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# THEORETICAL STUDY OF PROPERTIES OF SULFORAPHANE A CHEMO PREVENTIVE AGENT USING CHEMSKETCH AND CHEMICALIZE SOFTWARE

**K. Laxmi**

**Professor of Chemistry**

Department of Chemistry, Chaitanya Bharathi Institute of Technology (CBIT), Gandipet, Hyderabad -500 075, INDIA Email ID: klaxmi_chm@cbit.ac.in

***Abstract:*** Sulforaphane (SFN) is a powerful phytochemical found mostly in dark green vegetables like broccoli and cruciferous vegetables like kale, cabbage cauliflower, and Brussels sprouts. SFN is known for its antioxidant, anti-inflammatory, and anti-apoptotic properties. Keeping in view of its therapeutic effects structure and properties of Sulforaphane (SFN) were studied by using Chemsketch & Chemicalize software of Chemaxon and the data obtained is interpreted.

***Keywords:*** Sulforaphane, Properties, pka, Isoelectric Point, logP, logD, Solubility, Geometry, HNMR

## Introduction

Sulforaphane (SFN) is compound within the isothiocyanate group of organosulphur compounds(fig.1). Sulforaphane (SFN) is highly effective in blocking carcinogenesis[1-4]. In recent decades a wide research has been carried out on Sulforaphane considering it as a potential chemopreventive compound. Sulforaphane is also known for its efficient effect in the treatment of neurodegenerative disease, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. In view of its beneficial effects, Sulforaphane is recommended as a a supplement to neutralize neurodegenerative diseases [5,6] and for prevention and/or treatment of disorders like neoplasm and heart failure. SFN has been reported to conceal neurotoxicity induced by toxic factors like hydrogen peroxide, prion protein, hyperammonemia, and methamphetamine.

It has been reported that the progression of Alzheimer's disease, Parkinson's disease, cerebral ischemia, Huntington's disease, multiple sclerosis, epilepsy can be prevented by the use of SFN. This is possible by the potential effect of SFN in inhibiting the oxidative stress and neuro inflammation and also by promoting neurogenesis[7,8].

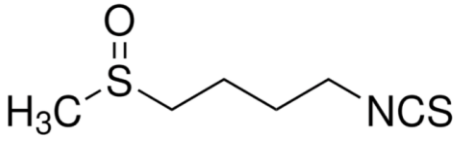



**Fig.1 structure of sulforaphane**

## Results and Discussions

### Hypothetical Study of Sulforaphane Using Chemsketch Software

ACD/Labs is one of the powerful software[9-11] used to obtain analytical data and to present reaction schemes. This software is used to focus on research as it is well equipped with prediction tools..A Chemical Naming Service is provided by ACD/Labs and this will use powerful software to quickly and accurately name compounds. ACD allows to generate systematic names according to IUPAC and CAS Index nomenclature rules.

ACD/ChemSketch enables to generate IUPAC names and also allows to calculate a variety of molecular descriptors.Molecular Formula of Sulforaphane is $C_6H_{11}NOS_2$ and its Molecular Weight is 177.28 . IUPAC Name of Sulforaphane [12,13](fig.2) is 1-isothiocyanato-4-(methanesulfinyl)butane. InChI name of Sulforaphane.(Table.1) is 1S/C6H11NOS2/c1-10(8)5-3-2-4-7-6-9/h2-5H2,1H3. The structure of chemical species using short ASCII strings.(Table.1) is described by using the simplified molecular-input line-entry system[14,15] (SMILES) . It is a specification in the form of a line notation. Smiles notation of Sulforaphane.(Table.1) is S=C=NCCCCS(=O)C

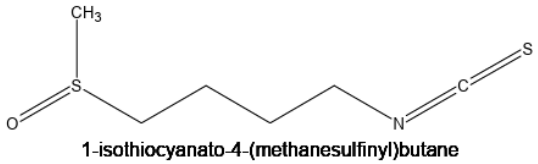



**Fig.2 structure of sulforaphane with IUPAC name**

**Table.1 chemical naming of sulforaphane as determined by ACD/chemsketch**

| | |
|---|---|
| **IUPAC name** | **1-isothiocyanato-4-(methanesulfinyl)butane** |
| **InChI** | **1S/C6H11NOS2/c1-10(8)5-3-2-4-7-6-9/h2-5H2,1H3** |
| **SMILES Notation** | **S=C=NCCCCS(=O)C** |

