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DECEMBER 2011

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2. K. L. Mittal, Ed., "*Solution Chemistry of Surfactants*", Plenum Press, New York (1984), Vols. 1-3, pp. 1-2173.

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The **SOUTHERN BRAZILIAN JOURNAL OF CHEMISTRY – *SCIENCO* (SOUTH. BRAZ. J. CHEM.)** publishes original research articles in chemistry and related interdisciplinary areas and is intended to fill a gap in terms of scientific information for Southern Brazil.

Occasionally the journal will include review papers and articles dealing with chemical education and philosophy and history of science. It will be published mainly in English, with abstracts in Portuguese and only occasional papers in other languages. At the present there are no page charges and the authors will receive twenty five reprints of their papers free of charge.

We have set high standards for the articles to be published by ensuring strong but fair refereeing by at least two reviewers. We hope that this journal will provide a forum for dissemination of high quality research in chemistry and related areas and are open to any questions and suggestions.

The Editor

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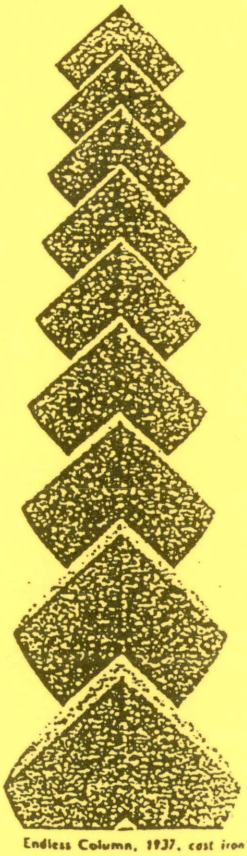

Endless Column, 1937, cast iron
CONSTANTIN BRÂNCUSI

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CONTENTS / CONTEÚDO

TADASHI TOKUHIRO, PROMINENT SPECIALIST IN NMR RELAXATION PHENOMENA AND MOLECULAR DYNAMICS
Lavinel G. Ionescu..... 1

ANTITUBERCULAR ACTIVITY OF SOME NEWER 6-PYRIDAZINONE DERIVATIVES
Asif Husain, Aftab Ahmad, Anil Bhandari and Veerma Ram..... 17

REACTION OF NITRILIMINES WITH SUBSTITUTED HYDRAZINES: SYNTHESIS OF 1, 2,4,5- TETRAAZA-3-PENTENES AND FORMAZANS
Hany M. M. Dalloul 25

SYNTHESIS AND CHARACTERIZATION OF Mn(II), Ni(II), Fe(III), Co(III), Cu(II), Zn(II) AND Cd(II) COMPLEXES OF o-HYDROXYBENZOIC ACID HYDRAZIDE
Vinnakota Srilalitha, Aluru Raghavendra Guru Prasad, Kakarla Raman Kumar, Vahi Seshagiri and Laxmana Rao Krishna Rao Ravindranath 35

ARTHUR F. FISHKIN, PROMINENT BIOCHEMIST AND EDUCATOR
Lavinel G. Ionescu 59

MINERALOGIC ASPECTS OF ARSENIC - THE ARSENATE MINERALS
Lavinel G. Ionescu, Paulo Cesar Pereira das Neves and Darcson Viera de Freitas..... 85

Author Index..... 107

SOUTHERN BRAZILIAN, JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM. , Vol. 19,No.19, 2011

TADASHI TOKUHIRO, PROMINENT SPECIALIST IN NMR RELAXATION PHENOMENA AND MOLECULAR DYNAMICS

Lavinel G. Ionescu
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Santa Fe, New Mexico, USA

ABSTRACT

Tadashi Tokuhiro was born in Yokohama, Japan in 1930 and passed away in Grapevine, Texas, USA in 2010. He obtained a Ph.D. in Chemical Physics from Tokyo Institute of Technology in 1962. He held faculty positions at many universities, including the University of Detroit, Massachusetts Institute of Technology and Missouri University of Science and Technology .His main research interest dealt with physical and engineering application of gels, nuclear magnetic resonance relaxation phenomena , molecular dynamics and characterization of biotissues by NMR methods. He published many scientific articles in widely respected journals from Japan, United States and Great Britain.

KEY WORDS: History of Chemistry, Physical Chemistry, Chemical Physics, NMR Spin Lattice Relaxation, Molecular Dynamics

RESUMO

Tadashi Tokuhiro nasceu in Yokohama, Japão em 1930 e faleceu em Grapevine, Texas, USA. Ele obteve o título de Ph D. em Química Física do Insituto de Tecnologia de Tóquio em 1962. Ocupou cargos de professor em várias universidades, incluindo University of Detroit, Massachusetts Institute of Technology e Missouri University of Science and Technology. As suas atividades de pesquisa trataram de propriedades físicas e aplicações de géis, fenômenos de relaxamento de ressonância magnética nuclear, dinâmica molecular e caracterização de tecidos biológicos com métodos de RMN. Ele publicou muitos artigos científicos em revistas de alto nível do Japão, Estados Unidos e Grã Bretanha.

PALAVRAS CHAVE: História da Química, Fisico-Química, Física Química, Relaxamento Espin-Rede de RMN, Dinâmica Molecular

DOI: 10.48141/SBJCHEM.v19.n19.2011.6_2011.pdf

Tadashi Tokuhiro, Prominent Specialist in Chemical Physics

Tadashi Tokuhiro was born in Yokohama, Japan on February 26, 1930 and passed away in Grapevine, Texas on August 10, 2010.

His father was a structural/architectural engineer for Japan's Sun (Shell) Oil Company with "Western " habits. Together with his sisters he spent the early years in Yokohama .

In 1956 he married Reiko, his wife for forty nine years. They had two children, a girl, named Asako and a boy, Akira.

He received the Bachelor of Science Degree in Chemistry from Tokyo University of Science in 1957. He obtained the Master of Science Degree in Physical Chemistry from the Tokyo Imperial Institute of Science and Technology (now , Tokyo Institute of Technology) in 1959 and was awarded the Doctor of Philosophy Degree in Chemical Physics from the same institution in 1962.

From 1962 to 1965, Tadashi Tokuhiro held the position of Research Associate at the Research Laboratory of Spectroscopy of the Tokyo Institute of Technology.

Early in his scientific career, in 1964, he was the recipient of the Matsunaga Science Foundation Award for Encouragement of Young Scientists for his work on nuclear quadrupole resonance in solid organic substances.

During that time, many promising young scientists from throughout the world were attracted to the United States, very much alike to what happened during the golden age of the Roman Empire, when the world's best scientists and engineers went to Rome.

Tadashi Tokuhiro went to the United States in 1965 with the recommendation and kindness of key individuals like Colonel ImObersteg (Pentagon) and Reverend R.C. Halverson of Washington, DC. He began postdoctoral work with Professor Gideon Fraenkel at The Ohio State University in 1965 and continued as

Research Associate until 1969 when he accepted a faculty position as Assistant Professor in the Chemistry Department of the University of Detroit. In 1974 he was promoted to Associate Professor. He worked at the University of Detroit for 15 years and played a very important role in the establishment of the Ph. D. Program in Chemistry.

PROF. DR TADASHI TOKUHIRO (1930-2010)

Prof. Dr. Tadashi Tokuhiro held faculty positions at other universities including Loyola University (Chicago), New Jersey School of Medicine and Dentistry, Massachusetts Institute of Technology and the University of Missouri, Rolla (now, Missouri University of Science and Technology).

He was also staff scientist at the following institutions: Argonne National

Laboratory (Solid State Science), MIT's Francis Bitter Magnet National Magnet Laboraory, Bruker BioSpin, Brucker Analytische Messtechnik, GMBH, Karlsruhe, Germany and Picker International (NMR/MRI).

At the Missouri University of Science and Technology he worked from 2002 to 2010, a few months before his death. He held the position of Adjunct Professor in the Graduate School and the Department of Chemistry.

His research interests dealt with physical science and engineering application of gels, nuclear magnetic resonance (NMR) relaxation phenomena, molecular dynamics and characterization of biotissues by NMR methods.

During the last ten years that he spent at the Missouri University of Science and Technology, he studied hydrogel/polymer gels using NMR and reported that the characteristic time scales of phenomena at the nano-scale were different from those in bulk aqueous phenomena.

Together with his son Akira Tokuhiro and Massimo Bertino, he was awarded various grants by the Department of Energy for nuclear energy engineering research (DOE NEER). They involved studies of metal binding capability of functional thermosensitive polymer networks and application of hydrogels to low level radioactive waste processing, enhancing reactor facility utilization at the University of Missouri-Rolla reactor.

Prof. Dr. Tadashi Tokuhiro was our colleague during our tenure as a faculty member in the Department of Chemistry of the University of Detroit, Detroit, Michigan from 1975 to 1978.

We shared the responsibility of teaching undergraduate lecture and laboratory courses to chemistry and chemical engineering students.

Eventually, we became good friends and collaborated in various research projects, the most important one being the study of the process of micellization in aqueous solutions. Our study of the ternary system cetyltrimethylammonium bromide-dimethyl sulfoxide-water (CTAB-DMSO-H_2O) , mainly by nuclear magnetic resonance spin-lattice relaxation and tensiometric techniques, eventually led to an unique model for a micelle. The preliminary results were presented at the *174th National Meeting of the American Chemical Society* in Chicago in 1977 and at the *52nd Colloid and Surface Science Symposium*, sponsored by the Oak Ridge National Laboratory, in Knoxville, Tennessee in 1978. A copy of the abstracts of the papers is given on the following pages.

The first diagram of the unique model was published in 1984 in *Surfactants in Solution*, K.L. Mittal and B. Lindman, Eds., Vol. 2, Plenum Press, New York, 1984. (Cf. *L. G. Ionescu, F. Nome and L.S. Romanesco, pp.789-801*).

Prof. Dr. Tadashi Tokuhiro was the best example that we have witnessed in terms of the preparation of experimental samples for precise measurements. He had an extraordinary patience, took a lot of care and seemed to feel a pleasure doing experiments. Like very few scientists, he managed to do research and experimental work up to the age of 80 years, a few months before his passing away.

ABSTRACTS OF PAPERS

174th ACS Meeting

American Chemical Society

Port City Press, Inc.
Baltimore, Md.

Chicago, Illinois
August 28-September 2, 1977

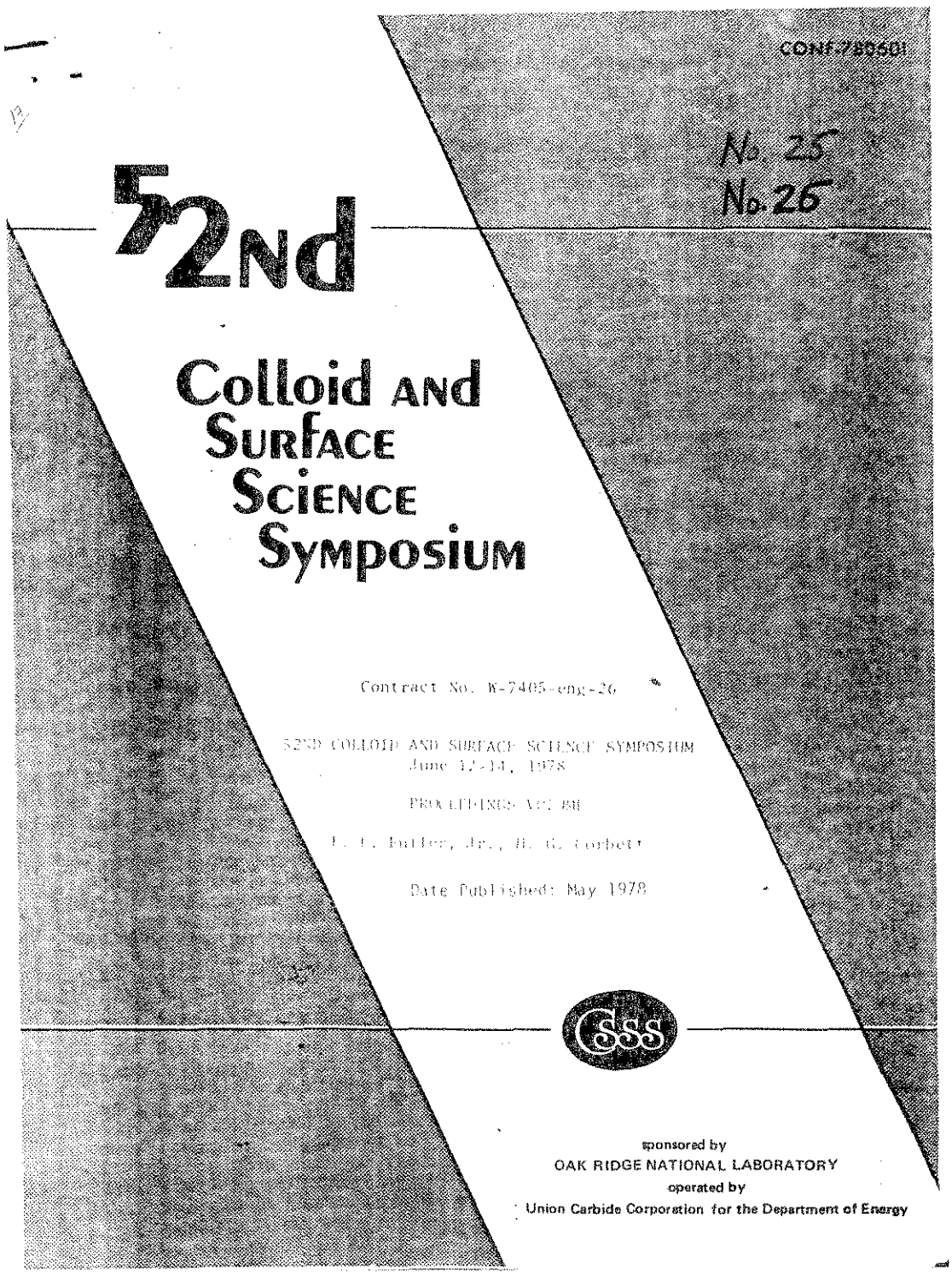
39. STUDY OF INTERMOLECULAR INTERACTIONS IN THE DMSO-H_2O SYSTEM AND THEIR EFFECTS ON THE FORMATION OF MICELLES OF CETYLTRIMETHYLAMMONIUM BROMIDE. Tadashi Tokuhiro, Daniel S. Fung, and Lavinel G. Ionescu, Department of Chemistry, University of Detroit, Detroit, Michigan 48221.

Surface tension measurements of water-dimethylsulfoxide (DMSO) solutions of cetyltrimethylammonium bromide (CTAB) indicate that the liquid structures of the solvent systems play an important role in the

formation of micelles. The addition of DMSO to water causes a significant increase in the critical micellar concentration (CMC) of CTAB. At a DMSO mole fraction (X) of 0.366, micelle formation was not observed. Proton spin-lattice relaxation rate ($1/T_1$) for the methylene groups, the methyl groups attached nitrogen and the end methyl group of CTAB were determined in D_2O and D_2O-DMSO-d_6 mixtures at 28°C. As compared to the $(1/T_1)(CH_2)$ values (0.017/s in D_2O), $(1/T_1)$ for both methyl protons were very large (~2/s). The $(1/T_1)(CH_2)$ values in both D_2O and D_2O-DMSO-d_6 mixtures above CMC were slightly greater than those below CMC. An increase in $(1/T_1)(CH_2)$ was caused by the addition of DMSO-d_6 to D_2O, i.e., 0.03/s (X=0.098) and 0.074/s (X=0.366). These results reveal that an increase in structuring of the solvent system apparently shifts the CMC to higher concentrations. Preliminary results obtained for CTAB in N,N-dimethylformamide-water solutions indicate a similar kind of intermolecular interactions.

40. CONDUCTANCE BEHAVIOR OF LONG-CHAIN AMINE HYDROCHLORIDES IN 2-METHOXYETHANOL. Barbara J. Barker and Thomas Mullin, Department of Chemistry, Hope College, Holland, MI 49423 and Joseph Rosenfarb, Department of Chemistry, University of Florida, Gainesville, FL 32611.

The behavior of a series of colloidal electrolytes in 2-methoxyethanol (methyl cellosolve), a medium of relatively low specific conductance (4-6 x 10^{-8} ohm^{-1} cm^{-1}) and dielectric constant (16.8) and moderate viscosity (1.54 cP), was investigated by conductance techniques at 25°C. Included in the study were octyl-, decyl-, dodecyl-, tetradecyl-, hexadecyl-, and octadecylamine hydrochlorides. All conductance data were evaluated by the Fuoss-Shedlovsky, Fuoss-Onsager, and Fernández-Prini expanded form of the Pitts and Fuoss-Hsia equations. As expected, the limiting equivalent conductances of the electrolytes decrease as the crystallographic radii of the cations of these salts increase. Little difference is observed in the extent of association of the six long-chain quaternary ammonium salts in 2-methoxyethanol; these salts appear to behave as simple 1:1 electrolytes within the concentration range of 1-28 x 10^{-4} M. Included in the present discussion are a summary of the previously investigated conductance behavior of these long-chain salts in water and a general review of colloidal electrolyte behavior in solution.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SOUTH. BRAZ. J. CHEM., Vol. 19,No.19, 2011

L. G. Ionescu

162
52nd Colloid and Surface Science Symposium
June 12-14, 1978
University of Tennessee, Knoxville, Tenn. 37196

EFFECT OF POLAR SOLVENTS ON THE FORMATION OF MICELLES OF CETYLTRIMETHYLAMMONIUM BROMIDE IN AQUEOUS SOLUTIONS. Lavinel G. Ionescu, Tadashi Tokuhiro and Benjamin J. Czerniawski, Department of Chemistry, University of Detroit, Detroit, Michigan 48221.

Long Abstract

Many properties of solutions of the surfactant cetyltrimethylammonium bromide (CTAB) in water have been studied in great detail. Of particular interest is the critical micellar concentration, CMC, which is the minimum concentration of surfactant at which micelles are formed. We have determined the critical micellar concentrations of aqueous solutions of CTAB containing various amounts of dimethylsulfoxide (DMSO), N, N-dimethylformamide (DMF) and N, N-dimethylacetamide (DMA) at 25° and 40°C by means of surface tensiometry. The experimental measurements were carried out with a Fisher Model 21 Surface Tensiomat. In general, the experimental results indicate that micelle formation is hindered by increasing the temperature. All three cosolvents, DMSO, DMF and DMA have an inhibitory effect on the formation of micelles of CTAB. This effect is relatively small at low cosolvent concentrations, but it increases dramatically as the mole fractions of DMSO, DMF and DMA approach 0.33. This mole fraction corresponds to the formation of the stoichiometric hydrates $DMSO \cdot 2H_2O$ and $DMF \cdot 2H_2O$. At cosolvent mole fractions higher than 0.33 the formation of CTAB micelles does not appear to take place. The inhibitory effect on micelle formation is most pronounced for mixtures of water and N,N-dimethylacetamide. The ΔG° values determined for the process of micellization in the mixed solvent systems are comparable to those determined for the formation of micelles in water. The values obtained for ΔS° micellization indicate than an increase in the ordering of the surfactant-water-cosolvent system takes place as the mole fraction of cosolvent is increased. This is consistent with a strong interaction, such as hydrogen bonding, between water and cosolvent. The inhibitory effect on micelle formation can be explained in terms of a decrease of hydrophobic forces in the ternary system due to interactions between water and cosolvent.

SOUTHERN BRAZILIAN, JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM., Vol. 19,No.19, 2011

163

52nd Colloid and Surface Science Symposium
June 12-14, 1978
University of Tennessee, Knoxville, Tenn. 37196

PROTON SPIN-LATTICE RELAXATION MEASUREMENT IN AQUEOUS MICELLAR SYSTEMS CONTAINING DIMETHYLSULFOXIDE. Tadashi Tokuhiro, Lavinel G. Ionescu and Daniel B. Fung, Department of Chemistry, University of Detroit, Detroit, Michigan, 48221.

Long Abstract

Although it is well recognized that the whole micellar structure is a bulk phase well distinct from the aqueous phase, information concerning molecular dynamics of surfactant monomers and molecules present in micelles is almost unavailable. In this work effect of intermolecular interactions on the formation of micelles and molecular motions of surfactant molecules were investigated by measuring proton spin-lattice relaxation rates for the methyl, N-methyl, and methylene groups of cetyltrimethylammonium bromide (CTAB) in water and water-DMSO mixtures at concentrations below and above the critical micellar concentration (CMC).

(1) Below CMC

The experimentally measurable relaxation rates for the above three proton groups (R) of CTAB $[(1/T_1)^S_{R(W \text{ or } B)}]$ consist of several contributions where W and B denote water and water-DMSO mixture. The values of these contributions are listed in Table I.

(2) Above CMC

The experimentally measurable relaxation rates can be expressed as

$$(1/T_1)^{expt}_{R(W \text{ or } B)} = (1/T_1)^{M}_{R(W \text{ or } B)}(1-CMC/C) + (1/T_1)^{S}_{R(W \text{ or } B)}(CMC/C) \quad (1)$$

where C is the total concentration of CTAB and M stands for micelles. There are several contributions to the first term in Eq.(1). The values of these are also listed in Table I.

Our previous study revealed that the addition of DMSO to water increased "structuring" in the liquid system[1] and this was attributed to a strong contribution from DMSO molecules which are directly involved in the structure of this binary liquid through hydrogen bonding with water protons. This increased "structuring" in the liquid system played an important role and disturbed the formation of micelles as manifested by the solvent-composition dependence of intra and intermolecular relaxation rates. (See the third and fourth column in Table I.) It is evident that the strength of intermolecular interactions between water and DMSO overcomes the "hydrophobic effect" which is the main driving force to form micelles in water.

From the values shown in Table I and various correlation times evaluated from $1/T_1$ values the "rigidity" or "fluidity" of micelles in water can be described as follows: 1) the "fluidity" of the methylene groups in micelles is comparable to that of monomers dispersed in water or liquid hydrocarbons, 2) within micelles, the "rigidity" of the tail part of the CTAB molecule is greater than that of the head group, and 3) the "fluidity" of the methylene group is larger than that of either the tail or the head groups by factors of over a few hundred.

SOUTHERN BRAZILIAN, JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM., Vol. 19,No.19, 2011

The generalized picture that emerges for the CTAB micelles consists of three well-delineated regions: 1) the center that contains the terminal methyl groups and is fairly rigid, 2) a fluid area containing most of the methylene groups and, 3) a relatively rigid surface consisting essentially of the N-methyl head groups and the corresponding counter ions.

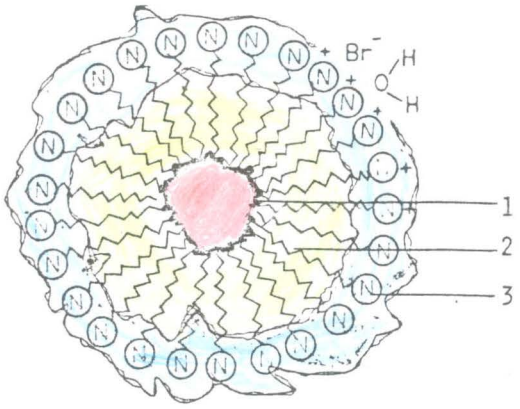
Table I. Intra and Intermolecular Proton Spin-Lattice Relaxation Rates at 28.2°C.

	X(DMSO)	$(\frac{1}{T_1})^S_R$(intra) x 10^2 (S^{-1})	$(\frac{1}{T_1})^{S(inter)}_{R\text{-CTAB}}$ x 10^2 (S^{-1})*	$(\frac{1}{T_1})^{S(inter)}_{R\text{-}H_2O}$ x 10^2 (S^{-1})	$(\frac{1}{T_1})^M_R$ x 10^2 (S^{-1})**	$(\frac{1}{T_1})^{M(inter)}_{R\text{-}H_2O}$ x 10^2 (S^{-1})
$(CH_2)_{15}$	0.	1.0	0.80	-	1.80	-
	0.098	2.5	0.52	-	3.54	-
	0.366	59.0	0.	-	-	-
CH_3	0.	102	44.0	1,260	236	~ 0.
	0.098	120	20.0	357	217	~0.
	0.366	188	0.	-	-	-
$N^+(CH_3)_3$	0.	105	43.0	1,740	275	~0.
	0.098	151	27.0	199	208	<620
	0.366	179	0.	-	-	

* C=3.2 mM

** $(1/T_1)^M_R = (1/T_1)^M_R(intra)+(1/T_1)^M_{R\text{-CTAB}}(inter)$ and at C = 13 mM.

1. T. Tokuhiro, L. Menafra and H. H. Szmant, J. Chem. Phys. 61, 2275 (1974).



1 - RELATIVELY RIGID CENTER CONTAINING TERMINAL METHYL GROUPS
2 - FLUID REGION CONTAINING MOST OF THE METHYLENE GROUPS
3 - RELATIVELY RIGID SURFACE CONSISTING MAINLY OF THE N-METHYL GROUPS AND BROMIDE COUNTERIONS

Structure proposed for micelles of cetyltrimethylammonium bromide (CTAB) on the basis of NMR spin lattice relaxation time measurements. (Cf. *Surfactants in Solution, Vol. 2, K.L.Mittal and B. Lindman, Eds, Plenum* Press, *New York, 1984*).

At the University of Detroit, he had the reputation of a good, tough and strict Professor. As we mentioned above, we shared the responsibility of teaching physical chemistry to chemistry and chemical engineering undergraduate students. We used to rotate the responsibility of the disciplines. In this way the students had a "democratic" choice to choose the professor. It was just the question of waiting a semester.

