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The Structure and Use of Dimethyl Sulfoxide

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by

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SUMMARY OF PHYSICAL PROPERTIES OF DMSO

Molecular weight	78.13
Boiling point at 760 mm Hg	189 °C (372 °F)
Melting point	18.55 °C (65.4 °F)
Specific gravity at 20 °C (68 °F)	1.1014 (9.18 lbs. per gal.)
Vapor pressure at 20 °C	0.36 mm Hg
Surface tension at 25 °C	42.85 dynes per cm
Specific heat at 29.4 °C	0.47 ± 0.015 cal/gm/°C
Heat of vaporization at 70 °C	260 BTU/lb 11.3 kcal/mole
Heat of solution at 20°C	60 ca/gm
Heat of fusion	44 cal/gm
Heat of combustion at 25 °C	6050 cal/gm
Coefficient of expansion	0.00088 per 1 °C
Dielectric constant (8 mc)	48.9 (20 °C)
Solubility parameter	13
Dipole moment	4.3 Debye Units
Conductivity 20 °C	3×10^{-8} ($ohm^{-1}cm^{-1}$)

THE STRUCTURE AND USE OF DIMETHYL SULFOXIDE

It is hard to talk about dimethyl sulfoxide (DMSO) without sounding like an old-time carnival snake-oil salesman. DMSO appears to be good for arthritis, simusitis, headaches, earaches, sprains, and burns. It reduces swellings, suppresses blisters, kills pain, tranquilizes, and fights germs. It enhances the action of other drugs. It can be swallowed, injected, rubbed one, or dripped in.

Dimethyl sulfoxide is one hundred years old. It was first synthesized by Alexander Saytzeff in Germany in 1866.[1] However, it remained a laboratory curiosity for about three-quarters of a century. No use was found for it until about ten years ago, when its powers as a solvent and antifreeze began to be appreciated by science and industry.

General Properties of DMSO. DMSO is a colorless, water-white liquid which mixes with and attracts water from other chemicals. It has a low order of toxicity and is essentially odorless; it has an osyter-sweet taste. The DMSO molecule is pyramidal with sulfur, oxygen, and carbon atoms at the corners:

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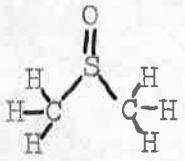
[1] C. D. Leake, "DMSO; Report on International Conference," Science, 152:1646, June 17, 1966.



The carbon-sulfur and carbon-hydrogen bonds are essentially normal single covalent bonds. However, the description of the sulfur-oxygen bonding has been the subject of uncertainity as to whether the structure is more nearly a covalent single bond or a double bond. The weight of the more recent data seems to favor the double bond. The bond shortening due to the second bond is attributed to 2p - 3d pi bonding.[2]

The molecular weight of DMSO is 78.13; the melting point is 18.45 °C and the boiling point is 189 °C (760 mm). Its density is 1.1014 (20 - liquid, 4 - water).[3] DMSO is very soluble in water, alcohol, ether, and acetone. Like ethanol, it mixes freely with water with the evolution of heat, and lowers the freezing points of aqueous solutions. Many of the characteristic properties of DMSO derive from the high polarity of the compound; the dielectric constant of DMSO is high for an organic liquid. The basicity of DMSO, which results from enhanced electron density at the oxygen atom, is slightly greater than that of water, acetone, or alcohols. DMSO forms

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[2]Warren S. MacGregor, The Reaction Solvent Characteristics of Dimethyl Sulfoxide, Drown Zellerbach Corporation, Chemical Products Division, Camas, Washington. p. 1.

[3]Handbook of Chemistry & Physics, Chemical Rubber Co., 47th edition, p. C-556.

crystalline salts with strong protic acids and coordinates with Lewis acids. It modifies hydrogen bonding.[4] Another characteristic of the molecule is the low acidity of the hydrogen atoms.

DMSO is a versatile and powerful solvent that will dissolve most aromatic and unsaturated hydrocarbons, organic nitrogen compounds, organo-sulfur compounds and many inorganic salts. It is miscible with most of the common organic solvents such as alcohols, ketones, lower ethers, chlorinated solvents and aromatics. However, saturated aliphatic hydrocarbons are virtually insoluble in DMSO. As a reaction solvent, DMSO is valuable for displacement, elimination, and condensation reactions involving anions.

