrimetric methods for DMSO determination is the use of toxic and aggressive reagents and the cumbersome experimental analytical procedure. The DMSO determination by these methods is hindered by the presence of some supplementary components entering into compositions.

*5.2. Optical Methods*

In 1972, Dizdar and Idjakovic [26] proposed a method for the spectrophotometric determination of DMSO based on the fact that the maximum in the electronic absorption spectrum of a ferric ammonium alum solution in 0.1 M aqueous sulfuric acid shifts in the presence of DMSO toward longer wavelengths. The DMSO concentration is determined by measuring the optical density of the shifted absorption peak at 410 nm. This method is simple in realization but possesses

low sensitivity. The DMSO determination by these methods is hindered by the presence of nickel(II), cobalt(II), chromium(III), uranium(VI), and iron(III) ions [26].

An alternative method [27] of the spectrophotometric determination of DMSO employs its ability to inhibit the color product formation in the reaction of malonic aldehyde (a lipid peroxidation product) with thiobarbituric acid ($\lambda_{max}$ = 535 nm); malonic aldehyde was obtained from rat brain homogenates. In 1972, Gnidets and Tereshchuk [28] proposed a method for determining DMSO by reaction with tryptophan and glycolic acid ($\lambda_{max}$ = 540 nm). In 1981, Shvidkii et al. [29] suggested a photometric method based on the color reaction of DMSO with sodium nitrite in the presence of acetyl chloride.

*5.3. Chromatographic Methods*

Presently, it is usually recommended to use GC for evaluating the quality of the parent substance of dimexide and determining the content of DMSO in biological fluids in the presence of metabolites and decomposition products [14, 15].

The GC columns employ high-polarity immobile liquid phases based on poly(ethylene glycol) (PEG) such as PEG with $M$ = 20 000 (Carbowax 20 M), PEG succinate, PEG adipate (and is analog Rheoplex 400). These proposed immobile phases exhibit close polarities and possess close values of the Rohrshneider and McReynolds constants: the PEG polarity according to Rohrshneider varies from 60 to 80; according to McReynolds, the polarity values are 2308 (Carbowax 20 M), 3300 (PEG succinate), and 2750 (PEG adipate) [30].

The maximum working temperatures of the PEG-filled GC columns do not exceed 220°C. The same temperature limit is established for DMSO, which exhibits disproportionation at higher temperatures [30, 31].

The GC analysis for DMSO is recommended at a column temperature of 120 – 220°C, an evaporator temperature of 150 – 250°C, and a plasma-ionization detector temperature of 150 – 220°C [13, 16, 32, 33, 34].

The GC method provides data both on the content of both the parent substance (DMSO) and the related impurities (dimethyl sulfide, dimethyl sulfone, and dimethyl sulfate). According to the normative documentation (ND 42-2980 – 98) for the dimexide ointment, the weight fraction of DMSO in the preparation is determined by subtracting the total contents of organic impurities and water. The organic impurities are determined by GC and the water content is evaluated by the Fischer method [35]. As follows from the above data, GC offers the most acceptable method for determining DMSO in the parent substance of dimexide, as well as in various medicinal forms and biological fluids.

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