We remember a chemical engineering student from Nigeria, Momoh, who took Physical Chemistry I with Professor Tokuhiro and failed. He was repeating the course with us. Momoh was almost late for the class that was early in the morning and at times he did not pay much attention.

On a certain date, we went to participate of a conference and our assistant gave an examination for us on the laws of thermodynamics. As usual, Momoh was late and when he got to the classroom he saw some strange people there. The room was used by a guest lecturer and the physical chemistry class was changed to a room in a nearby building. He did not see the note on the door, lost a lot of time finding the new place and failed the exam. He explained to us that he lost a lot of energy looking for the new classroom, his head got hot and could not think well. He became frightened at the idea of failing with us and having to repeat the course again with Professor T. Tokuhiro.

Since thermodynamics deals with the transformation of energy into heat and work, we gave Momoh a second chance and he eventually passed the course.

Prof. Dr. Tadashi Tokuhiro was active in community affairs and the propagation of science. He served as Vice-President and President of the Physical Sciences Section of the Michigan Academy of Sciences, Arts and Letters and participated in the "mokuyoki´ choral groups, He enjoyed classical music, especially the Bach Cantata and travelled widely.

Prof. Dr. Tadashi Tokuhiro lived some very difficult years as a youth during World War II, but was spared from major tragedies. His classes were often cancelled, he worked in a factory and saw B-29 bombers headed for Tokyo. The scenes he witnessed Tokyo in the part of the city hit by incendiary bombs left deep impressions that stayed with him for the rest of his life. He impressed people with his calm mood and his deep reflections.

Two of his doctoral students at the University of Detroit have contributed significantly to the development of chemistry in South America.

Dr. Luis Menafra, besides his effort in chemistry, was President (Rector) of the Universidad de la República, Montevideo, the most prestigious university in Uruguay.

Dr. Juanita Freer, faculty member at the Universidad de Concepción, made important contributions to the development of chemistry in Chile.

Prof. Dr. Tadashi Tokuhiro published a large number of articles dealing with chemistry, physical chemistry and chemical physics in widely respected journals in Japan, United States and Great Britain. A list of representative publications is given at the end of this article.

ACKNOWLEDGMENT. We thank Prof. Dr. Akira Tokuhiro of the University of Idaho for his help and assistance.

SOME REPRESENTATIVE PUBLICATIONS

1. T. Tokuhiro, A. T. Tokuhiro, "Characteristic role of cross-linker on thermally induced volumetric contraction-expansion processes in poly(*N*-isopropylacrylamide) networks and water systems", *J. App. Polymer Sci.* 112, 3177-3184 (2009)

2. T. Tokuhiro, A. T. Tokuhiro, "Temperature dependence of density of polymer gels :Effects of ionizable groups in copoly(*N*-isopropylacrylamide/acrylic acid or sodium acrylate) – water systems", *Polymer* 49, 525-533 (2008)

3. T. Tokuhiro, S. S. Akella, J. W. Carey, A. T. Tokuhiro, "Metal binding capability of functionalized thermo-sensitive polymer networks and application of hydrogels to low-level radioactive waste processing", Proceedings of 15th Intn'l Conf. Nucl. Eng., Nagoya, Japan (April, 2007), Paper#: 15-10163 (8 pages)

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ANTITUBERCULAR ACTIVITY OF SOME NEWER 6-PYRIDAZINONE DERIVATIVES

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ABSTRACT

*Two series of 6-pyridazinone derivatives (**17-30**) were synthesized and evaluated for antitubercular activities against Mycobacterium tuberculosis $H_{37}Rv$ strain. The results indicated that among the synthesized compounds, 5-(4-hydroxy-3-methoxybenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**23**) showed good antitubercular activity. Three more compounds, (**18, 25** & **27**) were significant in their antitubercular action. The present study reveals the antitubercular potential of 6-pyridazinones.*

KEY WORDS: Pyridazinone, antitubercular, mycobacteria, furanone.

RESUMO

*Duas séries de derivados de 6-piridazona foram sintetizados e avaliados para a atividade antitubercular contra Mycobacterium tuberculosis da cepa $H_{37}Rv$. Os resultados experimentais indicaram que o composto 5-(4-hidroxi-3-metoxibenzil)-3-fenil-1,6-dihidro-6-piridazinona (**23**) apresentou boa atividade antitubercular. Outros três compostos (**18, 25 e 27**) mostraram atividade antitubercular significativa. O presente estudo revela o potencial antitubercular de 6-piridazinonas.*

PALAVRAS-CHAVE: Piridazinona, atividade contra tuberculose, micobactéria, furanona.

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INTRODUCTION

Resistance of *Mycobacterium tuberculosis* strains to available antitubercular drugs is an increasing problem worldwide. New potent antimycobacterial drugs with new mechanisms of action have not been developed in the last forty years[1]. TB is considered by the WHO to be the most important chronic communicable disease in the world. About 32% of the world's population is currently infected with TB. The emergence of AIDS, decline of socioeconomic standards and a reduced emphasis on tuberculosis control programs contribute to the disease's resurgence in industrialized countries[2]. If the present trend continues, tuberculosis is likely to claim more than 30 million lives within the new decade. A great deal of research is being directed towards the development of new antitubercular drug.

During recent years pyridazinones have been a subject of intensive research due to their wide spectrum of biological activities. Substituted pyridazinones have been found to have potent antibacterial, antifungal and antiviral including anti-HIV activities[3-6]. Various 3-(2*H*)-pyridazinone derivatives have shown anticancer[6], analgesic & anti-inflammatory[6-8], anticonvulsant[9], cardiotonic & hypotensive[10,11] and antiulcer activities[12]. Now research efforts are toward the search of new antimycobacterial agents (new classes of compounds), which are structurally different from known antimycobacterial drugs[13,14]. The present work describes the synthesis of newer 2(3*H*)-pyridazinones with encouraging antitubercular activity.

MATERIALS AND METHODS

Synthesis

Melting points were determined in open capillary tubes and are uncorrected. Thin-layer chromatography was carried out to monitor the reactions using silica gel G plates. The IR spectra were recorded in potassium bromide pellets using a Perkin-Elmer 1725X spectrophotometer. Elemental analyses were performed on a Perkin-Elmer 240 analyzer and the values were in range of ±0.4% theoretical value for the element analyzed (C, H, N). ^{1}H-NMR spectra were recorded on Bruker spectropsin DPX-300 MHz in $CDCl_3$; chemical shift (δ) values are reported in parts per million (*ppm*). The splitting pattern abbreviations are as follows: *s*, singlet; *d*, doublet; *m*, multiplet. Mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing voltage with a VG Prospec instrument and are presented as m/z. Spectral data are consistent with the assigned structures.

Preparation of 3-(4-Chloro/methyl benozyl)propionic acid (1,2). The compounds, **1** and **2**, were synthesized according to the reported method[14].

Preparation of 3-Arylidene-5-(4-chloro/methyl phenyl)-2(3H)-furanones (3-16). Compounds (**3-16**) were synthesized from 3-(4-chloro/methyl benozyl)propionic acid (**1,2**) following literature method[14].

General Procedure for the synthesis of 5-(substituted benzyl)-3-aryl-1,6-dihydro-6-pyridazinones (17-30). 2(3*H*)-Furanones (**3-16**) (0.005 mole) and hydrazine hydrate (1-2 mL) in *n*-propanol (5-6 mL) were refluxed for 3h. After refluxing reaction mixture was poured onto crushed ice, a precipitate was obtained, which was filtered, dried and recrystallized from methanol to give TLC pure 5-(substituted benzyl)-3-aryl-1,6-dihydro-6-pyridazinone derivatives (**17-30**).

5-Benzyl-3-phenyl-1,6-dihydro-6-pyridazinone (**17**): Yield: 58%; m.p. 168-170 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.99 (s, 2H, CH_2), 7.26 (s, 1H, H-4, pyridazinone ring), 7.29-7.41 (m, 6H, 2xH-2,4,6, benzyl + phenyl), 7.58-7.65 (m, 4H, 2xH-3,5, benzyl + phenyl), 10.62 (s, 1H, NH); MS (*m/z*): 262(M^+); IR (cm^{-1}, KBr): 3186 (NH), 2949 (CH), 1683 (CO); Anal calcd. for $C_{17}H_{14}N_2O$ (CHN).

5-(2-Chlorobenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**18**): Yield: 63%; m.p. 210 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.42 (s, 2H, CH_2), 7.24 (s, 1H, H-4, pyridazinone ring), 7.26-7.64 (m, 9H, phenyl+ benzyl) 10.77 (s, 1H, NH); MS (*m/z*): 296/297 (M^+/M+1); IR (cm^{-1}, KBr): 3179 (NH), 2942 (CH), 1688 (CO), 726 (C-Cl); Anal calcd. for $C_{17}H_{13}ClN_2O$ (CHN).

5-(4-Chlorobenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**19**): Yield: 68%; m.p. 188 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.93 (s, 2H, CH_2), 7.24 (s, 1H, H-4, pyridazinone ring), 7.27 & 7.67 (d, each, $2xA_2B_2$, *p*-chlorophenyl), 7.30 (m, 1H, H-4, phenyl), 7.33 (m, 2H, H-2,6, phenyl), 7.46 (m, 2H, H-3,5, phenyl), 12.68 (s, 1H, NH); MS (*m/z*): 296/297(M^+/M+1); IR (cm^{-1}, KBr): 3173 (NH), 2936 (CH), 1672 (CO), 707 (C-Cl); Anal calcd. for $C_{17}H_{13}ClN_2O$ (CHN).

5-(3-Nitrobenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**20**): Yield: 58%, m.p. 178-180 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.89 (s, 2H, CH_2), 7.14 (s, 1H, H-4, pyridazinone ring), 7.26 (m, 1H, H-4, phenyl), 7.31 (m, 1H, H-4, phenyl), 7.44 (m, 1H, H-6, benzyl ring), 7.34 (m, 2H, H-2,6, phenyl), 7.50 (m, 2H, H-3,5, phenyl), 8.14 (m, 1H, H-5, benzyl ring), 8.16 (m, 1H, H-4, benzyl ring), 8.18 (m, 1H, H-2, benzyl ring), 10.98 (s, 1H, NH); MS (*m/z*): 307 (M^+); IR (cm^{-1}, KBr): 3178 (NH), 2942 (CH), 1686 (CO); Anal calcd. for $C_{17}H_{13}N_3O_3$ (CHN).

5-(4-Methoxybenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**21**): Yield: 52%; m.p. 186 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.82 (s, 3H, OCH_3), 3.93 (s, 2H, CH_2), 6.82 (s, 1H, H-4, pyridazinone ring), 6.83 & 7.41 (d, each, $2xA_2B_2$, *p*-methoxy benzyl ring), 7.21 (m, 1H, H-4, phenyl ring), 7.27 (m, 2H, H-2,6, phenyl ring), 7.65 (m, 2H, H-3,5, phenyl ring), 10.87 (s, 1H, NH); MS (*m/z*): 292 (M^+); IR (cm^{-1}, KBr): 3173 (NH), 2936 (CH), 1684 (CO); Anal calcd. for $C_{18}H_{16}N_2O_2$ (CHN).

5-(3,4-Dimethoxybenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**22**): Yield: 56%; m.p. 198-200 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.63 (s, 2H, $2xOCH_3$), 3.86 (s, 2H, CH_2), 7.26 (s, 1H, H-4, pyridazinone ring), 7.28 (m, 1H, H-4, phenyl ring), 7.38 (m, 1H, H-6, benzyl), 7.61 (m, 2H, H-3,5, phenyl ring), 7.64 (m, 1H, H-5, benzyl), 7.66 (m, 1H, H-2, benzyl), 11.31 (s, 1H, NH); MS (*m/z*): 322 (M^+); IR (cm^{-1}, KBr): 3167 (NH), 3002 (CH), 1673 (CO); Anal calcd. for $C_{19}H_{18}N_2O_3$ (CHN).

5-(4-Hydroxy-3-methoxybenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**23**): Yield: 62%; m.p. 191-193 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.48 (s, 2H, CH_2), 3.64 (s, 3H, OCH_3), 6.53 (s, 1H, H-4, pyridazinone ring), 7.07-7.29 (m, 5H, phenyl), 7.39-7.72 (3H, H-2,5,6, benzyl), 10.82 (s, 1H, NH); MS (*m/z*): 308 (M^+); IR (cm^{-1}, KBr): 3185 (NH), 2955 (CH), 1686 (CO); Anal calcd. for $C_{18}H_{16}N_2O_3$ (CHN).

5-(4-Fluorobenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**24**): Yield: 57%; m.p. 201 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.57 (s, 2H, CH_2), 7.09 (s, 1H, H-4, pyridazinone ring), 7.28 (m, 1H, H-4, phenyl), 7.29 (d, H-2,6, *p*-fluorobenzyl), 7.37 (m, 2H, H-2,6, phenyl), 7.53 (m, 2H, H-3,5, *p*-fluorobenzyl), 7.57 (m, 2H, H-3,5, phenyl), 11.73 (s, 1H, NH); MS (*m/z*): 280 (M^+); IR (cm^{-1}, KBr): 3182 (NH), 2949 (CH), 1673 (CO); Anal calcd. for $C_{17}H_{13}FN_2O$: (CHN).

5-(4-Hydroxy-3-ethoxybenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**25**): Yield: 65%; m.p. 180 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.46 (t, 3H, $OCH_2\underline{CH_3}$), 3.48 (s, 2H, CH_2), 4.07 (m, 2H, $O\underline{CH_2}CH_3$), 6.53 (s, 1H, H-4, pyridazinone ring), 7.07-7.29 (m, 5H, phenyl), 7.39-7.72 (3H, H-2,5,6, benzyl), 10.82 (s, 1H, NH); MS (*m/z*): 322 (M^+); IR (cm^{-1}, KBr): 3184 (NH), 2966 (CH), 1678 (CO); Anal calcd. for $C_{19}H_{18}N_2O_3$ (CHN).

5-(2-Chlorobenzyl-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone (**26**): Yield: 63%; m.p. 186-188 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.93 (s, 2H, CH_2), 7.21 (s, 1H, H-4, pyridazinone ring), 7.28 (m, 2H, H-4,6, phenyl), 7.38 (m, 1H, H-5, phenyl ring),7.40 & 7.59 (d, each, $2xA_2B_2$, *p*-chlorophenyl ring), 7.44 (m, 1H, H-3, phenyl), 11.52 (s, 1H, NH); MS (*m/z*): 330/331/333 (M^+/M+1/M+3); IR (cm^{-1}, KBr): 3185 (NH), 2952 (CH), 1676 (CO), 714 (C-Cl); Anal calcd. for $C_{17}H_{12}Cl_2N_2O$ (CHN).

5-(2-Hydroxybenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone (**27**): Yield: 58%; m.p. 182-184 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.61 (s, 2H, CH_2), 7.26 (s, 1H, H-4, pyridazinone ring), 7.34 (m, 1H, H-4, phenyl ring), 7.41 & 7.62 (d, each, $2xA_2B_2$, *p*-chlorophenyl), 7.64 (m, 2H, H-2,5, phenyl), 8.37 (m, 1H, H-3, phenyl), 8.57 (s, 1H, OH), 9.33 (s, 1H, NH); MS (*m/z*): 312/313 (M^+/M+1); IR (cm^{-1}, KBr): 3174 (NH), 2939 (CH), 1683 (CO), 718 (C-Cl); Anal calcd. for $C_{17}H_{13}ClN_2O_2$ (CHN).

5-(3-Hydroxybenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone (**28**): Yield: 54%; m.p. 189 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.64 (s, 2H, CH_2), 7.19 (s, 1H, H-4, pyridazinone ring), 7.42 & 7.55 (d, each, $2xA_2B_2$, *p*-chlorophenyl), 7.57 (m, 1H, H-6, benzyl), 7.98 (m, 1H, H-5, benzyl), 8.07 (m, 1H, H-4, benzyl), 8.17 (m, 1H, H-2, benzyl), 9.35 (s, 1H, NH); MS (*m/z*): 312/313 (M^+/M+1); IR (cm^{-1}, KBr): 3168 (NH), 2944 (CH), 1681 (CO), 722 (C-Cl); Anal calcd. for $C_{17}H_{13}ClN_2O_2$: (CHN).

5-(3-Nitrobenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone (**29**): Yield: 56%; m.p. 198 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.05 (s, 2H, CH_2), 7.15 (s, 1H, H-4, pyridazinone ring), 7.24 & 7.53 (d, each, $2xA_2B_2$, *p*-chlorophenyl), 7.55 (m, 1H, H-6, benzyl), 8.21 (m, 1H, H-5, benzyl), 8.31 (m, 1H, H-4, benzyl), 8.49 (m, 1H, H-2, benzyl), 9.23 (s, 1H, NH); MS (*m/z*): 341/342 (M^+/M+1); IR (cm^{-1}, KBr): 3180 (NH), 2934 (CH), 1687 (CO), 717 (C-Cl); Anal calcd. for $C_{17}H_{12}ClN_3O_3$ (CHN).

5-(3,4-Dimethoxybenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone (**30**): Yield: 59%; m.p. 186-188 °C; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.87 (s, 6H, 2x-OCH_3), 3.71 (s, 2H, CH_2), 6.81 (s, 1H, H-4, pyridazinone ring), 6.83 (m, 2H, H-2,6, benzyl), 7.26 (m, 1H, H-5, benzyl), 7.39 & 7.61 (d, each, $2xA_2B_2$, *p*-chlorophenyl), 11.54 (s, 1H, NH); MS (*m/z*): 356/357 (M^+/M+1); IR (cm^{-1}, KBr): 3176 (NH), 2959 (CH), 1681 (CO), 725 (C-Cl); Anal calcd. for $C_{19}H_{17}ClN_2O_3$ (CHN).

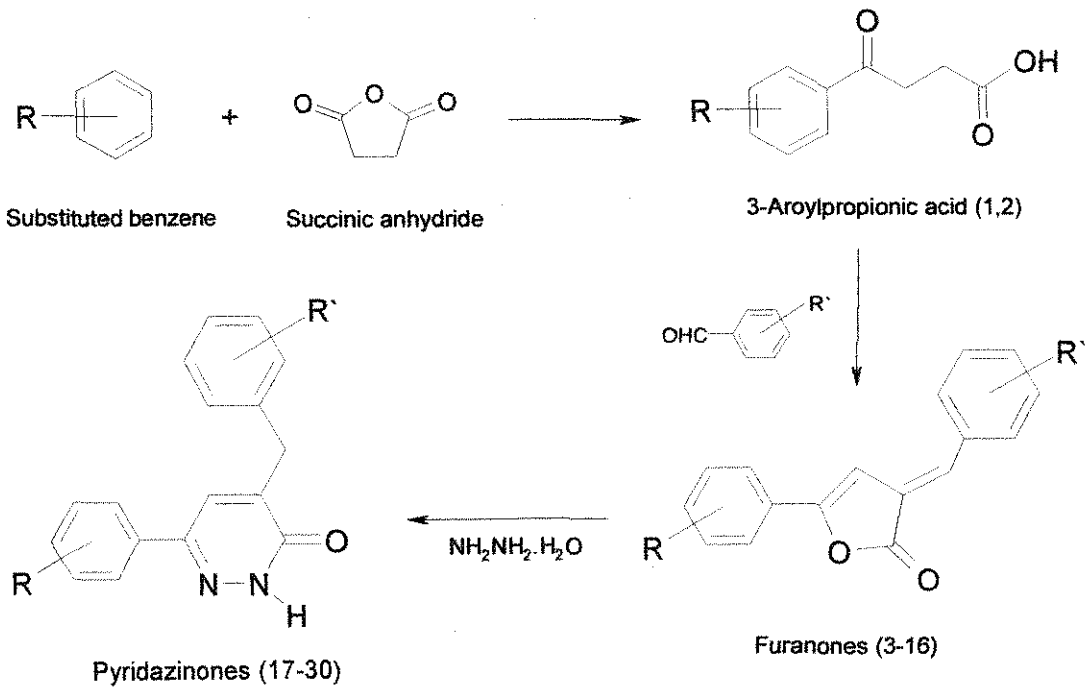
Antitubercular activity[15,16]

The antitubercular screening was carried out against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in Middle brook 7H11 agar medium with OADC (oleic acid albumin dextrose catalase) growth supplement. 10 fold serial dilutions of each test compound/drug (in DMSO/Water mixture) were incorporated into the agar medium. Inoculum of *M. tuberculosis* $H_{37}Rv$ were prepared from fresh Middlebrook 7H11 agar slants with OADC growth supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of approximately 10^7 cfu/mL. A 5 µL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 °C, and final readings were recorded after 30 days. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth. The MIC of the standard drug streptomycin was 10 µg/mL. The results are presented in **Table 1**.

RESULTS AND DISCUSSION

Synthesis

The starting material, 3-(4-chlorobenzoyl/benzoyl)propionic acid (**1,2**) was synthesized from dry benzene or chlorobenzene following Friedal Craft's acylation reaction conditions[14]. 2(3*H*)-Furanones (**3-16**) were prepared using 3-aroylopionic acid (**1,2**) following the previously



Scheme 1: Protocol for synthesis of title compounds

Table 1: Antitubercular activity of the 6-pyridazinone derivatives **17-30.**

Compound	R	R`	*MIC values*
17	H	H	50
18	H	2-Cl	25
19	H	4-Cl	50
20	H	3- NO_2	50
21	H	4-OCH_3	50
22	H	3,4-$(OCH_3)_2$	50
23	H	4-OH; 3-OCH_3	12.5
24	H	4-F	50
25	H	4-OH; 3-OC_2H_5	25
26	4-Cl	2-Cl	50
27	4-Cl	2-OH	25
28	4-Cl	3-OH	50
29	4-Cl	3- NO_2	50
30	4-Cl	3,4-$(OCH_3)_2$	50

benzyl)-3-aryl-1,6-dihydro-6-pyridazinone derivatives (**17-30**) (Scheme-1). Spectral data and microanalysis data were in agreement with the proposed structures.

Antitubercular activity

The antitubercular screening was carried out against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) (**Table 1**). The results indicated that 5-(4-hydroxy-3-methoxybenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**23**) showed best antitubercular activity among the synthesized compounds with *MIC*-12.5 μg/mL. Three compounds, 5-(2-chlorobenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**18**), 5-(4-hydroxy-3-ethoxybenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone (**25**) and 5-(2-hydroxybenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone (**27**) were also significant in their antitubercular action with *MIC*-25 μg/mL. Rests of the compounds showed *MIC*-values of 50 μg/mL. Disubstituted phenyl rings having hydroxyl group (**23** & **25**) at 5th position of pyridazinone ring showed good antitubercular activity than unsubstituted or mono-substituted phenyl rings. Among the mono-substituted phenyl rings at 5th position of pyridazinone ring, presence of 2-chloro or 2-hydroxyl group (**18** & **27**) showed significant antitubercular activity.

Conclusions

To sum up, among the synthesized 14 newer pyridazinones, compound **23**, 5-(4-hydroxy-3-methoxybenzyl)-3-phenyl-1,6-dihydro-6-pyridazinone emerged as lead compound with good antitubercular activity. The study showed the antitubercular potential of 6-pyridazinone derivatives.

