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Ameliorate QSPR Study of Alkyl Hydroperoxides[1]

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Abstract — A set of linear and nonlinear functions of one and several variables are determined to predict refractive index, molar refraction, and density for a representative set of alkyl hydroperoxides. Quite satisfactory predictions can be made on the basis of these equations and in some cases it is necessary to resort to higher-order equations to get a very good quantitative description of physical properties. Some possible further extensions of this study are pointed out in order to get a step head in the understanding of the quantitative structure–property relationships of alkyl hydroperoxides.

Hydroperoxides are derivatives of hydrogen peroxide with one hydrogen atom replaced by an organic radical:

$$\mathrm{H–O–O–H} \xrightarrow[-\mathrm{H}]{\mathrm{R}} \mathrm{R–O–O–H}.$$

Compounds in which R is an alkyl radical are termed alkyl hydroperoxides [1]. The chemistry of hydroperoxides had received strong development in 1950–1960s, following the firm establishment of these compounds as reactive intermediates in autooxidation of olefins [2–4]. Hydroperoxide research has not diminished in volume in the intervening years, and its most significant aspects have been published in the current literature [5]. Physical properties of alkyl hydroperoxides are well known, and they are very useful to elucidate many modes of their chemical decomposition.

One of the central topics in chemistry is the structure–property relationship [6], and it has fed a current trend in chemistry, pharmacology, toxicology, pharmaceutical drug design, and risk assessment of chemicals in order to predict behavioral properties of molecules from their structure [7]. The basic assumption underlying this field of research is that the structure of a molecule determines its behavior. It gave rise to the quantitative structure–property relationship approach (QSPR) [8]. This paradigm can be expressed by the general relationship

$$P = f(S),$$

where P is any physical property, and S may represent either an empirical property of the total molecular structure (or a relevant substructural fragment) or a theoretical structural descriptor quantitating some aspects of molecular structure [9]. There is a relatively large number of possibilities to choose S in the above equation, and a significant set is made up by quantum-chemical structural parameters calculated by *ab initio* or semiempirical methods [10].

The aim of this work is to present the results of a QSPR study of some alkyl hydroperoxides to calculate molar refraction, density, and refractive index resorting to quantum-chemical descriptors. The paper is organized as follows. First, basic definitions and the chosen algorithms are given. Next, the most significant results are discussed. Finally, conclusions are stated and possible future studies are pointed out.

The molecular properties currently used in correlations relate as directly as possible to the key physical properties of alkyl hydroperoxides studied here: molar refraction, density, and refractive index. These molecular properties are van der Waals-surface-bounded molecular volume (V), the log of the octanol–water partition coefficient ($\log p$), polarizability (P), solvent-accessible surface bounded molecular volume (SAG), and molar refraction (MR).

The calculation of $\log p$ was carried out using atomic parameters derived by Ghose *et al.* [12]. The computation of molar refraction (MR) was carried out by the same method as $\log p$. Ghose and Crippen [12, 13] presented atomic contributions to the refraction. The solvent-accessible surface bounded molecular volume (SAG) and the van der Waals-surface-bounded molecular volume (V) are based on the grid method described by Bodor *et al.* [14] using the atomic radii of Gavezotti [15]. The polarizability P was estimated by the additivity scheme given by

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Miller [16], where different increments are associated with different atom types. These quantum-mechanical descriptors were computed on a PC with the aid of ChemPlus software [17]. We have made complete regression analysis resorting to linear, quadratic, and cubic relationships in one, two, three, four, and five independent variables. The computations were carried out via Mathematica software [18].

Densities and molar refractions were studied for a set of 14 compounds: BuO_2H, *s*-BuO_2H, *n*-$C_5H_{11}O_2H$, $PrCH(Me)O_2H$, Et_2CHO_2H, *n*-$C_6H_{13}O_2H$, $BuCH(Me)O_2H$, $PrCH(Et)O_2H$, *n*-$C_7H_{15}O_2H$, *n*-$C_5H_{11}CH(Me)O_2H$, *n*-$C_8H_{17}O_2H$, *n*-$C_6H_{13}CH(Me)O_2H$, *n*-$C_9H_{19}O_2H$, and *n*-$C_{10}H_{21}O_2H$. Refractive indices were calculated for a set of 29 compounds: MeO_2H, PrO_2H, BuO_2H, *s*-BuO_2H, *i*-BuO_2H, *t*-BuO_2H, *n*-$C_5H_{11}O_2H$, $PrCH(Me)O_2H$, Et_2CHO_2H, *i*-$BuCH_2O_2H$, *n*-$C_6H_{13}O_2H$, *t*-$C_5H_{11}O_2H$, $BuCH(Me)O_2H$, $PrCH(Et)O_2H$, $PrC(Me)_2O_2H$, *n*-$C_7H_{15}O_2H$, *n*-$C_5H_{11}CH(MeO)_2H$, $BuCH(Et)O_2H$, Pr_2CHO_2H, $BuCH(Me)_2O_2H$, *n*-$C_8H_{17}O_2H$, *n*-$C_5H_{11}CH(Et)O_2H$, $BuCH(Pr)O_2H$, $BuCH(Et)CH_2O_2H$, *n*-$C_5H_{11}CH(Me)_2O_2H$, *n*-$C_6H_{13}CH(Me)_2O_2H$, $BuC(Me)(Pr)O_2H$, *n*-$C_9H_{19}O_2H$, and *n*-$C_{10}H_{21}O_2H$.

