



## ACCEPTED MANUSCRIPT

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## A simple computational approach for $pK_a$ calculation of organosulfur compounds

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**Abstract:** The present work is related to predicting the  $pK_a$  values of organosulfur compounds through Density Functional Theory (DFT). In this study 22 organosulfur compounds have been considered to calculate theoretical  $pK_a$  values. Main emphasis has been given on the substitution of different groups on the Sulfur atom. The computations were performed in the presence of Dimethyl sulfoxide (DMSO) as solvent. Experimentally the order of increase of acidity is; Sulfides < Sulfoxides < Sulfones. Our computed  $pK_a$  values also follow the same order. The theoretical  $pK_a$  values are computed using the DFT method B3LYP, with the basis sets 6-31G(d), 6-31+G(d,p) and IEFPCM bulk solvation model. The majority of computed  $pK_a$  values are in excellent agreement with the experimental ones through the diffuse function basis set. Hence this computational approach, B3LYP/6-31+G(d,p)/IEFPCM, could be utilized to predict the  $pK_a$  values of these types of organosulfur compounds.

**Keywords:** DFT method; Diffuse function basis set; DMSO solvent.

### INTRODUCTION

Acid dissociation constant ( $pK_a$ ) is an important property of many organic compounds and it is strongly related with their applications. Fast and accurate methods for determining aqueous  $pK_a$  values of organic compounds would have a wide range of applications. Aside from experimental measurements, theoretical determination of the acidity of a compound has been an important and challenging objective of computational chemistry.<sup>1,2</sup> The computations (theoretical calculations) are a reconfirmation of experimental results. A computation provides an idea of the structural information of a molecule in the vacuum (gas phase) which is difficult to obtain through experiments. Theoretical calculations are also helpful to provide information in determining the preferred protonation site when more than one site is available.<sup>3</sup>

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Organosulfur compounds have many important applications, and these are already reported in literature.<sup>4,5,6,7</sup> In this communication we are presenting a very easy computational approach for theoretical calculation of  $pK_a$  values. This theoretical model is employed for three types of organosulfur compounds i.e. Sulfides, Sulfoxides and Sulfones. Different kinds of substituents are selected which are attached on both sides of the Sulfur atom. The structures of compounds considered for  $pK_a$  calculation are shown in Figure 1. The significance of this computational model is that it could be applied for Sulfides, Sulfoxides and Sulfones uniformly.