ACD/ChemSketch calculates the properties like molar volume, molar refractivity, parachor ,of Sulforaphane (Table 2)from additive increments. The additive atomic increments were obtained using a database of density, surface tension, and calculated MW. Molar volume, molar refractivity, parachor ,of Sulforaphane as given in the table are 150.6 ± 7.0 $cm^3$ , 49.16 ± 0.5 $cm^3$ and 392.6 ± 8.0 $cm^3$ respectively.

ACD/ChemSketch calculates the density from MW and the calculated molar volume and it determines the refractive index from the molar volume and molar refractivity. Density of Sulforaphane is 1.17 ± 0.1 $g/cm^3$ and Index of Refraction is 1.566 ± 0.05.

ACD/ChemSketch calculates the dielectric constant from calculated MV and a proprietary empirical additive function. Polarizability is calculated from the Molar Refractivity (MR). Polarizability of Sulforaphane 19.49 ± 0.5 $10^{-24}cm^3$

Nominal Mass ($M_n$) is the sum of the approximated monoisotopic masses of the elements forming the structure. Nominal Mass ($M_n$) of Sulforaphane SFN is 177 Da .Average Mass ($M_{av}$) is the calculated mass of a particle based on the atomic weights of the elements from which it is comp. Average Mass ($M_{av}$) of SFN as determined by ACD/ChemSketch is 177.28 Da.

**Table 2 properties of sulforaphane as determined by acd/chemsketch**

| | |
|---|---|
| **Molecular Formula:** | **$C_6H_{11}NOS_2$** |
| **Formula Weight:** | **177.28** |
| **Composition:** | **C(40.65%) H(6.25%) N(7.90%) O(9.02%) S(36.17%)** |
| **Molar Refractivity:** | **49.16 ± 0.5 $cm^3$** |
| **Molar Volume:** | **150.6 ± 7.0 $cm^3$** |
| **Parachor:** | **392.6 ± 8.0 $cm^3$** |
| **Index of Refraction:** | **1.566 ± 0.05** |
| **Surface Tension:** | **46.2 ± 7.0 dyne/cm** |
| **Density:** | **1.17 ± 0.1 $g/cm^3$** |
| **Dielectric Constant:** | **Not available** |
| **Polarizability:** | **19.49 ± 0.5 $10^{-24}cm^3$** |
| **RDBE:** | **3** |
| **Monoisotopic Mass:** | **177.028204 Da** |
| **Nominal Mass:** | **177 Da** |
| **Average Mass:** | **177.28 Da** |
| **M+:** | **177.027655 Da** |
| **M-:** | **177.028753 Da** |
| **[M+H]+:** | **178.03548 Da** |
| **[M+H]-:** | **178.036578 Da** |
| **[M-H]+:** | **176.01983 Da** |
| **[M-H]-:** | **176.020928 Da** |

The logP prediction model of ACD/ChemSketch enables to estimate the value of the octanol-water partitioning coefficient (also referred to as $K_{OW}$) in the form of logarithmic ratio (logP) from structure. Chemists make use of ACD/LogP in different fields of chemical research. This is utilized even by the world's largest pharmaceutical companies like GlaxoSmithKline and Pfizer. Calculated log P of Sulforaphane is 0.23+/- 0.39.

**3D Viewer –3D Optimised Forms of Sulforaphane**

A powerfull modeling and visualization program ACD/3D Viewer, provides various styles of structure 3D representation. These can be displayed in various forms like Ball and cylinder form , ball and cylinder form with dots. The 3D forms of Sulforaphane are given in figure 3.

