International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 11 Issue 9 ǁ September 2023 ǁ PP. 134-143

A Review of the Physicochemical Approach to the Analysis of 2-Thiohydantoin

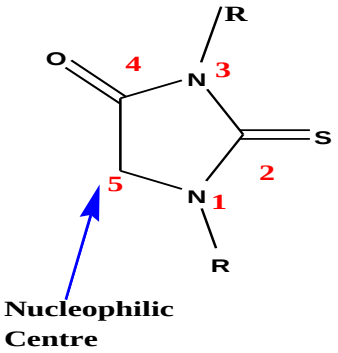
Prashant A. Gotmare[1*] and Dr. Sanjay V. Kolhe[2]
[1,2] *Department of Chemistry, Shri Shivaji Arts, Commerce and Science college, Akot, Dist.Akola-444101, (Maharashtra), India*
[*] *Corresponding Author E-Mail:prashantpatilchem2763@gmail.com*

ABSTRACT
Thiohydantoins and their derivatives are the most important sulfer anolog, which acts as a intermediate to making various drugs. Thiohydantoin attracted enormous attention of all researchers in the worldwide. In this review article, we focused our interest on the most important methods for the synthesis of 2-thiohydantoin derivatives, determine spectral data of them. We explored their physicochemical properties like density, viscosity, ultrasonic velocity, intermolecular free path, adiabatic compressibility etc.
Key words; *Thiohydantoin, density, physicochemical parameter etc*

Date of Submission: 07-09.2023 Date of acceptance: 20-09-2023

I. INTRODUCTION

Thiohydantoin is a sulfur analog, which having most important feature. In general, 2-thiohydantoin molecules contribute to drug discovery as they possess attractive features of their structures by owning a stereogenic center at position 5 as well as the feasibility of their synthesis. The number of groups like phenyl, benzyl etc. are attached to position 5 which increases the reactivity of thiohydantoin. [1-4]



2-Thiohydantoins are important class of compounds within pharmaceutical industries and exist in various pharmacologically active molecules that possess important bioactivities like antimicrobial [5], antiviral [6], fungicides [7], antiparasite, [8] and anticancer [9].
In 2017, Zuo and coworkers reported indoline thiohydantoin as a potent androgen receptor (AR) antagonist [10].
Buchynskyy *et al.* prepared the thiohydantoins 1-benzyl-3-aryl-2-thiohydantoins which acts as a anti-Trypanosoma brucei agents [11].
These molecules contribute to drug discovery and the importance of these compounds in bioactive, we have decided to synthesize the thiohydantoin and investigated its physicochemical properties because these properties explain the nature and reactivity towards drugs.

II. METHODS AND MATERIALS

2.1 General

The purity of resultant compound was check by using TLC. The IR spectra were recorded in KBr by using FT-(IR Perkin Elmer - Spectrum RX-IFTIR).Mass spectra were recorded on mass spectrometer while ^{1}HNMR were recorded on FT NMR Spectrometer (Bruker Avance Neo 500 MHz). Data are reported as

chemical shifts in parts per million downfield from TMS, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and assignment, respectively.

2.2 Synthesis

Aurone is a starting material was prepared from Chalcone. A mixture of aurone (0.01 M) and N-substituted thiourea (0.01 M) were taking in round bottom flask along with 10% KOH and Ethanol as a solvent. A reaction mixture was reflux about 3 hr. After 3 hr. cool the mixture and poured in to ice cold water and filter it by using suction pump. The final product recrystallized with Ethanol.

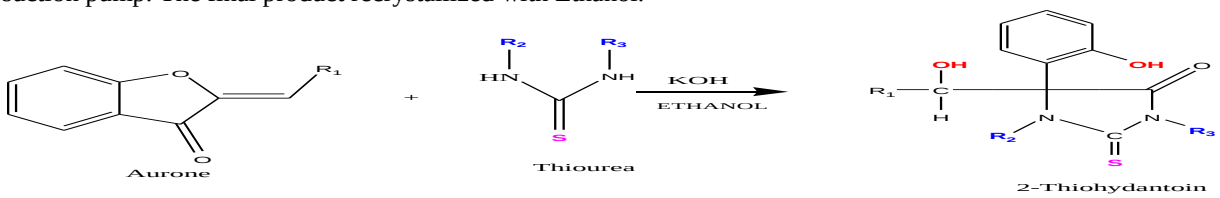


Table-01

Sr. no.	Compounds	R_1	R_2	R_3
1.	1a	C_7H_7	H	C_6H_5
2.	1b	C_4H_3O	C_6H_5	C_6H_5

2.2.1 Preparation of 5-(hydroxyl (p-tolyl)methyl)-5-(2-hydroxyphenyl)-3-phenyl-2-thioxoimidazolidin-4-one (1a)

2-(4-methylbenzylidene)benzofuran-3(2H)-one (0.01M) reflux with N-phenyl thiourea (0.01M) in presence of 10% KOH and appropriate ethanol solvent up to 3 hours. After completion of reaction, cooled the mixture and poured in to ice cold water. The solid product obtained which was filter and washed with dilute HCl and water. The product was crystallized by using ethanol.

