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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2023, Vol. 39, No.(5):
Pg. 1264-1271

Design of Novel Thiohydantoin Derivatives and Exploration Their Physico-Chemical Parameters

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http://dx.doi.org/10.13005/ojc/390520

(Received: August 28, 2023; Accepted: October 11, 2023)

ABSTRACT

Thiohydantoin analogues was heterocyclic non-aromatic five membered cyclic compounds obtained from aurones derivatives. In this article, we synthesized novel thiohydantoin derivatives and exploration of physicochemical parameters like density, viscosity, ultrasonic velocity, intermolecular free path, adiabatic compressibility etc. The structural elucidation of resultant compounds was done on the basis ^{1}HNMR, IR, Mass etc. The present study revealed that, thiohydantoin analogues shows more structure making capacity in DMSO than DMF.

Keyword: 2-Thiohydantoin, Physicochemical properties, Viscosity, Refractive index.

INTRODUCTION

2-Thiohydantoin is an important class of compounds within chemistry. It is a sulphur derivative of hydantoin which is obtained by replacing the oxygen atom of carbonyl group by sulphur. Thiohydantoin is a intermediate to synthesis of many drugs[1-12]. In solid state thiohydantoin shows π-π stacking, hydrogen bonding which is important in pharmaceutical industries.[13-16]

One of the most important things that drew the attention of researchers to synthesized thiohydantoin due to wide range of application like anti-inflammatory, anti-ulcer[17], antifungal, antibacterial[18], HIV[19], hypolipidemic[20], antimutagenic[21], against HSV[22], anticarcinogenic[23], on tuberculosis[24] and pesticide[25], derivatives of thiohydantoin are also used as a fungicide[26], N-phenyl derivative of 2-Thiohydantion shows antiparasitic activity against Trypanosoma brucei species[27].

K.H. Chikhalia *et al.,*[28] reported a series of thiohydantoin derivatives having ethyl linked 3,4-dimethoxyphenylethyl thiourea derivatives with styryl bridge possessing antibacterial properties as well as anti HIV activity. Abubshait S.A.[29] synthesized some 2-thiohydantoin drivatives and reported anticancer and antimicrobial properties against *Gram-positive* and *Gram-negative* bacteria. Kolhe S.V.[30] prepared 2-thiohydantoin derivatives by mixing aurones derivative with suitable thiourea by refluxing with KOH and ethaonol as a solvent and reported antimicrobial properties using microbes such as

Escherichia coli, *Staphylococcus aureus*, *Klebsilla, pseudomons*. Saied E.M. *et al.,*[31] synthesized 1, 3-disubstituted 2-thiohydantoin analogues and reported anti-inflammatory activity. Gotmare P.A. *et al.,*[32] synthesized 2-Thiohydantoin analogous and reported physicochemical properties.

Literature survey reveals that, substituted 2-thiohydantoin were found to be very instrumental in controlling the diseases in the field of medicine, agriculture. The present study has been undertaken to synthesis some new 2-thiohydantoin analogues and test them for their physico-chemical properties.

MATERIALS AND METHODS

All chemical s and reagents used in this research were commercially sourced and of analytical grade. 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-FTIR). Mass spectra were recorded on mass spectrometer while ^{1}HNMR were recorded on FT NMR Spectrometer (Bruker Avance Neo 500 MHz).

General Procedure for synthesis of 2-Thiohydantoin:-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 for 3 hours. After this period, the mixture was poured in to ice cold water and filter it by using suction pump. The final product recrystallized with Ethanol.