For conciseness, we present here only the best results which are given in Eqs. (1)–(22), for the free properties. Complete results are available from the authors.

Density

$$\delta = 9.5185\times10^{-1} - 1.2252\times10^{-4}V; \quad (1)$$

$$n\ 14,\ r^2\ 0.8851,\ ev = 1.8973\times10^{-5}.$$

$$\delta = 9.7464\times10^{-1} - 5.2691\times10^{-6}SAG - 1.4984\times10^{-6}(SAG)^2 + 2.2525\times10^{-9}(SAG)^3; \quad (2)$$

$$n\ 14,\ r^2\ 0.9299,\ ev\ 1.3879\times10^{-5}.$$

$$\delta = 1.5519 + 9.3708\times10^{-1}\log p - 3.1579\times10^{-1}(\log p)^2 + 3.5307\times10^{-2}(\log p)^3 - 2.8154\times10^{-1}P + 1.6571\times10^{-2}P^2 + 3.2535\times10^{-4}P^3; \quad (3)$$

$$n\ 14,\ r^2\ 0.9729,\ ev\ 7.6737\times10^{-6}.$$

$$\delta = 1.1857 + 3.2373\times10^{-1}\log p - 4.0028\times10^{-2}(\log p)^2 + 2.7817\times10^{-3}MR + 3.0481\times10^{-4}(MR)^2 - 9.8130\times10^{-2}P + 2.5151\times10^{-4}P^2; \quad (4)$$

$$n\ 14,\ r^2\ 0.9847,\ ev\ 4.3254\times10^{-6}.$$

$$\delta = -3.4395 + 1.8337\times10^{-1}SAG - 5.5427\times10^{-4}(SAG)^2 + 5.4843\times10^{-7}(SAG)^3 - 1.2037\times10^{-1}V + 2.3871\times10^{-4}V^2 - 1.54144\times10^{-7}V^3 + 9.0340\times10^{-1}P - 6.1427\times10^{-2}P^2 + 1.3307\times10^{-3}P^3; \quad (5)$$

$$n\ 14,\ r^2\ 0.9990,\ ev\ 4.5166\times10^{-7}.$$

$$\delta = 6.0276\times10^{-1} + 1.2640\times10^{-2}SAG - 2.2363\times10^{-5}(SAG)^2 - 6.6972\times10^{-3}V + 8.9752\times10^{-6}V^2 + 2.4770\times10^{-1}\log p - 3.4826\times10^{-2}(\log p)^2 - 4.7595\times10^{-2}P + 3.7182\times10^{-4}P^2; \quad (6)$$

$$n\ 14,\ r^2\ 0.9925,\ e = 9.9545\times10^{-6}.$$

$$\delta = 1.0595 - 2.3906\times10^{-3}SAG + 1.5400\times10^{-3}V + 1.2740\times10^{-2}\log p + 1.3886\times10^{-2}MR - 4.6241\times10^{-2}P \quad (7)$$

$$n\ 14,\ r^2\ 0.9600,\ ev\ 9.8981\times10^{-6}.$$

$$\delta = 3.9458\times10^{-1} + 1.1166\times10^{-2}SAG - 2.0003\times10^{-5}(SAG)^2 - 3.4823\times10^{-3}V + 5.3105\times10^{-6}V^2 + 2.2180\times10^{-1}\log p - 2.3676\times10^{-2}(\log p)^2 - 3.3743\times10^{-2}MR + 5.8736\times10^{-4}(MR)^2 - 1.8422\times10^{-2}P - 1.3641\times10^{-3}P^2; \quad (8)$$

$$n\ 14,\ r^2\ 0.9928,\ ev\ 4.7168\times10^{-6}.$$

Molar refraction

$$MR_{exp} = -17.9167 + 1.5645\times10^{-1}SAG; \quad (9)$$

$$n\ 14,\ r^2\ 0.9871,\ ev\ 1.0141.$$

$$MR_{exp} = 4.9712 + 1.8106P + 2.8171\times10^{-2}P^2; \quad (10)$$

$$n\ 14,\ r^2\ 0.9982,\ ev\ 0.1518.$$

$$MR_{exp} = -12.3596 + 2.2523MR + 3.8360(MR)^2 + 3.8496\times10^{-4}(MR)^3; \quad (11)$$

$$n\ 14,\ r^2\ 0.9992,\ ev\ 8.5043\times10^{-2}.$$

$$MR_{exp} = -2.0451 - 4.8383\log p + 3.5710P^2; \quad (12)$$

$$n\ 14,\ r^2\ 0.9998,\ ev\ 1.0205\times10^{-2}.$$

$$MR_{exp} = -1.1818 - 7.4778\times10^{-3}SAG - 4.7832\log p + 3.6842P; \quad (13)$$