Mol. Formula $C_{23}H_{20}O_3N_2S$: yellowish Crystalline solid, m.p 246^oC , yield 71%, Elemental analysis (%):C,68.30; H,4.98; N,6.93; O,11.87; S,7.93; IR (KBr cm-1) 3551.78 (O-H), 3414.58 (N-H), 1711.05 (C=O), 1638.5 (Ar C-H),ESI-MS[M+H]+ Calculated for $C_{23}H_{20}O_3N_2S$ *m/z* 404.12, 405.12.406,14, 407.12 ; ^{1}H-NMR (500 MHz, DMSO): δ 2.27 (3H, s), 5.50 (1H, s), 6.64 (1H, m, *J* = 8.3, 1.3, 0.5 Hz), 7.03 (1H, m, *J* = 8.0, 7.7, 1.3 Hz),

2.2.2 Preparation of 5-(furan-2-yl(hydroxy)methyl)-5-(2-hydroxyphenyl)-1,3-diphenyl-2-thioxoimidazolidin-4-one (1b)

2-(furan-2-ylmethylene)benzofuran-3(2H)-one (0.01M) reflux with N,N dIphenyl thiourea (0.01M) in presence of 10% KOH and appropriate ethanol solvent up to 3 hours. After completion of reaction, cooled the mixture and poured in to ice cold water. The solid product obtained which was filter and washed with dilute HCl and water. The product was crystallized by using ethanol.

Mol. Formula $C_{26}H_{20}O_4N_2S$: faint red Crystalline solid, m.p 238^oC, yield 73%, Elemental analysis (%):C,68.41; H,4.42; N,6.14; O,14.02; S,7.02, IR (KBr cm-1) 3616.5 (O-H), 3368.1 (N-H), 1720.42(C=O), 1436 (Ar C=C), ESI-MS[M+H]+ Calculated for $C_{26}H_{20}O_4N_2S$: *m/z* 456.10, 457.14, 458.16. ^{1}H-NMR (500 MHz, DMSO) : δ 5.86 (1H, s), 6.18-6.34 (2H, 6.24 (dd, *J* = 3.4, 1.1 Hz), 6.28 (dd, *J* = 3.4, 1.8 Hz)), 6.72 (1H, m, *J* = 8.3, 1.3, 0.5 Hz), 6.97-7.14 (2H, 7.04 (m, *J* = 8.0, 7.7, 1.3 Hz).

2.3 Physicochemical Properties of Thiohydantoin Derivatives*:*

Physico-chemical properties are essential indicators used in hazard, exposure and risk assessments, hence in this experiments the physico-chemical parameters were studied in different solvents, and different concentrations**,** with temperature 20 degree.

Density and Viscosity:

In fluid dynamics, viscosity is useful parameter to determine the thickness or thinness of any given fluid. It also useful to find out the intermolecular interaction between solute and solvent. Density is useful to measure the distance between two particles in a given fluid. Viscosity and density are the most important characteristics of a fluid. The density and viscosity were taken in different solvent like DMSO and DMF with different concentration and temperature at 20 degree. Densities of the solutions were measured using a 25 mL specific gravity bottle and the weight of the liquid was measured using an electronic balance (Model Shimadzu

AX200).The viscosity were measured by Ostwald viscometer and time by digital stop watch. The formula for viscosity, .

$$\eta_y = \eta_w \frac{d_y \times d_y}{d_w \times d_w}$$

Acoustic parameters:

The acoustic parameters were studied as follows.

Ultrasonic velocity was useful to determine the strength of material that is elastic moduli (measures the resistance of the material to elastic) as well as particle interaction in solution hence most of the scientist are attracted toward these parameters. Here ultrasonic parameters was measured using a single-crystal Interferometer (Mittal Enterprises) operating at 1MHz with an accuracy of ±1.0m/s.
The acoustic parameters were determine using fallowing formulae

a) Adiabatic compressibility (β):
In compression the heat is not absorb or release but the internal energy increases which effects on work done.

$$\beta = \frac{1}{\rho v^2}$$

b) Intermolecular free path length (L_f):
The mean free path or average distance between collisions for a molecule. In the liquid the mean free path is much probably less than one molecular diameter. There are 750 times more molecules in a given volume than there were in the gas state.

$$L_f = K\beta^{1/2},$$

Where K is the temperature dependent Jacobson's constant

c) Acoustic impedance (Z):
The acoustic impedance is the ratio of sound pressure to volume flow. Acoustic impedances explain, how much resistance an ultrasound beam encounters as it passes through a liquid.

$$Z = \rho V,$$

d) Relative association (RA):
It is a property which explain the interaction of molecules in liquid as well as measure extent of association in molecules.