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SOUTHERN BRAZILIAN, JOURNAL OF CHEMISTRY
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REACTION OF NITRILIMINES WITH SUBSTITUTED HYDRAZINES: SYNTHESIS OF 1,2,4,5-TETRAAZA-3-PENTENES AND FORMAZANS

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ABSTRACT

*A series of 1,2,4,5-tetraaza-3-pentenes **4a-j** were synthesized by the reaction of appropriate nitrilimines **2** with substituted hydrazines ($H_2NNHCOR$, R=Ph, OMe) **3**. Heating the compounds **4a-j** with activated charcoal in refluxing benzene oxidized to formazans **5a-j** and some formazans **5f,j** (R = OMe) gave s-tetrazinones **6f,j** in presence of lithium hydride. The microanalysis and spectral data of the synthesized compounds are in full agreement with their molecular structure.*

KEYWORDS
Nitrilimines, 1,2,4,5-tetraaza-3-pentenes, formazans, s-tetrazinones

RESUMO

*Uma série de 1,2,4,5-tetraazo -3-pentenos **4a-j** foram sintetizados pela reação das nitriliminas apropriadas **2** com hidrazinas substituídas ($H_2NNHCOR$, R=Ph, OMe) **3**. O aquecimento dos compostos **4a-j** com carvão ativado em benzeno quente levou á oxidação para formazanaos **5aj** e alguns formazanos **5f,j** (R=OMe) e na presença de LiH formaram s-tetrazinonas **6f,j** . As microanalises o os dados espectrais concordam com as estruturas moleculares dos compostos.*

PALAVRAS CHAVE:

Nitriliminas, 1,2,4,5 tetraazo -3-pentenos, formazanas, s-tetrazinonas

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GRAPHICAL ABSTRACT

Reaction of Nitrilimines with Substituted Hydrazines: Synthesis of 1,2,4,5-Tetraaza-3-pentenes and Formazans

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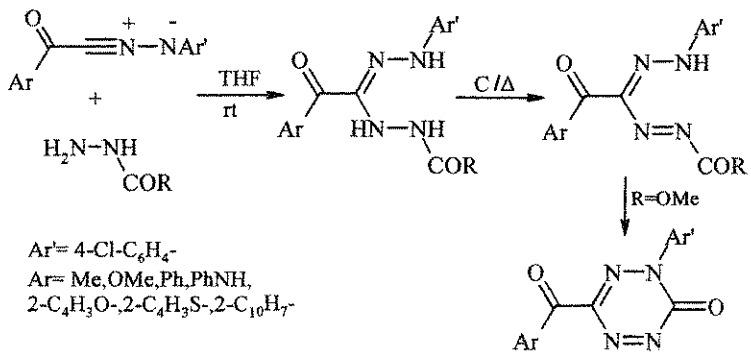


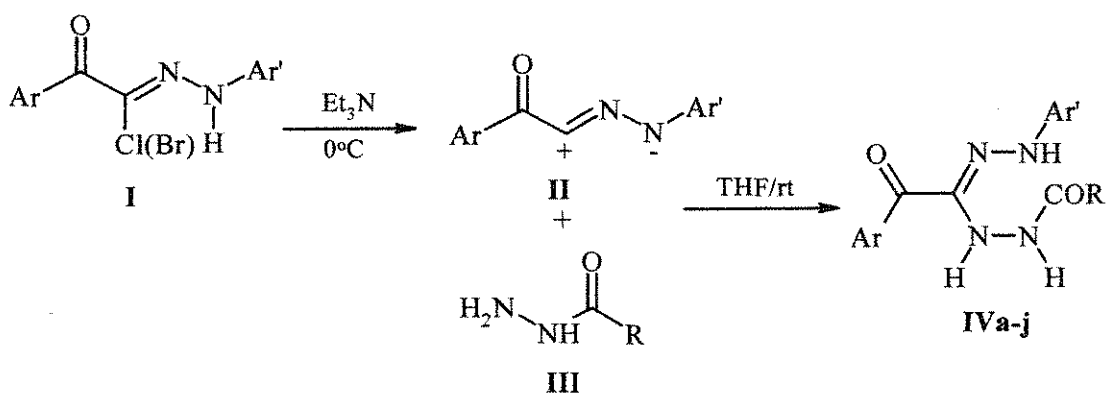
1. INTRODUCTION

The preparation of hydrazonoyl halides is well known because of their extensive use in 1,3-dipolar cycloaddition and cyclocondensation reactions. El-Haddad *et al.* [1] was reported the synthesis of 1-methoxycarbonyl-2-[1-(4-chlorophenyl)hydrazono-propan-2-one]hydrazine, which oxidized upon heating with charcoal in refluxing toluene to 3-acetyl-1-methoxy-carbonyl-5-(4-chlorophenyl)formazan.

The reactions nitrilimines and nitrile oxides were recently reviewed by Ferwanah *et al.* [2]. In a continuation of our work concerning the utility of nitrilimines in the synthesis of aza compounds, we investigated the reaction of different C-substituted-N-arylnitrilimines with benzoyl- and methoxycarbonyl hydrazines.

2. RESULTS AND DISCUSSION

The precursors of nitrilimines hydrazonoyl chlorides **I** employed in this study were prepared according to reported literature procedures [3-7]. The non isolable nitrilimines **II** immediately reacted with benzoyl and methoxycarbonyl hydrazines **III** affording the corresponding acyclic adducts, 1,2,4,5-tetraaza-3-pentenes **IVa-j** (Scheme 1) in good yields. Structural assignment of **IVa-j** was based on elemental analysis and spectral data. IR spectra of these compounds revealed the presence of the characteristic functional groups. The signals of the OCH_3 in both ^1H- and ^{13}C NMR spectra is of particular importance in support of the suggested acyclic structure. The spectral data of the obtained compounds **IVa-j** are presented in the experimental section.

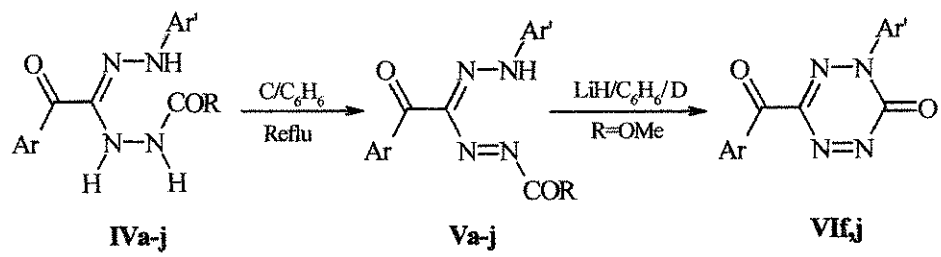


Ar' = 4-Cl-C_6H_4-

Ar/R = **a** Me/Ph; **b** Me/OMe; **c** MeO/Ph; **d** Ph/Ph; **e** PhNH/Ph; **f** PhNH/OMe; **g** 2-C_4H_3O/Ph; **h** 2-C_4H_3S/Ph; **i** 2-$C_{10}H_7$/Ph; **j** 2-$C_{10}H_7$/OMe

Figure 1. Synthetic pathway for the preparation of compounds **IVa-j.**

The acyclic adducts **Va-j** were oxidized to the corresponding formazans **Va-j** by heating them with activated charcoal in refluxing benzene or toluene for 6 hours (Scheme 2). No other cyclic products were observed using TLC. Structure elucidation of the obtained formazans **Va-j** was achieved by analytical and spectral data summarized in the experimental section. Their IR spectra revealed the absence of two NH absorption bands. Both and ^{1}H- and ^{13}C NMR spectra of compounds **Va-j** showed all the signals of the proposed structures, indicating the disappearance of HN-NH protons, however, the OCH_3 signal in compounds **Vb,f,j** does not disappeared which indicated that those compounds are oxidized to the formazans without further cyclization to the expected tetrazinones.



Ar' = 4-Cl-C_6H_4-; R = Ph, OMe
Ar = **a** Me; **b** Me; **c** MeO; **d** Ph; **e** PhNH; **f** PhNH; **g** 2-C_4H_3O; **h** 2-C_4H_3S; **i** 2-$C_{10}H_7$; **j** 2-$C_{10}H_7$

Figure 2. Synthetic pathway for the preparation of compounds **Va-j** and **VIf,j.**

The thermal cyclization of formazans **Vf,j** was performed by heating them with lithium hydride in benzene for 4 hours. New products were formed as indicated by TLC and found to be s-tetrazinones **VIf,j** (Figure 2). Structural assignment of compounds **VIf,j** is based on elemental analysis, mass spectra and NMR results. Elemental analysis and mass spectra showed a loss of methanol molecule. Further evidence was obtained from NMR measurements. The ^{1}H NMR indicate that the NH (δ = 11.40 ppm) and methoxy protons (δ = 3.90 ppm) are disappeared. Also the ^{13}C NMR data illustrated that compounds **VIf,j** have the assigned cyclic structure by the absence of signal for methoxy carbon (δ = 53.80 ppm) and the presence of the signal at δ = 159 ppm for the carbonyl carbon of tetrazinone ring.

3. EXPERIMENTAL SECTION

3.1. Reagents and Instrumentation

Melting points were determined on an A. Krüss Melting Point Meter equipped with a thermometer and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 Mid infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO-d_6 solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per millions (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on a Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. All compounds were analyzed satisfactorily for C, H and N. The hydrazonoyl halides **Ia-j** [3-7] were prepared according to literature procedures. Tetrahydrofuran (THF) and triethylamine were obtained from Across Company, Belgium. Benzoic acid hydrazide and methyl hydrazinocarboxylate were purchased from Avocado Research Chemicals, England, and used without further purification.

3.2. Synthesis of Compounds IVa-j

To a stirred solution of the appropriate hydrazonoyl halide **I** (10 mmol) and hydrazine **III** (20 mmol) in THF (70 mL), triethylamine (4mL, 30 mmol) in THF (10 mL) was dropwise added at 0 °C. The temperature of the reaction mixture was then allowed to rise slowly to room temperature, and stirring was continued overnight. The solvent was then evaporated *in vacuo*, and the residue washed with water (100 mL). The resulting crude solid product was collected and recrystallized from ethanol. The following compounds were prepared using this method:

3-Acetyl-1-benzoyl-5-(4-chlorophenyl)-1,2,4,5-tetraaza-3-pentene (IVa); Yield: 75%; m.p.: 177-179 °C; IR (KBr) ν_{max}: cm^{-1} 3432, 3342, 3315 (NH), 1693 (CH_3-C=O) 1675 (Ph-C=O), 1592 (C=N); ^{1}H NMR ($CDCl_3$): δ 9.50 (*s*, 1H, NH), 8.90 (*s*, 1H, NH), 8.27-7.26 (*m*, 9H, Ar-H), 7.31 (*s*, 1H, NH), 2.45 (*s*, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 192.3, 169.1, 141.0, 139.6, 135.6, 133.2, 130.8, 130.4, 129.3, 128.5, 120.4, 24.5; MS: *m/z* 330/332 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{16}H_{15}N_4O_2$ (330.78): C, 58.10; H, 4.57; N, 16.94; Found: C, 57.85; H, 4.45; N, 17.10.

3-Acetyl-5-(4-chlorophenyl)-1-methoxycarboyl-1,2,4,5-tetraaza-3-pentene (IVb): Yield: 78%; m.p.: 146-148 °C; IR (KBr) ν_{max}: cm^{-1} 3434, 3340, 3319 (NH), 1693 (CH_3-C=O) 1710 (O-C=O), 1596 (C=N); ^{1}H NMR ($CDCl_3$): δ 9.54 (*s*, 1H, NH), 8.86 (*s*, 1H, NH), 7.45-6.86 (*m*, 4H, Ar-H), 7.36 (*s*, 1H, NH), 3.61 (*s*, 3H, OCH_3), 2.42 (*s*, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 192.1, 156.9, 141.0, 139.1, 129.0, 128.2, 120.6, 52.3, 24.6; MS: *m/z* 284/286 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{11}H_{13}N_4O_3$ (284.70): C, 46.41; H, 4.60; N, 19.68; Found: C, 46.20; H, 4.72; N, 19.55.

1-Benzoyl-5-(4-chlorophenyl)-3-methoxycarbonyl-1,2,4,5-tetraaza-3-pentene (IVc): Yield: 76%; m.p.: 169-171 °C; IR (KBr) ν_{max}: cm^{-1} 3429, 3337, 3320 (NH), 1715 (O-C=O) 1675 (Ph-C=O), 1594 (C=N); ^1H NMR ($CDCl_3$): δ 9.56 (*s*, 1H, NH), 8.89 (*s*, 1H, NH), 8.22-7.21 (*m*, 9H, Ar-H), 7.38 (*s*, 1H, NH), 3.59 (*s*, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): *δ* 169.3, 157.1, 141.3, 139.7, 135.3, 133.0, 130.9, 130.2, 129.1, 128.7, 120.7, 52.6; MS: *m/z* 346/348 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{16}H_{15}N_4O_3$ (346.78): C, 55.42; H, 4.36; N, 16.16; Found: C, 55.70; H, 4.21; N, 15.05.

5-(4-Chlorophenyl)-1,3-dibenzoyl-1,2,4,5-tetraaza-3-pentene (IVd): Yield: 75%; m.p.: 182-184 °C; IR (KBr) ν_{max}: cm^{-1} 3427, 3337, 3322 (NH), 1677 (N-C=O), 1640 (Ph-C=O), 1598 (C=N); ^1H NMR ($CDCl_3$): δ 10.31 (*s*, 1H, NH), 8.31 (*s*, 1H, NH), 8.17-7.10 (*m*, 14H, Ar-H), 7.37 (*s*, 1H, NH); ^{13}C NMR ($CDCl_3$): *δ* 187.5, 169.1, 141.7, 139.5, 136.4, 135.6, 133.2, 132.2, 130.7, 130.1, 129.3, 128.5, 127.9, 127.1, 115.8; MS: *m/z* 392/394 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{21}H_{17}ClN_4O_2$ (392.85): C, 64.21; H, 4.36; N, 14.26; Found: C, 63.98; H, 4.50; N, 14.37.

1-Benzoyl-5-(4-chlorophenyl)-3-phenylaminocarbonyl-1,2,4,5-tetraaza-3-pentene (IVe): Yield: 77%; m.p.: 178-180 °C; IR (KBr) ν_{max}: cm^{-1} 3435, 3340, 3328, 3275 (NH), 1675 (Ph-C=O), 1655 (amide C=O), 1605 (C=N); ^1H NMR ($CDCl_3$): δ 10.36, (s, 1H, NH), 9.50 (*s*, 1H, NH), 8.92 (*s*, 1H, NH), 8.83 (*s*, 1H, NH), 8.27-7.26 (*m*, 14H, Ar-H), 7.31 (*s*, 1H, NH); ^{13}C NMR ($CDCl_3$): *δ* 169.3, 160.3, 142.5, 138.6, 135.6, 133.2, 130.8, 130.4, 129.4, 128.7, 128.5, 125.0, 123.6, 120.5, 116.2; MS: *m/z* 407/409 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{21}H_{18}ClN_5O_2$ (407.86): C, 61.84; H, 4.45; N, 17.17; Found: C, 62.05; H, 4.30; N, 17.00.

5-(4-Chlorophenyl)-1-methoxycarboyl-3-phenylaminocarbonyl-1,2,4,5-tetra-aza-3-pentene(IVf): Yield: 74%; m.p.: 158-160 °C; IR (KBr) ν_{max}: cm^{-1} 3433, 3335, 3325, 3270 (NH), 1725 (O-C=O), 1653 (amide C=O), 1600 (C=N); ^1H NMR ($CDCl_3$): δ 9.49 (*s*, 1H, NH), 8.91 (*s*, 1H, NH), 8.82 (*s*, 1H, NH), 7.45-6.86 (*m*, 9H, Ar-H), 7.36 (*s*, 1H, NH), 3.61 (*s*, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): *δ* 160.2, 157.6, 142.0, 138.1, 135.2, 129.7, 129.0, 128.2, 127.3, 125.1, 119.8, 52.3; MS: *m/z* 361/363 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{16}H_{16}ClN_5O_3$ (361.79): C, 53.12; H, 4.46; N, 19.36; Found: C, 52.86; H, 4.35; N, 19.45.

1-Benzoyl-5-(4-chlorophenyl)-3-(2-furoyl)-1,2,4,5-tetraaza-3-pentene (IVg): Yield: 73%; m.p.: 166-168 °C; IR (KBr) ν_{max}: cm^{-1} 3433, 3341, 3321 (NH), 1676 (Ph-C=O), 1665 (C=O), 1597 (C=N); ^1H NMR ($CDCl_3$): δ 9.49 (*s*, 1H, NH), 8.89 (*s*, 1H, NH), 8.21-7.13 (*m*, 12H, Ar-H), 7.33 (*s*, 1H, NH); ^{13}C NMR ($CDCl_3$): *δ* 174.2, 169.2, 141.6, 140.1, 139.1, 135.6, 135.1, 133.2, 130.8, 130.6, 129.0, 128.1, 127.9, 125.4, 120.6; MS: *m/z* 382/384 [M^+]; Anal. Calcd. for $C_{19}H_{15}ClN_4O_3$ (382.81): C, 59.62; H, 3.95; N, 14.64; Found: C, 59.40; H, 4.10; N, 14.55.

1-Benzoyl-5-(4-chlorophenyl)-3-(2-thenoyl)-1,2,4,5-tetraaza-3-pentene (IVh): Yield: 75%; m.p.: 159-161 °C; IR (KBr) ν_{max}: cm^{-1} 3436, 3340, 3325 (NH), 1678 (Ph-C=O), 1660 (C=O), 1596 (C=N); ^1H NMR ($CDCl_3$): δ 9.46 (*s*, 1H, NH), 8.87 (*s*, 1H, NH), 8.30-7.10 (*m*, 12H, Ar-H), 7.31 (*s*, 1H, NH); ^{13}C NMR ($CDCl_3$): *δ* 174.6, 169.3, 141.3, 140.2, 139.3, 135.1, 134.9, 133.2, 130.8, 130.4, 129.3, 128.3, 128.0, 125.3, 120.4; MS: *m/z* 398/400 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{19}H_{15}ClN_4O_2S$ (334.38): C, 57.21; H, 3.79; N, 14.05; Found: C, 57.45; H, 3.90; N, 13.95.

1-Benzoyl-5-(4-chlorophenyl)-3-(2-naphthoyl)-1,2,4,5-tetraaza-3-pentene (IVi): Yield: 71%; m.p.: 171-173 °C; IR (KBr) ν_{max}: cm^{-1} 3424, 3331, 3309 (NH), 1693 (CH_3-C=O) 1675 (Ph-C=O), 1592 (C=N); ^1H NMR ($CDCl_3$): δ 9.50 (*s*, 1H, NH), 8.90 (*s*, 1H, NH), 8.77-7.26 (*m*, 16H, Ar-H), 7.36 (*s*, 1H, NH); ^{13}C NMR ($CDCl_3$): *δ* 183.3, 169.2, 141.4, 139.6, 135.9, 133.8, 133.1, 132.4, 132.2, 130.3, 129.9, 129.1, 128.7, 128.6, 127.9, 127.8, 127.7, 127.4, 126.6, 125.5, 124.3; MS: *m/z* 442/444 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{25}H_{19}ClN_4O_2$ (442.91): C, 67.80; H, 4.32; N, 12.65; Found: C, 68.05; H, 4.20; N, 12.50.

5-(4-Chlorophenyl)-1-methoxycarbonyl-3-(2-naphthoyl)-1,2,4,5-tetraaza-3-pentene (IVj): Yield: 74%; m.p.: 179-181 °C; IR (KBr) ν_{max}: cm^{-1} 3430, 3333, 3311 (NH), 1693 (CH_3-C=O) 1675 (O-C=O), 1592 (C=N); ^1H NMR ($CDCl_3$): δ 9.49 (*s*, 1H, NH), 8.86 (*s*, 1H, NH), 8.75-7.24 (*m*, 11H, Ar-H), 7.32 (*s*, 1H, NH), 3.57 (*s*, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): *δ* 183.6, 157.8, 141.4, 139.1, 135.6, 134.1, 132.5, 132.3, 130.5, 129.9, 129.2, 128.4, 127.8, 127.7, 126.5, 125.6, 124.4, 53.1; MS: *m/z* 396/398 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{20}H_{19}ClN_4O_3$ (396.84): C, 60.53; H, 4.32; N, 14.12; Found: C, 60.35; H, 4.40; N, 14.05.

3.3. Synthesis of formazans Va-j

Compounds **IVa-j** (5 mml) were refluxed in benzene or toluene (50 mL) and activated charcoal (1.0 g) for 6 hours. After cooling the reaction was then filtered and the solvent was removed under reduced pressure and the residual solid was collected and recrystallized from chloroform/petroleum ether (b.p. 40-60 oC) to give formazans **Va-j**. The following compounds were prepared using this method:

3-Acetyl-1-benzoyl-5-(4-chlorophenyl)formazan (Va): Yield: 76%; m.p.: 149-151 °C; IR (KBr) ν_{max}: cm^{-1} 3348 (NH), 1685 (CH_3-C=O) 1679 (Ph-C=O), 1590 (C=N); ^1H NMR ($CDCl_3$): δ 11.49 (*s*, 1H, NH), 7.40-7.29 (*m*, 11H, Ar-H), 2.60 (*s*, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$): *δ* 193.9 (CH_3-C=O), 169.1 (N-C=O), 150.5 (C=N), 26.6 ($COCH_3$); MS: *m/z* 328/330 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{16}H_{13}ClN_4O_2$ (328.76): C, 58.46; H, 3.99; N, 17.04; Found: C, 58.25; H, 4.10; N, 16.90.

3-Acetyl-5-(4-chlorophenyl)-1-methoxycarboylformazan (Vb): Yield: 79%; m.p.: 136-138 °C; IR (KBr) ν_{max}: cm^{-1} 3347 (NH), 1720 (O-C=O), 1686 (CH_3-C=O), 1590 (C=N); ^1H NMR ($CDCl_3$): δ 11.51 (*s*, 1H, NH), 7.42-7.31 (*m*, 11H, Ar-H), 3.91 (*s*, 3H, OCH_3), 2.61 (*s*, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$): *δ* 193.9 (CH_3-C=O), 153.8 (N-C=O), 150.4 (C=N), 53.9 (OCH_3), 26.6 ($COCH_3$); MS: *m/z* 282/284 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{11}H_{11}ClN_4O_3$ (282.69): C, 46.74; H, 3.92; N, 19.82; Found: C, 46.60; H, 4.05; N, 19.70.

1-Benzoyl-5-(4-chlorophenyl)-3-methoxycarbonylformazan (Vc): Yield: 80%; m.p.: 127-129 °C; IR (KBr) ν_{max}: cm^{-1} 3325 (NH), 1725 (O-C=O), 1673 (Ph-C=O), 1586 (C=N); ^1H NMR ($CDCl_3$): δ 11.43 (*s*, 1H, NH), 7.45-7.21 (*m*, 11H, Ar-H), 3.92 (*s*, 3H, OCH_3), 2.61 (*s*, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$): *δ* 168.8 (N-C=O), 158.4 (O-C=O), 149.7 (C=N), 53.9 (OCH_3); MS: *m/z* 344/346 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{16}H_{13}ClN_4O_3$ (344.76): C, 55.74; H, 3.80; N, 16.25; Found: C, 55.90; H, 3.72; N, 16.33.

5-(4-Chlorophenyl)-1,3-dibenzoylformazan (Vd): Yield: 81%; m.p.: 176-178 °C; IR (KBr) ν_{max}: cm^{-1} 3322 (NH), 1673 (Ph-C=O), 1645 (Ar-C=O), 1585 (C=N); ^1H NMR ($CDCl_3$): δ 11.43 (*s*, 1H, NH), 7.75-7.20 (*m*, 11H, Ar-H); ^{13}C NMR ($CDCl_3$): *δ* 185.5 (Ph-C=O), 168.7 (N-C=O) 149.2 (C=N); MS: *m/z* 390/392 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{21}H_{15}ClN_4O_2$ (390.83): C, 64.54; H, 3.87; N, 14.34; Found: C, 64.40; H, 3.75; N, 14.50.

1-Benzoyl-5-(4-chlorophenyl)-3-phenylaminocarbonyl formazan (Ve): Yield: 76%; m.p.: 198-200 °C; IR (KBr) ν_{max}: cm^{-1} 3328, 3245 (NH), 1675 (Ph-C=O), 1655 (Ar- C=O), 1592 (C=N); ^1H NMR ($CDCl_3$): δ 11.36, (s, 1H, NH), 8.92 (*s*, 1H, NH), 8.31-7.26 (*m*, 14H, Ar-H); ^{13}C NMR ($CDCl_3$): *δ* 168.3 (N-C=O), 161.4 (Ar-C=O), 150.3 (C=N); MS: *m/z* 405/407 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{21}H_{16}ClN_5O_2$ (405.85): C, 62.15; H, 3.97; N, 17.26; Found: C, 61.95; H, 4.10; N, 17.35.

5-(4-Chlorophenyl)-1-methoxycarboyl-3-phenylaminocarbonylformazan (Vf): Yield: 79%; m.p.: 188-190 °C; IR (KBr) ν_{max}: cm^{-1} 3325, 3236 (NH), 1722 (O-C=O), 1650 (Ar-C=O), 1590 (C=N); ^1H NMR ($CDCl_3$): δ 11.39 (*s*, 1H, NH), 8.96 (*s*, 1H, NH), 7.45-7.18 (*m*, 9H, Ar-H), 3.90 (*s*, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): *δ* 161.2 (Ar-C=O), 158.6 (O-C=O), 150.1 (C=N), 53.8 (OCH_3); MS: *m/z* 359/361 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{16}H_{14}ClN_5O_3$ (359.77): C, 53.42; H, 3.92; N, 19.47; Found: C, 53.60; H, 4.05; N, 19.35.

1-Benzoyl-5-(4-chlorophenyl)-3-(2-furoyl) formazan (Vg): Yield: 81%; m.p.: 172-173 °C; IR (KBr) ν_{max}: cm^{-1} 3329 (NH), 1673 (Ph-C=O), 1660 (Ar-C=O), 1591 (C=N); ^1H NMR ($CDCl_3$): δ 11.36 (*s*, 1H, NH), 7.45-6.71 (*m*, 11H, Ar-H); ^{13}C NMR ($CDCl_3$): *δ* 173.4 (Ar-C=O), 168.9 (N-C=O), 150.2 (C=N); MS: *m/z* 380/382 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{19}H_{13}ClN_4O_3$ (380.79): C, 59.93; H, 3.44; N, 14.71; Found: C, 60.15; H, 3.30; N, 14.60.

1-Benzoyl-5-(4-chlorophenyl)-3-(2-thenoyl) formazan (Vh): Yield: 82%; m.p.: 165-167 °C; IR (KBr) ν_{max}: cm^{-1} 3325 (NH), 1673 (Ph-C=O), 1665 (Ar-C=O), 1593 (C=N); ^1H NMR ($CDCl_3$): δ 11.37 (*s*, 1H, NH), 7.45-6.71 (*m*, 11H, Ar-H); ^{13}C NMR ($CDCl_3$): *δ* 174.6 (Ar-C=O), 168.7 (N-C=O), 150.7 (C=N); MS: *m/z* 396/398 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{19}H_{13}ClN_4O_2S$ (334.38): C, 57.50; H, 3.30; N, 14.12; Found: C, 57.32; H, 3.42; N, 13.98.

