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Tables of proposed values for the Orientational Parameter of the Substituent I. Monoatomic, Diatomic, Triatomic, n-C_nH_{2n+1}, O-n-C_nH_{2n+1}, NRR', and Cycloalkanes (with a single ring) substituents

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ABSTRACT

Longtime ago, and from the analysis of the rotational partition function, a mathematical expression for the orientational parameters of the substituent was obtained [1, 2]. This parameter is purely geometrical and does not depend on any electronic property. As a preliminary physical interpretation we suggested that these terms represent the fraction of molecules attaining the proper orientation to interact with a given site. Given the necessity of having at hand "standard" numerical values for this parameter, we present here the first group of Tables for monoatomic, diatomic, triatomic, n-C_nH_{2n+1}, O-n-C_nH_{2n+1}, NRR', and cycloalkanes (with a single ring) substituents. Several relationships between the orientational parameters values are discussed.
Keywords: Orientational effect, substituent effect, QSAR, SAR, standard values, rotational partition function.

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INTRODUCTION

Longtime ago, and from the analysis of the statistical-mechanical definition of the drug-receptor equilibrium constant, a relationship with some atomic reactivity indices was developed [3]. This original expression was later expanded and considerably improved [4-7]. The subsequent analysis of the molecular rotational partition function led to the following definition of the Orientational Parameter of substituent "t", ϕ_t :

$$\phi_t = \sum_{p=1}^{n} m_{p,t} R_{p,t}^2 \qquad (1)$$

where the summation over p includes the n atoms composing substituent p, $m_{p,t}$ is the mass of the p-th atom belonging to substituent t and $R_{p,t}$ being the distance from the p-th atom to the atom to which the substituent is attached [2]. This approximation allowed us to transform a molecular property into a substituent's property. In several QSAR studies this orientational parameter (OP) appeared with different degrees of statistical significance [2, 8-19]. To elucidate the possible physical meaning for the OPs, let us consider the following very simple example. Fig. 1 shows the benzene molecule with the three moments of inertia around the principal axis of rotation (AM1 geometry optimization). We shall assume that this molecule is the most active one of a series of molecules that are recognized by a certain site and that the aromatic moiety is the part of the molecule that is recognized by the site.

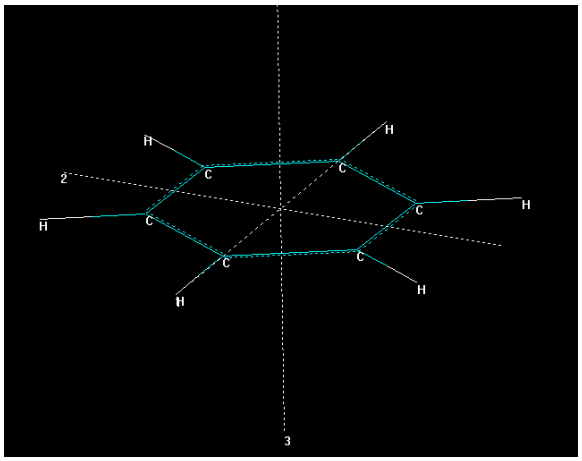

Figure 1: Benzene molecule.

In a biological setting (a laboratory experiment or a living organism), and close to the interaction site, the group of benzene molecules has a distribution of rotational and translational velocities that depends on the temperature and composition of the *milieu*. On the other hand, there is a window of time of limited duration during which the recognition and guiding of the benzene molecules toward the interaction site can be accomplished. In simple terms, the site needs to brake and to orientate the molecule during the window of time. For explanatory effects, we shall accept that the rest of the active molecules must achieve a similar pattern of rotation than the benzene molecule to be recognized and orientated toward the site. Now let us consider the *n*-pentyl-benzene and methoxybenzene (anisole) molecules shown in Fig. 2 (with AM1 geometry optimization).

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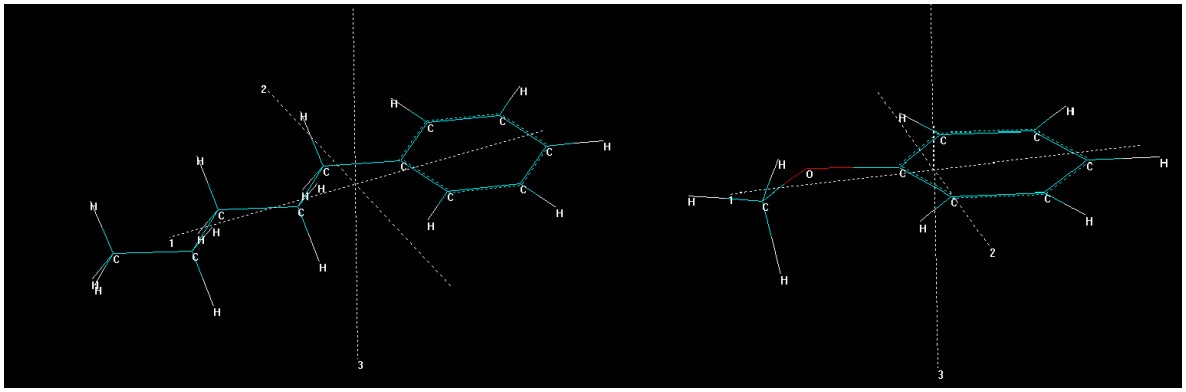

Figure 2: *N*-pentylbenzene (left) and methoxybenzene (right) molecules.