$$RA = \left(\frac{\rho}{\rho_0}\right)\left(\frac{v_0}{v}\right),$$

e) Ultrasonic attenuation (α/f^2):
Ultrasound intensity is continuously reduces by the cohesive forces present in liquid molecules.

$$\alpha/f^2 = \frac{8\pi^2\eta}{\rho v^3}$$

f) Relaxation time (τ):
It is related to both the elasticity and viscosity of the material. Relaxation time means rate of relaxation.it is inversely proportional to velocity.

$$\tau = \frac{4\eta}{3\rho v^2}$$

III. RESULTS AND DISCUSSION

The physico-chemical properties of thiohydantoin derivatives were given below

3.1 Compound 1a

Solvent: DMF Temp. 20^0 C

Conc. (M) Mol/dm^3	Density(ρ) Kg/m^{-3}	Viscosity(η) $\times 10^3$ NSm^{-2}	Ultasonic velocity(v) m/s	Refractive Index
0.000	970.76	0.94577	1415.0	1.4305
0.001	971.04	1.22993	1513.92	1.4306
0.002	971.84	1.29764	1592.82	1.4308
0.003	972.24	1.34708	1600.28	1.4309
0.004	972.92	1.48921	1648.72	1.4310

0.005	973.68	1.62742	1704.81	1.4314

Ultrasonic parameters in DMF

Conc. (M) Mol/dm^3	Adiabetic compressibility (β) $\times 10^{-10}$	Intermolecular Free path (L_f) $\times 10^{-11}$	Acoustic impedances (Z) $\times 10^{6}$	Relative Association (RA)	Ultrasonic Attenuation $(\frac{\propto}{f^2})$ $\times 10^{-14}$	Relaxation Time (τ) $\times 10^{-13}$
0.000	5.14488	4.62265	1.37362	1.00000	2.71240	6.48780
0.001	4.49320	4.32011	1.47007	0.93492	2.87928	7.36845
0.002	4.05574	4.10443	1.54796	0.88934	2.60620	7.01720
0.003	4.01636	4.08445	1.55585	0.88556	2.66674	7.21384
0.004	3.78119	3.96307	1.60407	0.86014	2.69393	7.50798
0.005	3.53371	3.83118	1.65994	0.83250	2.66074	7.68355

Solvent: DMSO Temp. 20^0 C

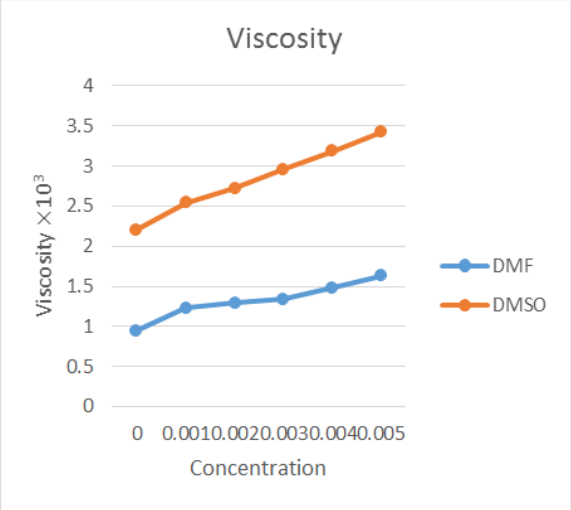
Conc. (M) Mol/dm^3	Density(ρ) Kg/m^{-3}	Viscosity(η) $\times 10^3$ NSm^{-2}	Ultasonic velocity(v) m/s	Refractive Index
0.000	1126.28	2.2026	1553.0	1.4740
0.001	1128.27	2.5426	1563.24	1.4742
0.002	1128.96	2.7287	1584.54	1.4745
0.003	1129.42	2.9642	1596.48	1.476
0.004	1129.86	3.1874	1608.74	1.4748
0.005	1130.32	3.4217	1618.56	1.4749