1-Benzoyl-5-(4-chlorophenyl)-3-(2-naphthoyl)formazan (Vi): Yield: 76%; m.p.: 189-191 °C; IR (KBr) ν_{max}: cm^{-1} 3326 (NH), 1672 (Ph-C=O), 1645 (Ar-C=O), 1591 (C=N); ^1H NMR ($CDCl_3$): δ 11.40 (*s*, 1H, NH), 8.63-7.49 (*m*, 11H, Ar-H); ^{13}C NMR ($CDCl_3$): *δ* 183.7 (Ar-C=O), 168.5 (N-C=O), 149.9 (C=N); MS: *m/z* 440/442 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{25}H_{17}ClN_4O_2$ (440.89): C, 68.11; H, 3.89; N, 12.71; Found: C, 67.95; H, 4.00; N, 12.60.

5-(4-Chlorophenyl)-1-methoxycarbonyl-3-(2-naphthoyl)formazan (Vj): Yield: 78%; m.p.: 176-178 °C; IR (KBr) ν_{max}: cm^{-1} 3326 (NH), 1671 (Ph-C=O), 1645 (Ar-C=O), 1591 (C=N); ^1H NMR ($CDCl_3$): δ 11.43 (*s*, 1H, NH), 8.65-7.51 (*m*, 11H, Ar-H), 3.90 (*s*, 3H, OCH_3);; ^{13}C NMR ($CDCl_3$): *δ* 183.7 (Ar-C=O), 153.9 (N-C=O), 149.8 (C=N), 53.8 (OCH_3); MS: *m/z* 394/396 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{20}H_{15}ClN_4O_3$ (394.82): C, 60.84; H, 3.83; N, 14.19; Found: C, 60.65; H, 3.72; N, 14.10.

3.4. Thermal cyclization of compounds V(f,j) to s-tetrazinones VI(f,j)

To a stirred solution of compounds **Vf,j** (5 mmol) in benzene (50 mL) was carefully added lithium hydride (0.08 g, 10 mmol) at r. t. The resulting reaction mixture was refluxed for 4 hours. After cooling excess lithium hydride was destroyed with some drops of glacial acetic acid . The solvent was evaporated under reduced pressure and the residue was washed with water and then triturated with ethanol (10 mL). The resulting solid product was collected and recrystallized from diethyl ether/petroleum ether (b.p. 40-60 oC) to give s-tetrazinones **VIf,j**. The following compounds were synthesized using this method:

1-(4-Chlorophenyl)-3-phenylaminocarbonyl-s-tetrazinone (VIf): Yield: 84%; m.p.: 158-160 °C; IR (KBr) ν_{max}: cm^{-1} 3276 (NH), 1655 (Ar-C=O), 1598 (C=N); ^1H NMR (DMSO-d_6): δ 8.86 (*s*, 1H, NH), 7.45-7.18 (*m*, 9H, Ar-H); ^{13}C NMR (DMSO-d_6): *δ* 159.8 (C=O), 157.8 (PhNH-C=O), 139.8 (C=N); MS: *m/z* 327/329 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{15}H_{10}ClN_5O_2$ (327.73): C, 54.97; H, 3.08; N, 21.37; Found: C, 55.15; H, 2.95; N, 21.45.

1-(4-Chlorophenyl)-3-(2-naphthoyl)-s-tetrazinone (VIj): Yield: 82%; m.p.: 168-170 °C; IR (KBr) ν_{max}: cm^{-1} 1645 (Ar-C=O), 1599 (C=N); ^1H NMR (DMSO-d_6): δ 8.60-7.48 (*m*, 11H, Ar-H); ^{13}C NMR (DMSO-d_6): *δ* 184.3 (Ar-C=O), 159.7 (C=O), 140.3 (C=N); MS: *m/z* 362/364 [M^+, Chlorine isotopes]; Anal. Calcd. for $C_{19}H_{11}ClN_4O_2$ (362.78): C, 62.91; H, 3.06; N, 15.44; Found: C, 63.10; H, 2.98; N, 15.53.

4. CONCLUSION

The nitrilimines **IIa-j** reacted with benzoyl and methoxycarbonyl hydrazines **III** affording the 1,2,4,5-tetraaza-3-pentenes **IVa-j**, which underwent thermal oxidation to the corresponding formazans **Va-j**. The treatment of formazans **Vf,j** with lithium hydride in refluxing benzene gave s-tetrazinones **VIf,j**.

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SYNTHESIS AND CHARACTERIZATION OF Mn(II), Ni(II), Fe(III), Co(III), Cu(II), Zn(II) AND Cd(II) COMPLEXES OF o-HYDROXYBENZOIC ACID HYDRAZIDE

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ABSTRACT
A series of complexes of o-Hydroxybenzoic acid hydrazide (HBH) with Mn(II), Ni(II), Fe(III), Co(III), Cu(II), Zn(II) and Cd(II) were synthesized. The stoichiometry and structures for the complexes have been established by elemental analysis, electrical conductivity measurements, magnetic moment measurements and spectral (UV-Vis, IR and NMR) studies.

KEYWORDS
Metal Complexes, Hydroxybenzoic acid hydrazide Ligand, Characterization, Stoichiometry and Geometry

RESUMO
Uma série de complexos da hidrazida do ácido o-hidroxibenzóico (HBH) com Mn(II), Ni(II), Fe(III), Co(III), Cu(II), Zn(II) e Cd(II) foram sintetizados. A estequiometria e a estrutura dos complexos foram estabelecidas usando análise elementar, medidas de condutância elétrica, momento magnético e estudos espectroscópicos de uv-visível, infravermelho e ressonância magnética nuclear.

PALAVRAS-CHAVE
Complexos metálicos, Hidrazida do ácido hidroxibenzóico com ligante, Caracterização, Estequiometria e Geometria

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INTRODUCTION

In the recent past, there has been a growing interest in the synthesis and characterization of metal complexes of hydrazides. The obvious reason being the metal coordinated complexes of hydrazides act as effective antimicrobial agents[1,2]. Various research articles have described the fungicide and bactericide properties of metal complexes of hydrazides and hydrazones[3-8]. They have indicated that, hydrazides have remarkable antimicrobial, anticonvulsant, analgesic, anti inflammatory and antitumorial activities[9-15]. The biological activity is due to the existence of potential sites for metal ions[16-18] namely $-\overset{|}{C}=O$, N-H and $-NH_2$ that can be engaged in complexation with the transition metal ions[19,20]. Isonicotinic acid hydrazide is a drug of proven therapeutic importance and is used against a wide spectrum of bacterial ailments e.g., tuberculosys[21]. Agarwal et al have investigated the coordinating ability of hydrazide derivatives with metal ions[22]. Many such articles reported in the literature serve as the testimony for the versatility of these compounds to their potential chelating and antimicrobial abilities. In view of the versatile importance of hydrazides, the authors made an attempt to synthesize and characterize certain metal complexes of HBH.

EXPERIMENTAL

All chemical and reagents used were analytical grade obtained from Merck, India.

The stock solutions Mn(II), Ni(II), Fe(III), Co(III), Cu(II), Zn(II) and Cd(II) were prepared by dissolving appropriate amounts manganous sulphate, nickel(II) sulphate, ferric chloride,

cobalt(II) nitrate [Cobalt(II) solution by aerial oxidation is converted to cobalt(III)], copper(II) sulphate, zinc(II) sulphate and cadmium(II) sulphate in required amount of double distilled water.

An Elico pH meter supplied by ELICO Private Limited, Hyderabad, India used for pH measurements.

Synthesis of o-Hydroxybenzoic acid hydrazide (HBH)

Required amounts of methyl salicylate, hydrazine hydrate and 100 mL of methanol were taken in a 250 mL round bottom flask. The contents of the flask were refluxed for about 2 hours at 35-40°C. A white crystalline solid separated out after cooling was filtered and washed with aqueous methanol. The crude sample was recrystallysed from aqueous methanol. (Melting point: 147°C)

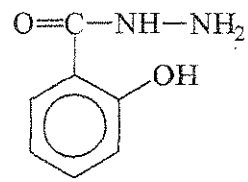


Figure 1. Structure of o-Hydroxybenzoic acid hydrazide

Synthesis of Metal-HBH complex

A methanolic solution containing the metallic salt and HBH in required concentrations was refluxed for about one hour in a 250 mL round bottomed flask. The crystalline sample (pale pink-Mn(II)-HBH; light green-Ni(II)-HBH; dark brown-Fe(III)-BAH; dark pink- Co(III)-HBH;

bluish green-Cu(II)-HBH; light yellow-Zn(II)-HBH and yellow-Cd(II)-BAH) obtained on cooling was filtered, washed with distilled water and finally dried in vacuo.

RESULTS AND DISCUSSION

Elemental analysis

The elemental analysis and magnetic moment data of HBH and its metal complexes under investigation are presented in Table 1.

Table 1. Analytical data of complexes under investigation.

S.No.	Complex	Colour	Melting point °C	Molecular weight	Found (Cal)%				μ_{eff} BM	Molar Conductivity $ohm^{-1} cm^2 mole^{-1}$
					C	H	N	M		
1.	HBH	Yellow	220	152	55.20 (55.26)	5.19 (5.26)	18.39 (18.42)	-	-	-
2.	Mn(II)-HBH	Pale yellow	194	428	39.21 (39.28)	3.20 (3.30)	13.01 (13.09)	12.63 (12.83)	5.20	12.6
3.	Fe(III)-HBH	Dark brown	206	509	49.45 (49.53)	4.05 (4.15)	16.43 (16.50)	10.89 (10.97)	1.96	14.8
4.	Co(III)-HBH	Dark pink	117	512	49.12 (49.23)	4.03 (4.13)	16.33 (16.40)	11.30 (11.50)	Diamagnetic	-
5.	Ni(II)-HBH	Light green	110	432	38.83 (38.93)	3.17 (3.27)	12.90 (12.97)	13.41 (13.59)	3.20	28.4
6.	Cu(II)-HBH	Bluish green	121	366	45.88 (45.96)	3.76 (3.86)	15.24 (15.32)	17.18 (17.37)	2.05	22.5
7.	Zn(II)-HBH	Light yellow	181	368	45.66 (45.74)	3.74 (3.84)	15.18 (15.24)	17.59 (17.78)	Diamagnetic	-
8.	Cd(II)-HBH	Yellow	283	415	40.50 (40.55)	3.30 (3.40)	13.45 (13.51)	26.94 (27.10)	Diamagnetic	-

The elemental analysis data of the complexing agent and its complexes were in agreement with the theoretically calculated values shown in the parenthesis. The stoichiometry of the complexes have been deduced from the data and was found to be 1:2 (Metal : Ligand) for the

Mn(II), Ni(II), Zn(II), Cu(III) and Cd(II)-HBH complexes and 1:3 (Metal : Ligand) for Co(III) and Fe(III)-HBH complex.

Molar conductivity data

The molar conductivity values of the metal complexes determined in dimethylformamide solutions of concentration 1×10^{-3} M are presented in Table 1. The molar conductivity values were in the range 12.6 – 28.4 ohm^{-1} cm^2 $mole^{-1}$. This suggests the non-electrolytic behavior[23] of the metal complexes under investigation.

Electronic spectral details

UV-Vis spectra of the complexes were recorded in the solid phase and are presented in Table 2 and in Figure 2 – Figure 6.

Table 2. Electronic spectral data

Complex	Frequency			ν_2/ν_1	B	β
	ν_1	ν_2	ν_3			
Mn(II)-HBH	15506	17730	22701	1.143	860	1.1631
Fe(III)-HBH	9852	11383	18215	1.155	1015	0.6241
Co(III)-HBH	-	19724	27435	-	1065	-
Ni(II)-HBH	11167	18832	24845	1.686	1030	0.6586
Cu(II)-HBH	17778	27100	-	1.524	-	-
Zn(II)-HBH	-	-	-	-	-	-
Cd(II)-HBH	-	-	-	-	-	-

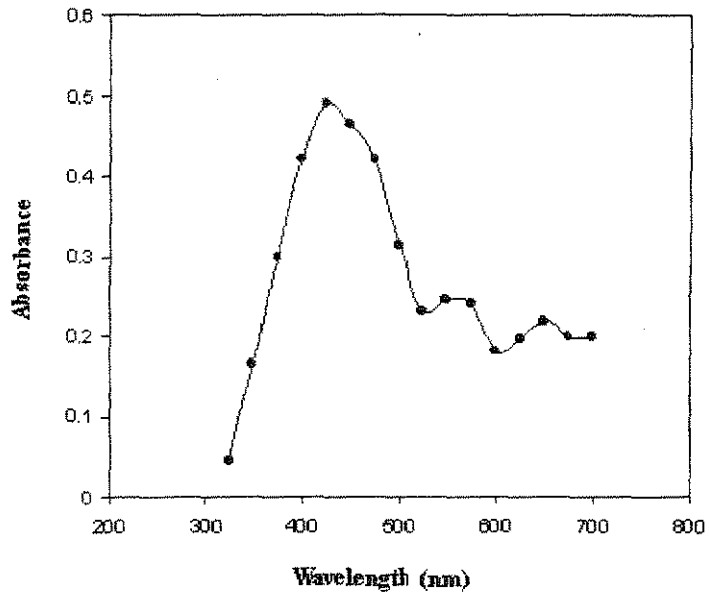


Figure 2. UV-Vis spectrum of Mn(II)-HBH complex

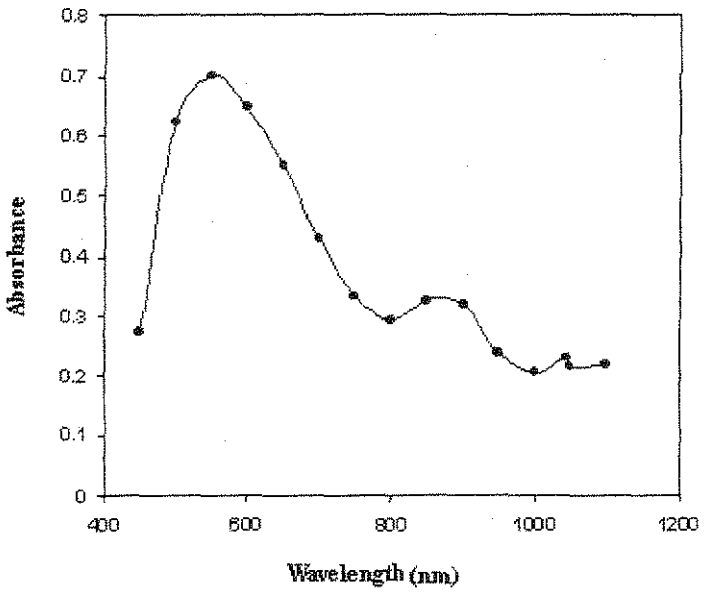


Figure 3. UV-Vis spectrum of Fe(III)-HBH complex

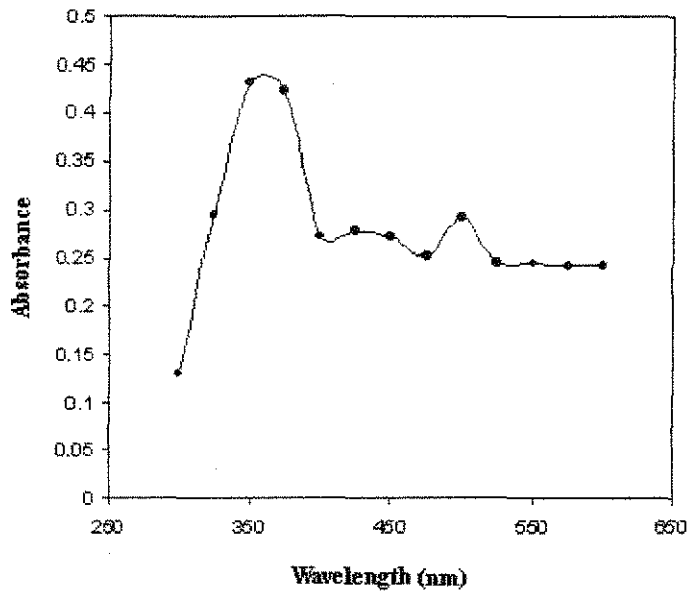


Figure 4. UV-Vis spectrum of Co(III)-HBH complex

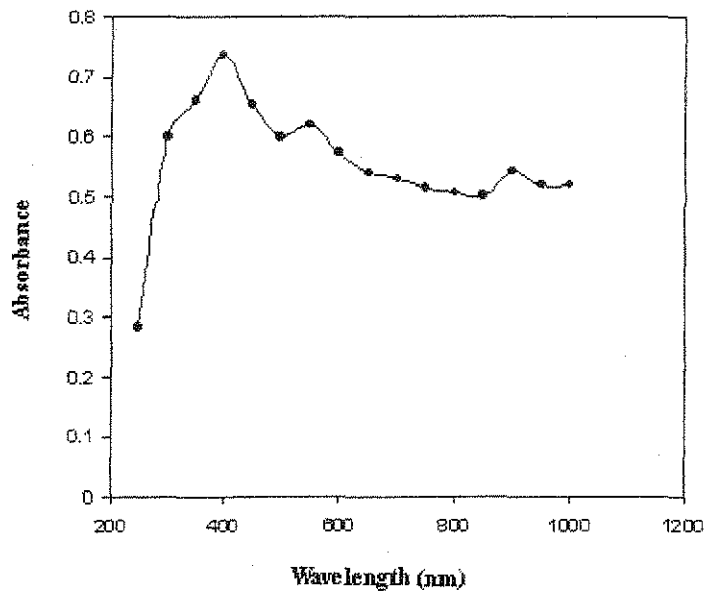


Figure 5. UV-Vis spectrum of Ni(II)-HBH complex

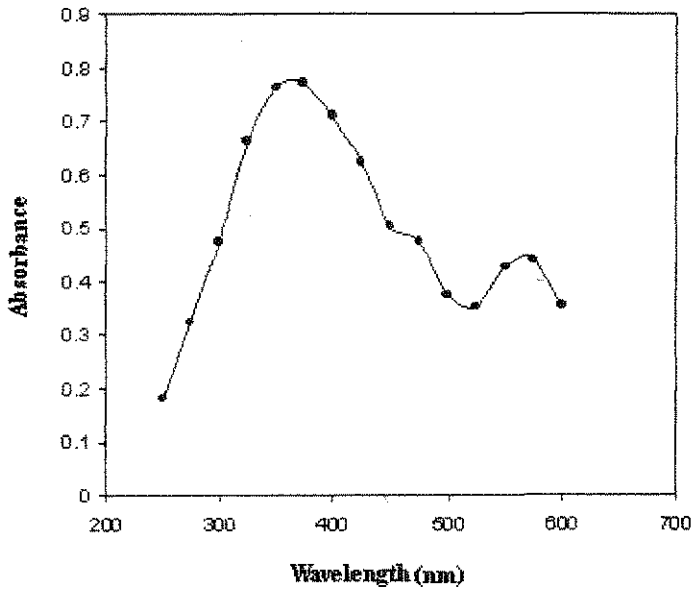


Figure 6. UV-Vis spectrum of Cu(II)-HBH complex

Majority of manganese (II) complexes are found in octahedral structure. The ground state of Mn(II) (d^5) in high spin octahedral coordination is $^6A_{1g}$. The alteration of the electron distribution in the octahedral coordination results in the pairing of electrons. Due to weak spin orbit interactions, weak absorption bands that might correspond to $^6A_{1g} \rightarrow {}^4T_{1g(G)}$, $^6A_{1g} \rightarrow {}^4T_{2g(G)}$ and $^6A_{1g} \rightarrow {}^4E_{g(G)}$[24-26] transitions may occur. The spectrum of Mn(II)–HBH complex contains three bands at 15516, 17730 and 22701 cm^{-1} and correspond to $^6A_{1g} \rightarrow {}^4T_{1g(G)}$, $^6A_{1g} \rightarrow {}^4T_{2g(G)}$ and $^6A_{1g} \rightarrow {}^4E_{g(G)}$ transitions respectively indicating the octahedral geometry. The magnetic moment value of 5.20 BM also supports the octahedral geometry for Mn(II)–HBH complex.[8]

Fe(III) ion is isoelectronic with Mn(II) ion. The spectral bands observed are 9852, 11383, 18215 cm^{-1}. Fe(III) is high spin in majority of its octahedral complexes. The ground state of Fe(III) is $^6A_{1g}$ and correspondingly four weak transitions are expected[27]. However low spin complexes with t_{2g}^5 configuration possess $^2T_{2g}$ ground state and as such in this case also four transitions are expected[28]. Further, in low spin complexes, a high degree of covalence and electron delocalization were observed. The magnetic moment value is 1.96 BM. The greatest loss of exchange energy occurs when the d^5 configuration is forced to pair up during the formation of low spin complexes. Further in low spin complexes, the ligands approach the empty e_g orbitals more closely. This is justified by the greater observed value of μ_{eff} 2.09 BM.

Based on the electronic spectral data and magnetic moment data, an octahedral geometry was suggested for Fe(III)-HBH complex.

In general, all known Co(III) complexes are octahedral. The energy level features of free Co(III) ion (d^6) is qualitatively same as that of Fe(II). All Co(III) complexes are expected to possess bands characteristic of transition from $^1A_{1g}$ ground state to other singlet states. The two absorption bands observed in the visible region at 19724 and 27435 cm^{-1} correspond to such transitions namely, $^1A_{1g} \rightarrow {}^1T_{1g}$ and $^1A_{1g} \rightarrow {}^1T_{2g}$ respectively. The electronic spectral data and diamagnetic behavior of the complex suggest an octahedral structure for Co(III)–HBH complex.

The ground state of Ni(II) ion in octahedral coordination is $^3A_{2g}$ ($t_{2g}^6e_g^2$). In the present investigations, the spectrum of Ni(II)–HBH complex in dimethylformamide solution contains three peaks at 11167, 18832 and 24845 cm^{-1}. These absorption bands correspond to transitions $^3A_{2g} \rightarrow {}^3T_{2g}$, $^3A_{2g} \rightarrow {}^3T_{1g(F)}$ and $^3A_{2g} \rightarrow {}^3T_{1g(P)}$ respectively [29]. The value of ν_2/ν_1 was found to be 1.686[30,31] which is lower than that of 1.800 observed for the regular octahedral nickel aquo complex. The lower value of ν_2/ν_1 is attributed to the asymmetric environment around Ni(II). The Racah parameter value and nephelauxetic factor (β) suggest the delocalization of d-orbitals and covalency of the metal-ligand bond in metal complexes. The ground state of regular octahedral complex is $^3A_{2g}$. In such a case, the μ_{eff} value should be equal to spin only value (2.8 BM) as the orbital angular momentum contribution to the magnetic moment is zero. The reason being the fact that the ground state $^3A_{2g}$ is usually be non degenerate. The slightly greater observed value of 3.2 BM observed for Ni(II)–HBH complex in the present investigation was due to the spin orbit coupling between the ground state $^3A_{2g}$ and the first excited state $^3T_{2g}$. The data supports octahedral geometry for the Ni(II) complex[32-34].

Cu(II) complexes usually have distorted octahedral with a limiting structure of either square planar or tetrahedral. The ground term in square planar geometry is $^3B_{1g}$ and the excited terms are $^2A_{1g}$, $^2B_{2g}$ and ^2E_g. Corresponding to these three transitions, the spectrum of square planar copper(II) complex is expected to contain three peaks. However these peaks usually overlap to give one or two broad peaks[35,36]. The d-d bands of square planar complexes[37,38] are observed in the range 14000 and 22000 cm^{-1}. In the present investigation two bands, one at 17778 cm^{-1} and

the other at 27100 cm^{-1} are observed. The band at 17778 cm^{-1} may be attributed either to $^2B_{1g} \rightarrow {}^2B_{2g}$ or $^2B_{1g} \rightarrow {}^2E_g$ transition. The band at 27100 cm^{-1} may be attributed to the ligand to metal charge transfer transition. The absence of bands below 10000 cm^{-1} rules out the tetrahedral or pseudo tetrahedral environment for this complex[39]. Irrespective of stereochemistry, Cu(II) complexes possess one unpaired electron. Figgis and Lewis[40] have predicted a magnetic moment value less than 1.90 BM (spin only value) for square planar geometry. Usually the magnetic moment values for square planar complexes would be slightly greater than the spin only value of 1.90 BM. The magnetic moment value of 2.05 BM observed in the present studies could be due to spin-orbit coupling.

Based on elemental analysis data, the electronic spectral data and magnetic moment value, a square planar geometry is proposed for the complex.

Zn(II) and Cd(II) complexes possess d^{10} configuration and hence do not show spectral absorptions due to d-d transitions. The complexes are diamagnetic in nature. Based on the elemental analysis, conductance and infrared spectral data[41], tetrahedral geometry is suggested for the Zn(II) and Cd(II)–HBH complexes.

IR spectral studies

The IR spectra of the ligand and its metal complexes under investigation are presented in Figure 7–Figure 14. The important absorption assignments observed in the respective spectra are given in the Table 3.