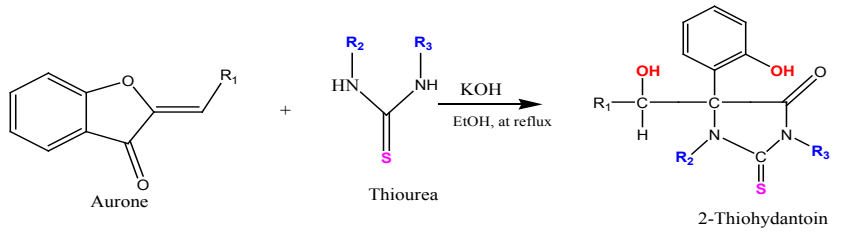


Table: 1

Sr. No	Compounds	R_1	R_2	R_3
1	1a	C_4H_3O	C_6H_5	C_6H_5
2	1b	C_6H_4Cl	C_6H_5	H

Preparation of 5-(hydroxyl(4-methoxyphenyl) methyl)-5-(2-hydroxyphenyl)-1,3-diphenyl-2-thioxoimidazolidin-4-one(1a)

2-(4-methoxybenzylidene)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 $C_{29}H_{24}O_4N_2S$: Yellowish Crystalline solid. m. p. 258°C yield 70%, Elemental analysis (%): C, 70.14; H, 4.87; N, 5.64; S, 6.46; O, 12.89; IR (KBr cm^{-1}) 3617.5 (O-H), 3016 (=CH), 1614 (C=N), 1438 (Ar C=C), ESI-MS[M+H]$^+$ Calculated for $C_{29}H_{24}O_4N_2S$: m/z 496.15, 497.15, 498.15; ^{1}H-NMR (500 MHz, DMSO) 3.76 (s, 3H), 5.68 (s, 1H), 6.86-7.38 (m, *J*=8.4,1.1 Hz, 11H), 7.43 7.70 (m, 6H).

Preparation of 5-((4-chlorophenyl)(hydroxy) methyl)-5-(2-hydroxyphenyl)-3-phenyl-2-thioxoimidazolidin-4-one (1b)

2-(4-chlorobenzylidene)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 $C_{22}H_{17}O_3N_2SCl$: faint yellowish Crystalline solid, m.p. 228°C, yield 74%, Elemental analysis (%): C,62.19; H,4.03; N, 6.59; O, 11.30; S, 7.55;Cl,8.34. IR (KBr cm^{-1}) 3616.5 (O-H), 3268.1 (N-H), 1682(Amide C=O), 1436 (Ar C=C), 755.2 (C-Cl); ESI-MS[M+H]$^+$ Calculated for $C_{22}H_{17}O_3N_2SCl$: m/z 424.06, 426.06, 425.07, 427.07. ^{1}H-NMR (500 MHz, DMSO) 5.58 (s, 1H), 7.04 (m, *J*=8.0,7.8 Hz, 1H), 7.48 (m, *J*=8.3,1.6,0.5 Hz, 8H), 8.02(m, *J*=8.0,1.4 Hz, 1H).

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°C.

Density and Viscosity

Viscosity and density are affected by temperature. Which implies, for any given fluid, when the temperature is raised, the particle in it start to move apart, bringing down fluid density thereby the value of viscosity also falls down or fluid becomes less viscous. The density and viscosity were taken in different solvent like DMSO and DMF with different concentration and temperature at 20 degree. The density was measured by using pycnometer and viscosity by Ostwald viscometer using fallowing formula.

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

Acoustic parameters

Ultrasonic velocity was useful to determine the strength of material 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

Adiabatic compressibility (β)

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

Intermolecular free path length (L_f)

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

Where *K* is the temperature dependent Jacobson's constant

Acoustic impedance (*Z*) is given as follows:

$$Z = \rho V,$$

Relative association (RA)

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

Ultrasonic attenuation (α/f^2)

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

Relaxation time (τ)

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

RESULTS AND DISCUSSION:

The physico-chemical properties of thiohydantoin derivatives were given below

Compound 1a
Solvent: DMF Temperature 20°C

Conc. (M) Mol/dm^3	Density(ρ)Kg/m^{-3}	Viscosity(∝)×10^3 NSm^{-2}	Ultasonic velocity(v) m/s	Refractive Index
0.000	970.76	0.94577	1415	1.4305
0.001	972.46	1.19646	1434.4	1.422
0.002	972.94	1.2428	1558.8	1.424
0.003	973.88	1.30469	1603.2	1.425
0.004	974.68	1.40073	1632	1.426
0.005	976.2	1.5086	1694.8	1.426