Ultrasonic parameters in DMSO

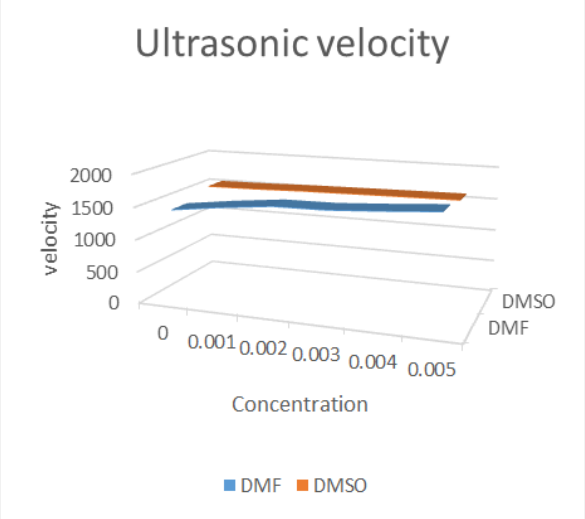
Conc. (M) Mol/dm^3	Adiabetic compressibility (β) $\times 10^{-10}$	Intermolecular Free path (L_f) $\times 10^{-11}$	Acoustic impedances (Z) $\times 10^{6}$	Relative Association (RA)	Ultrasonic Attenuation $(\frac{\propto}{f^2})$ $\times 10^{-14}$	Relaxation Time (τ) $\times 10^{-13}$
0.000	3.68138	3.910414	1.749110	1	4.11835	10.8115
0.001	3.62690	3.881372	1.763756	0.995204	4.653046	12.2956
0.002	3.52778	3.828032	1.788882	0.982427	4.792002	12.8354
0.003	3.47390	3.798622	1.803096	0.975477	5.087577	13.7297
0.004	3.41987	3.768928	1.817650	0.968420	5.344458	14.5337
0.005	3.37707	3.745324	1.829490	0.962936	5.631233	15.4071

GRAPHICAL REPRESENTATION

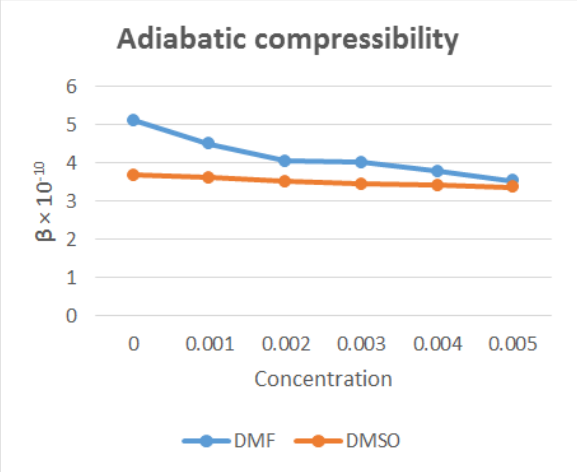
1. Viscosity



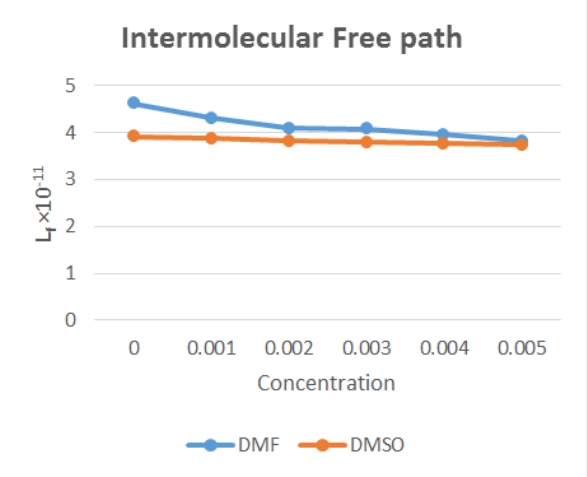
2. Ultrasonic velocity



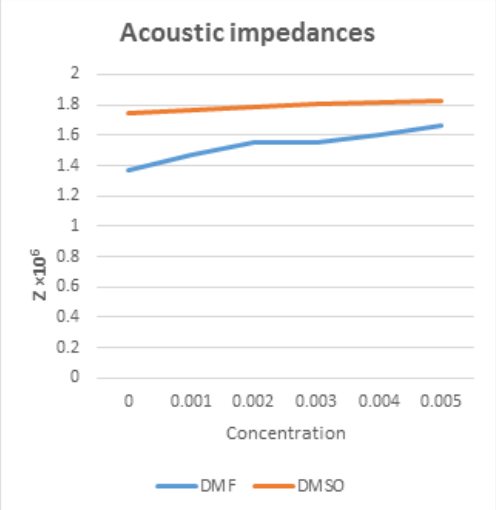
3. Adiabatic compressibility (β)



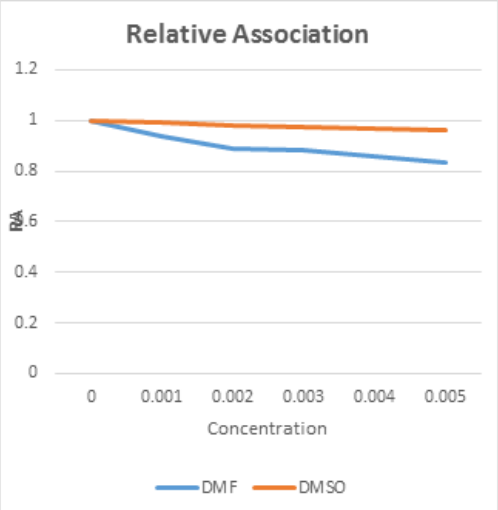
4. Intermolecular Free path (L_f)