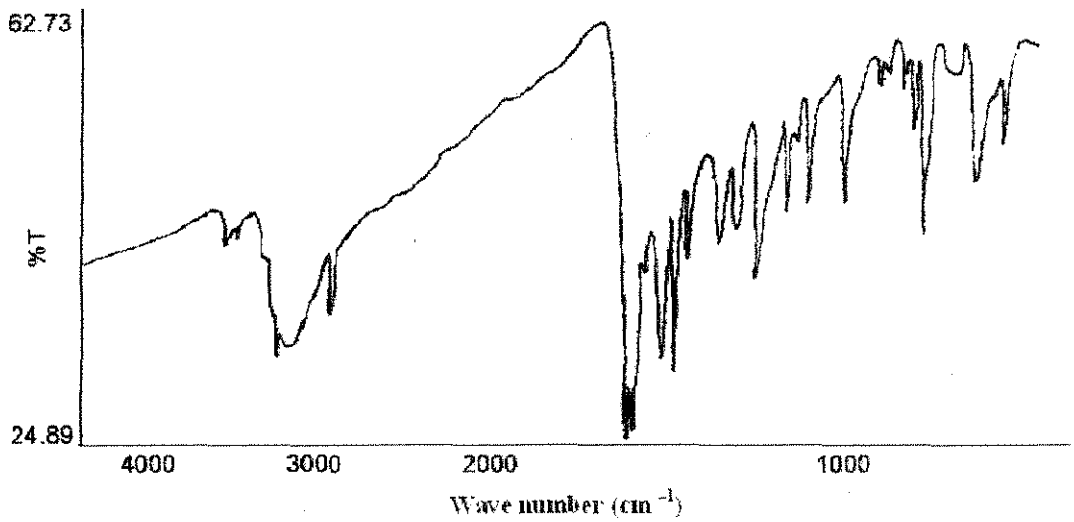


Figure 7. IR spectrum of HBH

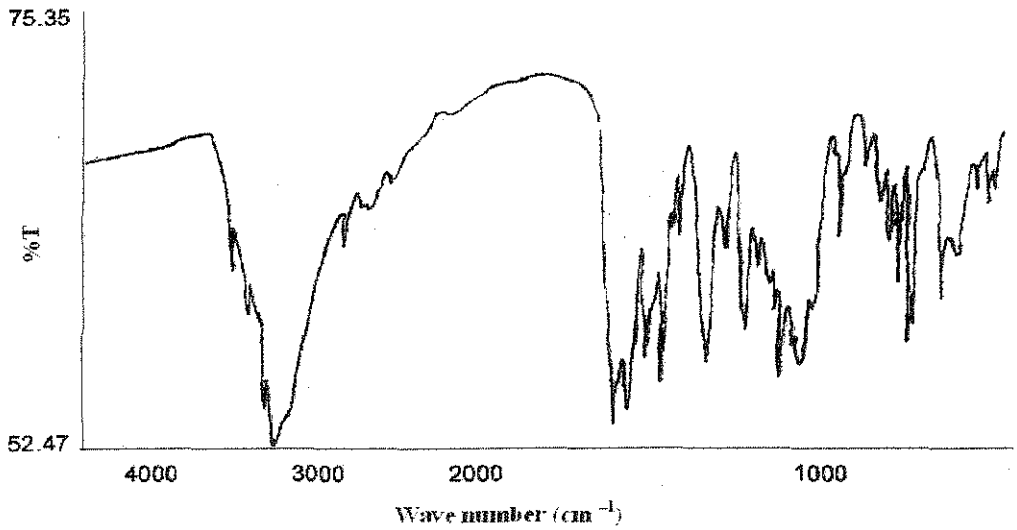


Figure 8. IR spectrum of Mn(II)-HBH complex

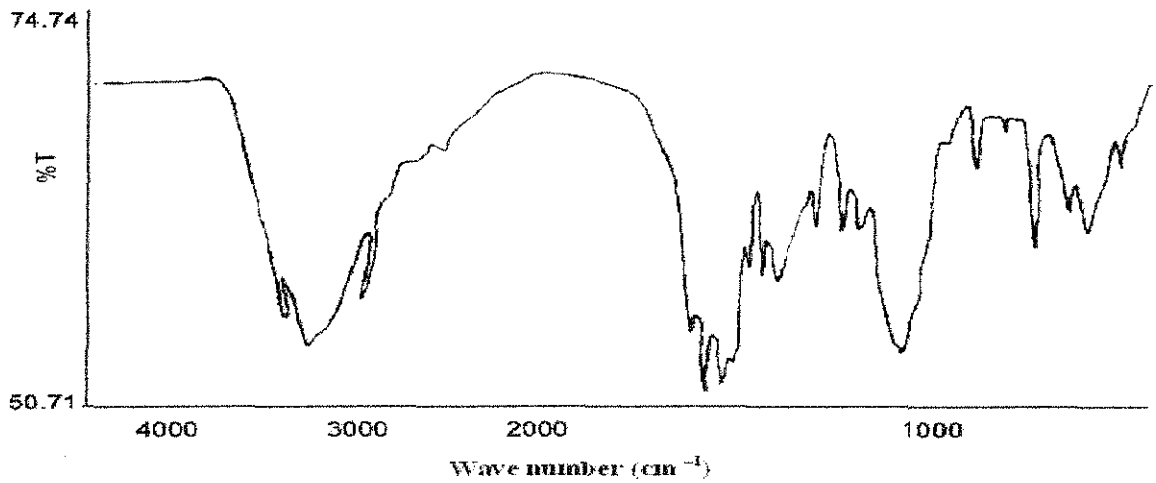


Figure 9. IR spectrum of Ni(III)-HBH complex

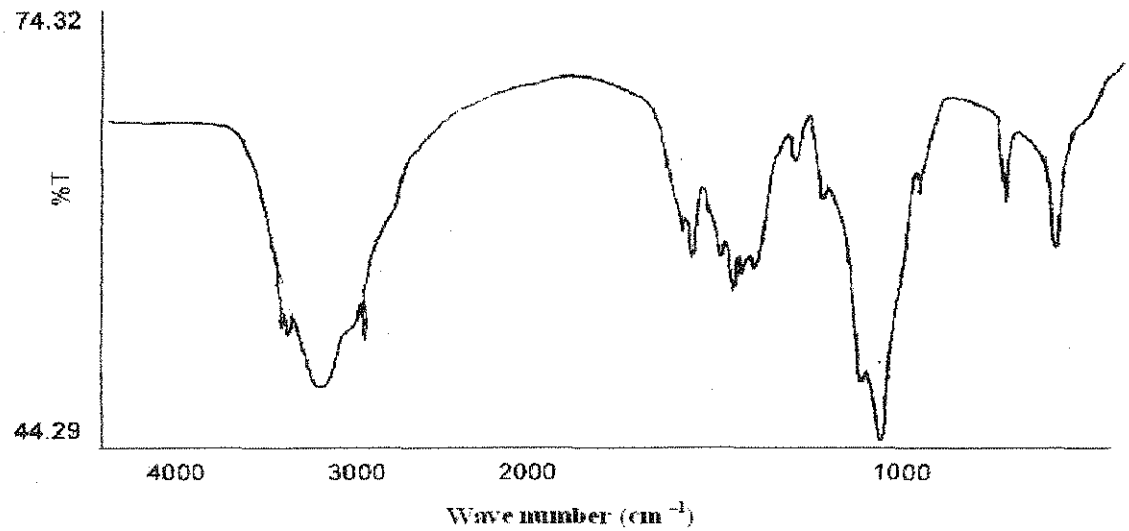


Figure 10. IR spectrum of Fe(III)-HBH complex

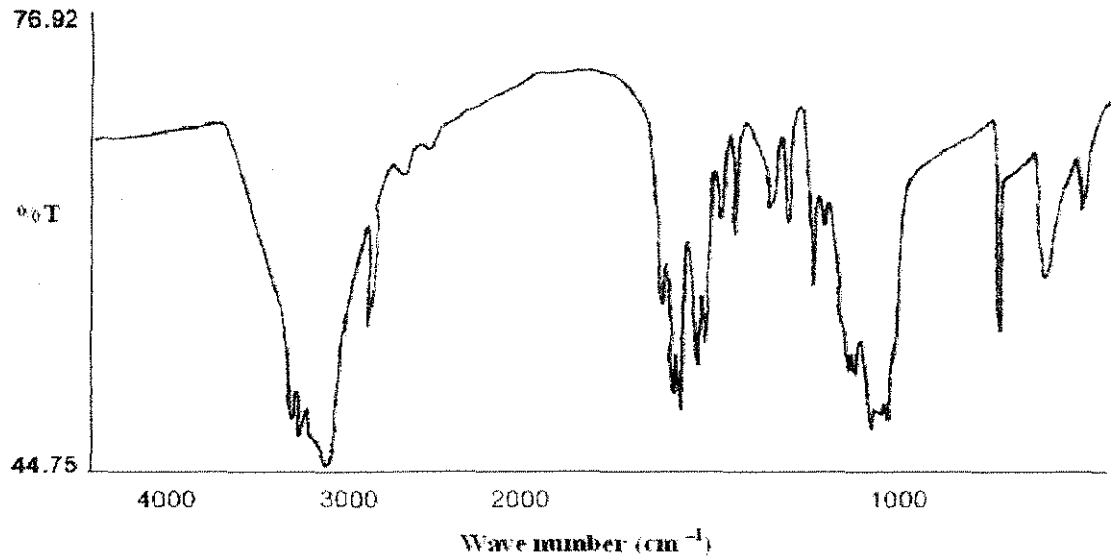


Figure 11. IR spectrum of Co(III)-HBH complex

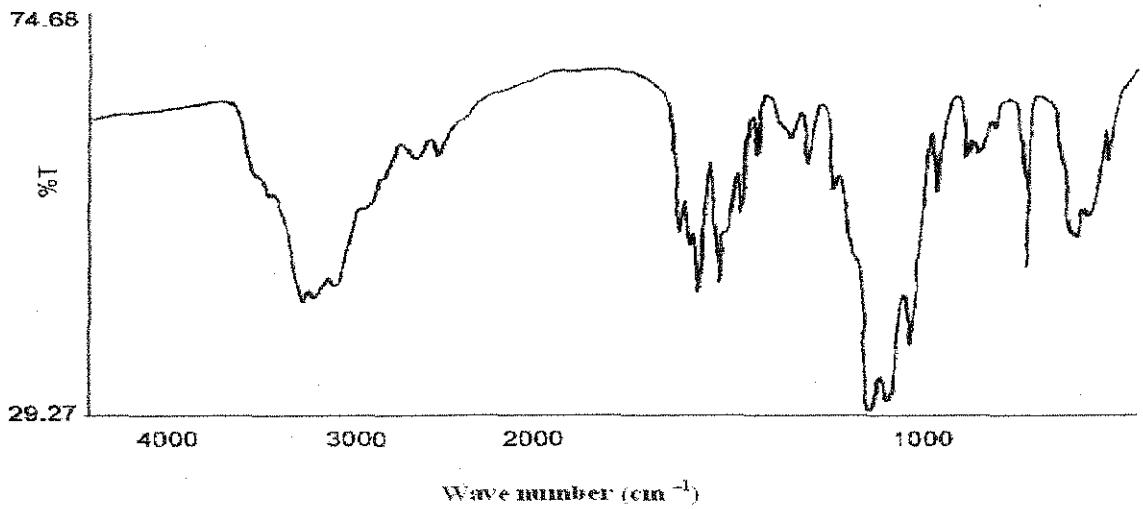


Figure 12. IR spectrum of Zn(II)-HBH complex

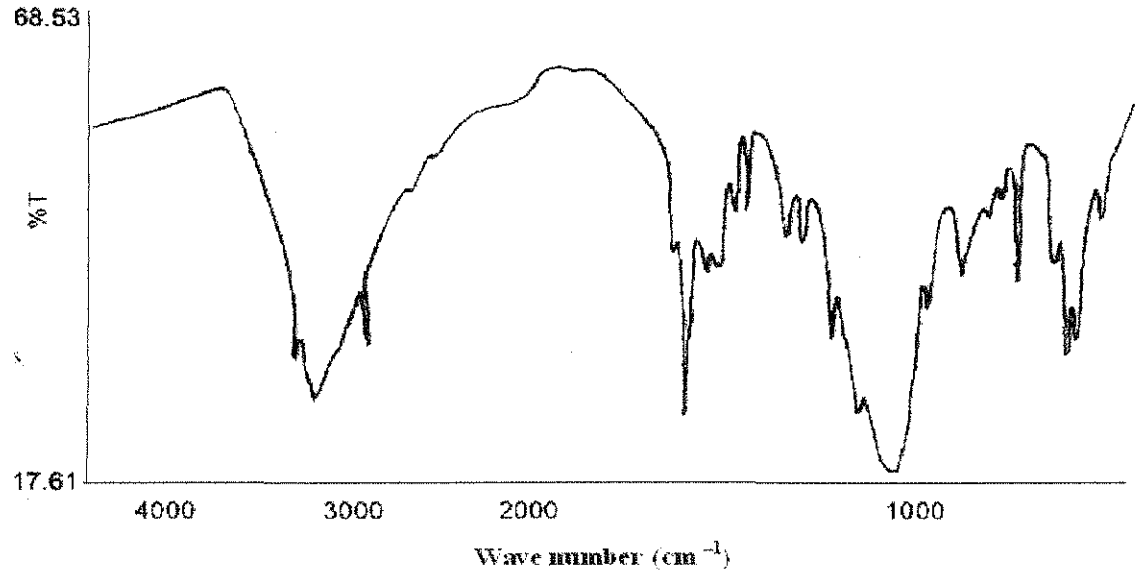


Figure 13. IR spectrum of Cd(II)-HBH complex

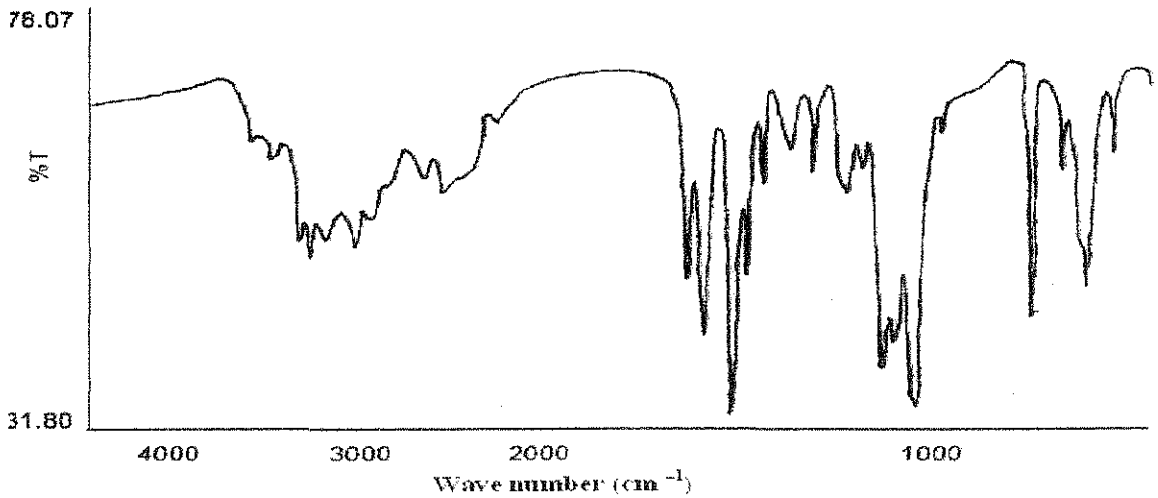
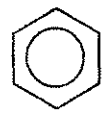
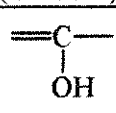


Figure 14. IR spectrum of Cu(II)-HBH complex

Table 3. Characteristic IR absorption frequencies (cm^{-1}) and their assignments

	Reagent (HBH)	**Mn(II)-HBH**	**Fe(III)-HBH**	**Co(III)-HBH**	**Ni(II)-HBH**	**Cu(II)-HBH**	**Zn(II)-HBH**	**Cd(II)-HBH**
ϕ-OH	3245	-	-	-	-	-	-	-
>C=O	1645	-	-	-	-	-	-	-
-NH	3290	-	-	-	-	-	-	-
$-NH_2$	3495 3395	3450 3321	3445 3325	3445 3330	3440 3320	3435 3312	3440 3320	3445 3328
	1450 1490 1540 1595	1440 1486 1534 1586	1442 1492 1532 1595	1459 1496 1544 1567	1456 1497 1530 1563	1457 1496 1537 1570	1457 1495 1554 1609	1460 1494 1531 1567
$-NH_2$ (amide II)	-	1590	1590	1590	1590	1590	1590	1590
	-	2850	2845	2860	2840	2870	2860	2845
>C=N	-	1608	1604	1609	1609	1608	1609	1606
N-N	980	979	980	978	980	981	981	980
M-O	-	529	565	516	529	530	530	522
M-N	-	748	752	748	752	746	747	748

A doublet noticed at 3495 cm^{-1} and 3395 cm^{-1} is attributed to the presence of $-NH_2$ group in the molecule. Another band at 3290 cm^{-1} is ascribed to the $-\overset{|}{N}H$ group attached to the carbonyl group. A band at 3245 cm^{-1} is due to the phenolic –OH (ϕ-OH). A band at 1645 cm^{-1} may be ascribed to the ν (C=O). The bands observed at 1450, 1490, 1540, 1595 cm^{-1} are ascribed to the benzene skeleton.

The important IR frequencies exhibited by Mn(II)-HBH and Ni(II)-HBH complexes and their assignments are shown in the Table 3 and in Figure 8 and Figure 9 respectively. The

appearance of a new band at 2930 cm^{-1} in Mn(II)-HBH spectrum and 2933 cm^{-1} in Ni(II)-HBH spectrum may be attributed to the enolic –OH group. This suggests that the reagent in these complexes is in the enolic form but not in the keto form as is present in the free ligand. The bands at 3495 and 3395 cm^{-1} corresponding to $-NH_2$ group are shifted to lower wave numbers by about 75 cm^{-1} in the spectra of both these complexes. This shift is ascribed to the strong intra molecular hydrogen bonding between nitrogen of $-NH_2$ and hydrogen of enolic –OH. The appearance of a new band at 1590 cm^{-1} in both the complexes may be attributed to amide-II NH_2 group. The bands due to benzene skeleton present in the free ligand are not displaced in the spectra of complexes. A band at 1645 cm^{-1} due to the amide carbonyl group is absent in the spectra of complexes. This further suggests that the reagent in these complexes is in the enolic form. Similarly a band at 3290cm^{-1} due to $-\overset{|}{N}H$ stretching is absent in the spectra of complexes suggesting that not only the reagent is present in the enolic form but the nitrogen of the $-\overset{|}{N}H$ group is involved in coordination with the metal ion. The bands that are not observed in the spectrum of free ligand and observed at 1608 and 1609 cm^{-1} in the spectrum of the complex may be attributed to the presence of azomethine (>C=N-) group in the complexes. The bands at 748, 752 cm^{-1} may be due to ν_{M-N}[42,43] vibrations respectively in the complexes. A shift in ν_{N-N} to higher wave numbers is observed in the spectra of complexes and this may be explained by the fact that the ligand coordinates in a bidentate manner via azomethine nitrogen[44,45].

The elemental analysis data predicts 1:2 metal to ligand ratio for the complexes. Further, magnetic moment value[46], elemental analysis data and IR spectral data reaffirms the octahedral structure. Out of six coordination sites, two nitrogen atoms occupy two coordinate positions, two oxygen atoms occupy the other two coordinate positions and two solvent molecules occupy remaining two coordinate positions (Figure 15).

The IR spectral data of Fe(III) and Co(III)–HBH complexes are presented in Table 3 and the spectra are shown in Figure 10 and Figure 11. The behavior is almost same as described for Mn(II) and Ni(II)–HBH complexes. The elemental analysis data predicts a stoichiometry of 1:3 (M:L) for these complexes. Based on the IR spectral and elemental analysis data, an octahedral structure is proposed for these complexes (Figure 15).

The IR spectrum of Zn(II) and Cd(II)–HBH complexes are shown in Figure 12 and Figure 13 and the data is presented in Table 3. The same scenario of IR spectral bands was observed for these complexes also. The most preferred geometry for d^{10} systems is tetrahedral. Further keeping in view the experimental data, a tetrahedral geometry was suggested for Zn(II) and Cd(II) complexes (Figure 15). Based on the elemental analysis data, IR and electronic spectral data[47,48], a square planar geometry is suggested for Cu(II)–HBH complex (Cu(II) has d^9 configuration). The stoichiometry of the complexes determined from elemental analysis data is found to be 1:2 (Figure 15).

NMR spectral studies

The ^{1}H NMR spectral data of the ligand and its metal complexes studied in DMSO d^6 using TMS as an internal standard is given in the Table 4.

The ^{1}H NMR signal at 4.80 ppm was assigned to phenolic –OH. Broad peaks observed at 6.10 ppm and 11.20 ppm were attributed to amino (-NH_2) and imino (-$\overset{|}{N}H$) groups respectively.

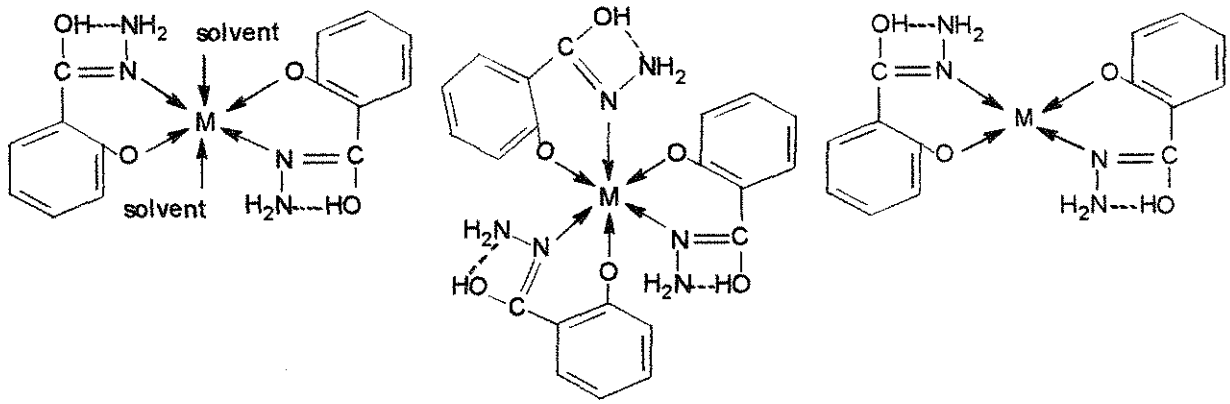
Table 4. ^{1}H NMR spectral data (δ ppm) and their assignments

S.No.	Compound	H_a	H_b	H_c	-$\overset{|}{N}$H	-NH_2	-OH (phenolic)	-OH (enolic)
1.	HBH	7.50	7.10	6.80	11.20	6.10	4.80	-
2.	Mn(II)-HBH	7.95	7.50	7.10	-	5.90	-	5.60
3.	Fe(III)-HBH	8.20	8.00	7.70	-	5.80	-	5.62
19.	Co(III)-HBH	8.19	7.99	7.69	-	5.70	-	5.73
5.	Ni(II)-HBH	8.18	7.98	7.68	-	5.75	-	5.78
6.	Cu(II)-HBH	8.40	8.20	7.90	-	5.85	-	5.65
7.	Zn(II)-HBH	7.70	7.50	7.20	-	5.90	-	5.68
8.	Cd(II)-HBH	8.00	7.80	7.50	-	5.80	-	5.70

The complex multiplet noticed in the ^{1}H NMR spectra of the complexes in the range 7.10 – 8.40 ppm were attributed to the aromatic protons H_a, H_b and H_c[49]. The signal corresponding to the phenolic –OH (4.80 ppm) were absent in the spectra of complexes, thereby indicating the coordination of phenolic oxygen atom to the metal[50]. The spectra of all metal complexes studied contain signal in the range of 5.60 – 5.78 ppm and this was absent in the spectrum of free ligand. This may be attributed to the presence of an enolic –OH in the complexes. The signals observed for the amino protons in the ligand were unaffected in the spectra of complexes. However, the signal for imino proton found in the spectrum of free ligand was absent in the

spectra of metal complexes. This fact further confirms the presence of enolic –OH in the metal complexes.

Based on the above studies following structures have been assigned for the complexes under investigation.



(a)M = Mn^{2+} and Ni^{2+} (b) M = Fe^{3+} and Co^{3+} (c) M = Zn^{2+}, Cd^{2+} and Cu^{2+}

Figure 15. Structure of Metal-HBH complexes under investigation

CONCLUSION

Mn(II), Ni(II), Fe(III), Co(III), Cu(II), Zn(II) and Cd(II) complexes of o-Hydroxybenzoic acid hydrazide were synthesized and characterized. The metal complexes were characterized by elemental analysis, molar conductivity, UV-Vis spectral, IR spectral and NMR spectral studies and stoichiometry was established in each case. In all the cases, the ligand acts a neutral bidentate ligand and coordinates to the metal via N and O.

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ARTHUR F. FISHKIN, PROMINENT BIOCHEMIST AND EDUCATOR

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ABSTRACT

Arthur Frederic Fishkin was born on May 27, 1930 in New York City, USA and passed away peacefully in his sleep in Omaha, Nebraska on his 80th birthday, on May 27, 2010. He attended elementary and secondary school in New York , obtained a B.A. in Zoology from Indiana University in 1951 and a M.A. in 1953. He was awarded the Ph. D. Degree in Biochemistry from the University of Iowa in 1957. He held faculty positions at Louisiana State University, New Mexico State University and Creighton University. His research activities dealt with enzymes and glycoproteins in connective tissues. He contributed to the training of thousands of students in the medical sciences for almost half a century.