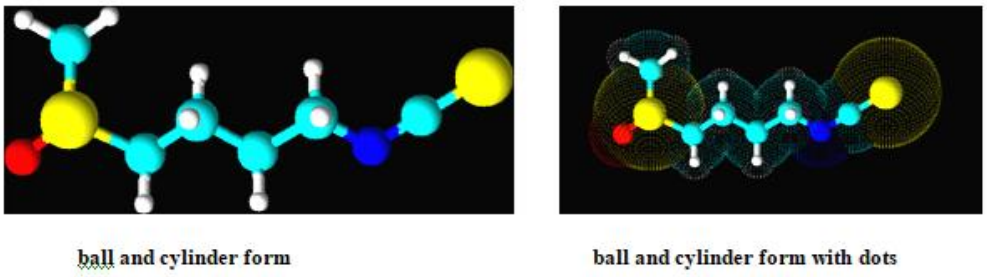



**Fig. 3. 3D optimized structure of sulforaphane**

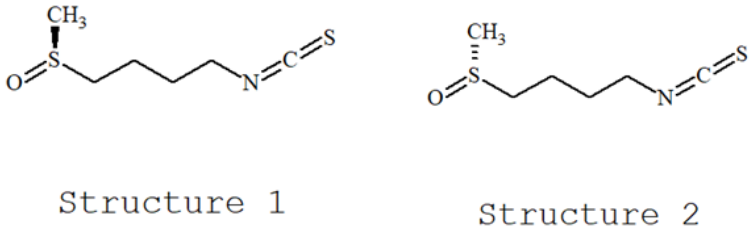



**Fig.4 R/S forms of sulforaphane**

R,S-Sulforaphane is a synthetic isothiocyanate while R form of Sulforaphane is the naturally-occurring isomer, found in broccoli (Fig.4). R-Sulforaphane is known for its anticancer chemotherapeutic, and chemopreventive , neuromodulatory, anti-inflammatory, antioxidative, neuroprotective, activities. Mirror images of 3D optimized forms of Sulforaphane as indicated by 3D Viewer of Chemsketch is given in Fig.5.

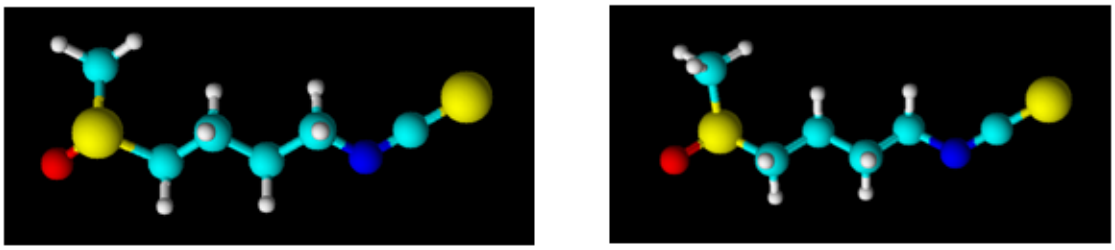


**Fig. 5 mirror images of 3D optimized forms of sulforaphane**

**Hypothetical Study of Sulforaphane using Chemicalize Software**

**Basic properties of Sulforaphane**

The structure of Sulforaphane is drawn as the input and from the data [16,17] given (Table 3) it is clearly evident that the formula of Sulforaphane is $C_6H_{11}NOS_2$ and its composition is C=40.65% ,H=6.25%,N=7.90%, S (36.17%). The molar mass of Sulforaphane (SFN) is 177.28 g/mol and its exact mass is 177.028206326 Da.

**Table 3. properties of sulforaphane as determined by chemicalize software**

| | |
|---|---|
| Input | Sulforaphane |
| Molar mass | 177.28 g/mol |
| Exact mass | 177.028206326 Da |
| Formula | C6H11NOS2 |
| Composition | C (40.65%), H (6.25%), N (7.90%), O (9.02%), S (36.17%) |

**Structural Properties of Sulforaphane**

The evaluation of various topology-related characteristics, hydrogen bonding, and other physical properties.is done by the Structural calculations.

Data of structural properties of Sulforaphane(SFN) were presented in Table.4. The atom count of 21 of Sulforaphane is in agreement with the number of atoms as given in chemical formula of $C_6H_{11}NOS_2$

In this there are 6 carbons , 1 nitrogen, 1 oxygen and 2 sulphurs which are the heavy atoms and the sum of these is in agreement with the total heavy atom count of 10 atoms( fig 1&2 ). There is one asymmetric atom and Sulforaphane has five rotatable bonds[18-20]. The topological polar surface area[21,22] of Sulforaphane is 29.43 $Å^2$. Molar refractivity of Sulforaphane is indicated to be 49.57 $cm^3$/mol.

