

Does Incorporation of Silicon Increases Lipophilicity? A Theoretical Perspective



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Abstract

Quantum chemical calculations have been carried out using MP2/6-311++G** level of theory to calculate lipophilicity, i.e., octanol-water partition coefficient (LogP) of some alcohols and their silicon derivatives. Very good correlation has been obtained between the experimental LogP values against our calculated one. Moreover, incorporation of Si atom into the C atom attached to the -OH group dramatically increases the lipophilicity of the compounds. This finding may have wide implications towards designing new Si incorporated drugs.

Introduction

The lipophilicity, which refers to the ability of a compound to dissolve in fats, oils, lipids and non polar solvents such as hexane or toluene, is an important parameter for a drug to successfully pass through clinical development [1-3]. The lipophilicity is a measure of all the intermolecular forces between solute and two phases between which it partitions [4]. Generally, the lipophilicity is expressed experimentally as the octanol-water partition coefficient P (logP) or as distribution coefficients (logD). The logP describes the partition equilibrium of an un-ionized solute, while logD determines the ratio of the sum of the concentrations of all forms of the compound (pH-dependent mixture of ionized and unionized forms) in each of the two phases. Accurate determination of LogP is very important requirement in drug design. Theoretical calculation of LogP has been practiced for a long time. In practice, theoretical LogP values evaluated using quantitative structure-activity relationship (QSAR) models are practiced more often rather than expensive experimental measurements [5-6]. However, screening based on QSAR models often lead to erroneous results [7-8].

Herein, we have undertaken a theoretical study on the direct and accurate measurement of LogP values based on the following equation

$$\text{LogP} = (\Delta G_{\text{water}} - \Delta G_{\text{n-octanol}}) / RT$$

Where values are the free energies in respective solvent [9], the calculated values of LogP were then compared with the available experimental data from Khadikar and co-workers [10]. Recently, it has been speculated that substitution of C atom by Si increases

the lipophilicity of different drugs [11]. This is intriguing by the fact that Si is the biostere of C as Si has similar physicochemical properties and similar biological activity in broad sense. Herein, we are also interested in testing the speculation by carrying out high level *abinitio* calculations.

Computational Details

All these structures were fully optimized without any symmetry constraints at MP2/6-311++G** level of theory [12]. Harmonic frequency calculations were also carried out to understand the nature of the stationary states. All structures were found to be at the local minimum with all real frequencies. Solvent calculations were performed using the prescribed salvation model using density (SMD) approach. All calculations were performed using GAUSSIAN16 suite of program [13].

Results and Discussions

Figure 1 shows the optimized geometries of the molecules considered in this study. The geometries shown here are for the gas phase. All these structures are local minima on the potential energy surface. It should be noted that many isomeric forms of these structures are possible; however, we have considered the lowest energy isomer of all these molecules. These gas phase geometries are taken as the starting geometry for further geometry optimization in different solvent (water and n-octanol) medium using SMD approach. Table 1 contains the calculated values of LogP of the selected molecules. The experimental LogP values are taken from Khadikar and co-workers [10]. It is evident from

Table 1 that the values calculated with MP2/6-311++G** level of theory lies between -0.3 to 3.3 and follows a similar trend as the experimental values. However, the magnitudes of calculated values are different from the experimental one. We, therefore, adopted regression analysis between the calculated and experimental LogP values. Figure 2 shows the plot of the regression analysis. It is

evident from Figure 2 that there is a very good correlation between the calculated and experimental values with regression coefficient, $R^2 = 0.97$. Interestingly, incorporation of Si atom into the alcohols dramatically increases the LogP value which is consistent with the recent speculation.

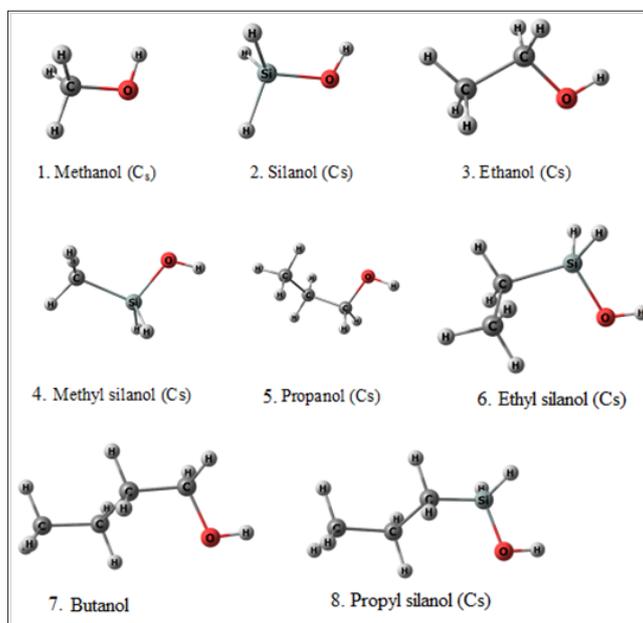


Figure 1: Local minimum structures of the investigated molecules calculated at MP2/6-311++G** level of theory.