Chemically, DMSO is stable up to 100 °C in alkaline, acidic or neutral conditions. At temperatures approaching its boiling point of 189 °C, DMSO is stable in neutral or alkaline conditions. In fact, it can be distilled away from solid caustic at atmospheric pressure. Prolonged refluxing at atmospheric pressure will cause slow decomposition of DMSO. If this occurs it can be readily detected by the odor of trace amounts of methyl mercaptan and bis-(methylthio)methane.[5] The rate of decomposition is a time-temperature function that can be accelerated by the addition of acids and retarded by bases. Dimethyl

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[4]C. D. Leake, op. cit., p. 1646.

[5]Dimethyl Sulfoxide Technical Bulletin, Crown Zellerbach Corporation, Chemical Products Division, Camas, Washington. p. 1.

sulfoxide is very hydroscopic and must be protected from atmospheric moisture.

Dimethyl sulfoxide is a relatively stable solvent of low toxicity. DMSO by itself presents less hazard than many chemicals and solvents commonly used in industry. However, DMSO has the ability to penetrate the skin and may carry with it certain chemicals with which it is combined under certain conditions. This ability presents a potential hazard to be guarded against. The toxicity of DMSO solutions will depend on the nature and toxicity of the other chemicals used and the degree of penetration. The degree of penetration is determined by the concentration of DMSO and water in the solution and the length of time of skin contact. Not all chemicals can be carried through the skin, even though the DMSO may penetrate. A 10% solution of DMSO in water causes only slight increase in skin penetration over the same solution without DMSO.[6]

Preparation of DMSO. The Crown Zellerbach Corporation has a patent on the manufacturing process that produces DMSO from lignin. Lignin is something of a mystery substance that cements the cellulose fibers of wood together. One thirty-five pound log will produce enough lignin for about four ounces of DMSO.[7] Until Crown Zellerbach learned how to synthesize DMSO, Kraft process legnin was almost worthless. Now

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[6]Ibid., p. 23.

[7]Andrew Hamilton, "Report on DMSO; Dimethyl Sulfoxide," Science Digest, 58:80, August, 1965.

the 15,000,000 tons a year that are produced in paper products manufacturing have taken on a new value. As an industrial solvent, DMSO sells for fifty cents a pint; but as a medicine, the cost of DMSO will be several times higher, reflecting the cost of research and purification of the chemical. Crown Zellerbach, manufacturers of DMSO and the nation's second largest paper firm, and the Oregon State Board of Higher Education have a fifty-fifty profit-sharing arrangement on the potential pharmaceutical applications of the chemical.

In the Kraft process the wastes of paper manufacture are evaporated, burned, and many chemicals recovered. DMSO is manufactured from the black liquor of the Kraft pulp process. It is not a component of the liquor, but the liquor furnishes lignin, which in turn furnishes the methyl group. Sulfur is added to this giving dimethyl sulfide; this is oxidized to give demethyl sulfoxide. The industrial process requires many heatings, distillations, and purifications. DMSO can also be made from a number of organic materials and is inexpensively produced.

Early in 1961, Dr. Stanley Jacob, of the University of Oregon, and Dr. Robert J. Herschler, of the Crown Zellerbach Corporation, accidentally learned of DMSO's strange medicinal properties in the course of some experiments involving animal tissue freezing. They acidentally spilled some of the substance on their arms; when they noticed a sweetish taste in their mouths a few minutes later, they realized that the

chemical had passed through the skin. The strange absorption property of DMSO is probably through the blood stream. Doctors still do not know what becomes of DMSO in the human body. Some of it gets broken down to dimethyl sulfide, which causes the garlic breath and might be responsible for more serious undesirable effects. A drop on the skin is completely absorbed in fifteen to thirty minutes.[8]

Applications of DMSO. The major applications of DMSO are dependent upon its characteristics as a solvent, a reaction medium, and a chemical reactant. Its ability to depress the freezing point of water, its humectancy, its dispersing ability, and its ability to form complexes with many inorganic salts play lesser but still vital roles in the use of this compound.

Dr. Herschler started looking for new uses for DMSO as a solvent. It was tried first on notoriously hard to dissolve substances like pesticides. DMSO dissolved them easily. Then the solution was checked on trees. The pesticides began to move around with amazing speed. Pesticides were piped into trees the way intravenous drips are put in the arms of patients. They spread to protect leaves and fruit from mildews, blights, scabs, and cankers.