**Table 4. structural properties of Sulforaphane as determined by Chemicalize**

| | |
|---|---|
| **Atom count** | **21** |
| **Heavy atom count** | **10** |
| **Asymmetric atom count** | **1** |
| **Rotatable bond count** | **5** |
| **Ring count** | **0** |
| **Aromatic ring count** | **0** |
| **Hetero ring count** | **0** |
| **FSP3** | **0.83** |
| **Hydrogen bond donor count** | **0** |
| **Hydrogen bond acceptor count** | **2** |
| **Formal charge** | **0** |
| **Topological polar surface area** | **29.43 $Å^2$** |
| **Polarizability** | **19.27 $Å^3$** |
| **Molar refractivity** | **49.57 $cm^3$/mol** |

**Names and Identifiers of Sulforaphane**

The following names of Sulforaphane(SFN) were given by the chemcalise software.other details like SMILES, InChI, InChIKey ,CAS Registry numbers of Sulforaphane were also obtained(Table 5)

The name of the compound according to the International Union of Pure and Applied Chemistry nomenclature and the commonly used trivial or traditional name is also shown

**Table 5. names and identifiers of sulforaphane given by chemicalize software**

| | |
|---|---|
| **IUPAC name** | **1-isothiocyanato-4-methanesulfinylbutane** |
| **Traditional name** | **sulforaphane** |
| **Common names** | **(+/-)-sulforaphane; DL-sulforaphane; SFN; sulforafan; sulforaphane; sulforathane** |
| **SMILES** | **CS(=O)CCCCN=C=S** |
| **InChI** | **InChI=1/C6H11NOS2/c1-10(8)5-3-2-4-7-6-9/h2-5H2,1H3** |
| **InChIKey** | **SUVMJBTUFCVSAD-UHFFFAOYNA-N** |

**pKa of Sulforaphane**

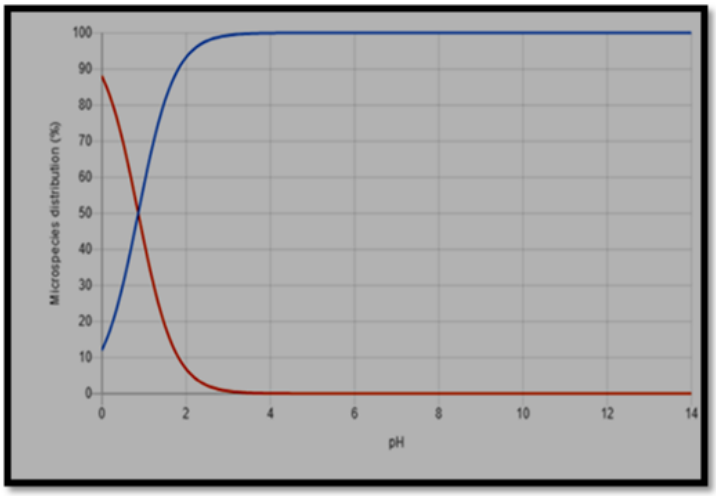
pKa is the measure of the acid dissociation constant given as pKa = - log 10 (K) and it is a measure of the strength of an acid in solution quantitatively [23-27]. In chemcalise the pKa values of Sulforaphane is found to be 0.87 thereby indicating its strong basic nature( Fig 6.). This is attributed to the dissociation of protons of -NH group.

$$pK_a = -\log_{10}(K)$$

$$pK_a = pH + \log_{10}\left(\frac{[AH]}{[A^-]}\right)$$

$$\Rightarrow \mathbf{pK_a = pH + \log_{10}\frac{[conjugated\ acid]}{[conjugated\ base]}}$$

$$pK_a = pH + \log_{10}\left(\frac{[RNH_3^+]}{[RNH_2]}\right)$$



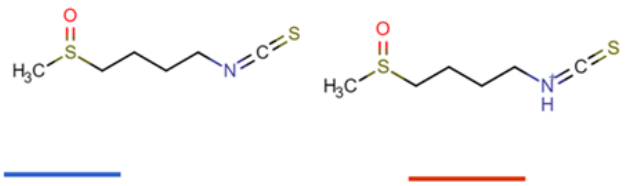




**Fig.6 distribution of pH for the different microspecies of sulforaphane as given by chemicalize software**

## Isoelectric Point of Sulforaphane

The isoelectric point is the pH at which a particular molecule or surface carries no net electrical charge. The gross charge distribution of a molecule as a function of pH is calculated as well.