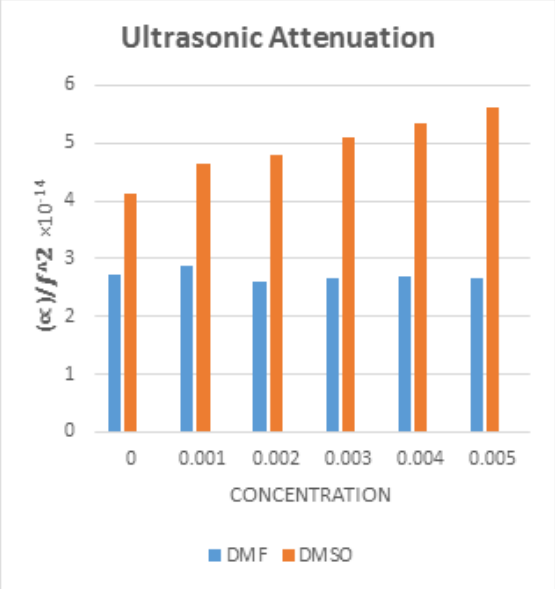
5. Acoustic impedances (Z)



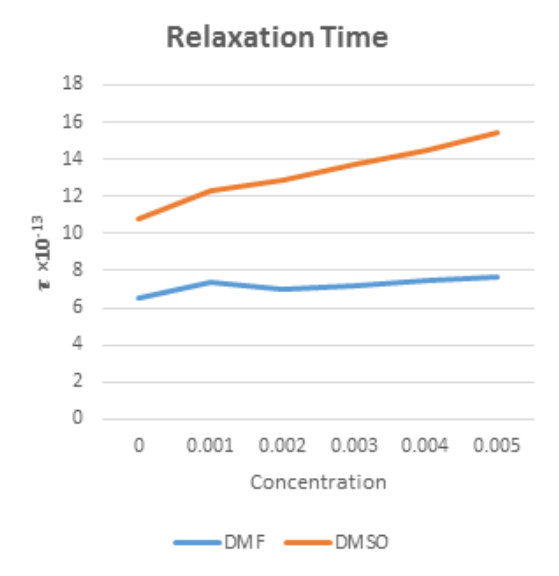
6. Relative Association (RA)



7. Ultrasonic Attenuation($\frac{\propto}{f^2}$)



8. Relaxation Time (τ)



3.2 Compound 1b

Solvent: DMF Temp. 20^0 C

Conc. (M) Mol/dm^3	Density(ρ) Kg/m^{-3}	Viscosity(η) ×10^3 NSm^{-2}	Ultasonic velocity(v) m/s	Refractive Index
0.000	970.76	0.94577	1415.0	1.4305
0.001	971.24	1.19423	1462.53	1.4306
0.002	971.86	1.27421	1513.20	1.4308
0.003	972.41	1.29946	1572.24	1.4309
0.004	972.91	1.32764	1618.51	1.4310
0.005	973.42	1.48742	1666.71	1.4312

Ultrasonic parameters in DMF

Conc. (M) Mol/dm^3	Adiabetic compressibility (β) × 10^{-10}	Intermolecular Free path (L_f) ×10^{-11}	Acoustic impedances (Z) ×10^6	Relative Association (RA)	Ultrasonic Attenuation ($\frac{\propto}{f^2}$) ×10^{-14}	Relaxation Time (τ) ×10^{-13}
0.000	5.14488	4.62265	1.37362	1.00000	2.71240	6.48783
0.001	4.81352	4.47145	1.42047	0.96797	3.10024	7.66460
0.002	4.49368	4.32034	1.47062	0.93615	2.98467	7.63453
0.003	4.16018	4.15692	1.52886	0.90151	2.71210	7.20799
0.004	3.92369	4.03705	1.57467	0.87619	2.53868	6.94566
0.005	3.69810	3.91928	1.6224	0.85129	2.60316	7.33418

Solvent: DMSO Temp. 20^0 C

Conc. (M) Mol/dm^3	Density(ρ) Kg/m^{-3}	Viscosity(η) ×10^3 NSm^{-2}	Ultasonic velocity(v) m/s	Refractive Index
0.000	1126.28	2.2026	1553.0	1.4740
0.001	1128.62	2.2733	1590.24	1.4744

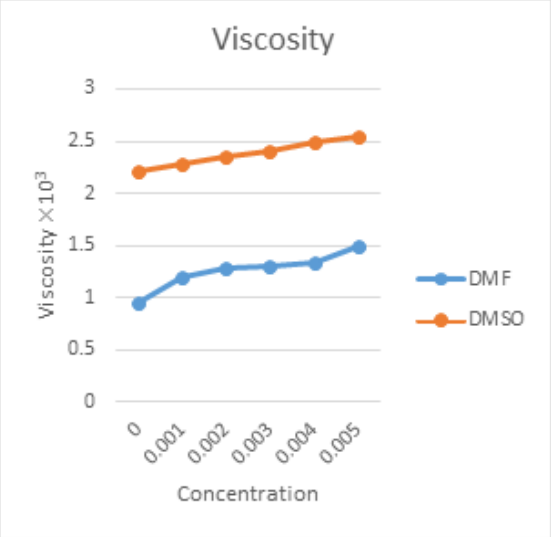
0.002	1129.04	2.3475	1598.72	1.4746
0.003	1129.92	2.4082	1604.57	1.4748
0.004	1130.42	2.4976	1615.54	1.4750
0.005	1131.28	2.5489	1624.82	1.4751

