Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *86* (2) 165–170 (2021)
JSCS–5412
Short communication

SHORT COMMUNICATION

A simple computational approach for pK_a calculation of organosulfur compounds

SYED TAHIR ALI*, ANEESA CHOUDHARY[1], SYED MAJID KHALIL[2]
and ARIF ZUBAIR[3]

[1]Department of Chemistry, Federal Urdu University of Arts Science and Technology, Karachi, Pakistan, [2]Bosch Pharmaceutical Private Limited, Plot No. 209, Sector 23, Korangi Industrial Area, Karachi, Pakistan and [3]Department of Environmental Science, Federal Urdu University of Arts Science and Technology, Karachi, Pakistan

(Received 18 May, accepted 7 July 2020)

Abstract: The present work is related to predicting the pK_a values of organosulfur compounds through the density functional theory (DFT). In this study, 22 organosulfur compounds were considered to calculate the theoretical pK_a values. The main emphasis was 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. The herein computed pK_a values also follow the same order. The theoretical pK_a values were computed using the DFT method B3LYP, with the basis sets 6-31G(d), 6-31+G(d,p) and the IEFPCM bulk solvation model. The majority of the pK_a values computed through the diffuse function basis set were in excellent agreement with the experimental ones. 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

The acid dissociation constant (pK_a) is an important property of many organic compounds and it is strongly related to 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.[1,2] The computations (theoretical calculations) are a reconfirmation of experimental results. A

---

* Corresponding author. E-mail: stahir.ali@fuuast.edu.pk

https://doi.org/10.2298/JSC200518042A

Available on line at www.shd.org.rs/JSCS/
(CC) 2021 SCS.

computation provides an idea of the structural information of a molecule in vacuum (gas phase), which is difficult to obtain through experiments. Theoretical calculations are also helpful in providing information for the determination of the preferred protonation site when more than one site is available.[3]

Organosulfur compounds have many important applications, which have already been reported in literature.[4–7] 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 were selected that were attached on both sides of the sulfur atom. The structures of compounds considered for pK_a calculation are shown in Fig. 1. The significance of this computational model is that it could be uniformly applied for sulfides, sulfoxides and sulfones.

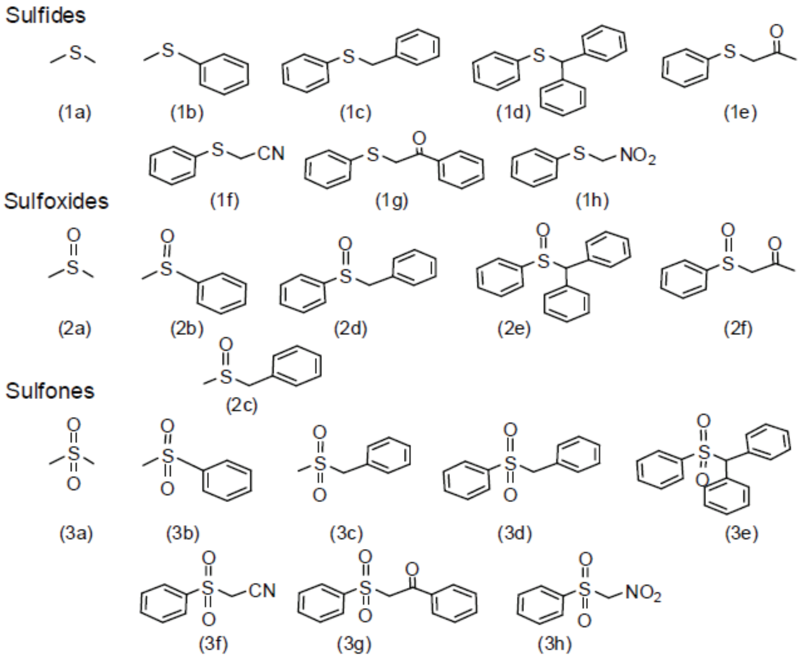

Fig. 1. Compounds considered for the theoretical pK_a calculations.

This computational protocol was developed in previous studies related to pK_a calculations.[8,9] In these studies, it was shown 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 the solvent.

(CC) 2021 SCS.