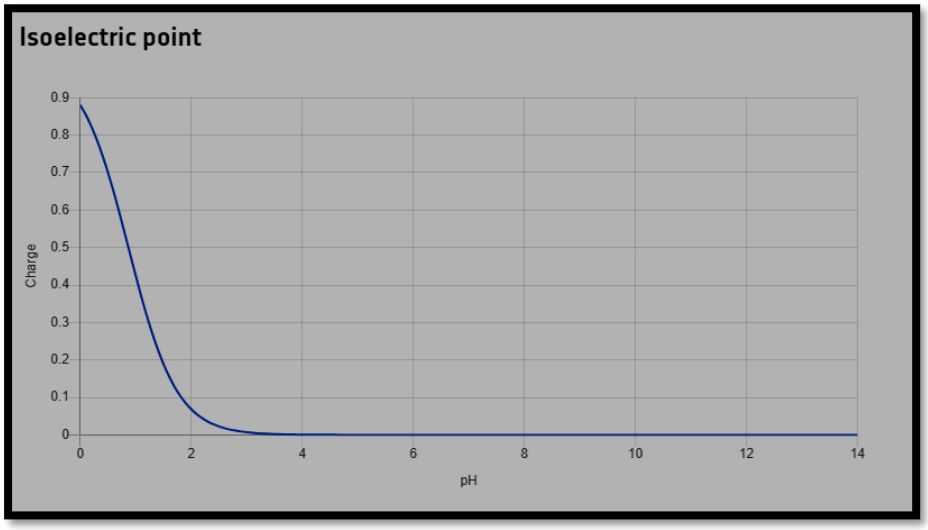



**Fig.7 Distribution of charge with pH of Sulforaphane as given by chemicalize software**

**Table.6 data of distribution of charge with pH of Sulforaphane as given by chemicalize software**

| pH | Charge |
|---|---|
| 1.7 | 0.13 |
| 4.6 | 0 |
| 6.5 | 0 |
| 7.4 | 0 |
| 8 | 0 |

The distribution of charge with pH of Sulforaphane(SFN) is graphically depicted in the fig7. and the coressponding data is given in the Table.6. From the above graph (Fig.7) it is evident that Sulforaphane is electrically neutral with zero electric charge within the pH range of 4.6 to 8 indicating the isoelecrtric point[28,29]

## log P and log D of Sulforaphane

### logP

The partition coefficient is a ratio of concentrations of an un-ionized compound in the two phases of immiscible solvents (water and n-octanol) at equilibrium. logP is the 10-base logarithmic measure of the coefficient.

$$log\ P_{oct/wat} = log\left(\frac{[solute]_{octanol}}{[solute]^{un-ionized}_{water}}\right)$$

### logD

Compounds having ionizable groups exist in solution as a mixture of different ionic forms. The ionization of those groups, thus the ratio of the ionic forms depends on the pH. Since logP describes the hydrophobicity of one form only, the apparent logP value can be different. The octanol-water distribution coefficient, logD represents the compounds at any pH value.

$$log\ D_{oct/wat} = log\left(\frac{[solute]_{octanol}}{[solute]^{ionized}_{water} + [solute]^{neutral}_{water}}\right)$$

The hydrophilic-lipophilic balance number (HLB number) measures the degree of a molecule being hydrophilic or lipophilic. This number is calculated based on identifying various hydrophil and liphophil regions in the molecule. This number is a commonly used descriptor in any workflow in which lipid based delivery can be an option (e.g. lipid-based drug delivery, cosmetics). HLB number of Sulforaphane is 10.77

logP is the octanol-water partition for the neutral (un-ionized) form of the compound. logP value of Sulforaphane [30-32] is found to be 0.22. log D is a log of partition of a chemical compound between the lipid and aqueous phases.The following figure shows the variation of the log D value of Sulforaphane with pH. It is observed that the log D value is same being 0.22 within the pH range o f 4.6 to 8 and further log D value increases as the pH increases.( Fig 8 &Table 7 ) . The column and the line graph showing variation of log D with pH is given in the figure 9.