Ultrasonic parameters in DMSO

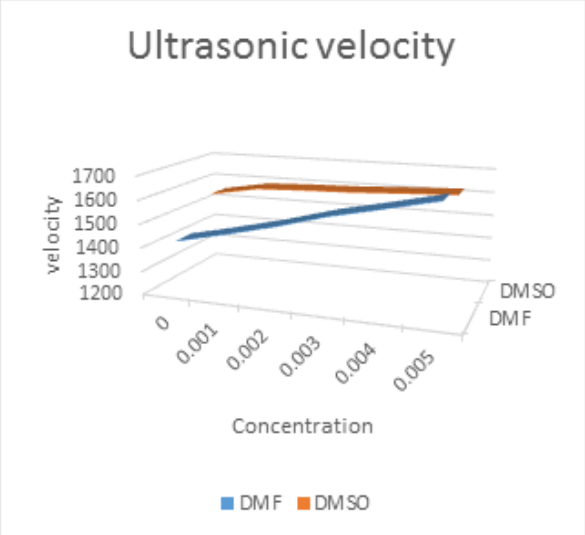
Conc. (M) Mol/dm^3	Adiabetic compressibility (β) $\times 10^{-10}$	Intermolecular Free path (L_f) $\times 10^{-11}$	Acoustic impedances (Z) $\times 10^{6}$	Relative Association (RA)	Ultrasonic Attenuation $(\frac{\propto}{f^2})$ $\times 10^{-14}$	Relaxation Time (τ) $\times 10^{-13}$
0.000	3.68138	3.910414	1.749110	1.00000	4.11835	10.8115
0.001	3.50370	3.81488	1.79477	0.97861	3.95066	10.61994
0.002	3.46534	3.79393	1.80501	0.97378	4.01354	10.84651
0.003	3.43744	3.77863	1.81303	0.97098	4.06928	11.03739
0.004	3.38941	3.75214	1.82623	0.96482	4.13313	11.28720
0.005	3.34826	3.72929	1.83812	0.96004	4.14301	11.37917