$$n\ 14,\ r^2\ 0.9999,\ ev\ 9.5567\times10^{-3}.$$

$$MR_{exp} = -1.5625 + 8.3147\times10^{-3}SAG - 1.3352\times10^{-2}V - 4.7396\log p + 3.8012P; \quad (14)$$

$$n\ 14,\ r^2\ 0.9999,\ ev\ 9.9754\times10^{-3}.$$

$$MR_{exp} = -1.4843 + 8.7654\times10^{-3}SAG - 1.4221\times10^{-2}V - 4.6849\log p + 4.4849\times10^{-2}MR + 3.6947P; \quad (15)$$

$$n\ 14,\ r^2\ 0.9999,\ ev\ 1.1211\times10^{-2}.$$

Refractive index

$$\eta = 1.3751 + 1.9106\log p; \quad (16)$$

$$n\ 29,\ r^2\ 0.9094,\ ev\ 2.3547\times10^{-5}.$$

$$\eta = 1.3270 + 4.2403\times10^{-3}MR - 4.1684\times10^{-5}(MR)^2; \quad (17)$$

$$n\ 29,\ r^2\ 0.9897,\ ev\ 2.7796\times10^{-6}.$$

$$\eta = 1.3216 + 1.2213P - 4.0783\times10^{-4}P^2 + 4.1349\times10^{-6}P^3; \quad (18)$$

$$n\ 29,\ r^2\ 0.9908,\ ev\ 2.5891\times10^{-6}.$$

$$\eta = 1.3385 + 2.0011\times10^{-2}\log p - 3.7880\times10^{-3}(\log P)^2 + 2.2688\times10^{-3}MR - 1.1699\times10^{-5}(MR)^2; \quad (19)$$

$$n\ 29,\ r^2\ 0.9928,\ ev\ 2.1115\times10^{-6}.$$

$$\eta = 1.3208 + 3.7376\times10^{-3}\log p + 2.5320\times10^{-3}(\log p)^2 - 7.4559\times10^{-4}(\log p)^3 - 5.7215\times10^{-2}MR + 1.3583\times10^{-3}(MR)^2 - 9.7826\times10^{-6}(MR)^3 + 1.5459\text{–}10^{-1}P - 8.9500\text{–}10^{-3}P^2 + 1.5978\text{–}10^{-4}P^3; \quad (20)$$

$$n\ 29,\ r^2\ 0.9948,\ ev\ 1.9308\times10^{-6}.$$

$$\eta = 1.3803 - 2.7725\times10^{-4}SAG + 2.1010\times10^{-4}V + 1.0127\times10^{-2}\log p + 1.2641\times10^{-4}MR; \quad (21)$$

$$n\ 29,\ r^2\ 0.9930,\ ev\ 2.4268\times10^{-5}.$$

$$\eta = 1.3533 - 1.3786\times10^{-3}SAG + 1.5384\times10^{-6}(SAG)^2 + 1.1788\times10^{-3}V - 9.4422\times10^{-7}V^2 + 7.1879\times10^{-3}\log p - 5.1353\text{–}10^{-4}(\log p)^2 - 2.1101\text{–}10^{-2}MR + 3.6639\times10^{-4}(MR)^2 + 5.0629\times10^{-2}P - 2.1726\times10^{-3}P^2; \quad (22)$$

$$n\ 14,\ r^2\ 0.9960,\ ev\ 1.5532\times10^{-6}.$$

The correlations for density show that predictions for one- and two-variable formulas are not quite satisfactory, while for three, four, and five variables they are all quite satisfactory, especially at the third-order equations. Molar refraction can be nicely predicted even for one-variable expressons and from the first-order relations, while for several variables and higher orders the correlation coefficient is almost equal to unity. A similar situation happens with refractive index, although to get very good results one must resort to second- and third-order equations even though using several-variable formulas.

We can see that the selected quantum-chemical descriptors are suitable to predict the examined properties and that higher order relationships provide an appropriate quantitative tool to analyze refractive indices, densities, and molar refractions of alkyl hydroperoxides. Our results show the importance of employing second- and third-order equations to obtain a satisfactory predictive power with regression analysis.

One of the widely used data reduction techniques, multiple regression analysis, often gives valuable insights into structure–property relationships. However, most often a direct interpretation of the results of such analysis is rather difficult. It is generally understood that structure–property correlations at best suggest a parallel between the quantities involved (evaluators and responses) and that they do not necessarily reflect a cause–effect relationship [19]. The physical properties of alkyl hydroperoxides studied in this paper via the quantum-mechanical descriptors *SAG*, *V*, log *p*, *MR*, and *P*, depend not only on the structure in general terms but also on more subtle quantities some of which are directly related to the chosen descriptors. This work is the first attempt to thoroughly study the influence of the intimate molecular structure on the physical properties of alkyl hydroperoxides. Our present results suggest a dependence between the above quantum-mechanical descriptors and the examined physical properties. In order to advance a step further, the next question to be analyzed should be the degree of correlation between the variables. It is well known that the degree of interrelatedness depends upon the polynomials, and it is always present [20]. Work along this line of research is now in progress in our laboratories, and the results will be given elsewhere in the near future.

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