EXPERIMENTAL

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

$$\begin{tikzcd}
\mathbf{HA}_{(gas)} \arrow[r, "\Delta G_{gas}"] \arrow[d, "\Delta G_{solv}(\mathbf{HA})"'] & \mathbf{A}^{-}_{(gas)} \arrow[d, "\Delta G_{solv}(\mathbf{A}^{-})"'] & + & \mathbf{H}^{+}_{(gas)} \arrow[d, "\Delta G_{solv}(\mathbf{H}^{+})"] \\
\mathbf{HA}_{(solv)} \arrow[r, "\Delta G"'] & \mathbf{A}^{-}_{(solv)} & + & \mathbf{H}^{+}_{(solv)}
\end{tikzcd}$$

Scheme 1. The thermodynamic cycle utilized for Eqs. (1) and (2).

$$\mathrm{p}K_a = \Delta G/(2.303RT) \tag{1}$$

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

RESULTS AND DISCUSSION

The data set of experimental pK_a values shows that changing the methyl group with a phenyl or a benzyl group increases the acidity of the considered organosulfur compounds. Electron withdrawing substituents also have the same effect (see Table I). 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 calculations, by the B3LYP method using the basis set, 6-31G(d). Solvation energies were obtained by single point computations with the same basis set. The calculated pK_a values obtained through this computational approach and the experimental pK_a values are summarized in Table I.

---

* 1 kcal = 4184 J

TABLE I. Comparison of experimental and calculated pK_a values

Sulfide				Sulfoxide				Sulfone			
Comp.	Exp.	Calcd.^{a}	Calcd.^{b}	Comp.	Exp.	Calcd.^{a}	Calcd.^{b}	Comp.	Exp.	Calcd.^{a}	Calcd.^{b}
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^2		0.99	0.98			0.83	0.99			0.89	0.91

^{a}B3LYP/6-31G(d)/IECPCM; ^{b}B3LYP/6-31+G(d,p)/IECPCM

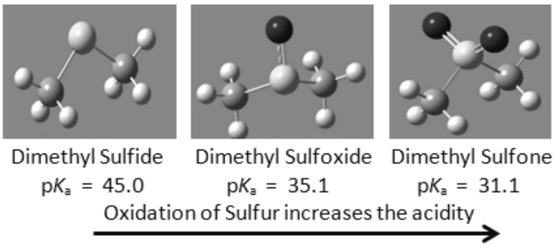

Fig. 2. Addition of oxygen atoms increases the acidity.

A comparison of the experimental and computed pK_a values shows that the pK_a values computed through B3LYP/6-31G(d)/IEFPCM procedure are large than experimental pK_a values. 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, the correlation coefficients (R^2) are somehow better in each series (>0.8).

Addition of a diffuse function in the basis set subsequently improved the results. The *MAD* values decreased significantly in each series (<2pK_a – unit) and the R^2 values also improved (>0.9). The data obtained through the B3LYP/6-31+G(d,p)/IEFPCM computational approach shows an excellent agreement between the experimental and computed pK_a values (see Table I). 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 are presented in Fig. 3.

CONCLUSIONS

The DFT method was employed to calculate theoretical pK_a values of organosulfur compounds using two different basis sets. The diffuse function basis set provided the best calculated pK_a values and these are in excellent agreement with

(CC) 2021 SCS.

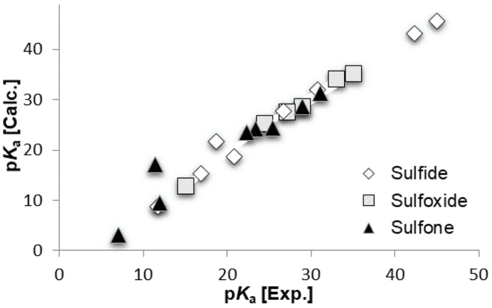

Fig. 3. Plot of experimental and computed pK_a through B3LYP/6-31+G(d,p)/IEFPCM.

the majority of the 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 was 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.

Acknowledgement. The authors are thankful to Higher Education Commission (HEC), Pakistan, for financial support.