Assuming that the real conformation of the n-pentyl and methoxy substituents during the window of time is the one shown in Fig. 2, it is easy to understand that it is more difficult to brake *n*-pentylbenzene than methoxybenzene. Is in this sense that we suggested that the physical interpretation of these parameters is related to the fraction of molecules attaining the proper orientation to interact with a given site.

MODELS AND CALCULATIONS

The molecules were built with Hyperchem software [20]. First, a benzene molecule lacking a hydrogen atom was built. For the calculation of the OP value of a particular substituent, we attached it to the free valence of the benzene ring and the option "model build" of Hyperchem was used to get the final structures. This choice is arbitrary and based only on the simplicity of work. The carbon which originally lacked an H atom was chosen as the origin of the Cartesian coordinate system (the (0,0,0) point). OPs were calculated with the STERIC software [21]. We employed the standard atomic weights of year 2015 (http://www.ciaaw.org/atomic-weights.htm) in Eq. 1. For the *n*-C_nH_{2n+1} hydrocarbons (Table 2, below), monoatomic substituents (Table 1, below), O-*n*-C_nH_{2n+1} substituents (Table 3, below) and diatomic and triatomic substituents (Table 5, below) we used the abovementioned option "model build". Also, for *n*-C_nH_{2n+1} and O-*n*-C_nH_{2n+1} substituents, we calculated the OP of the most extended structure. In the case of some substituents, marked * in Table 4, we carried out a molecular mechanics optimization to eliminate some small H-H distances. We are aware that we are introducing a small distortion in the OP values due to the fact that geometry optimization included the phenyl ring.

RESULTS AND DISCUSSION

Table 1 shows the OP proposed values for monoatomic substituents.

Table 1: Monoatomic substituents.

Substituent	ϕ (amu·Å^2)		Substituent	ϕ (amu·Å^2)
H	1.18		Cs	1261.56 (3.081 Å)
Li	26.68 (1.960 Å)		F	40.00 (1.451 Å)
Na	118.38 (2.270 Å)		Cl	105.08 (1.723 Å)
K	297.86 (2.761 Å)		Br	279.89 (1.872 Å)
Rb	714.44 (2.891 Å)		I	539.43 (2.062 Å)

Considering that we used a X-C (aromatic) bond to calculate the OPs, we included in the Table the C-X distance. In the case of cations, the OP values should be used with caution because normally the molecules carrying them are fully dissociated in a biological environment. As Fig. 3 shows, a polynomial fit of degree two with zero intercept works good for groups of elements 1 and 17. There are small discrepancies for the case of group 1 that could be perhaps an indication that some distances are not the exact ones. Possibly more exact OP values for this group can be obtained from crystallographic data if needed.

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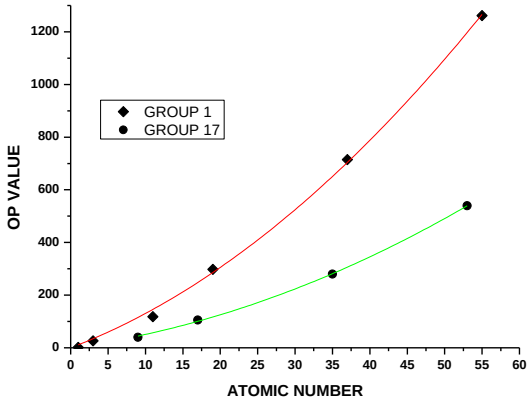

Figure 3: Polynomial fit of atomic number *vs.* OP value.

Table 2 shows the OP values for linear hydrocarbons in their fully extended form.

Table 2: *n*-C_nH_{2n+1} hydrocarbons (fully extended form).

Substituent	ϕ (amu·Å^2)		Substituent	ϕ (amu·Å^2)
CH_3	41.59		*n*-C_8H_{17}	5054.52
C_2H_5	138.96		*n*-C_9H_{19}	7090.21
n-C_3H_7	362.03		*n*-$C_{10}H_{21}$	9358.66
n-C_4H_9	730.62		*n*-$C_{11}H_{23}$	11905.71
n-C_5H_{11}	1313.98		*n*-$C_{12}H_{25}$	14744.26
n-C_6H_{13}	2131.21		*n*-$C_{13}H_{27}$	17976.98
n-C_7H_{15}	3281.72		*n*-$C_{14}H_{29}$	21548.08

Table 3 displays the OP values for the O-*n*-C_nH_{2n+1} substituents.

Table 3: O-*n*-C_nH_{2n+1} substituents (fully extended conformation).