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 (α/f^2)×10^{-14}	Relaxation Time(τ)×10^{-13}
0.000	5.14488	4.622658	1.373625	1.000000	2.7124	6.4869
0.001	4.99790	4.556149	1.394896	0.988202	3.28825	7.9731
0.002	4.22993	4.191512	1.516618	0.909788	2.66007	7.0094
0.003	3.99502	4.073461	1.561324	0.885446	2.56637	6.9498
0.004	3.85210	3.999935	1.590677	0.870535	2.60784	7.1944
0.005	3.56635	3.848718	1.654463	0.839585	2.50397	7.1737

Solvent: DMSO Temperature 20 °C

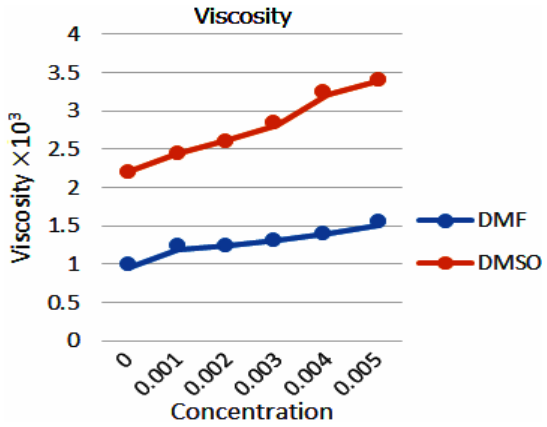
Conc. (M)Mol/dm^3	Density(ρ)Kg/m^{-3}	Viscosity($\propto$)×10^3 NSm^{-2}	Ultasonic velocity(v)m/s	Refractive Index
0.000	1126.28	2.2026	1553.0	1.4740
0.001	1129.04	2.4404	1566.2	1.4742
0.002	1129.86	2.6248	1594.6	1.4744
0.003	1130.12	2.8067	1604.0	1.4748
0.004	1130.98	3.2115	1734.2	1.4751
0.005	1131.06	3.3924	1788.2	1.4752

Ultrasonic parameters in DMSO

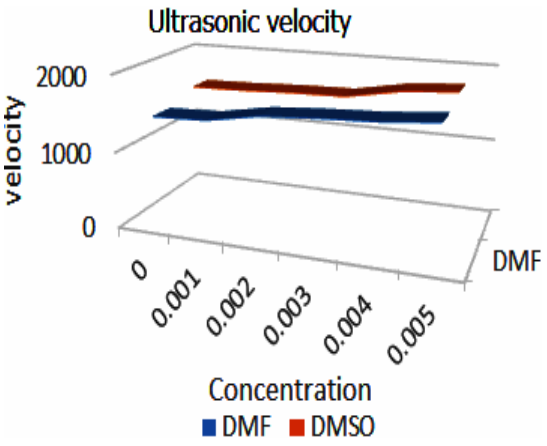
Conc. (M) Mol/dm^3	Adiabetic compressibility (β)×10^{-10}	Intermolecular Free path(L_f)×10^{-11}	Acoustic impedances(Z)×10^6	Relative Association(RA)	Ultrasonic Attenuation^{-14} ($\propto/f^2$)×10^{10}	Relaxation Time(τ)×10^{-13}
0.000	3.68138	3.910414	1.749110	1	4.11835	10.8115
0.001	3.61074	3.872715	1.768302	0.994001	4.43771	11.7489
0.002	3.48074	3.802360	1.801674	0.977024	4.51924	12.1817
0.003	3.43897	3.779470	1.812872	0.971591	4.74645	12.8695
0.004	2.94000	3.494549	1.961345	0.899266	4.29442	12.5891
0.005	2.76492	3.388900	2.022560	0.872172	4.13954	12.5063