KEYWORDS: History of Chemistry and Biochemistry, Glycoproteins in Blood Vessels, Enzymes, Medical Education

RESUMO

Arthur F. Fishkin nasceu em New York, Estados Unidos em 27 de Maio de 1930 e faleceu serenamente no dia de seu 80º aniversário durante o sono em Omaha, Nebraska, Estados Unidos em 27 de Maio de 2010.Ele recebeu os títulos de B.A. e M.A. em Zoologia da Universidade de Indiana em 1951 e 1953, respectivamente e o título de Ph.D. em Bioquímica da Universidade de Iowa em 1957. Ocupou cargos de professor em Louisiana State University, New Mexico State University e Creighton University. As suas atividades de pesquisa trataram de enzimas e glicoproteínas em vasos sanguíneos. Ele contribuiu na preparação de milhares de profissionais na área da saúde por quase meio século.

PALAVRAS CHAVE: História da Química e Bioquímica, Glicoproteínas em Vasos Sanguíneos, Enzimas, Educação Médica

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Arthur Frederic Fishkin was born on May 27, 1930 in New York City, USA and passed away peacefully in his sleep in Omaha, Nebraska, on his 80th birthday, on May 27, 2010.

He was an only child. His parents were Sidney Leonard Fishkin and Ruth Schneiderman Fishkin. His father was a successful lawyer in New York. His grandfather was originally from Edinet (Yedintzi), in the northern part of the present day Republic of Moldova and immigrated to the United States of America towards the end of the 19th century (1899).

Arthur F. Fishkin attended Public School 192 and Junior High School 43 in Manhattan. His Bar Mitzvah was held at the Park Avenue Synagogue in New York in 1943. He completed secondary education at the Bronx High School of Sciences and graduated in 1948. He was a member of the Boy Scouts in Manhattan, was elected to the *Order of the Arrow* and as a youngster enjoyed sports, especially baseball.

He graduated from Indiana University and obtained a Bachelor of Arts Degree in Zoology in 1951. Two years later, in 1953 he was awarded the Master of Arts in Zoology by Indiana University.

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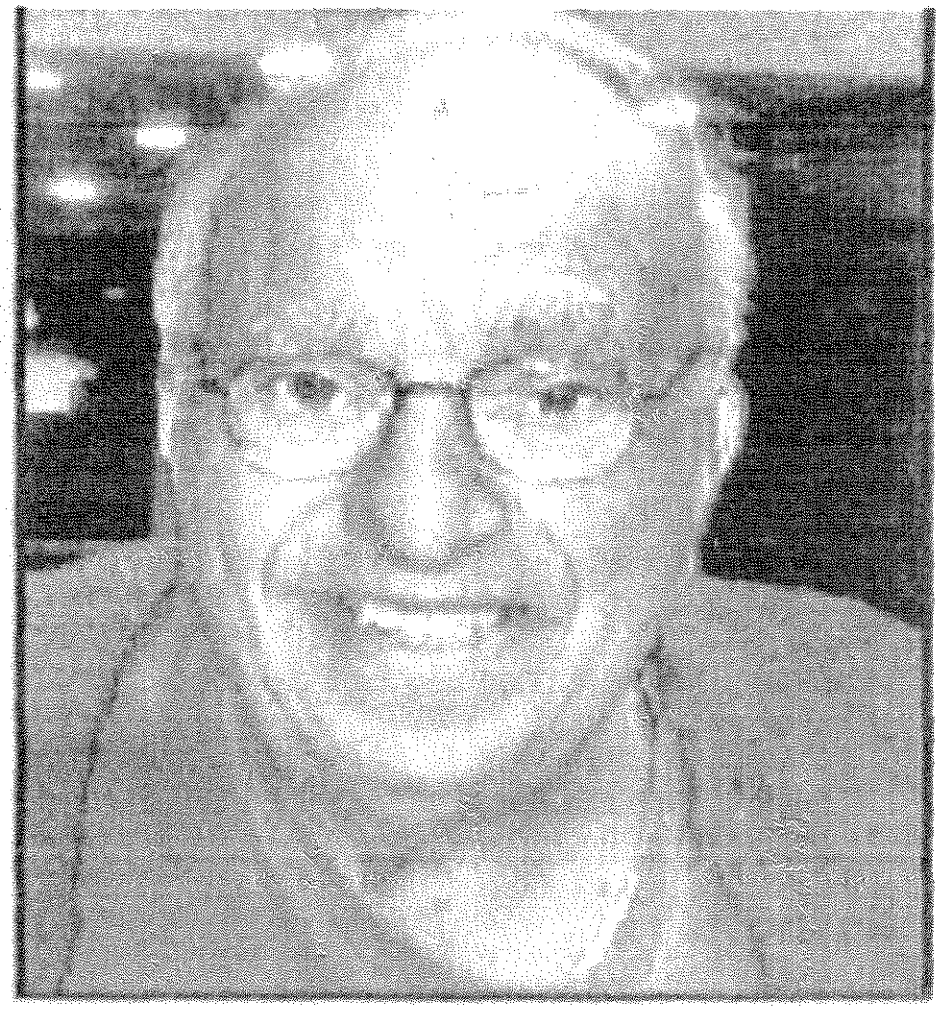
L. G. Ionescu



PROF. Dr. ARTHUR F. FISHKIN (1930-2010)

Arthur F. Fishkin continued his graduate studies at the University of Iowa, where he originally intended to study for a doctorate in zoology. His interest in biochemistry was sparked by his interaction with Prof. Henry Bull and by his course in physical biochemistry. He was awarded the Doctor of Philosophy Degree in Biochemistry in 1957. His research advisor was Professor Gene Lata and his doctoral dissertation involved the investigation of hormones and enzymes. Enzymology was an area in which Prof. Dr. A. F., Fishkin had profound and continuous interest for the rest of his life.

He met Jane Leslie Paul at the University of Iowa and they were married in September 1956 at her home in Bangor, Maine. They were married for 53 years and she survives him. They had four children: Paul A.S. Fishkin, M.D., an oncologist and hematologist of Peoria, Illinois; Charles A. Fishkin, a Senior Vice-President of Alliance Bernstein in New York (married to Suzanne Tinley of Chappaqua, N.Y.): James A. Fishkin, a partner in legal antitrust practice at Dechert LLP of Washington, D.C.; and Joel A. Fishkin, an economist for the Indiana Utility Regulatory Commission. He was blessed with five grandchildren.

Prof. Dr. Arthur F. Fishkin was extremely proud of his children and grandchildren. As a father, he was very encouraging and allowed each one of his sons to find his interests and develop his talents. As a grandfather, he was very gentle and followed with care and interest the development of his grandchildren.

From 1957 to 1958, Dr. A. F. Fishkin was the recipient of a Postdoctoral Fellowship and worked as an Associate Scientist at the Southwest Foundation for Research and Education in San Antonio, Texas.

In 1958 he joined the Louisiana State University School of Medicine in New Orleans as Instructor of Biochemistry and Medicine and collaborated with Professor Gerald S. Berenson doing research on glycoproteins in blood vessels.

In 1962, Dr. Arthur F. Fishkin was promoted to Assistant Professor of Biochemistry and Medicine, a position that he held until 1964.

From 1964 to 1968 he held the academic appointment of Assistant Professor of Chemistry at New Mexico State University in Las Cruces and played an important role in the establishment of the Doctoral Program in Chemistry and Biochemistry.

In 1968, Prof. Dr. Arthur F. Fishkin moved to Omaha, Nebraska and accepted the position of Associate Professor of Biomedical Sciences in the School of Medicine at Creighton University. He worked in the Biochemistry Department of Creighton University for almost four decades and was promoted to Professor Emeritus of Biomedical Sciences in 2008.

Creighton President the Rev. John P. Schlegel, S.J., presents Fishkin with a plaque, honoring his promotion to professor *emeritus*, during the 2008 President's Convocation ceremony.

At Creighton University, well known for its "student-centered" approach, Prof. Dr. A.F. Fishkin epitomized this approach. He was always willing to give whatever time was needed to mentor and help students that were having problems in the classroom or in life in general.

He taught biochemistry classes to undergraduate and graduate students in the College of Arts and Sciences, School of Medicine, School of Dentistry, School of Pharmacy and School of Nursing.

During his academic career, Prof. Dr. Arthur F. Fishkin was instrumental in the preparation and education of literally thousands of health professionals over a period that spanned almost half of century, of which about forty years at Creighton University. Sometimes, his students came from two different generations. One interesting case is that of a wedding in Florida, where the bride , Constance Faro, MS'97, MD'02 and the father of the bride, Richard Faro, MD'72 were Prof. Fishkin's medical students.

Prof. Dr. Arthur Fishkin held many administrative positions at Creighton University. Among them we mention, Head of the Division of Biochemistry, Director of Animal Research, Departmental Graduate Coordinator, University Rank and Tenure Committee, Minority Student Committee, Medical School Admissions Committee, Committee on Scholarship and Student Services and others.

A more complete description of Prof. Dr. Arthur F. Fishkin's service to Creighton University is given in the *FOUNDERS DAY CONVOCATION* of February 12, 2008, reproduced on the following page.

SOUTHERN BRAZILIAN, JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM. , Vol. 19,No.19, 2011

Creighton UNIVERSITY

FOUNDERS DAY CONVOCATION 2008
February 12, 2008 • 4 p.m.

Award Citations In Order of Presentation

Arthur F. Fishkin, Ph.D.
Professor *Emeritus* of Biomedical Sciences

Dr. Arthur F. Fishkin's service to Creighton University, its Health Science schools and the College of Arts and Sciences has been substantial and extensive, covering four decades.

Prior to joining Creighton in 1968, Dr. Fishkin held teaching posts at Louisiana State University School of Medicine and at New Mexico State University. He earned his doctor of philosophy degree in biochemistry at the University of Iowa in 1957.

At Creighton, Dr. Fishkin has taught molecular and cell biology classes for the School of Medicine. For students in the Health Science Schools, he has taught undergraduate and graduate level biochemistry courses in the classroom, as well as online. His foundation course in human nutrition, entitled Nutrition Facts and Fads, has been an important resource for students in the College of Arts and Sciences.

Since the formation of the Department of Biomedical Sciences, Dr. Fishkin has served as a mentor for junior faculty and is held in highest regard by his department colleagues.

In addition, Dr. Fishkin has given valuable input to the School of Medicine's Admissions Committee, which is a challenging responsibility. In a given year, the hours spent reviewing applications, participating in meetings and conducting student interviews can easily add up to 200 hours.

Dr. Fishkin is an active member of the American Society of Biochemistry and Molecular Biology, and of the American Chemical Society. He serves as a judge of abstracts for the Midwest Student Medical Forum.

For outstanding contributions and length of service, it is with pride and gratitude that Creighton University confers the rank Professor *Emeritus* of Biomedical Sciences upon Dr. Arthur F. Fishkin.

We first met Prof. Dr. Arthur F. Fishkin in August of 1965 in Las Cruces. We had just completed the studies for the M.S. Degree in Chemistry doing research on organic liquid scintillators under the supervision of Prof. Guido H. Daub of the University of New Mexico and Dr. Francis Newton Hayes of the Los Alamos Scientific Laboratory and were beginning the studies for the Ph.D. Degree with Prof. John J. Monagle, who was chairman of the Chemistry Department at New Mexico State University and was working with phosphorus organic compounds.

The Chemistry Department at NMSU was one big happy family at the time. Both the faculty and the graduate students were enthusiastic about the new Doctoral Program in Chemistry that had just begun. All of the young faculty members, including Prof. Dr. A. F. Fishkin , were working very hard to establish research groups, research laboratories and obtain research grants.

Two faculty members were responsible the biochemistry area: A. F. Fishkin and O. B. Weeks and both joined NMSU in 1964. Dr. Owen B. Weeks had a joint appointment as Research Professor of Chemistry and Biology, was really a microbiologist and spent most of

his time in the Research Center and the Department of Biology.

We remember Prof. Dr. Arthur F. Fishkin as a very friendly person. He talked to almost all of the graduate students, used to go drink coffee with them in the Student Union, tell jokes or engage in serious discussions and conversations about many topics. He was an erudite person and some people were considering him a "walking encyclopedia".

He told us that he came to Las Cruces to help establish the program in biochemistry and to continue the research on glycoproteins in blood vessels in cows, since the genetics in the bovine species was much better documented than in humans.

Unfortunately and surprisingly, in the middle of 1966, Prof. John J. Monagle announced that he was leaving to the University of Alabama, Tuscaloosa, to become Chairman of the Chemistry Department. It was part of a strong and general effort of Governor George C.Wallace to strengthen science and engineering and attract industry to the State of Alabama.

The impact of J.J. Monagle's decision was not a very good one for the Chemistry Department at NMSU and eventually it affected the lives of many people.

In September of 1966 we enrolled in Medical School and after completing the first year we spent the summer of 1967 working with Prof. John J. Monagle as a Technical Assistant at the University Alabama.

In September of 1967, we decided to return to Las Cruces and complete the studies for the Ph.D. in Physical Chemistry under the supervision of Prof. Dr. Gordon J. Ewing, investigating the interaction of leguminous hemoglobin with nitrogen and xenon. Leguminous hemoglobin, leghemoglobin or legoglobin is a protein and respiratory pigment found in the root nodules of many plants that fix nitrogen. It was during this period (1967-68) that we interacted more with Prof. Arthur F. Fishkin and he helped us with the extraction and separation of leguminous hemoglobin from soybean root nodules.

The atmosphere in the Chemistry Department at NMSU had changed completely. There was animosity among the younger faculty members and one could feel the presence of envy, pettiness, jealousy and vanity, characteristic of the ivory towers of universities throughout the world. The new chairman (1967-71), Basil G. Anex, a specialist in reflectance spectroscopy, who had come from Yale, was not a very efficient administrator and later it took a lot of effort on the

part of Prof. Latimer R. Evans and Ralph G. Wilkins to normalize the situation.

Prof. Dr. Arthur F. Fishkin had managed to set up the best equipped laboratory, had research grants from NASA and NIH and the largest research group (10-15 graduate students). We needed his help and assistance in the separation of leguminous hemoglobin from the root nodules. The process was a rather complicated, laborious and repetitive one and involved, among others, precipitation, fractionation, sedimentation with an ultracentrifuge, dialysis and gel electrophoresis. Prof. Fishkin's only condition for his help was that we go first to drink coffee in the Student Union.

It was during our trips to the Student Union that we got to know each other relatively well. Since I was not formally his student, he felt very much at ease. We used to talk about many topics other than science, including history of the United States, Mexico, Bessarabia, Romania and Russia, literature, art, wine, politics, the news of the day and other subjects.

During the 1960's the United States returned to Mexico a small strip of El Paso that became part of the United States after the Rio Grande River changed its course (El Chamizal). The Mexican

Government celebrated the event and built a shopping center, hotel, museums, monuments, water falls, parks, etc. in part of El Chamizal (PRONAF-Programa Nacional Fronterizo). Prof. A. F. Fishkin used to say that this was Juarez's answer to Fifth Avenue and that it was a damned good one. Many students from New Mexico State University used to visit Mexico to see "Fishkin's Fifth Avenue" in Ciudad Juárez.

Some peoples have a high resistance and tolerance to alcohol, while ohers get drunk easily. Prof. A. F. Fishkin, who was a specialist in enzymology, had a theory on resistance or tolerance to alcohol. The metabolism of alcohol depends on enzymes. According to him, peoples that have consumed alcohol for many generations developed more and better enzymes.

He was an adept of the pheromone theory (today's *Chemistry of Love*) and used to give as an example a medical student who sensed the phermones that his girl friend sent from hundreds of miles away.

As we mentioned above, in 1967 Prof. Dr. Arthur Fishkin had the largest number of graduate students and had research grants from NASA and NIH. He had a lot of research money and all of them had research assistantships. About half of them were working on

glycoproteins from cattle and the other half on the extraction of proteolytic enzymes from dermestid beetles. The fad of the time was to make trips in the Gila Wilderness, especially on horse back. Most of Prof. Fishkin's students were going on weekly mounted expeditions and were renting the horses. After some time, they decided that it was more convenient to buy horses. Each one of them had a horse and they used to keep them at stables in Mesilla Park. Some of them began neglecting research work in the laboratory and this used to upset Prof. A. F. Fishkin. He used to say jokingly that perhaps he should change research from cows to horses and that he was the only "*Assistant Professor West of the Pecos River with a Mounted Cavalry Unit*".

The photograph on the following page was taken during a visit to NASA's headquarters in Houston in 1964. It probably had to do with NASA's support of the Biochemistry Program at NMSU and the donation of laboratory equipment to the Chemistry Department after the closing of the Primate Facility near Alamogordo. It is well known that the first astronaut was LAIKA, the female shepherd dog that the Russians sent to space. The first American astronauts were

Picture taken in 1964 at NASA's Manned Space Center in Houston Texas, now called the Johnson Space Center.

From left to right: Owen B. Weeks, Scott Carpenter (Gemini Astronaut), Paul Purser (Senior NASA Official), Arthur F. Fishkin and James Weiss (Director of the Research Center, New Mexico State University).

two chimpanzees, HAM and ENOS, trained at the Primate Facility and sent to space in 1961.

Two graduate students, Peter N, Spangler and Philip J. Witt completed their Master of Science theses with Prof. Dr. A. F. Fishkin as advisor at New Mexico State University in 1968. These were probably the first graduate theses in biochemistry at NMSU.

Peter N. Spangler's work dealt with glycoproteins in fetal and adult cattle aortas and part of it was published in *Nature* in 1968.

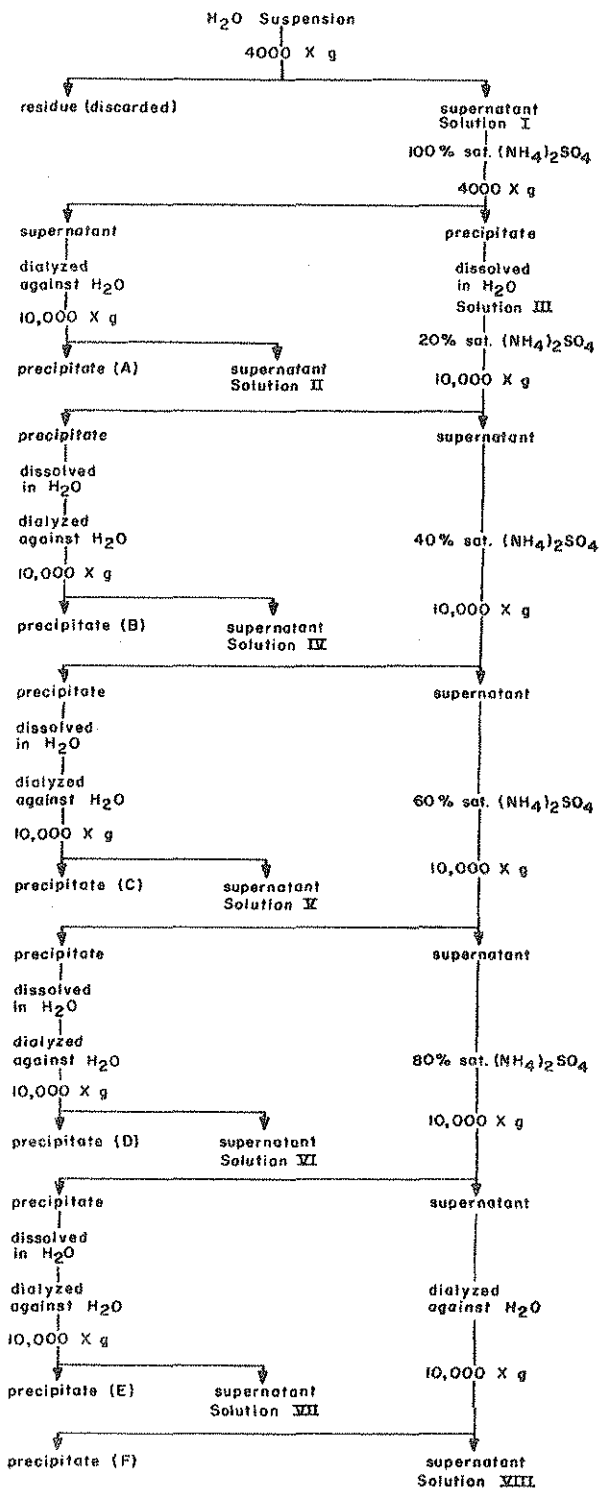
Philip J. Witt worked in a new area and studied the selected proteolytic activity by of dermestid beetle larvae. This was a new area of research that Prof. A. F. Fishkin began in Las Cruces, remained in the initial stages and apparently he was not able to continue at Creighton University.

Dermestid beetles are part of the family of *Coleoptera.* They are scavengers that feed on plant and animal material and are sometimes employed to clean bones and skeletons and are known to contain proteolytic enzymes. The idea was to isolate, characterize and study the activity and property of these enzymes.

In the following pages we reproduce some figures, tables and diagrams that deal with these two topics and that we have received through the courtesy of Charles A. Fishkin, son of Prof. A. F. Fishkin and Senior Vice-President of Alliance Bernstein, New York, USA.

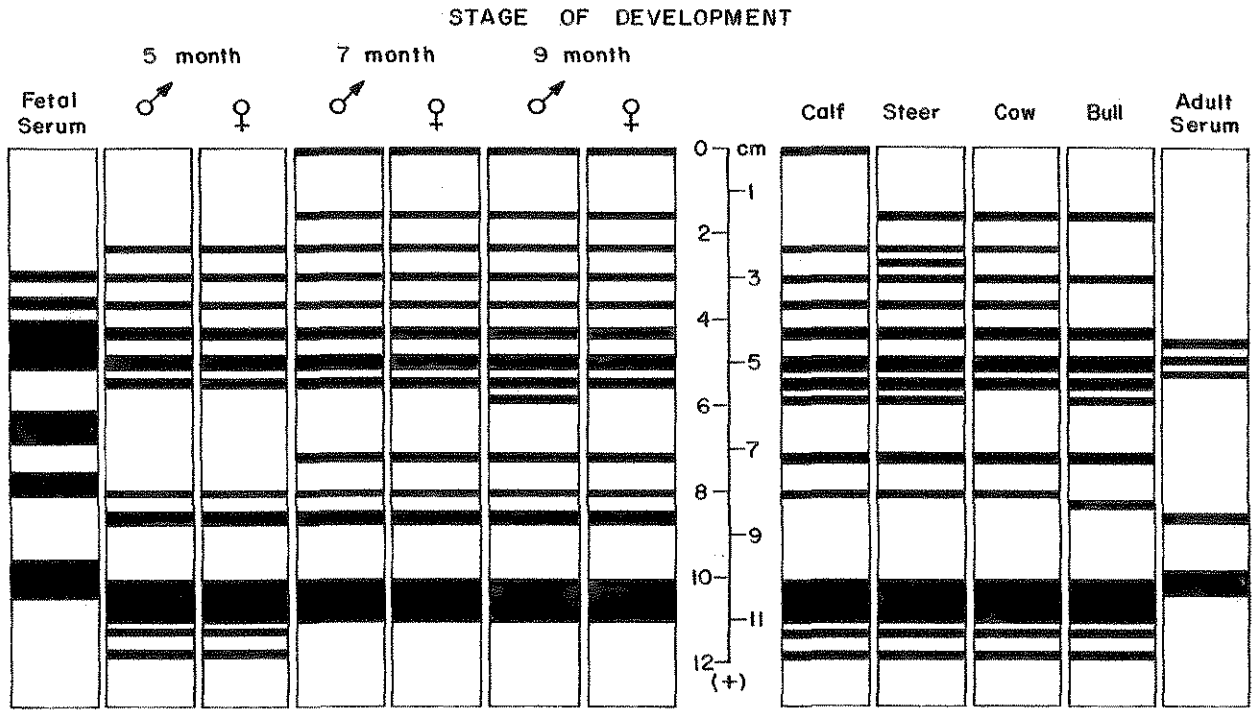
The material is self-explanatory and needs no additional comments.