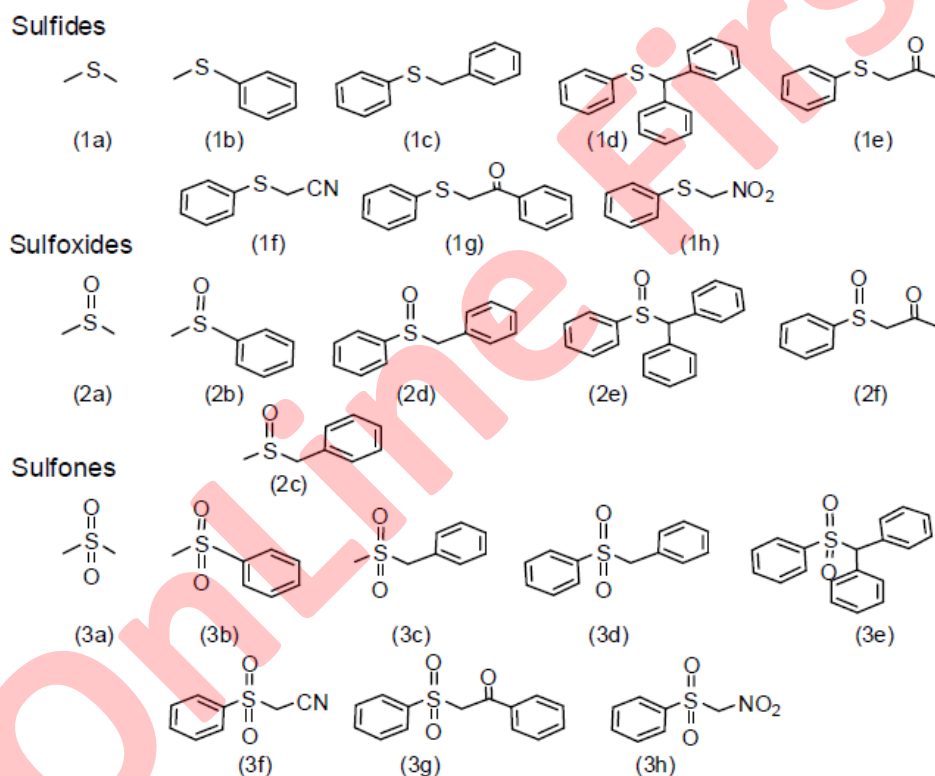
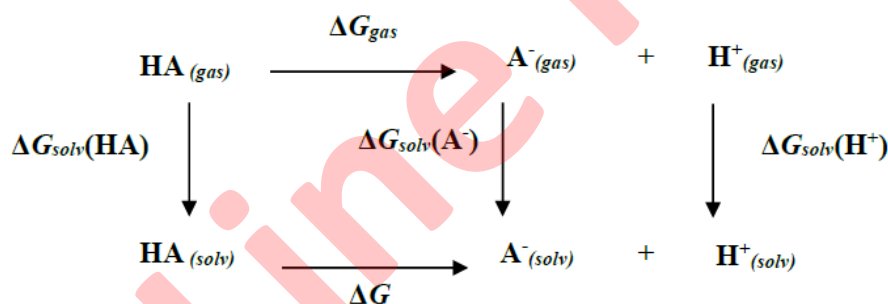


Fig 1. Compounds considered for theoretical  $pK_a$  calculation

In our previous studies related to  $pK_a$  calculations,<sup>8,9</sup> this computational protocol was developed. In these studies we showed that the theoretically calculated  $pK_a$  values could be utilized to resolve discrepancies in experimental  $pK_a$  values. These computational studies were performed with different solvation models but only water was used as a solvent.

## EXPERIMENTAL

The experimental  $pK_a$  values of different derivatives of Sulfide, Sulfoxide and Sulfone have been obtained from literature.<sup>10-13</sup> These experimental  $pK_a$  values are determined in DMSO as solvent. The series starts with the simple form i.e. dimethyl sulfide, dimethyl sulfoxide and dimethyl sulfone. Other derivatives are set by variation of different groups (See Fig. 1). First of all, the geometries of all considered compounds have been drawn with help of GaussView 6.<sup>14</sup> Then the molecular modelling software Gaussian 16<sup>15</sup> is employed for all quantum calculations. For the computation of  $pK_a$  values, the Gibbs free energies in the gas phase ( $\Delta G_{gas}$ ) have been calculated through DFT method, B3LYP, with the basis sets 6-31G(d) and 6-31+G(d,p). Solvation free energies ( $\Delta G_{solv}$ ) in DMSO have been obtained by single point computations on gas phase geometries, using the bulk solvation model, IEFPCM (Integral Equation Formalism Polarizable Continuum Model). The calculations of  $pK_a$  values is performed by using a well known thermodynamic cycle (Scheme 1, Equation 1 and 2).<sup>16</sup> The Gibbs free energy of the gas phase proton<sup>17</sup> was taken from the Sackur-Tetrode equation as  $G_{gas}(H^+) = -6.28 \text{ kcal mol}^{-1}$ ; for the Gibbs free energy of hydration of the proton the experimental value,<sup>18</sup>  $\Delta G_{solv}(H^+) = -270.0 \text{ kcal mol}^{-1}$ , was used. The usual correction term of  $1.9 \text{ kcal mol}^{-1}$  was applied for standard state conversion between 1 atm in gas phase and  $1 \text{ mol L}^{-1}$  in solution.<sup>19</sup>