GRAPHICAL REPRESENTATION

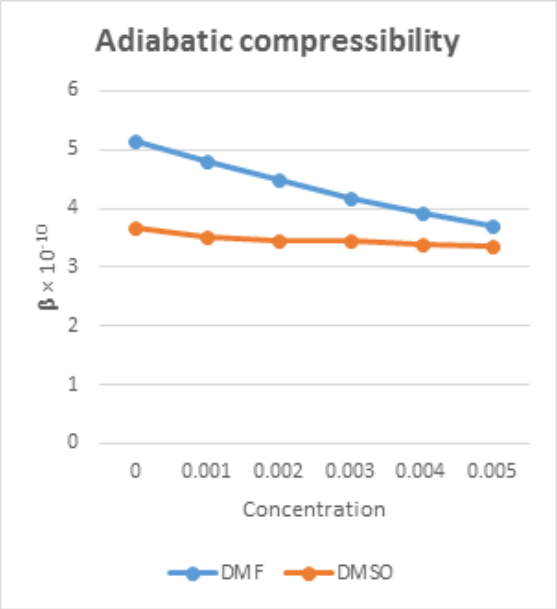
1. Viscosity



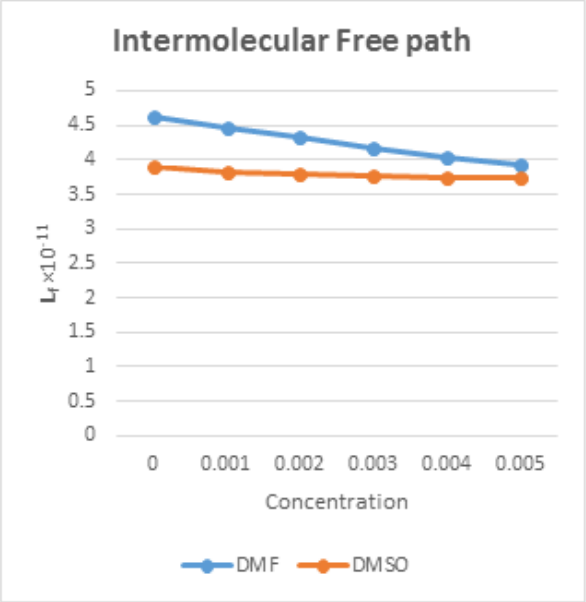
2. Ultrasonic velocity



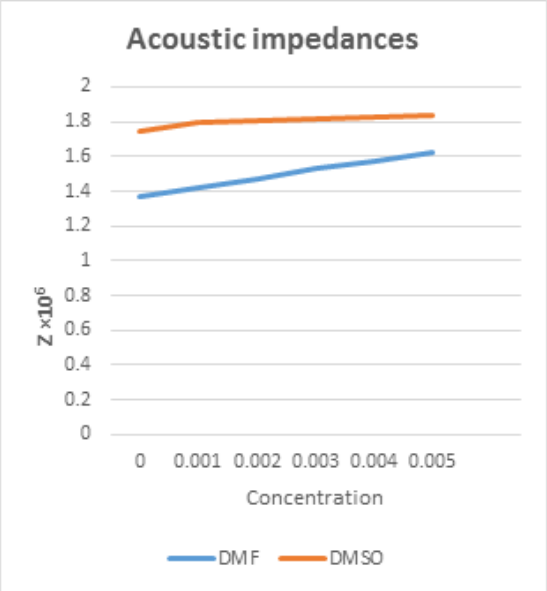
3. Adiabatic compressibility (β)



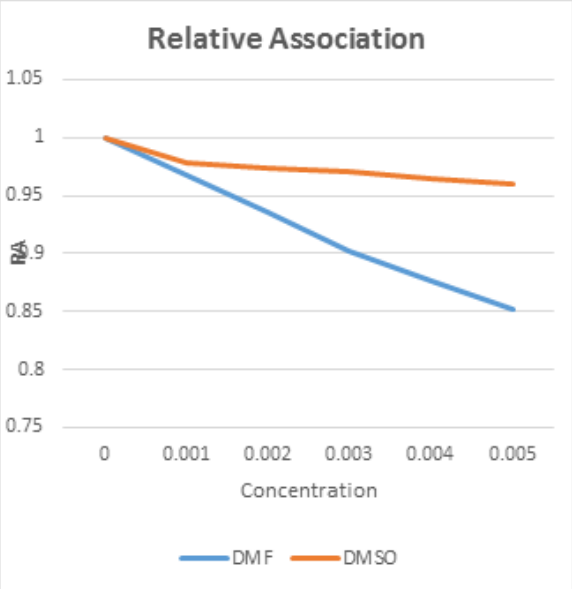
4. Intermolecular Free path (L_f)



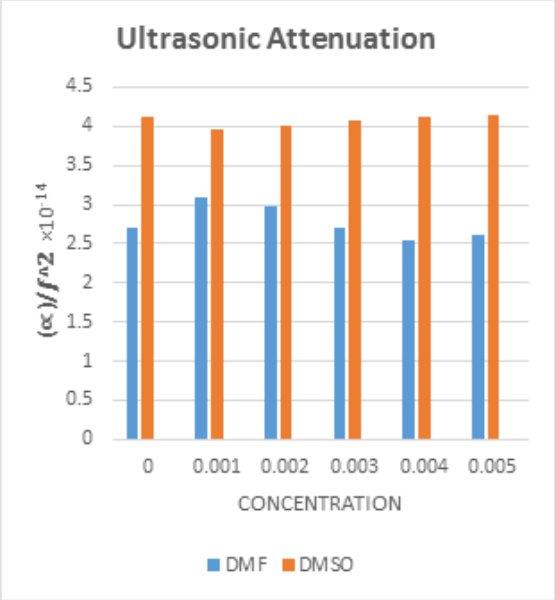
5. Acoustic impedances (Z)



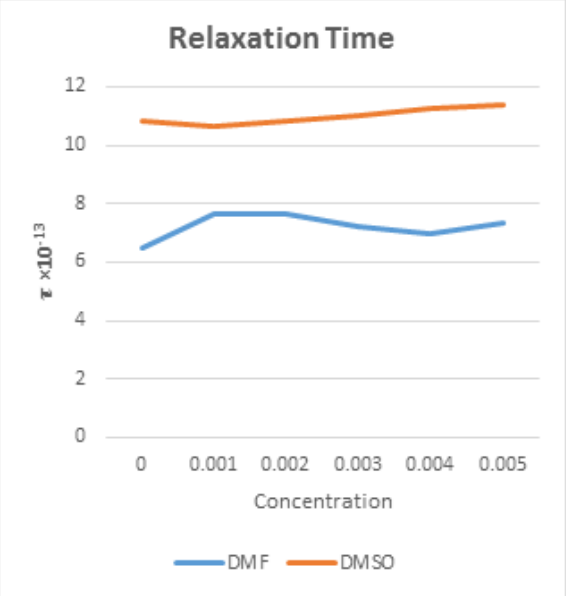
6. Relative Association (RA)



7. Ultrasonic Attenuation($\frac{\propto}{f^2}$)



8. Relaxation Time (τ)



Physico-chemical meaning that they are dependent on, or produced by, the combined actions of physical and chemical attributes. The physicochemical properties can be useful to manufacturing, food and beverages, and other chemical or biological product-based industries. The most important properties of an ideal drug are: effectiveness, safety, and selectivity. Here Thiohydantoin acts as good drugs for Cancer. It shows properties like antimicrobial, anticancer, antimalarial etc. The Thiohydantoin shows different physico-chemical properties in different solvent as well as different concentration which indicated that the different interaction of thiohydantoin molecules in different solvents.