Dimethyl sulfoxide is of great interest to researchers in plant pathology. Plant experiments are much slower than medical ones due to the fact that there is only one growing

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[8]Ibid., p. 80.

season a year and investigators have to work in that annual cycle. Experimenters are working on disease and insect controls of orchard trees by injecting DMSO in combination with other chemicals into the tree. DMSO increases the action of some insecticides, requiring less insecticide and even activating some compounds that have not previously been considered as insect killers.

Dimethyl sulfoxide is an extensively used commercial and industrial chemical with a wide range of uses. Some of these are: (1) It is a solvent for spinning synthetic fibers, extracting petroleum impurities, carrying dyes, dissolving pesticides, resin, and paint strippers. (2) It is used as a reaction medium in many industrial processes; by speeding reaction rates, it reduces costs. (3) It is a chemical reactant and aids in the manufacture of new or existing compounds. (4) It is useful in the biological field in preventing damage to cells and tissues during storage by freezing. Researchers have used it in preserving blood cells, bone marrow, and bovine spermatozoa.[9]

Medical Applications of DMSO. The greatest medical use of DMSO will probably be as a carrier and action increaser of other drugs, getting them inside the cells where they can act best. Only time and experiments will tell. As a penetrant carrier, DMSO increases penetration of various substances

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[9]W. B. Morse, "DMSO; Fact and Fancy," American Forests, 70:6-7, September, 1964.

through biological membranes. This kind of rapid penetrating power is known to exist in certain poisons, but it had never before been found in a non-poisonous material. Experiments on animal bladders indicate that DMSO can increase the penetration of various drugs through membranes, including cell walls: (1) As a local analgesic agent, DMSO penetrates human skin relieving pain in several conditions. (2) It can be used for anti-inflammation in a variety of skin, burn and surgical conditions. (3) DMSO acts against a few forms of bacteria. (4) Application of DMSO appears to have a tranquilizing effect.

Because of the drug's ability to penetrate the skin, some researchers feel the most exciting potential use of DMSO will be as a new way of administering drugs and vaccines. Dr. Richard Stoughton of Western Reserve has found that DMSO not only speeds the absorption of such steroid hormones as cortisone into the skin, but also increases their effectiveness.[10] While DMSO will transport many substances through the skin, others, because of the size or complicated structure of their molecules, are left behind. In tests so far, insulin is one of those complex molecules that will not effectively penetrate the skin barrier.

The original hope was that it could penetrate all body membranes. This set up great excitement among medical re-

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[10]"Too Good To Be True; Strange Medicinal Properties," Newsweek, 65:109-10, May 10, 1965.

searchers who hoped they could use DMSO to reach inaccessible tissues, such as the interior of the eyeball, which so far cannot be reached by antibiotics and other medications. But in every test so far, the drug has failed to penetrate the dense layers of the eyeball.

Some medical uses of DMSO already in effect are:

1. For fungal infections such as ringworm and athlete's foot, DMSO transports the basic anti-fungal drug and helps to spread clearing of the infection.

2. DMSO also helps in scleroderma, or "hidebound disease," in which the skin's fibrous middle layer becomes thickened and so hard that the victim cannot clench his hands. DMSO has restored the use of the hands and healed fingertip ulcers. Microscopic sections of the skin of patients with scleroderma have been studied before and after treatment with DMSO. These studies demonstrated definite improvement with DMSO therapy.

3. A big question about DMSO is its usefulness in rheumatoid arthritus, the most disabling form of joint inflammation. The best results to date have been in patients in the early stages of the disease, especially those invovling the small joints of the hands. Dr. Heinz John of Schering Corporation in West Berlin reported the drug was of unequivocal benefit to eighty-one percent of a group of three hundred and eight

patients with acute muscular-skeletal injuries.[11] Not all investigators, however, have gotten the same results in their tests. Dr. Daniel Bachman of the University of Oregon has reported skepticism about the drug's effectiveness in patients with rheumatoid arthirtus. But Dr. Jacob feels that the negative results in at least some trials were the result of low dosage. About an ounce a day is necessary for real effectiveness.[12]

Side Effects of DMSO. An important question about any drug is toxicity. There is no such thing as a non-toxic drug. DMSO has its side effects. The major clinical side effect of dimethyl sulfoxide is the possibility that an occasional patient may be allergic. Systematic allergic reactions to DMSO have been reported, some of a severe nature with at least one death which occurred in Ireland. The systematic allergic reactions consisted of generalized urticaria (an inflammatory disease of the skin accompanied by itching; hives), respiratory distress, angioneurotic edema, and anaphylaxis (excessive susceptibility; especially, protein sensitization). The lone death in Ireland claimed by Dr. Joseph F. Sadusk, Jr., to be connected with DMSO has not been verified, said Dr. Stanley Jacob. The woman in question had been taking several different drugs besides DMSO and he reported that there was no evidence

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[11] Ibid., p. 110.