Scheme 1. Thermodynamic cycle utilized for equation 1 and 2

$$pK_a = \Delta G / 2.303RT \quad (1)$$

$$\Delta G = \Delta G_{gas} + \Delta G_{solv}(A^-) + \Delta G_{solv}(H^+) - \Delta G_{solv}(HA) \quad (2)$$

## RESULTS AND DISCUSSION

The data set of experimental  $pK_a$  values shows that the change of methyl group by phenyl or benzyl increases the acidity of considered organosulfur compounds. The electron withdrawing substituents also have the same effect (See Table 1). Addition of Oxygen atoms on Sulfur also increases the acidity from Sulfide to Sulfoxides and Sulfones (see Fig. 2).

Initially all structures were fully optimized with frequency calculation, by the method B3LYP and using the basis set, 6-31G(d). Solvation energies have been obtained by single point computations with the same basis set. The calculated  $pK_a$  values obtained through this computational approach and experimental  $pK_a$  values are summarized in Table 1.

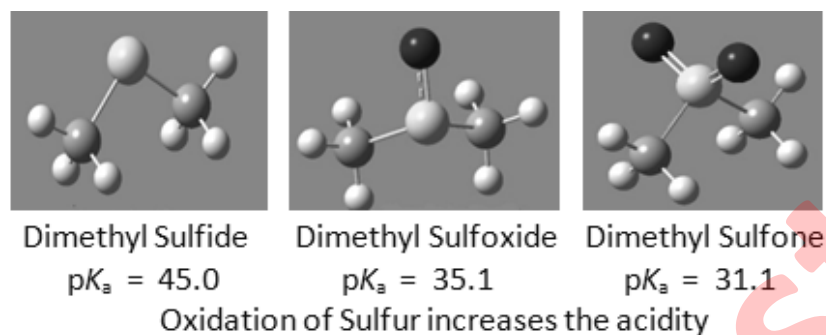


Fig 2. Addition of Oxygen atoms increases the acidity

TABLE I. Comparison of experimental and calculated  $pK_a$  values

		$pK_a$									
Sulfide		Sulfoxide				Sulfone					
Comp.	Exp.	Calc. <sup>a</sup>	Calc. <sup>b</sup>	Comp.	Exp.	Calc. <sup>a</sup>	Calc. <sup>b</sup>	Comp.	Exp.	Calc. <sup>a</sup>	Calc. <sup>b</sup>
1a	45.0	55.7	45.7	2a	35.1	46.9	35.1	3a	31.1	38.2	31.3
1b	42.4	51.3	43.2	2b	29.0	35.3	28.6	3b	25.4	30.2	24.4
1c	30.8	37.6	32.0	2c	33.0	53.5	34.1	3c	29.0	36.5	28.6
1d	26.7	32.0	27.7	2d	27.2	33.8	27.6	3d	23.4	29.8	24.1
1e	20.8	24.5	18.6	2e	24.5	30.3	25.3	3e	22.3	32.1	23.4
1f	18.7	24.9	21.7	2f	15.1	21.9	12.8	3f	12.0	15.2	9.4
1g	16.9	25.2	15.4					3g	11.4	24.5	17.0
1h	11.8	15.7	8.7					3h	7.1	10.1	3.0
MAD		6.8	1.7			9.6	0.83			6.8	1.9
R <sup>2</sup>		0.99	0.98			0.83	0.99			0.89	0.91

<sup>a</sup> B3LYP/6-31G(d)/IECPCM; <sup>b</sup> B3LYP/6-31+G(d,p)/IECPCM

The comparison of experimental and computed  $pK_a$  values shows that the computed  $pK_a$  values are large than experimental  $pK_a$  values through B3LYP/6-31G(d)/IEFPCM procedure. The mean absolute deviations (MAD) are also large ( $<7pK_a$ – units) in Sulfide, ( $<9pK_a$ – units) in Sulfoxide and ( $<7pK_a$ – units) in Sulfone. However, correlation coefficient ( $R^2$ ) is somehow better in each series ( $>0.8$ ).