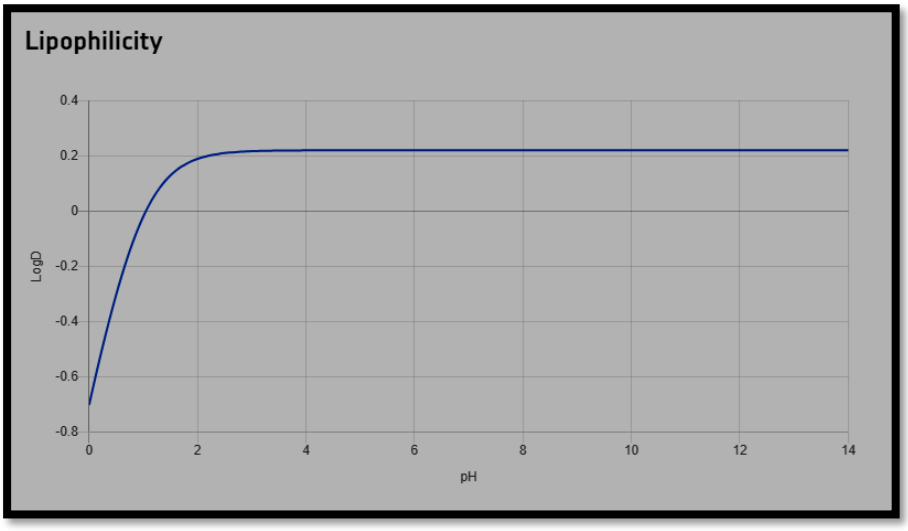



**Fig.8 distribution of log D with pH of sulforaphane as given by chemicalize software**

**Table.7 data of distribution of log D with pH of sulforaphane**

| pH | log D |
|---|---|
| 1.7 | 0.16 |
| 4.6 | 0.22 |
| 6.5 | 0.22 |
| 7.4 | 0.22 |
| 8 | 0.22 |

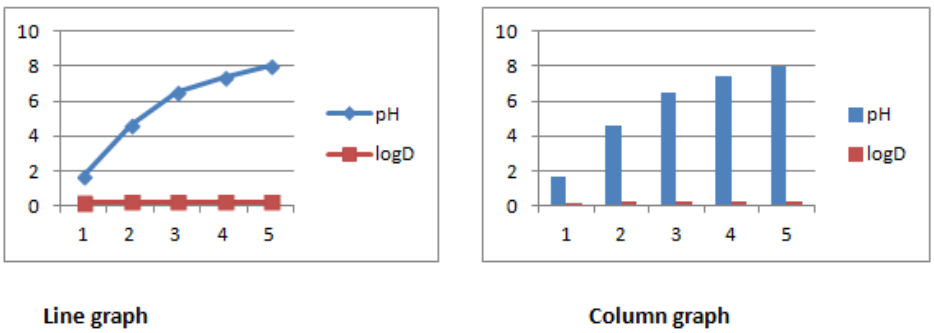



**Fig.9 distribution of log D with pH as given by chemicalize software**

**Solubility of Sulforaphane (log S)**

Solubility is a chemical property referring to the ability for a given substance, the solute, to dissolve in a solvent.*logS* is the 10-based logarithm of the solubility measured in mol/l.

The following graph shows the distribution of log S with pH (Fig.10) and the data (Table.8) indicates that Sulforaphane[33-36] is of High solubility category with Intrinsic solubility of -1.313. The column and the line graph showing variation of Solubility of Sulforaphane (log S) with pH is given in the figure 11.