[12] Ibid., p. 109.

that her death was caused by DMSO.

Another possible side effect from the use of DMSO is eye damage. Human eye problems resulting from its use have been described as: "Blurring of vision," "like wearing dark glasses," "pain in one eye," "double vision," "impaired vision of a rather vague type" and "decreasing vision."

A more minor, but still an impressive, side effect was skin trouble that resulted from DMSO use. One study of more than 900 patients showed that in seven percent of the cases, skin problems were so severe as to require discontinuing use of the drug.[13]

Dr. Sadusk now says that his office has received forty-six reports of adverse reactions in the central nervous system. For the most part these have been minor--headaches, dizziness, vertigo, and drowisness--but in one instance "severe mental confussion" was reported.

Thirty-one other deaths have been listed as occurring during or after DMSO therapy, says Dr. Sadusk, who hastens to add that no casual relationship has been established. However, an asthma patient being treated with DMSO died and Sasusk conceded that it was possible that the death occurred from the use of the drug.

Some experiments have shown that DMSO is capable of

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[13]Robert G. Sherrill, "Razz-Ma-Tazz in the Drug Industry; Lessons of the DMSO Case," Nation, 202:425, April 11, 1966.

causing deformities in chicks and of reducing the size of rat litters. The point about possible damage to unborn individuals has not been answered with DMSO. Dr. Jacob feels that no drug should be given to a woman known to be pregnant unless it is life saving.

Not the least remarkable feature of DMSO is its apparent harmlessness. Massive doses have been given orally and by injection in laboratory animals without apparent harm; however, long-term effects are still unknown. Dogs have been given up to twice the daily dose for humans for up to eighteen months without showing toxic effects.[14]

The dangers of self-medication with DMSO are spelled out by medical experts: The main feature of DMSO is its ability to pass through human skin rapidly and to enter the bloodstream. Few other substances act this way, and probably none quite so fast. So far, DMSO in its pure state does not appear to have toxic, or harmful effects. However, the purity of the commercial grade, which was never intended to have medical application, may be open to serious question. It may, and often does, contain impurities known to be harmful internally. If these harmful materials are dissolved in DMSO somewhere during the manufacturing or distribution process--and DMSO is an excellent solvent--they too can be carried through the bloodstream. Toxic substances entering the body can cause

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[14]"Too Good To Be True," op. cit., p. 110.

all sorts of complications, some serious, and even death. There may be damage to the kidneys, liver, blood-forming organs, and other vital parts of the body.[15]

The FDA and DMSO. In 1964 the Food and Drug Administration authorized limited investigational use of DMSO in treating humans, but in the ensuing months the drug was widely publicized and widely used despite a lack of evidence of its safety. Application of DMSO to the skin was the only use the FDA had authorized, but many patients received the drug orally, by injection, and in combination with other drugs for a variety of purposes not covered in investigational plans.

The DMSO case is a classic illustration of how the powerful drug industry can undermine the effeciency of the Food and Drug Administration with publicity. An application for distribution of DMSO as an Investigational New Drug was placed with the FDA on October 25, 1963. The FDA advised Crown Zellerbach that there was no evidence that clinical testing would be safe; they did not think that testing on animals had gone far enough to permit even experimental use of the drug on human beings. Newsweek, Life and the Saturday Evening Post gave the story of DMSO's miraculous powers to the public. This brought enough public pressure to soften up FDA a little and they agreed to allow very limited experiments, involving

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[15]Lester David, "Promise and Perils of the Miraculous DMSO," Good Housekeeping, 161:68, August, 1965.

no more than a couple of hundred patients, with the testing done by experts under controlled hospital conditions. Before the FDA knew what was happening, more than 1,000 doctors were giving DMSO to perhaps 50,000 patients under the most slap-dash conditions. Most of these doctors knew little more about the drug than what they had read in the magazine articles.