Addition of diffuse function in the basis set subsequently improved the results. The MADs decreased significantly in each series ( $<pK_a$ – unit) and the  $R^2$  value also improved ( $>0.9$ ). The data obtained through B3LYP/6-31+G(d,p)/IEFPCM computational approach shows an excellent agreement between the experimental and computed  $pK_a$  values (See Table 1). Hence this computational model is excellent in predicting the  $pK_a$  values of these kinds of organosulfur compounds. All investigated data obtained through B3LYP/6-31+G(d,p)/IEFPCM computational model is presented in Figure 3.

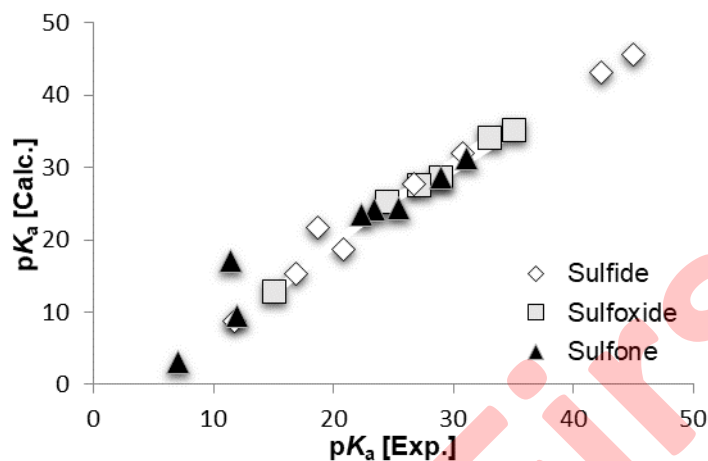


Fig 3. Plot of experimental and computed  $pK_a$  through B3LYP/6-31+G(d,p)/IEFPCM

#### CONCLUSION

The DFT method was employed to calculate theoretical  $pK_a$  values of organosulfur compounds with two different basis sets. The diffuse function basis set provided best calculated  $pK_a$  values and these are in excellent agreement with the majority of experimental  $pK_a$  values. Oxidation of Sulfur and substitution of electron withdrawing and aromatic groups increase the acidity of considered organosulfur compounds. The predicted  $pK_a$  values showed the same phenomenon regarding the acidity of organosulfur compounds. Finally it is concluded that the proposed computational approach B3LYP/6-31+G(d,p)/IEFPCM is predictive and could be utilized to calculate theoretical  $pK_a$  values of these kinds of small organosulfur compounds. For large and flexible organosulfur compounds conformational analysis will be required.

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#### ИЗВОД

#### ЈЕДНОСТАВАН РАЧУНАРСКИ ПРИСТУП ИЗРАЧУНАВАЊУ $pK_a$ ОРГАНОСУМПОРНИХ ЈЕДИЊЕЊА

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Овај рад се односи на предвиђање  $pK_a$  вредности органосумпорних једињења помоћу Теорије Функционала Густине (DFT). У овој студији су разматрана 22 органосумпорна једињења за израчунавање теоријских  $pK_a$  вредности. Нагласак је стављен на супституцију различитих група на атому сумпора. Израчунавања су урађена за присуство диметил-сулфоксида (DMSO) као растварача. Експериментални редослед пораста киселости је; Сулфиди < Сулфоксиди < Сулфони. Наше израчунате  $pK_a$

вредности такође следе овај поредак. Теоријске  $pK_a$  вредности израчунате су користећи DFT метод B3LYP, са базисима 6-31G(d), 6-31+G(d,p) и IEFPCM помоћни солватациони модел. Већина  $pK_a$  вредности, израчунatih помоћу дифузног базиса, су у изврсној сагласности са експерименталним. Отуда се овај рачунарски приступ, B3LYP/6-31+G(d,p)/IEFPCM, може користити за предвиђање  $pK_a$  вредности овог типа органосумпорних једињења.

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