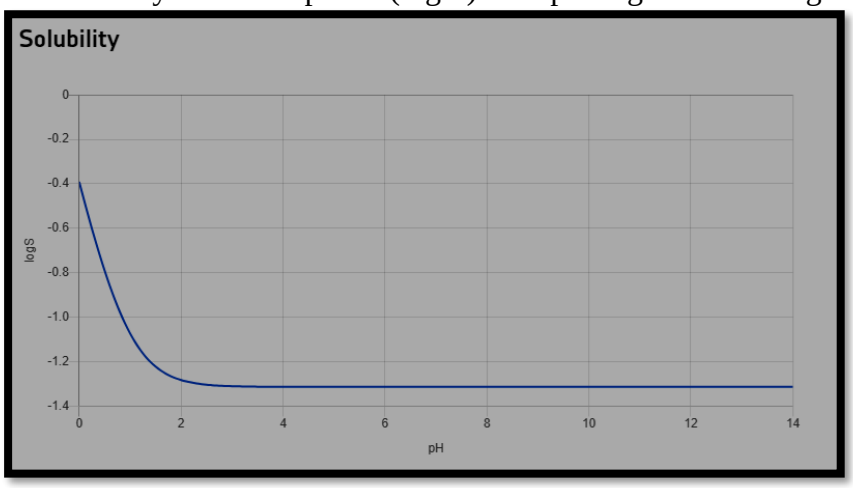



**Fig.10 distribution of log S with pH of sulforaphane as given by chemicalize software**

**Table.8 data of Distribution of log S with pH of sulforaphane as given by chemicalize software**

| pH | Solubility [logS] |
|---|---|
| 1.7 | -1.25 |
| 4.6 | -1.31 |
| 6.5 | -1.31 |
| 7.4 | -1.31 |
| 8 | -1.31 |

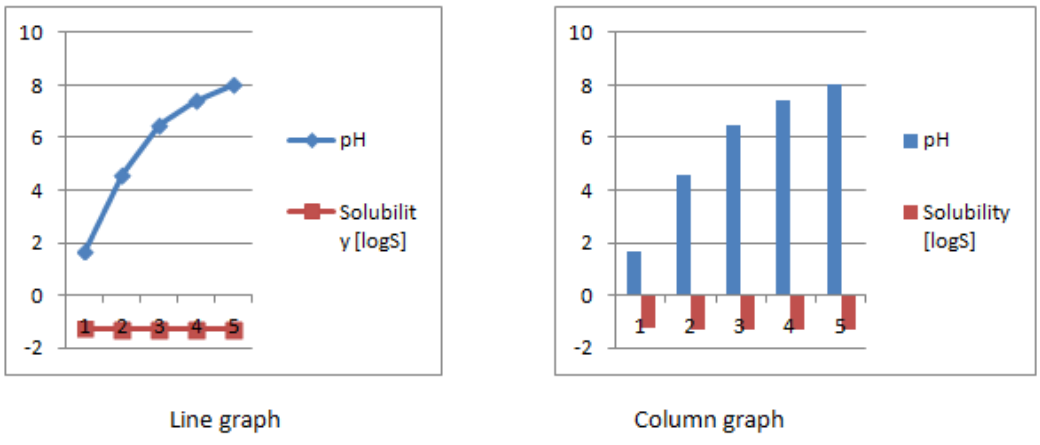



**Fig.11 distribution of log S with pH of sulforaphane as given by chemicalize software**

## Geometry of Sulforaphane

By using the chemicalize software the following information of vanderwaals volume, surface area ,projection area projection radius of Sulforaphane were obtained[37].

**Table. 9 data of of volume, surface area ,projection area and projection radius of sulforaphane as given by chemicalize software**

| | |
|---|---|
| **Van der Waals volume** | **158.99 $Å^3$** |
| **Van der Waals surface area** | **267.14 $Å^2$** |
| **Solvent accessible surface area** | **395.44 $Å^2$** |
| **Topological polar surface area** | **29.43 $Å^2$** |
| **Minimum projection area** | **24.4 $Å^2$** |
| **Maximum projection area** | **58.03 $Å^2$** |
| **Minimum projection radius** | **3.2 Å** |
| **Maximum projection radius** | **6.86 Å** |

## H-NMR Spectrum of Sulforaphane

NMR spectra for standard organic molecules is predicted by the NMR Predictor in ChemAxon.A mixed HOSE and linear model based on topological description scheme is used for estimating the chemical shifts[38,39]. This estimation is done in relation to the chemical shift of tetra methylsilane (TMS = 0ppm)H-NMR spectrum of Sulforaphane(SFN) is given in the figure 12.