ИЗВОД

ЈЕДНОСТАВАН РАЧУНАРСКИ ПРИСТУП ИЗРАЧУНАВАЊУ pK_a ОРГАНОСУМПОРНИХ ЈЕДИЊЕЊА

SYED TAHIR ALI, ANEESA CHOUDHARY[1], SYED MAJID KHALI[2] и ARIF ZUBAIR[3]

[1]*Department of Chemistry, Federal Urdu University of Arts Science and Technology, Karachi, Pakistan,*
[2]*Bosch Pharmaceutical Private Limited, Plot No. 209, Sector 23, Korangi Industrial Area, Karachi,*
Pakistan и [3]*Department of Environmental Science, Federal Urdu University of Arts Science and*
Technology, Karachi, Pakistan

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, израчунатих 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.

(Примљено 18. маја, прихваћено 7. јула 2020)

REFERENCES

1. A. Onufriev, D. A. Case, G. M. Ullmann, *Biochemistry* **40** (2001) 3413 (https://doi.org/10.1021/bi002740q)

(CC) 2021 SCS.

2. K. S. Alongi, G. C. Shields, *Ann. Rep. Comp. Chem.* **6** (2010) 113 (https://doi.org/10.1016/S1574-1400(10)06008-1)
3. G. J. Paul, J. S. Walter, *J. Chem. Phys.* **83** (1985) 2984 (https://doi.org/10.1063/1.449201)
4. M. K. Syed, C. Murray, M. Casey, *Eur. J. Org. Chem.* **25** (2014) 5549 (https://doi.org/10.1002/ejoc.201402584)
5. M. K. Syed, M. Casey, *Eur. J. Org. Chem*. **35** (2011) 7207 (https://doi.org/10.1080/09168451.2017.1407235)
6. B. Cheng, Y. Li, T. Wang, X. Zhang, H. Li, Y. Li, H. Zhai, *Chem. Comm.* **55** (2019) 14606 (https://doi.org/10.1039/c9cc08326j)
7. X. Yang, X. Li, K. Adair, H. Zhang, X. Sun, *Elect. Chem. Energy Rev.* **1** (2018) 239 (https://doi.org/10.1007/s41918-019-00044-4)
8. S. T. Ali, S. Karamat, J. Kóňa, W. M. F. Fabian, *J. Phys. Chem., A* **114** (2010**)** 12470 (https://doi.org/10.1021/jp102266v)
9. S. T. Ali, S. Jahangir, S. Karamat, W. M. F Fabian, K. Nawara, J. Kóňa, *J. Chem. Theor. Comput.* **6** (2010) 1670 (https://doi.org/10.1021/ct9003355)
10. F. G. Bordwell, *Acc. Chem. Res.* **21** (1988) 456 (https://doi.org/10.1021/ar00156a004)
11. F. G. Bordwell, G. E. Drucker, N. H. Andersen, A. D. Denniston, *J. Am. Chem. Soc.* **108** (1986) 7310 (https://doi.org/10.1021/ja00283a028)
12. X. M. Zhang, F. G. Bordwell, *J. Am. Chem. Soc.* **116** (1994) 968 (https://doi.org/10.1021/ja00082a018)
13. F. G. Bordwell, X. M. Zhang, *J. Am. Chem. Soc.* **114** (1992) 7623 (https://doi.org/10.1021/ja00046a003)
14. R. Dennington, T. A. Keith, J. M. Millam, *GaussView 6*, Semichem Inc., Shawnee Mission, KS, 2016
15. *Gaussian 16, Revision C.01*, Gaussian, Inc., Wallingford, CT, 2016
16. C. P. Kelly, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem., A* **110** **(**2006) 2493 (https://doi.org/10.1021/jp055336f)
17. I. D. Cunningham, K. Bhaila, D. C. Povey, *Comp. Theor. Chem.* **1019** (2013) 55 (https://doi.org/10.1016/j.comptc.2013.06.031)
18. J. Ho, M. L. Coote, *Theor. Chem. Acc.* **125** (2010) 3 (https://doi.org/10.1007/s00214-009-0667-0)
19. M. D. Tissandier, K. A. Cowen, W. Y. Feng, E. Gundlach, M. H. Cohen, A. D. Earhart, V. C. James, T. R. Tuttle, *J. Phys. Chem., A* **102** (1998) 7787 (https://doi.org/10.1021/jp982638r).

(CC) 2021 SCS.