There was no adequate scientific data to justify these glowing accounts. But the publicity excited interest in the medical profession, as well as the laity. DMSO was readily available in many communities, in commercial grades as an industrial solvent. So anyone who wanted to try the substance had a source of supply. These factors greatly complicated the problem of confining the use of the substance for drug purposes to the realm of the qualified and careful clinical investigator. Up to 50,000 patients in the U. S. (and perhaps 500,000 world-wide)[16] have been treated with the super-permeable drug since in burst upon the public and medical profession more than two years ago.

The Food and Drug Administration decided on September 19, 1965, to halt the drug's uncontrolled use and quietly issued a federal ban on further clinical studies. DMSO was banned from interstate shipment and its production halted. The FDA order was based partly on reports of possible human eye damage. Monkeys, mice, rats, rabbits, hamsters, and chicks have been

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16"Some Scientists Hold Dim View of DMSO Ban," Chemical & Engineering News, 44:25, March 21, 1966.

used in DMSO toxicity studies. Eye changes were observed in all animals that were given the drug internally, but changes were less pronounced when DMSO was applied only to the skin. In rabbits, swine, and dogs, dimethyl sulfoxide was shown to produce poorly understood changes in the lens of the eye. These changes are not cataracts. They do not cause blindness. Whether or not they are reversible probably depends on the length of time they are present before the medication is stopped. No similar side effects have been found in humans receiving DMSO.

To disprove the eye damage, another report concluded that high doses of most any effective pharmaceutical will produce some form of toxicity in small animals. In rabbits, using amounts comparable to those commonly recommended for human therapy, tests failed to produce any retinoscopic changes.[17]

Guidelines set by the Food and Drug Administration for new clinical studies provide that:

1. Prior approval by the FDA will be required before any investigational plan is undertaken. Approval will be on the basis of submitted protocols for studies rather than on a patient-by-patient basis as in the recent past.

2. Use of DMSO will be restricted to cutaneous application in serious conditions--such as scleroderma, persistent

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[17]L. F. Ruben and P. A. Mattis, "DMSO; Lens Changes in Dogs During Oral Administration," Science, 155:404, January 27, 1967.

herpes zoster and severe rheumatoid arthritis--for which no satisfactory therapy is now available.

3. Studies will be permitted only in centers with adequate facilities and well-trained, experienced personnel.

4. All subjects must receive a full examination (including an eye evaluation by an ophthalmologist) prior to receiving the drug, at periodic intervals during a study, and three months after discontinuing the drug. Laboratory monitoring of patients must include periodic liver function tests and blood tests.

5. Patient-consent requirement must be carefully observed. Patients must be fully informed of the effects of DMSO in animals and told of the possibility that these may occur in humans.[18]

Dr. James L. Goddard, Commissioner of Food and Drugs, said new studies under these controls will permit sound investigation of the possible therapeutic value of DMSO while at the same time safeguarding patients who may receive the drug.

DMSO and the Future. How soon will you be able to obtain a prescription for DMSO? Dr. Kenneth L. Milstead, special assistant to the U. S. Commissioner of Food and Drugs in Washington has answered that question: "DMSO is an experimental drug authorized for limited investigational use by qualified

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[18]FDA Release, Food and Drug Administration, U. S. Department of Health, Education, and Welfare, December 22, 1966, pp. 2-3.

scientific researchers. It has not been licensed for general medical use."[19] This must not be interpreted as meaning that the drug is unsafe or ineffective--only that the burden of proof lies upon the researchers, who have not yet proved their case.

Before a new drug can be approved for sale, it must pass recently stiffened regulations designed to prevent such disasters as the baby deformities caused abroad by the sedative thalidomide. The famous woman physician and pharmacologist, Dr. Frances O. Kelsey, whose stubborn refusal to approve thalidomide for sale in the U. S. helped to prevent a national calamity, is carefully sifting evidence on DMSO now being submitted by research scientists.

How long before approval can be expected? The American Medical Association Journal answers: "It may well be two years, or even longer, before the drug is available to patients."[20] Indeed, FDA sources candidly state there can be no assurance that the drug will ever be approved. At this point enough is not known about its effects upon the human body. A substance such as this, which offers an entirely new technique of treating medical problems, will receive the most thorough-going scrutiny before general distribution is legalized.

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[19]David Lester, op. cit., p. 69.

[20]Ibid., p. 69.

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