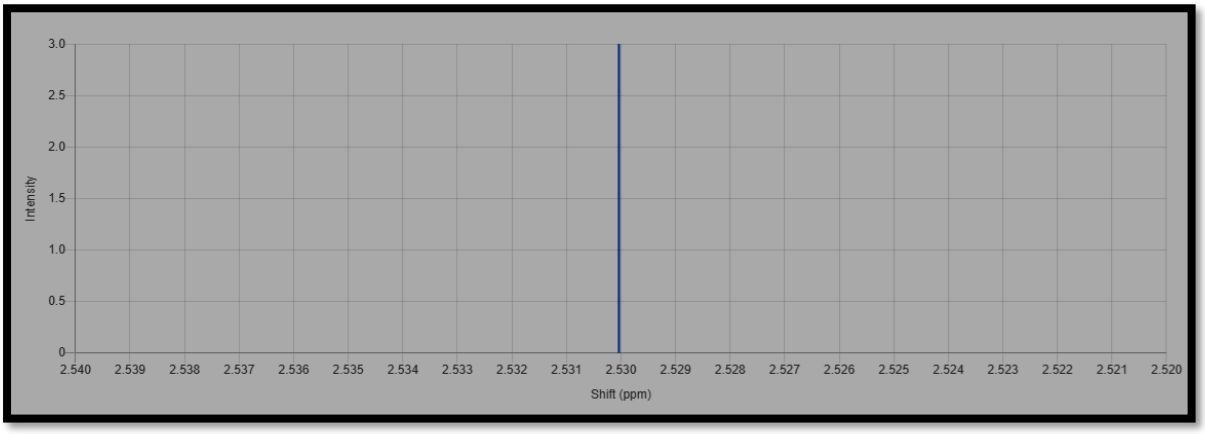
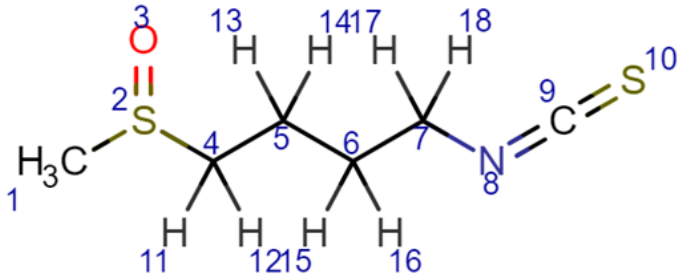



**Fig.12 1HNMR spectrum of sulforaphane as given by chemicalize software**

**Table 10. shifts caused by the protons of sulforaphane and the intensity and quality for each shift and corresponding protons as given by chemicalize software**




| Atoms | Shift | Intensity | Multiplet | Quality |
|---|---|---|---|---|
| 15 | 1.870 ppm | 1 | n | medium |
| 13 | 1.899 ppm | 1 | p | medium |
| 16 | 2.098 ppm | 1 | n | medium |
| 14 | 2.261 ppm | 1 | p | medium |
| 11 | 2.290 ppm | 1 | t | medium |
| 1, 1, 1 | 2.530 ppm | 3 | s | good |
| 12 | 3.010 ppm | 1 | t | medium |
| 17 | 3.330 ppm | 1 | t | medium |
| 18 | 3.726 ppm | 1 | t | medium |

The above table 10 shows the shifts caused by the protons of Sulforaphane and it also indicates the intensity and quality for each shift. The shift observed at 2.530 ppm corresponds to protons of methyl group.

## Conclusions

Structural and physicochemical aspects of Sulforaphane is well understood by the information provided by chemsketch study. Different styles of 3D representation of structure, mirror images and R/S forms of Sulforaphane were well visualized by applying ACD/3D Viewer integrated with ACD/ChemSketch

As indicated by data of chemicalize software from pKa values and 1HNMR spectral data it is understood that Sulforaphane is of strongly basic nature having one dissociable proton. Graphical interpretation showing distribution of log D, log S, solubility in mg/L with pH of Sulforaphane enabled the study of variation of these properties with pH . Geometrical studies of Sulforaphane done using chemcalise software provided the data of properties like vanderwaals area,vanderwaals volume, projection area projection radius.

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