Graphical representation

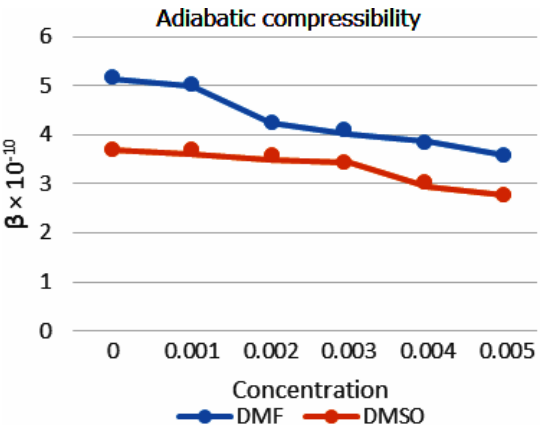
1. Viscosity



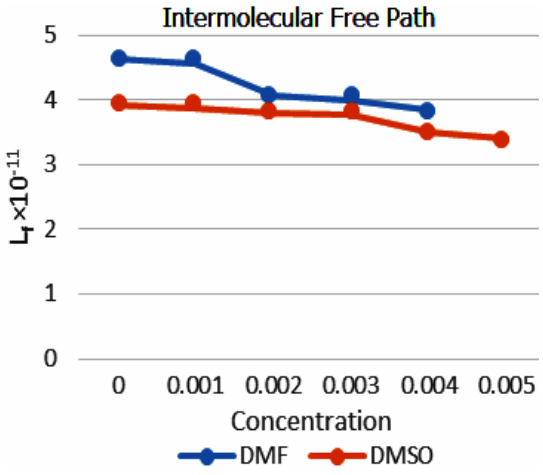
2. Ultrasonic velocity



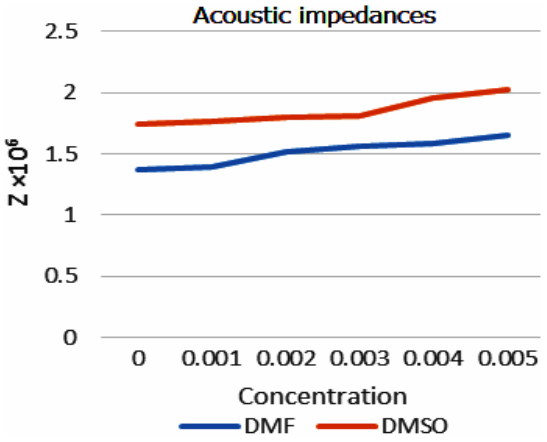
3. Adiabatic compressibility (β)



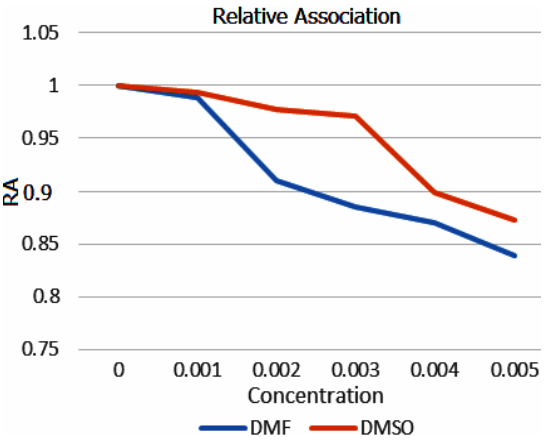
4. Intermolecular Free path (L_f)



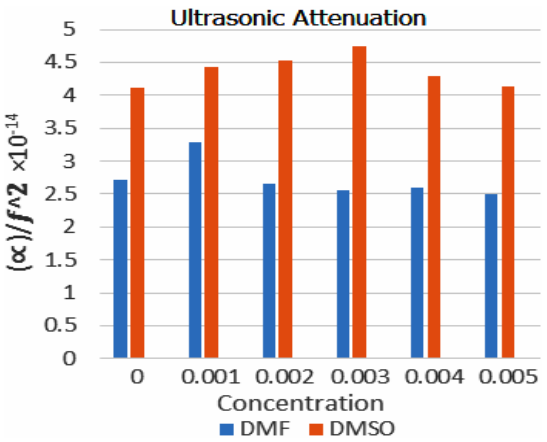
5. Acoustic impedances (Z)