Figure 2. Procedure for Ammonium Sulfate Fractionation



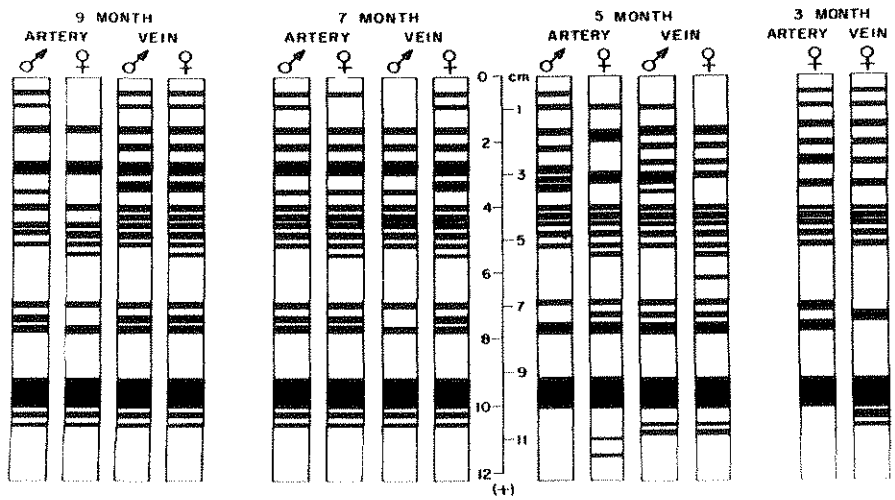
Peter N. Spangler, "*Glycoproteins in Fetal and Adult Cattle Aortas*", M.S. Thesis, New Mexico State University, April 8, 1968
Advisor: Prof. Arthur F. Fishkin

Figure 3.
ELECTROPHORETIC PATTERNS OF AORTA GLYCOPROTEIN



UMBILICAL BLOOD VESSEL GLYCOPROTEINS

ELECTROPHORETIC PATTERNS



PERCENT COMPOSITION OF GLYCOPROTEIN FRACTIONS

	Umbilical Artery	Umbilical Vein
Neutral Sugars	3.0	3.5
Hexosamine	1.4	1.6
Sialic Acid	3.4	3.3
Nitrogen	14.4	15.2

SOUTHERN BRAZILIAN, JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM. , Vol. 19,No.19, 2011

Arthur F. Fishkin, Prominent Biochemist and Educator

78

NEW MEXICO STATE UNIVERSITY

COLLEGE OF ARTS AND SCIENCES
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Abstract for ACS Meeting-in-Minature on April 15, 1967

Gelatinolytic Activity of Extracts from the Larvae of Dermestid Beetles

P. J. Witt and A. F. Fishkin
Department of Chemistry
New Mexico State University

Recently enzymes which hydrolyze collagen and its degradation product gelatin have been demonstrated in developing animal systems Collagen is a ubiquitous and important structural component of all connective tissue. The catabolyc steps by which this macromolecular species is handled is nobtwell understood. The larvae of dermestid beetles are known to subsist on collagenous substrates. It would appear that these larvae could provide a source of enzymes which catalyze the degradation of collagen and gelatin. Water extracts of the larvae of Dermestes maculatus hydrolyze a 0.5% solution of gelatin. Fractional precipitation with ammonium sulfate yields three fractions capable of hydrolyzing gelatin. One fraction is precipitated by 20% saturated ammonium sulfate; the other two, which seem quite similar to each other, precipitate in excess of 40% saturation. The fraction precipitating at 60% saturation exhibited a 30 fold increase in specific activity as compared with the initial crude extract. The enzyme fractions lost approximately 50% of their activity after considerable freezing and thawing over a period of two months. Assay of the gelatinolytic activity was made by a viscometric method. This work was supported in part by NASA grant NGR 32-003-027 to New Mexico State University.

SOUTHERN BRAZILIAN, JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM., Vol. 19,No.19, 2011

L.G. Ionescu

Philip James Witt, "*Selected Proteolytic Activity by Extracts of Dermestid Larvae*", M.S. Thesis, New Mexico State University, May 9, 1968
Advisor: Prof. Arthur F. Fishkin

ABSTRACT

The larvae of the beetle Dermestes maculatus DeGeer can subsist on a diet consisting largely of protein. Studies have been undertaken to investigate the nature of the proteolytic enzymes. A water extract of the larvae yielded a crude preperation which hydrolyses gelatin, hide powder, hemoglobin substrate, benzoyl-DL-arginine p-nitroanilide and glutaryl-L-phenylalanine p-nitroanilide. Enzyme activity was found in a non-dialysable, heat- and acid-labile portion of the extracts. Fractionation with ammonium sulfate of the crude extract yielded two fractions with high specific activity towards gelatin. These are precipitated between 40% to 60% saturation of ammonium sulfate and 60% to 80% saturation. The higher specific activity was observed in the 40%-60% fraction. These results suggest that the larvae of these dermestids contain proteolytic enzymes with actions similar to mammalian trypsin and chymotrypsin. The results also suggest that other proteolytic enzymes may be present as well.

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In 1968, forced by circumstances, Prof. Dr. Arthur F. Fishkin left Las Cruces and went to the School of Medicine of Creighton University in Omaha, Nebraska, where he remained for the rest of his life.

He was sad about the fact that his *Research Group* and his *Research Laboratory* , built with so much effort, would be dismantled. He knew that at Creighton University, an institution mainly devoted to teaching and the training of health professionals, he would have less time and fewer collaborators to continue his research. It was, after all, a question of survival and he had the responsibility of the life and and education of his wife and four small children and this was much more important.

Besides his effort of almost half a century in the training of health professionals, Prof. Dr. Arthur F. Fishkin made important contributions to science. His discovery of the racial differences in the composition of blood vessels and their relationship to cardiovascular disease, led to the Bogalusa Heart Study led by Gerald S. Berenson that lasted more than thirty years. He had ample research support from the Louisiana Heart Association, National Institutes of Health and the National Aeronautics and Space Administration.

He was a member of the New York Academy of Sciences, Phi

Lambda Upsilon, Sigma Xi-The Scientific Research Society of America, American Society for Biochemistry and Molecular Biology, American Institute of Chemists, Society for Complex Carbohydrates and the American Chemical Society.

Prof. Dr. Arthur Fishkin liked people and liked to talk to people. He had a quality called empathy and in many ways he was an archetype. He was a great person, teacher, mentor, educator and friend.

ACKNOWLEDGMENT. We thank Charles A. Fishkin, Senior Vice-President, Bernstein Alliance, New York, USA for his help and assistance.

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SOUTH. BRAZ. J. CHEM. , Vol. 19,No.19, 2011

MINERALOGICAL ASPECTS OF ARSENIC – THE ARSENATE MINERALS

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ABSTRACT

Arsenic is an element known since ancient times. It is the 52nd element in order of chemical abundance in the Earth's crust with 1.8 ppm (grams per metric ton). Arsenic combines relatively easy with chlorine sulfur, oxygen and many metals. This article describes some of the uses and properties of arsenic and arsenic compounds and presents a synopsis of the two hundred and seventy eight (278) arsenate minerals known at the present time.

KEY WORDS: Arsenic, Mineralogical Aspects, Arsenates, Uses of Arsenic

RESUMO

O arsênio é um elemento conhecido desde a antiguidade. Está na qüinquagésima segunda (52ª) colocação em ordem de abundância química na crosta terrestre com 1.8 ppm (gramas por tonelada). O arsênio combina facilmente com cloro, enxofre, oxigênio e muitos metais. Este trabalho descreve algumas das propriedades e usos do arsênio e seus compostos e apresenta uma sinopse das duzentos e oitenta (280) espécies mineralógicas de arseniatos conhecidas até a presente data.

PALAVRAS CHAVE: Arsênio , Aspectos mineralógicos, Arseniatos, Usos do Arsênio

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INTRODUCTION

This article represents a continuation of our work dealing with the mineralogy of the elements of the Periodic Table. We have already published a series of papers dealing with mineralogical aspects of silver, copper, gold, lead, platinum, lithium, hydrogen, uranium and the rare earths.[1-8]

Arsenic is an element known since ancient times. It occurs in nature in many minerals, mainly in combination with sulfur and a large number of metals. In general, the arsenic minerals are subdivided into two large groups, those that posses arsenic in a metallic form and the arsenates. In particular, this work describes mainly the arsenate minerals.

The main minerals containing arsenic, other than the arsenates are native arsenic (As), arsenopyrite (iron arsenide sulfide), cobaltite (cobalt iron arsenic sulfide), enargite (copper arsenic sulfide), erythrite (hydrated cobalt arsenate), orpiment (arsenic sulfide), proustite (silver arsenic sulfide), realgar (arsenic sulfide) and tennantite (copper arsenic sulfide).[9-17]

One of the most common minerals is mispickel arsenopyrite, FeSAs, from which upon heating, arsenic sublimes leaving ferrous sulfide. Arsenic is relatively common in volcanic ash and ground waters, due to weathering of mineral ores.

It also occurs in various organic compounds found in nature in bacteria, molds, fish, algae and other plants, the most common ones being trimethyl arsine and arsenobetaine.[18-20]

Arsenic is also present in nature in the elemental state and it occurs in two solid modifications, yellow and grey or metallic with specific gravities of 1.97 and 5.73, respectively. The more common allotropic form is the steel-grey variety that has a

bright metallic luster. Under normal pressure it sublimes before melting, but under pressure it melts at 817 °C. It burns with a blue flame at 180 °C forming As_2O_3, arsenic trioxide.

Arsenic combines relatively easy with chlorine, sulfur and certain metals. The most common compound is arsenic trioxide, As_2O_3, sometimes called *white arsenic* or simply arsenic. The valence of arsenic ranges from -3 to +5. Both As_2O_3 and As_2O_5 are hygroscopic, readily soluble in water and form acidic solutions. The corresponding acids H_3AsO_3 , arsenious acid for As (III) and H_3AsO_4, arsenic acid for As(V) are weak acids and the corresponding salts are called arsenites and arsenates, respectively. Some of the more common ones are Paris Green - copper(II) acetoarsenite, calcium arsenate and lead hydrogen arsenate and have been widely used as dyes, agricultural insecticides and poisons.[10-17]

At the present time China is the top producer of arsenic, followed by Chile, Peru and Morocco. Arsenic is mainly recovered as a side product from copper, gold and lead smelters. Most of the operations in Europe and the United States have been discontinued for environmental reasons.[15-17] Some properties of arsenic are given in Table I.

The word arsenic probably derives from the Persian *Zarnik* or *Zarnikh* that means yellow orpiment. Arsenic sulfides, orpiment (As_2S_3); realgar (As_4S_4) and arsenic oxides have been known and used as stimulants, poisons and dyes since ancient times.

Zosimos described about 300AD the roasting of sandarach (realgar) to obtain a cloud of arsenic (arsenious oxide) which was then reduced to metallic arsenic.[9]

Table I. Some Properties of Arsenic

Atomic weight	**74.92180 g/mol**
Electronic configuration	**(Ar) $4s^2$ $3d^{10}$ $4p^3$**
Density at room temperature	**5.727 g/cm^3**
Density of liquid at m.p.	**5.22 g/cm^3**
Sublimation point	**615 °K**
Critical Point	**1673°K, ? MPa**
Triple point	**817°C, 3628 kPa**
Heat of fusion (grey As)	**24.44 kJ/mol**
Oxidation states	**+5,+3,2,+1,-3**
Ionization energy	**1st 947.0 kJ/mol 2nd 1798 kJ/mol 3rd 2735 kJ/mol**
Atomic radius	**119 pm**
Van de Waals radius	**185 pm**
Covalent radius	**119 pm**
Young modulus	**8 GPa**

The word orpiment comes from the Latin *aurumpigmentum* (*aurum* and *pigmentum* - pigment of gold) and describes the lemon-yellow color the mineral.

The Persian word Zarnik eventually lead to the Greek arsenikon and the Latin arsenicum. *Zerni-zar* is the Persian word for gold.

During the Bronze Age, arsenic was added to the Cu-Sn alloy in order make the bronze harder. It is generally accepted that the first to isolate the metal was Albert the Great (Albertus Magnus, 1193-1280) who obtained it by heating orpiment (As_2S_3) with soap.

The Chinese Encyclopedia on Materia Medica (Pen Ts'ao Kan-Mu or Kang-mu) of about 1600 described properties and uses of arsenic.

In 1760, Louis Claude Cadet de Gassicourt prepared what is sometimes considered the first synthetic organometallic compound (Cadet's fuming liquid, impure cacodyl) by reacting potassium acetate with arsenic trioxide.

In ancient times, arsenic and arsenic compounds in small doses were used as stimulants and in large doses as poisons. The addition of arsenic to bronze (Cu-Sn alloy) in order to make it harder was well known. The use of arsenic compounds as pigments and dyes was also widespread.

As we mentioned earlier, arsenic compounds were used as medicines during the middle ages in Europe and also in the Orient.[9] Their use incosmetics was also common.

A large number of arsenic compounds were synthesized during the 18th and 19th centuries. For Example, *Paris Green*, also known as *Emerald Green*, used in wallpaper, printing ink and also employed widely by Cézanne and Van Gogh in their paintings, was first prepared in 1814 by reacting copper(II) acetate with

arsenic trioxide. It was originally used in large scale to kill rats in the Parisian sewers. During the 1950's, Paris Green was used in the United States and Europe as an insecticide in apple orchards and in 1945 it was spread by airplanes in Sardinia and Corsica to control malaria.

At the present time the toxicity of arsenic to insects, bacteria, fungi, plants and higher organisms is well documented. In spite of this, wood is still treated with chromated copper arsenate (CCA or Tanalith) and a large number of agricultural insecticides contain arsenic. Their use is still common in rice and rubber plantations.

Arsphenamine and neosalvarsan were introduced in the beginning of the twentieth century by Paul Ehrlich for the treatment of syphilis and trypanosomiasis and Thomas Fowler used arsenic trioxide for the treatment of psoriasis. As recently as the year 2000, the United States Food and Drug Administration approved As2O3 for the treatment of patients with acute promyelocytic leukemia.

Until very recently, arsenic was added to animal food to prevent disease and stimulate growth. One compound used widely as nutritional supplement for chickens is *Roxarsone*. The use of arsenic as a stimulant by athletes and mountain climbers is still in practice.

One of the main uses of arsenic is for the improvement of nonferrous metal alloys, especially those containing copper and lead. Lead parts in automotive batteries are significantly strengthened by the addition of small quantities of metallic arsenic. Lead alloys used for lead shots and bullets contain up to 2% of arsenic. It is also used in bronzing and pyrotechnics. Small quantities of arsenic

are added to alpha-brass to make it resistant to dezincification. This type of brass is used to manufacture plumbing fittings and other parts that are in constant contact with water.

Galium arsenide is a very important semiconductor material employed in integrated circuits. It is prepared by chemical vapor deposition. Circuits made from gallium arsenide (GaAs) are much faster and more expensive than those made from silicon. Unlike silicon, it has a direct band gap and can be used in laser diodes and light emitting diodes (LEDs) to convert directly electricity into light.

Arsenic is also used for taxonomic sample preservation and for the manufacture of optical glass.

Military uses of arsenic include stockpiles of chemical weapons. Trimethyl arsine, $As(CH_3)_3$, was used as a nerve gas in World War I and lewisite, ($ClCH=CHAs_2Cl_2$), that is a vesicant (blister agent) and lung irritant was employed in World War II and other recent conflicts.

The high affinity of As (III) for thiols is one of the causes of its high toxicity. The –SH group is part of the amino acid cysteine that is located at the active site of many enzymes.

Several tissue culture studies have shown that As(III) blocks the IKr and IKs channels and activates the IK-ATP channels.

Arsenic also disrupts ATP production by several mechanisms. At the level of the citric acid cycle, arsenic inhibits pyruvate dehydrogenase. By competing with phosphate it uncouples oxidative phosphorylation and inhibits energy linked reduction of NAD+, mitochondrial respiration and ATP synthesis.

Arsenate can replace phosphate in the glycolysis step that produces 1,3-diphosphoglycerate, forming 1-*arseno*-3-phosphoglycerate. This molecule is unstable and hydrolyzes quickly forming 3-phosphopglycerate, the next intermediate in the pathway. Glycolysis proceeds, but the ATP molecule that Would be generated from 1,3-diphosphoglycerate is not formed and is lost. Arsenate thus is an uncoupler of glycolysis and this explains its toxicity.

Various species of bacteria obtain their energy by oxidizing fuel compounds while reducing arsenate too arsenite. Under oxidative environmental conditions, some bacteria can use arsenite and oxidize it to arsenate as a fuel for their metabolism. The enzymes involved in this process are known as *Arsenate Reductases* (Arr). In 2008, R. S. Orelmand and his collaborators discovered a strain of bacteria (PHS-1 related to the gamma-*Proteobacterium echtothiorodospira Shapóshnikovii*) that employs a version of photosynthesis in the absence of oxygen was discovered. For the case of this bacterium, arsenites act as electron donors, producing arsenates, just like ordinary photosynthesis uses water as an electron donor, producing molecular oxygen.

Upon entering the food chain, inorganic arsenic and its compounds are metabolized thorough methylation reactions. The mold Scopulariopsis produces trimethyl arsine. Marine species such as algae, fish, clams, oisters and some species of mushrooms contain large amounts of the organic compound arsenobetaine.

In 2010 a group form the NASA Astrobiology Institute led by Felisa Wolfe Simon in collaboration with Ronald S. Oremland of the U.S. Geological Survey published an article in Science in which they claimed that the microbe strain

GFAJJ-1 of the *Gammaproteobacteria* (*Halomonadaceae*) from arsenic rich Mono Lake in California incorporates arsenic into its DNA backbone and in ATP.[20,21]

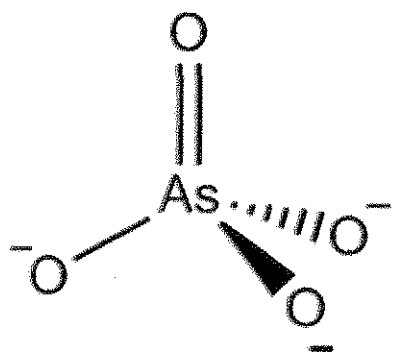
The bacterium was cultured in an environment high in arsenic and low in phosphorus. The group performed a battery of tests including x-ray absorption studies and mass spectrometry and concluded that the organism used arsenic and introduced it in the backbone of the DNA in the place of phosphorus. The arsenate esters supposedly form in the DNA back bone in place of the phosphate esters and As replaces P as one of the six elements of which living things are made (C,N, H, O. S and P). This claim, if true would alter the basic and fundamental understanding of carbon based life and would provide more perspectives to the possibility of extraterrestrial life based on elements different from those on Earth.[20-22]

At the present time there is considerable debate about this claim and many scientists that study the origin of life, arsenic metabolism and synthetic biology echo a chorus of skepticism.

ARSENATE MINERALS

The formula of the arsenate ion is ASO_4^{-3}. Any compound that contains this ion is called an arsenate. The arsenic atom in arsenate has a valence of +5 and is commonly known as pentavalent arsenic As(V).

Arsenate is similar to phosphate in many respects, since As and P occur in the same group in the Periodic Table. The arsenate ion has tetrahedral symmetry and its structural represented in Figure 1. In strongly acidic solutions it exists as arsenic acid, H_3AsO_4; in weakly acidic solutions as the dihydrogen arsenate ion,H_2AsO4^-; in weakly basic solutions as the hydrogen arsenate ion, $HAsO_4^{-2}$ and in strongly basic conditions as the arsenate ion, AsO_4^{-3}.



IUPAC name	
arsorate	
Identifiers	
CAS number	12523-21-6
PubChem	27401
Jmol-3D images	Image 1 (http://chemapps.stolaf.edu/jmol/jmol.php?model=%5BO-%5D%5BAs%5D%28%3DO%29%28%5BO-%5D%29%5BO-%5D)
SMILES	
[O-][As](=O)([O-])[O-]	

Figure 1. Structure of Arsenate

By the end of 2008, the International Mineralogical Associataion – IMA, had validated officially 280 (two hundred and eighty) species of arsenate. They are listed in Table II that follows along with their chemical formula and the crystal system.

Table II. The Arsenate Species Validated by the International Mineralogical Association – IMA.

MINERAL	CHEMICAL FORMULA	CRYSTAL SYSTEM
abernathyite	$K[(UO_2)(AsO_4)](H_2O)$	Tetragonal
adamite	$Zn_2(AsO_4)OH$	Orthorhombic
adelite	$CaMg(AsO_4)OH$	Orthorhombic
aerugite	$Ni_{8.5}As_3O_{16}$	Trigonal
agardite-(Ce)	$Ce,Cu_6(AsO_4)_3(OH)_6.3H_2O$	Hexagonal
agardite-(La)	$(La,Ca)Cu_6(AsO_4)_3(OH)_6.3H_2O$	Hexagonal
agardite-(Y)	$(Y,Ca)Cu_6(AsO_4)_3(OH)_6.3H_2O$	Hexagonal
akrochordite	$(Mn,Mg)_5)(AsO_4)_2(OH)_4.4H_2O$	Monoclinic
alarsite	$AlAsO_4$	Trigonal
allactite	$Mn_7(AsO_4)_2(OH)_8$	Monoclinic
alumopharmacosiderite	$KAl_4(AsO_4)_3(OH)_4.6.5H_2O$	Cubic
andyrobertsite	$KCdCu_5(AsO_4)_4[As(OH)_2O_2].2H_2O$	Monoclinic
angelellite	$Fe^{3+}{}_4(AsO_4)_2O_3$	Triclinic
annabergite	$Ni_3(AsO_4)_2.8H_2O$	Monoclinic
arakiite	$(Zn,Mn^{2+})(Mn^{2+},Mg)_{12}(Fe^{3+},Al)_2(As^{3+}O_3)(As^{5+}O_4)_2(OH)_{23}$	Monoclinic
arhbarite	$Cu_2Mg(AsO_4)(OH)_3$	Triclinic
arsenbrackebuschite	$Pb_2Fe^{3+}(AsO_4)_2(OH)$	Monoclinic
arsendescloizite	$PbZn(AsO_4)OH$	Orthorhombic
arseniopleite	$NaCaMn^{2+}(Mn^{2+},Mg)_2(AsO_4)_3$	Monoclinic
arseniosiderite	$Ca_2Fe^{3+}{}_3(AsO_4)_2O_2.3H_2O$	Monoclinic
arsenoclasite	$Mn^{2+}{}_5(AsO_4)_2(OH)_4$	Orthorhombic
arsenocrandallite	$CaAl_3(AsO_4)_2(OH,H_2O)_6$	Trigonal
arsenoflorencite-(Ce)	$CeAl_3(AsO_4)_2(OH,H_2O)_6$	Trigonal
arsenogorceixita	$HBaAl_3(AsO_4)_2(OH,H_2O)_6$	Trigonal
arsenogoyazite	$SrAl_3(AsO_4)_2(OH)_6$	Trigonal

arsenovanmeersscheite	$U(UO_2)_3(AsO_4)_2(OH)_6.4H_2O$	**Orthorhombic**
arsentsumebite	$Pb_2Cu(AsO_4)(SO_4)(OH)$	**Monoclinic**
arsenuranospathite	$Al_{1-x}\square_x[(UO_2)(AsO_4)]_2(H_2O)_{20+3x}F_{1-3x}$	**Tetragonal**
arsenuranylite	$Ca(UO_2)_4(AsO_4)_2(OH)_4.6H_2O$	**Orthorhombic**
arthurite	$CuFe^{3+}{}_2(AsO_4)_2(OH)_2.4H_2O$	**Monoclinic**
asselbornite	$(Pb,Ba)(UO_2)_6(BiO)_4(AsO_4)_3(OH)_{12}.3H_2O$	**Cubic**
atelestite	$Bi_2O(OH)(AsO_4)$	**Monoclinic**
attikaite	$Ca_3Cu_2Al_2(AsO_4)_4(OH)_4.2H_2O$	**Orthorhombic**
auriacusite	$Fe^{3+}Cu^{2+}(AsO_4)O$	**Orthorhombic**
austinite	$CaZn(AsO_4)(OH)$	**Orthorhombic**
barahonite-(Al)	$(Ca,Cu,Na,Fe^{3+},Al)_{12}Al)_{12}Al_2(AsO_4)_8(OH,Cl)_x.nH_2O$	**Monoclinic**
barahonite-(Fe)	$(Ca,Cu,Na,Fe^{3+},Al)_{12}Fe^{3+}{}_2Al)_{12}(AsO_4)_8(OH,Cl)_x.nH_2O$	**Monoclinic**
bariopharmacosiderite	$Ba_{0.5}Fe^{3+}{}_4(AsO_4)_3(OH)_4.6H_2O$	**Cubic**
bayldonite	$PbCu_3(AsO_4)_2(OH)_2$	**Monoclinic**
bearsite	$Be_2(AsO_4)(OH).4H_2O$	**Monoclinic**
bergslagite	$CaBe(AsO_4)(OH)$	**Monoclinic**
berzeliite	$(Ca,Na)_3(Mg,Mn^{2+})_2(AsO_4)_3$	**Cubic**
betpakdalite	$H_8[K(H_2O)_6]_4[Ca(H_2O)_6]_8[Mo^{6+}{}_{32}Fe^{3+}{}_{12}As^{5+}{}_8O_{148}].8H_2O$	**Monoclinic**
beudantite	$PbFe_3[(As,S)O_4]_2(OH,H_2O)_6$	**Trigonal**
bouazzerite	$Bi_6(Mg,Co)_{11}Fe_{14}[AsO_4]_{18}O_{12}(OH)_4(H_2O)_{86}$	**Monoclinic**
bradaczekite	$NaCu_4(AsO_4)_3$	**Monoclinic**
braithwaiteite	$NaCu_5(Ti,Sb)_{202}(AsO_4)[AsO_3(OH)]_2.8H_2O$	**Triclinic**
brandtite	$Ca_2(Mn^{2+},Mg)(AsO_4)_2.2H_2O$	**Monoclinic**
brassite	$Mg(AsO_3OH).4H_2O$	**Orthorhombic**
bukovskyite	$Fe^{3+}{}_2(AsO_4)(SO_4)(OH).7H_2O$	**Triclinic**
bulachite	$Al_2(AsO_4)(OH)_3.3H_2O$	**Orthorhombic**
cabalzarite	$Ca(Mg,Al,Fe)_2(AsO_4)_2(H_2O,OH)_2$	**Monoclinic**
cafarsite	$Ca_8(Ti,Fe^{2+},Fe^{3+},Mn)_{6-7}(As^{3+}O_3)_{12}.4H_2O$	**Cubic**
cahnite	$Ca_2B(AsO_4)(OH)_4$	**Tetragonal**