In above experiment clear that the ρ, η and U values increased linearly with concentration (C), due to specific molecular interactions. The variation of adiabatic compressibility with concentration. Here the concentration increases and adiabatic compressibility decreases due to formation of large cluster molecules. The aggregation of solvent molecules around the solute, supporting solute-solvent interaction. The intermolecular free path is a clear evidence for strong interactions between solvent and compound molecules in DMSO and DMF. Such interactions may be due to Ionic-dipole, dipole-dipole, dipole-induced-dipole interactions.

Relative association decreases with increase in concentration for a thiohydantoin in DMSO and DMF. This may be due to the breaking up of the associated solvent molecules on addition of solute which indicates the structure-forming tendencies of solutes decreases at higher concentration in both the solvents. In DMF solvent the thiohydantoin molecules shows weak association than DMSO and less tendency to form structure. If relaxation time (τ) increasing with concentration which supports structure making capacity of the solute. Here the concentration of thiohydantoin increases which increase structure making capacity in DMSO than DMF.

IV. CONCLUSION

The synthesized Thiohydantoin might show different effect in DMSO and DMF. The good correlations are observed between density, viscosity and other physicochemical parameters and concentration in different solvents .The linear or nonlinear increases or decreases of acoustical parameters indicate the existence of strong molecular interactions in the solutions that depend on the interaction between solute and solvent molecules and structure formation tendency of solute. The polarity of DMSO is slightly higher than DMF due to which DMSO shows more structure making capacity than DMF.

ACKNOWLEDGEMENT:

We are thankful to Principal Dr. S.H. Pande sir and Department of chemistry Shri Shivaji Arts Commerce and Science College Akot for providing lab equipment's. Also thankful to Shri D. M. Jakate for his cooperation. We are also thankful to CIL and SAIF, Panjab University, Chandigarh for providing spectral data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Prashant A. Gotmare : https://orcid.org/0000-0002-0869-4313

REFERENCES

[1]. A.A. El-Barbary, A.I. Khodair, E.B. Pedersen, C. Nielsen, J. Med. Chem., **1994**, 37, 73–77. **[crossref], [Google Scholar], [Publisher]**

[2]. S. Cortes, Z.K. Liao, D. Watson, H. Kohn, J. Med. Chem., **1985**, 28, 601-606. **[crossref],[Google Scholar], [Publisher]**

[3]. S. Süzen, B. T. Demircigil, E. Buyukbingol, S.A. Özkan. New Journal of Chemistry, **2003**, 27, 1007–1011. **[crossref], [Google Scholar], [Publisher]**

[4]. B. Gregg, K. Golden, J. Quinn, D. Tymoshenko, W. Earley, D. Maynard, D. Razzano, W. Rennells, J.Butcher, J. Comb. Chem. ,**2007**, 9, 1036–1040. **[crossref], [Google Scholar], [Publisher]**

[5]. J. Marton, J. Enisz, S. Hosztafi, T. Timar, J. Agric. Food Chem., **1993**, 41, 148–152.[CrossRef], [Google Scholar], [Publisher]

[6]. J.R. Chérouvrier, F. Carreaux, J.P. Bazureau. Molecules, **2004**, 9, 867−875. [CrossRef], [Google Scholar], [Publisher]

[7]. K. Kobyłka, G. Żuchowski, W. Tejchman, K.K. Zborowski, J. Mol. Model., **2019**, 25, 268. [CrossRef], [Google Scholar], [Publisher]

[8]. A. Buchynskyy, J.R. Gillespie, Z.M. Herbst, R.M. Ranade, F.S. Buckner, M.H. Gelb, ACS Med. Chem. Lett., **2017**, 8, 886–891. [CrossRef], [Google Scholar], [Publisher]

[9]. A.M. Al-Obaid, H.I. El-Subbagh, A.I. Khodair, M. M. Elmazar, Anti-Cancer Drugs, **1996**, 7, 873−880. [CrossRef], [Google Scholar], [Publisher]

[10]. M. Zuo, X. Xu, Z. Xie, R. Ge, Z. Zhang, Z. Li, J. Bian, European Journal of MedicinalChemistry, **2017**, 125,1002–1022. [CrossRef], [Google Scholar], [Publisher]

[11]. S. Süzen, B. T. Demircigil, E. Buyukbingol, S.A. Özkan. New Journal of Chemistry, **2003**, 27, 1007–1011. [CrossRef], [Google Scholar], [Publisher]