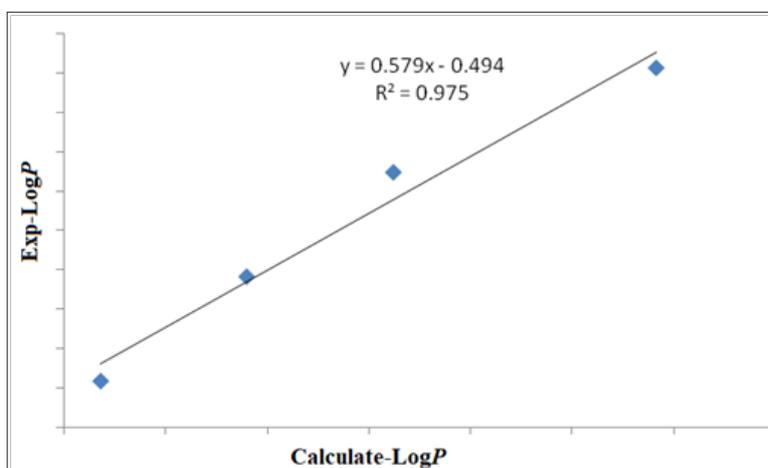


Figure 2: Correlation plot between the experimental and calculated LogP values.

Table 1: MP2/6-311++G** calculated values of LogP.

Molecule	LogP	
	Calculated	Experimental ¹⁰
Methanol	-0.317	-0.764
Silanol	0.359	
Ethanol	0.400	-0.235
Methyl silanol	0.805	
Propanol	1.121	0.294

Ethyl silanol	1.164	
Butanol	2.412	0.823
Propyl silanol	3.311	

Conclusion

Abinitio calculations at MP2/6-311++G** level of theory has been carried out for the theoretical calculation of lipophilicity parameter LogP. A nice linear correlation has been obtained for the set of alcohols studied in this work. The most important outcome of

this work is the theoretical verification of the previous speculation that incorporation of Si atom into the carbon containing drugs may increase the lipophilicity and hence, may increase the physiological activity of the Si containing drugs.

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References

- Lombardo F, Shalaeva MY, Tupper KA, Gao F, Abraham MH (2000) ElogPoct: a tool for lipophilicity determination in drug discovery. *J Med Chem* 43(15): 2922-2928.
- Sârbu C, Naşcu-Briciu RD, Casoni D, Kot-Wasik A, Wasik A, et al. (2012) Chromatographic lipophilicity determination using large volume injections of the solvents non-miscible with the mobile phase. *J Chromatogr A* 1266: 53-60.
- Komsta Ł, Skibiński R, Berecka A, Gumieniczek A, Radkiewicz B, et al. (2010) Revisiting thin-layer chromatography as a lipophilicity determination tool-a comparative study on several techniques with a model solute set. *J Pharmaceut Biomed* 53(4): 911-918.
- (1997) IUPAC, Compendium of Chemical Terminology, (2nd Edition), Blackwell Scientific Publications, Oxford.
- (2016) Molinspiration Cheminformatics, Bratislava, Slovak Republic.
- Estrada-Tejedor R, Sabaté N, Broto F, Nonell S (2013) the validation of quantum chemical lipophilicity prediction of alcohols. *Afinidad* 70: 564.
- Liao SY, Chen JC, Qian L, Shen Y, Zheng KC (2008) QSAR, action mechanism and molecular design of flavone and isoflavone derivatives with cytotoxicity against HeLa. *Eur J Med Chem* 43(10): 2159-2170.
- Khan AU (2016) Descriptors and their selection methods in QSAR analysis: paradigm for drug design. *Drug Discov Today* 21(18): 1291-1302.
- Garrido NM, Economou IG, Queimada AJ, Jorge M, Macedo EA (2012) Prediction of the n-hexane/water and 1-octanol/water partition coefficients for environmentally relevant compounds using molecular simulation. *AIChE J* 58(6): 1929-1938.
- Khadikar PV, Sharma V, Varma RG (2005) Novel estimation of lipophilicity using ¹³C NMR chemical shifts as molecular descriptor. *Bioorg Med Chem Lett* 15(2): 421-425.
- Ramesh R, Reddy DS (2017) Quest for Novel Chemical Entities through Incorporation of Silicon in Drug Scaffolds. *J Med Chem*.
- Møller C, Plesset MS (1934) Note on an Approximation Treatment for Many-Electron Systems. *Physn Rev* 46: 618-622.
- Frisch MJ, Trucks GW, Schlegel HB, GE Scuseria GE, Robb MA, et al. Cioslowski J and Fox DJ Gaussian 16, Revision A.03, Gaussian, Inc. Wallingford CT.



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