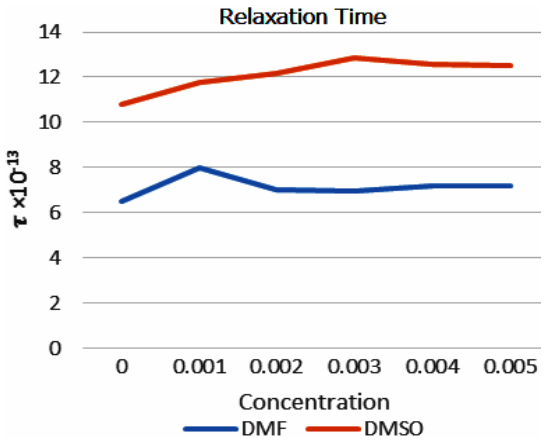
6. Relative Association (RA)



7. Ultrasonic Attenuation(α/f^2)



8. Relaxation Time (τ)



Compound 2a
Solvent: DMF Temperature 20°C

Conc. (M)Mol/dm^3	Density(ρ)Kg/m^{-3}	Viscosity($\propto$)×103 NSm-2	Ultasonic velocity(v) m/s	Refractive Index
0.000	970.76	0.94577	1415	1.4305
0.001	971.68	1.15997	1438.72	1.4306
0.002	971.91	1.22426	1452.81	1.4308
0.003	972.18	1.30241	1464.86	1.4309
0.004	972.82	1.42826	1506.91	1.4311
0.005	973.52	1.51763	1585.68	1.4312

Ultrasonic parameters in DMF

Conc. (M) Mol/dm^3	Adiabetic compressibility^{-10} (β)×10	Intermolecular Free path(L_f)×10^{-11}	Acoustic impedances (Z)×10^6	Relative Association(RA)	Ultrasonic Attenuation($\propto/f^2$)×10^{14}	Relaxation Time(τ)×10^{-13}
0.000	5.14488	4.622658	1.373625	1.000000	2.71240	6.4878
0.001	4.97192	4.544431	1.397975	0.984445	3.16187	7.6897
0.002	4.87479	4.499826	1.412000	0.975128	3.24019	7.9574
0.003	4.79359	4.462190	1.424107	0.967375	3.16000	8.3243
0.004	4.52681	4.336246	1.465952	0.941000	3.38424	8.6206
0.005	4.08530	4.119357	1.543691	0.894898	3.08406	8.2666

Solvent: DMSO Temperature 20°C

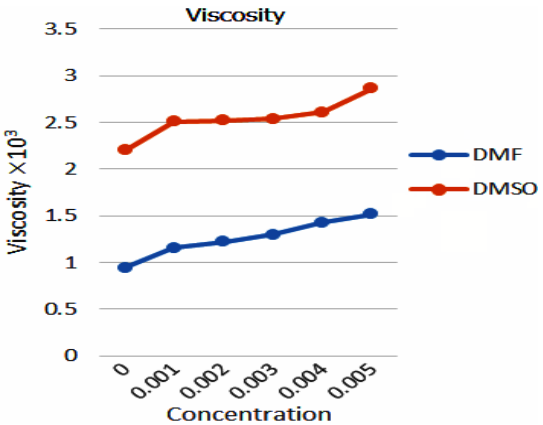
Conc. (M)Mol/dm^3	Density(ρ)Kg/m^{-3}	Viscosity(∝)×10^3 NSm^{-2}	Ultasonic velocity(v) m/s	Refractive Index
0.000	1126.28	2.2026	1553.0	1.4740
0.001	1127.26	2.5128	1609.0	1.4742
0.002	1127.98	2.5247	1612.22	1.4746
0.003	1128.48	2.5382	1614.20	1.4747
0.004	1128.82	2.6141	1618.70	1.4748
0.005	1129.72	2.8663	1622.0	1.4750