calcioandyrobertsite	$KCaCu_5(AsO_4)_4[As(OH)_2O_2].2H_2O$	**Orthorhombic/Monoclinic**
camgasite	$CaMg(AsO_4)(OH).5H_2O$	**Monoclinic**
carminite	$PbFe^{3+}{}_2(AsO_4)_2(OH)_2$	**Orthorhombic**
caryinite	$NaCaCa(Mn^{2+},Mg)_2)(AsO_4)_3$	**Monoclinic**
ceruleite	$Cu_2Al_7(AsO_4)_4(OH)_{13}.11.5H_2O$	**Triclinic**
chalcophyllite	$Cu_9Al[(OH)_{12}(SO_4)_{1.5}(AsO_4)_2].18H_2O$	**Trigonal**
chenevexite	$Cu^{2+}{}_2Fe^{3+}{}_2(AsO_4)_2(OH)_4.H_2O$	**Monoclinic**
chernovite-(Y)	$YAsO_4$	**Tetragonal**
chistyakovaite	$Al(UO_2)_2(AsO_4)_2F.6.5H_2O$	**Monoclinic**
chlorophoenicite	$(Mn,Mg)_3Zn_2[AsO_3(OH)](OH)_8$	**Monoclinic**
chudobaite	$(Mg,Zn)_5[AsO_3(OH)]_2(AsO_4)_2.10H_2O$	**Triclinic**
chursinite	$Hg_3(AsO_4)$	**Monoclinic**
clinoclase	$Cu^{2+}{}_3(AsO_4)(OH)_3$	**Monoclinic**
clinomimetite	$Pb_5(AsO_4)_3Cl$	**Monoclinic**
cobaltarthurite	$Co^{2+}Fe^{3+}{}_2(AsO_4)_2(OH)_2.4H_2O$	**Monoclinic**
cobaltaustinite	$CaCoAsO_4(OH)$	**Orthorhombic**
cobaltkoritnigite	$(Co,Zn)(As^{5+}O_3)(OH).H_2O$	**Triclinic**
cobaltlotharmeyerite	$Ca(Co,Fe^{3+},Ni)_2(AsO_4)_2(OH,H_2O)_2$	**Monoclinic**
cobaltneustädtelite	$Bi_2Fe^{3+}Co^{2+}O(OH)_3(AsO_4)_2$	**Triclinic**
cobalttsumcorite	$Pb(Co,Fe^{3+})(AsO_4)_2(H_2O,OH)_2$	**Monoclinic**
conichalcite	$CaCu^{2+}(AsO_4)(OH)$	**Orthorhombic**
coparsite	$Cu_4O_2[(As,V)O_4]Cl$	**Orthorhombic**
cornubite	$Cu^{2+}{}_5(AsO_4)_2(OH)_4$	**Triclinic**
cornwallite	$Cu^{2+}{}_5(AsO_4)_2(OH)_4$	**Monoclinic**
dixenite	$Cu^{1+}\ Mn^{2+}{}_{14}Fe^{3+}(As^{3+}O_3)_5(SiO_4)_2(As^{5+}O_4)(OH)_6$	**Trigonal**
duftite	$PbCu(AsO_4)(OH)$	**Orthorhombic**
dugganite	$Pb_3Zn_3Te^{6+}O_6)(AsO_4)_2$	**Trigonal**
durangite	$NaAl(AsO_4)F$	**Monoclinic**
dussertite	$BaFe^{3+}{}_3\ Fe^{3+}(\ AsO_4)_2(OH,H_2O)_6$	**Trigonal**

erythrite	$Co_3(AsO_4)_2.8H_2O$	**Monoclinic**
esperanzaite	$NaCa_2Al_2(AsO_4)_2F_4(OH).H_2O$	**Monoclinic**
euchroite	$Cu^{2+}{}_2(AsO_4)(OH).3H_2O$	**Orthorhombic**
scorodite	$Fe^{3+}AsO_4.2H_2O$	**Orthorhombic**
eveite	$Mn^{2+}{}_2(AsO_4)(OH)$	**Orthorhombic**
feinglosite	$Pb_2Zn(AsO_4)(SO_4)(OH)$	**Monoclinic**
fermorite	$(Ca,Sr)_5(AsO_4,PO_4)_3(OH)$	**Monoclinic**
ferrarisite	$Ca_5H_2(AsO_4)_{4.9}(H_2O)$	**Triclinic**
ferrilotharmeyerite	$CaZn(Fe^{3+})(AsO_3OH)_2(OH)_3$	**Monoclinic**
ferrisymplesite	$Fe^{3+}{}_3(AsO_4)_2(OH)_3.5H_2O$	**Monoclinic**
filatovite	$K(Al,Zn)_2(As,Si)_2O_8$	**Monoclinic**
flinkite	$Mn^{2+}{}_2Mn^{3+}(AsO_4)(OH)_4$	**Orthorhombic**
fluckite	$CaMn^{2+}H_2(AsO_4)_2.2H_2O$	**Triclinic**
gabrielsonite	$PbFe^{2+}AsO_4(OH)$	**Orthorhombic**
gaitite	$Ca_2Zn(AsO_4)_2.2H_2O$	**Triclinic**
gallobeudantite	$PbGa_3[(AsO_4),(SO_4)]_2(OH)_6$	**Trigonal**
gartrellite	$PbCuFe^{3+}(AsO_4)_2[(H_2O)(OH)]$	**Triclinic**
gasparite-(Ce)	$(Ce,La,Nd)AsO_4$	**Monoclinic**
geigerite	$Mn^{2+}{}_5(As^{5+}O_4)_2(As^{5+}O_3OH)_2.10H_2O$	**Triclinic**
gerdtremmelite	$ZnAl_2(AsO_4)(OH)_5$	**Triclinic**
gilmarite	$Cu_3(AsO_4)(OH)_3$	**Triclinic**
goudeyite	$(Al,Y)Cu^{2+}{}_6(AsO_4)_3(OH)_6.3H_2O$	**Hexagonal**
graulichite-(Ce)	$CaFe^{3+}{}_3(AsO_4)_2(OH)_6$	**Trigonal**
grischunite	$NaCa_2Mn^{2+}{}_4(Mn^{2+}Fe^{3+})(AsO_4)_6.2H_2O$	**Orthorhombic**
guanacoite	$Cu_2Mg_2(Mg_{0.5}Cu_{0.5})(OH)_4(H_2O)_4(AsO_4)_2$	**Monoclinic**
guèrinite	$Ca_5H_2(AsO_4)_4.9H_2O$	**Monoclinic**
haidingerite	$Ca(AsO_3OH).H_2O$	**Orthorhombic**
hedyphane	$Pb_3Ca_2(AsO_4)_3Cl$	**Hexagonal**
heinrichite	$Ba(UO_2)(AsO_4)_2.10\text{-}12H_2O$	**Tetragonal**

helmutwincklerite	$PbZn_2(AsO_4)_2.2H_2O$	Triclinic
hematolite	$(Mn^{2+},Mg,Al)_{15}(AsO_3)(AsO_4)_2(OH)_2$	Trigonal
holdenite	$(Mn^{2+},Mg)_6Zn_3(AsO_4)_2(SiO_4)(OH)_8$	Orthorhombic
hörnesite	$Mg_3(ASO_4)_2.8H_2O$	Monoclinic
hügelite	$Pb_2(UO_2)_3(AsO_4)_2(OH)_4.3H_2O$	Monoclinic
irhtemite	$Ca_4NgH_2(AsO_4)_4.4H_2O$	Monoclinic
jamesite	$Pb_2Zn_2Fe^{3+}{}_5(AsO_4)_5O_4$	Triclinic
jarosewichite	$Mn^{2+}{}_3Mn^{3+}(AsO_4)(OH)_6$	Orthorhombic
johillerite	$Na(Mg,Zn)_3Cu^{2+}(AsO_4)_3$	Monoclinic
johnbaumite	$Ca_5AsO_4)_3(OH)$	Hexagonal
juanitaite	$(Cu,Ca,Fe)_{10}Bi(AsO_4)_4(OH)_{11}.H_2O$	Tetragonal
kaatialaite	$Fe(H_2AsO_4)_3.5H_2O$	Monoclinic
kahlerite	$Fe^{2+}(UO_2)_2(AsO_4)_2.10\text{-}12H_2O$	Tetragonal
kaňkite	$Fe^{3+}(AsO_4).3.5H_2O$	Monoclinic
karibibite	$Fe^{3+}2As^{3+}4(O,OH)_9$	Orthorrhombic
kemmlitzite	$SrAl_3[(As,S)O_4]_2(OH,H_2O)_6$	Trigonal
keyite	$Cu^{2+}{}_3(Zn,Cu^{2+})_4Cd_2(AsO_4)_6(H_2O)_2$	Monoclinic
kolfanite	$Ca_2Fe^{3+}{}_3O_2(AsO_4)_3.2H_2O$	Monoclinic
kolicite	$Mn^{2+}{}_7Zn_4(AsO_4)_3.2H_2O$	Orthorrhombic
koritnigite	$Zn(AsO_3)(OH).H_2O$	Triclinic
köttigite	$Zn_3(AsO_4)_2.8H_2O$	Monoclinic
kraisslite	$Mn_{24}Zn_4(AsO_4)(SiO_4)_8(OH)_{12}$	Hexagonal
krautite	$Mn^{2+}(AsO_3)(OH).H_2O$	Monoclinic
kuznetsovite	$Hg^{1+}2Hg^{2+}Cl(AsO_4)$	Cubic
lammerite	$Cu_3(AsO_4)_2$	Monoclinic
lavendulan	$NaCaCu^{2+}5(AsO_4)_4Cl.5H_2O$	Orthorrhombic
lazarenkoite	$(Ca,Fe^{2+})Fe^{3+}As^{3+}{}_3O_7.3H_2O$	Orthorrhombic
legrandite	$Zn_2(AsO_4)(OH).H_2O$	Monoclinic
leiteite	$ZnAs^{3+}{}_2O_4$	Monoclinic

lemanskiite	$NaCaCu_5(AsO_4)_4Cl.5H_2O$	**Tetragonal**
leogangite	$Cu_{10}(AsO_4)(SO_4)(OH)_6.8H_2O$	**Monoclinic**
lindackerite	$Cu_5(AsO_3OH)_2(AsO_4)_2.10H_2O$	**Monoclinic**
liroconite	$Cu^{2+}{}_2Al(AsO_4)(OH)_4.4H_2O$	**Monoclinic**
liskeardite	$(Al,Fe^{3+})_3(AsO_4)(OH)_6.5H_2O$	**Monoclinic/Orthorrhombic**
lotharmeyerite	$Ca(Zn,Mn^{3+})_2(AsO_4)_2(OH,H_2O)_2$	**Monoclinic**
luetheite	$Cu^{2+}{}_2Al_2(AsO_4)_2(OH)_4.H_2O$	**Monoclinic**
lukhranite	$CaCuFe^{3+}(AsO_4)_2[(H_2O)(OH)]$	**Triclinic**
magnesiochlorophoenicite	$(Mg,Mn)_3Zn_2(AsO_4)(OH,O)_6$	**Monoclinic**
mahnertite	$(Na,Ca)(Cu^{2+}{}_3(AsO_4)_2Cl.5H_2O$	**Tetragonal**
manganberzeliite	$(Ca,Na)_3(Mn^{2+},Mg)_2(AsO4)_3$	**Cubic**
manganohörnesite	$(Mn,Mg)_3(AsO_4)_2.8(H_2O)$	**Monoclinic**
manganolotharmeyerite	$Ca(Mn^{3+},Zn)_2(AsO_4)_2(OH,H_2O)_2$	**Monoclinic**
manganostibite	$(Mn^{2+}, Fe^{2+})_7(SbO_4)(AsO_4,SiO_4O_4)$	**Orthorrhombic**
mansfieldite	$AlAsO_4.2H_2O$	**Orthorrhombic**
mapimite	$Zn_2Fe^{3+}{}_3(AsO_4)_3(OH)_4.10H_2O$	**Monoclinic**
mawbyite	$Pb(Fe^{3+},Zn)_2(AsO_4)_2(OH,H_2O)_2$	**Monoclinic**
maxwellite	$NaFe^{3+}(AsO_4)F$	**Monoclinic**
mcgovernite	$Zn_3(Mn^{2+},Mg)_{42}(As^{3+}O_3)_2(As^{5+}O_4)_4(SiO_4)_8(OH)_{40}$	**Trigonal**
mcnearite	$NaCa_5H_4(AsO_4)_5.4H_2O$	**Triclinic**
medenbachite	$Bi_2Fe^{3+}(Cu,Fe^{2+})(O,OH)_2(OH)_2(ASO_4)_2$	**Triclinic**
metaheinrichite	$Ba(UO_2)_2(AsO_4)_2.8H_2O$	**Tetragonal**
metakhalerite	$Fe^{2+}(UO_2)_2(AsO_4).8H_2O$	**Tetragonal**
metakirchheimerite	$Co(UO_2)_2(AsO_4)_2.8H_2O$	**Tetragonal**
metaköttigite	$(Zn,Fe^{3+})(Zn,Fe^{3+},Fe^{2+})_2(AsO_4)_2.8(H_2O,OH)$	**Triclinic**
metalodèvite	$Zn(UO_2)_2.10H_2O$	**Tetragonal**
metanovácëkite	$Mg(UO_2)_2(AsO_4)_2.4\text{-}8H_2O$	**Tetragonal**
metauranospinite	$Ca(UO_2)_2(AsO_4)_2.8H_2O$	**Tetragonal**
metazeunerite	$Cu^{2+}(UO_2)_2(AsO_4)_2.8H_2O$	**Tetragonal**

mimetite	$Pb_5(AsO_4)_3Cl$	Hexagonal
mixite	$BiCu^{2+}{}_6(AsO_4)_3(OH)_6.3H_2O$	Hexagonal
natrobetkdalite	$(Na,Ca)_3Fe^{3+}{}_2(As_2O_4)(MoO_4)_6.15H_2O$	Monoclinic
natropharmacosiderite	$(Na,K)_2Fe^{3+}{}_4(AsO_4)_3(OH)_5.7H_2O$	Cubic
natrouranospinite	$(Na_2,Ca)(UO_2)_2(AsO_4)_2.5H_2O$	Tetragonal
neustädtelite	$Bi_2Fe^{3+}Fe^{3+}O_2(OH)_2(AsO_4)_2$	Triclinic
nickelaustinite	$CaNiAsO_4(OH)$	Orthorrhombic
nickellotharmeyerite	$Ca(Ni,Fe^{3+})_2(AsO_4)_2(H_2O,OH)_2$	Monoclinic
nickelschneebergite	$BiNi_2(AsO_4)_2[(H_2O)(OH)]$	Monoclinic
nicknichite	$Na_{0,8}Ca_{0,4}Cu_{0,4}(Mg,Fe^{3+})_3(AsO_4)_3$	Monoclinic
novácëkite I	$Mg(UO_2)_2(AsO_4)_2.12H_2O$	Cubic
novácëkite II	$Mg(UO_2)_2(AsO_4)_2.10H_2O$	Monoclinic
nyholmite	$Cd_3Zn_2(AsO_4)_2(HASO_4)_2.4H_2O$	Monoclinic
o'danielite	$Na(Zn,Mg)_3H_2(AsO_4)_3$	Monoclinic
ogdensburgtite	$Ca_2Fe^{3+}{}_4(Zn,Mn)^{2+}(AsO_4)_4(OH)_6.6H_2O$	Orthorrhombic
ojuelaite	$ZnFe^{3+}{}_2(AsO_4)_2(OH)_2.4H_2O$	Monoclinic
olivenite	$Cu^{2+}{}_2(AsO_4)(OH)$	Monoclinic
orthowalpurgite	$(UO_2)Bi_4O_4(AsO_4)_2.2H_2O$	Orthorrhombic
paganoite	$NiBi^{3+}As^{5+}O_5$	Triclinic
parabrandtite	$Ca_2Mn^{2+}(AsO_4)_2.2H_2O$	Triclinic
paradamite	$Zn_2(AsO_4)(OH)$	Triclinic
paranaiite-(Y)	$Ca_2Y(AsO_4)(WO_4)_2$	Tetragonal
parascorodite	$Fe^{3+}AsO_4.2H_2O$	Hexagonal
parasymplesite	Fe 2+3(AsO4)2.8H2O	Monoclinic
parwelite	$(Mn,Mg)_5Sb^{5+}As^{5+}SiO_{12}$	Monoclinic
paulmooreite	$Pb_2As^{3+}{}_2O_5$	Monoclinic
petewilliamsite	$(Ni,Co)_{30}(As_2O_7)15$	Monoclinic
pharmacolite	$CaHAsO_4.2H_2O$	Monoclinic
phaunoxite	$Ca_3(AsO_4).2H_2O$	Triclinic

philipsbornite	$PbAl_3(AsO_4)_2(OH,H_2O)_6$	Trigonal
philipsburgite	$(Cu,Zn)_3(AsO_4)_2(OH)_6.H_2O$	Monoclinic
pitticite	(Fe,AsO_4,SO_4,H_2O)	Amorphous
plumboagardite	$(Pb,REE,Ca)Cu_6(AsO_4)_3(OH)_6.3H_2O$	Hexagonal
pradetite	$CoCu_4(AsO_3OH)_2(AsO_4)_2.9H_2O$	Triclinic
preisingerite	$Bi_3O(OH)(AsO_4)_2$	Triclinic
prosperite	$CaZn_2H(AsO_4)_2OH$	Monoclinic
pushcharovskite	$Cu(AsO_3OH).H_2O$	Triclinic
radovanite	$Cu_2Fe^{3+}(AsO_4)(As^{3+}O_2OH)_2.H_2O$	Orthorrhombic
rappoldite	$Pb(Co,Ni)_2(AsO_4)_2.2H_2O$	Triclinic
rauenthalite	$Ca_3(AsO_4)_2.10H_2O$	Triclinic
reinerite	$Zn_3(As^{3+}O_3)_2$	Orthorrhombic
retzian-(Ce)	$Mn^{2+}{}_2Ce(AsO_4)(OH)_4$	Orthorrhombic
retzian-(La)	$(Mn^{2+},Mg)_2(La,Ce,Nd)(AsO_4)(OH)_4$	Orthorrhombic
richelsdorfite	$Ca_2Cu^{2+}{}_3Sb^{5+}(AsO_4)_4Cl(OH)_6.6H_2O$	Monoclinic
rollandite	$Cu_3(AsO_4)_2.4H_2O$	Orthorhombic
rooseveltite	$BiAsO_4$	Monoclinic
roselite	$Ca_2Co(AsO_4)_2.2H_2O$	Monoclinic
roselite-beta	$Ca_2(Co^{2+},Mg)(AsO_4)_2.2H_2O$	Triclinic
rösslerite	$MgHAsO_4.7H_2O$	Monoclinic
rouseite	$Pb_2Mn^{2+}(As^{3+}O_3)_2.2H_2O$	Triclinic
Sahlinite	$Pb_{14}(AsO_4)_2O_9Cl_4$	Monoclinic
sailaufite	$(Ca,Na,\square)Mn^{3+}{}_3(AsO_4)_2(CO_3)O_2.3H_2O$	Monoclinic
sainfeldite	$Ca_5(AsO_4)_2(AsO_3OH)_2.4H_2O$	Monoclinic
sarkinite	$Mn^{2+}{}_2(AsO_4)(OH)$	Monoclinic
sarmientite	$Fe^{3+}{}_2(AsO_4)(SO_4)(OH).5H_2O$	Monoclinic
schlegelite	$Bi_7O_4(MoO_4)_2(AsO_4)$	Orthorrhombic
schneebergite	$BiCo_2(AsO_4)_2[(H_2O)(OH)]$	Monoclinic
schneiderhönite	$Fe^{2+}Fe^{3+}{}_3As^{3+}{}_5O_{13}$	Triclinic

schultenite	$PbHAsO_4$	**Monoclinic**
seelite	$Mg(UO_2)_2(As^{3+}O_3)_{1.4}(As^{5+}O_4)_{0.6}.7H_2O$	**Monoclinic**
segnitite	$PbFe^{3+}{}_3H(AsO_4)_2(OH)$	**Trigonal**
sewardite	$CaFe^{3+}{}_2(AsO_4)_2(OH)_2$	**Orthorrhombic**
shubnikovite	$Ca_2Cu^{2+}{}_8(AsO_4)_6Cl(OH).7H_2O$	**Orthorrhombic (?)**
smolyaninovite	$Co_3(Fe^{3+})_2(AsO_4)_4.11H_2O$	**Orthorrhombic**
sterlinghillite	$Mn^{2+}{}_3(AsO_4)_2.4H_2O$	**Monoclinic**
dstranskiite	$Zn_2Cu^{2+}(AsO_4)_2$	**Triclinic**
dtranshimirite	$Cu^{2+}{}_8(AsO_4)_4(OH)_4.5H_2O$	**Monoclinic**
svabite	$Ca_5(AsO_4)_3F$	**Hexagonal**
svenekite	$CaH_4(AsO_4)_2$	**Triclinic**
symplesite	$Fe^{2+}{}_3(AsO_4)_2.8H_2O$	**Triclinic**
synadelphite	$(Mn^{2+},Mg,Ca,Pb)_9(As^{3+}O_3)(As^{3+}O_4)_2(OH)_9.2H_2O$	**Orthorrhombic**
talmessite	$Ca_2Mg(AsO_4)_2.2H_2O$	**Monoclinic/Triclinic**
tetrarooseveltite	$Bi^{3+}AsO_4$	**Tetragonal**
theisite	$Cu_5Zn_5[(As,Sb)O_4]_2(OH)_{14}$	**Trigonal**
theoparacelsite	$Cu_3(OH)_2As_2O_7$	**Orthorrhombic**
thometzekite	$PbCu_2(AsO_4)_2.2H_2O$	**Triclinic**
tilasite	$CaMg(AsO_4)F$	**Monoclinic**
trippkeite	$Cu^{2+}As^{3+}{}_2O_4$	**Tetragonal**
tröggerite	$(H_3O)[(UO_2)(AsO_4)](H_2O)_3$	**Tetragonal**
tsumcorite	$Pb(Zn,Fe^{3+})_2(AsO_4)_2(H_2O,OH)_2$	**Monoclinic**
turneaureite	$Ca_5[(As,P)O_4]_3Cl$	**Hexagonal**
tyrolite	$CaCu^{2+}{}_5(AsO_4)_2(CO_3)(OH)_4.6H_2O$	**Orthorrhombic**
uramarsite	$NH_4(UO_2)AsO_4.3H_2O$	**Tetragonal**
uranospinite	$Ca(UO_2)_2(AsO_4)_2.10H_2O$	**Tetragonal**
urusovite	$Cu[AlAsO_5]$	**Monoclinic**
vajdakite	$(MoO_2)_2(H_2O)_2As^{3+}2O_5.H_2O$	**Monoclinic**
villyaellenite	$(Mn^{2+},Ca,Zn)_5(AsO_4)_2[AsO_3(OH)]_2.4H_2O$	**Monoclinic**

vladimirite	$Ca_5H_2(AsO_4)_4.5H_2O$	**Monoclinic**
wallkilldellite	$Ca_4Mn^{2+}_6(AsO_4)_4(OH)_8.18H_2O$	**Hexagonal**
wallkilldellite-Fe	$(Ca,Cu)_4Fe_6[(As,Si)O_4]_4(OH)_8.18H_2O$	**Hexagonal**
walpurgite	(BiO)4(UO2)(AsO4)2.2H2O	**Triclinic**
warikhanite	$Zn_3(AsO_4)_2.2H_2O$	**Triclinic**
weilite	$Ca(AsO_3OH)$	**Triclinic**
wendwilsonite	$Ca_2(Mg,Co)(AsO_4)_2.2H_2O$	**Monoclinic**
wilhelmkleinite	$ZnFe^{3+}_2(AsO_4)_2(OH)_2$	**Monoclinic**
xanthiosite	$Ni_3(AsO_4)_2$	**Monoclinic**
yanomamite	$InAsO_4.2H_2O$	**Orthorrhombic**
yazganite	$NaMg(Fe^{3+})_2(AsO_4)_3.H_2O$	**Monoclinic**
yukonite	$Ca_2Fe^{3+}_2(AsO_4)_3(OH)_4.4H_2O$	**Orthorrhombic**
yvonite	$Cu(AsO_3OH).2H_2O$	**Triclinic**
zálesiite	$CaCu_6[(AsO_4)_2(AsO_3OH)(OH)_6].3H_2O$	**Hexagonal**
zdnëkite	$NaPbCu_5(AsO_4)_4Cl.5H_2O$	**Tetragonal**
zeunerite	$Cu^{2+}(UO_2)_2(AsO_4)_2.10\text{-}16H_2O$	**Tetragonal**
zincgartrellite	$Pb(Zn,Fe,Cu)_2(AsO_4)_2(H_2O,OH)_2$	**Triclinic**
zincolivenite	CuZnAsO4(OH)	**Orthorrhombic**
Zincroselite	$Ca_2Zn(AsO_4)_2.2H_2O$	**Monoclinic**

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SOUTHER BRAZILIAN JOURNAL OF CHEMISTRY

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VOLUME NINETEEN, NUMBER NINETEEN DECEMBER 2011

AUTHOR INDEX / ÍNDICE DE AUTORES

Ahmad, Aftab 17

Bhandari, Anil 17

Dalloul, Hany M. M. 25

Freitas, Darcson Vieira 85

Husain, Asif 17

Ionescu, Lavinel G. 1, 59, 85

Kumar, Kakarla Raman 35

Neves, Paulo Cesar Pereira 85

Ram, Veerma 17

Ravindranath, Laxmana Rao Khrisna Rao 35

Prasad, Aluru Raghavendra Guru 35

Seshagiri, Vahi 35

Srilalitha, Vinnakota 35