Ultrasonic parameters in DMSO

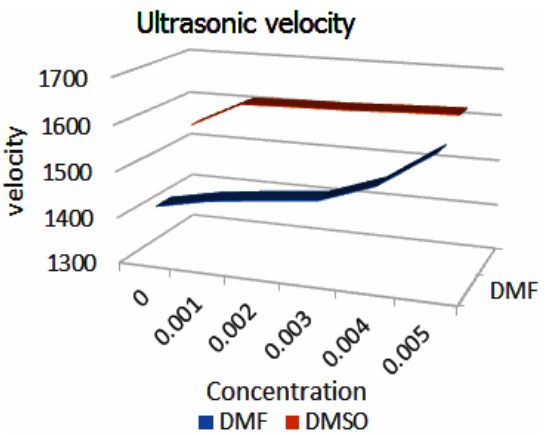
Conc. (M) Mol/dm^3	Adiabetic compressibility (β)×10^{-10}	Intermolecular Free path (L_f)×10^{-11}	Acoustic impedances (Z)×10^6	Relative Association (RA)	Ultrasonic Attenuation (∝/f^2)×10^{-14}	Relaxation Time (τ)×10^{-13}
0.000	3.68138	3.910414	1.749110	1	4.11835	10.8115
0.001	3.426603	3.772675	1.813761	0.966035	4.22099	11.4808
0.002	3.410751	3.763938	1.818551	0.964721	4.21303	11.4817
0.003	3.400881	3.758488	1.821592	0.963965	4.21802	11.5094
0.004	3.380980	3.747475	1.827220	0.961575	4.30687	11.7846
0.005	3.645538	3.738360	1.832405	0.960384	4.39528	12.0510

Graphical representation

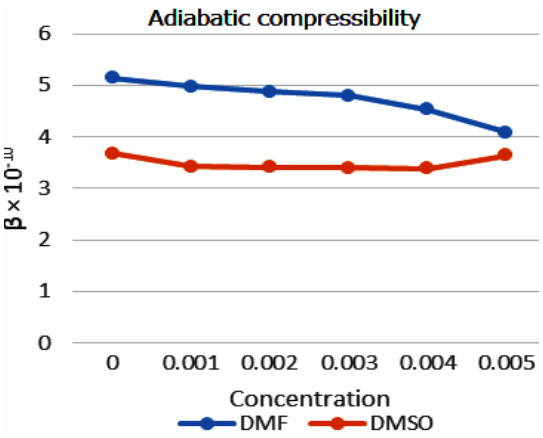
1. Viscosity



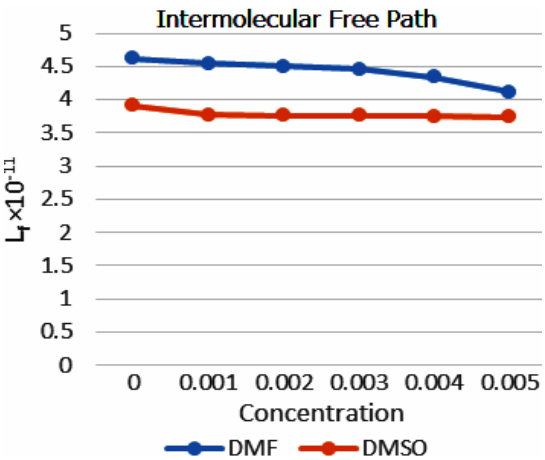
2. Ultrasonic velocity



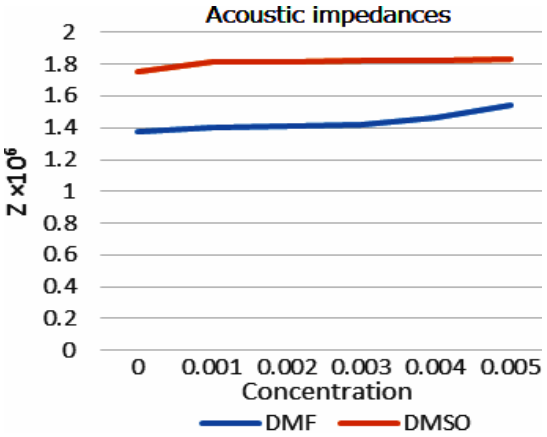
3. Adiabatic compressibility (β)



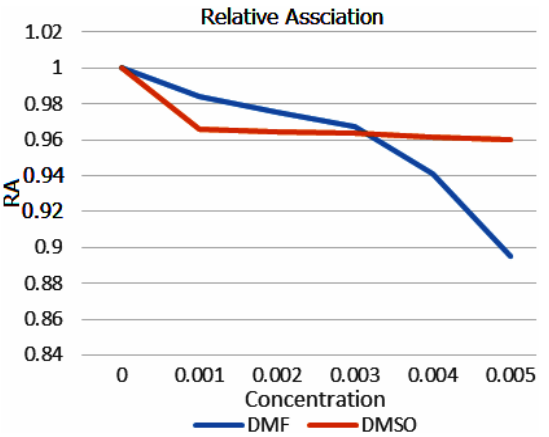
4. Intermolecular Free path (L_f)



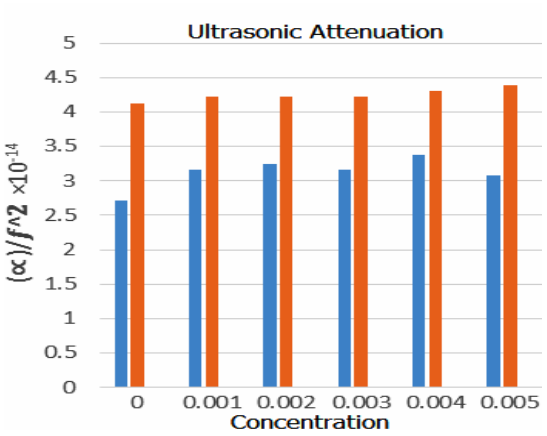
5. Acoustic impedances (Z)



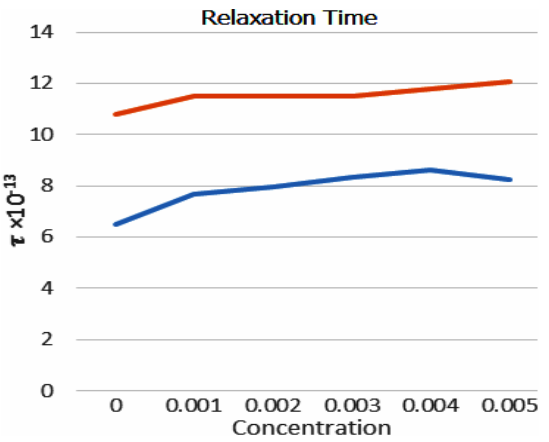
6. Relative Association (RA)



7. Ultrasonic Attenuation(α/f^2)



8. Relaxation Time (τ)



Physicochemical properties are a key to determinant of pharmacokinetic and pharmacodynamics profile, and essential to increasing the success rate of drug sample candidates within the preclinical development process. The importance of the physicochemical properties for active transport. The density and viscosity are depends on temperature and concentration, here the density and viscosity increases by increasing concentration but solvent changes change the density and viscosity that means density as well as viscosity affected by solvent.

Ultrasonic velocity in which sound waves travel through liquid sample. Here Ultrasonic velocity increases by increasing concentration due to an increase of cohesive forces which is created due to strong molecular interactions. The experimental Ultrasonic velocity values are different for the same compound in the two different solvents. This suggests that solvent plays an important role in solutions, molecular interactions exists which differs with different solvents. In this case thiohydantoins shows higher Ultrasonic velocity in DMSO solvent than DMF because in DMSO samples shows strong interaction with solvent DMSO.

If intermolecular free path decreases with increase of concentration, explain that the distance between solute and solvent molecules decrease due to increase in solute-solvent interactions, which causes velocity to increase. It is supported by compressibility and relaxation time. Here relaxation time increases by increasing concentration. Compressibility is a measure of the relative volume change of a sample as a response to a pressure change. Here compressibility decreases by increasing concentration that means concentration increases which increase strong interaction between solute and solvent.

CONCLUSION

It is concluded that physicochemical properties of a thiohydantoin derivatives depends on its structure, concentration and solvents in which it is dissolved. In this case DMSO and DMF shows different values for same compound due to interactions changes in different solvents thereby affecting properties. Further, position of substitution in a compound also affects physicochemical properties. In DMSO solvent, strong solute solvent interaction appear 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.

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