Substituent	ϕ (amu·Å^2)		Substituent	ϕ (amu·Å^2)
OCH_3	85.72		O-*n*-C_8H_{17}	6969.23
OC_2H_5	285.12		O-*n*-C_9H_{19}	9294.23
O-*n*-C_3H_7	622.79		O-*n*-$C_{10}H_{21}$	11911.50
O-*n*-C_4H_9	1166.44		O-*n*-$C_{11}H_{23}$	14712.24
O-*n*-C_5H_{11}	1937.74		O-*n*-$C_{12}H_{25}$	18028.60
O-*n*-C_6H_{14}	3041.33		O-*n*-$C_{13}H_{27}$	21687.32
O-*n*-C_7H_{15}	4876.30		O-*n*-$C_{14}H_{29}$	25703.51

Figure 4 shows that a polynomial fit of degree two with zero intercept works good for both substituents.

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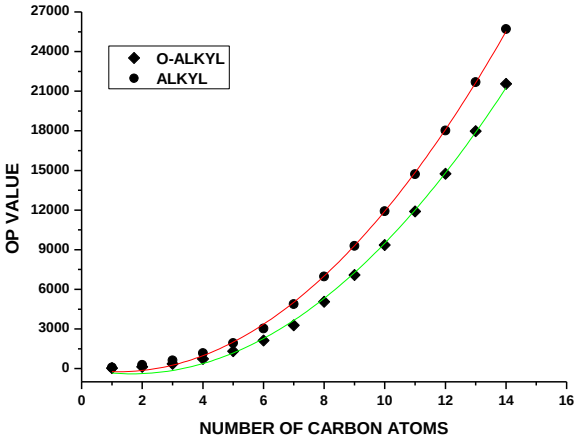

Figure 4: Polynomial fit of number of carbon atoms *vs.* OP value for *n*-C_nH_{2n+1} (fully extended form, green line) and O-*n*-C_nH_{2n+1} substituents (red line).

Table 4 shows the OP values for N(H)R and NRR substituents. Figure 5 shows the plot of the number of carbon atoms *vs.* the OP value for N(H)R and NRR substituents.

Table 4: NRR' substituents

Substituent	ϕ (amu·Å^2)		Substituent	ϕ (amu·Å^2)
N(H)CH_3	124.64		N(C_2H_5)(*n*-C_3H_7)	1033.55*
N(CH_3)$_2$	216.63		N(H)(*n*-C_4H_9)	1246.26
N(H)C_2H_5	330.74		N(*n*-C_4H_9)$_2$	2303.03*
N(C_2H_5)$_2$	671.82*		N(CH_3)(*n*-C_4H_9)	1395.25*
N(CH_3)(C_2H_5)	444.11*		N(C_2H_5)(*n*-C_4H_9)	1619.40*
N(H)(*n*-C_3H_7)	687.06		N(*n*-C_3H_7)(*n*-C_4H_9)	1780.36*
N(*n*-C_3H_7)$_2$	1394.66*		N(H)(*n*-C_5H_{11})	2044.54*
N(CH_3)(n-C_3H_7)	810.73*		N(*n*-C_5H_{11})$_2$	3830.77*

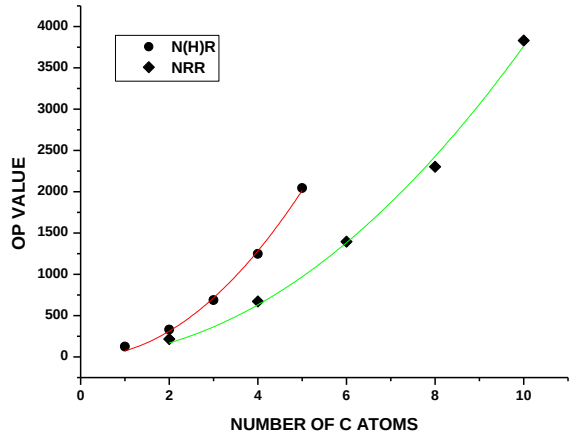

Figure 5: Polynomial fit of number of carbon atoms *vs.* OP value for N(H)R (red line) and NRR substituents (green line).

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We can see that in this case, despite geometry optimization, we may calculate the OP value for longer substituents using the fitting formula instead of carrying out the full procedure. Table shows the OP values for some diatomic and triatomic substituents.

Table 5: Some diatomic and triatomic substituents.

Substituent	ϕ (amu·Å^2)		Substituent	ϕ (amu·Å^2)
OH	33.23		C(H)O	116.95
SH	109.35		C≡CH	123.44
CN	120.71		PH_2	117.73
NO_2	212.68		PO_2	418.25
NS_2	486.79		BH_2	38.69
N(S)O	349.70		NH_2	32.66

Table 6 shows the OP values for cycloalkanes with a single ring and Figure 6 displays the plot of number of carbon atoms *vs.* the OP value.

Table 6: Cycloalkanes with a single ring.

Substituent	ϕ (amu·Å^2)		Substituent	ϕ (amu·Å^2)
c-C_3H_5	243.16		*c*-C_7H_{13}	951.36
c-C_4H_7	390.47		*c*-C_8H_{15}	1390.53
c-C_5H_9	636.75		*c*-C_9H_{17}	1855.79
c-C_6H_{11}	660.28		*c*-$C_{10}H_{19}$	1890.18

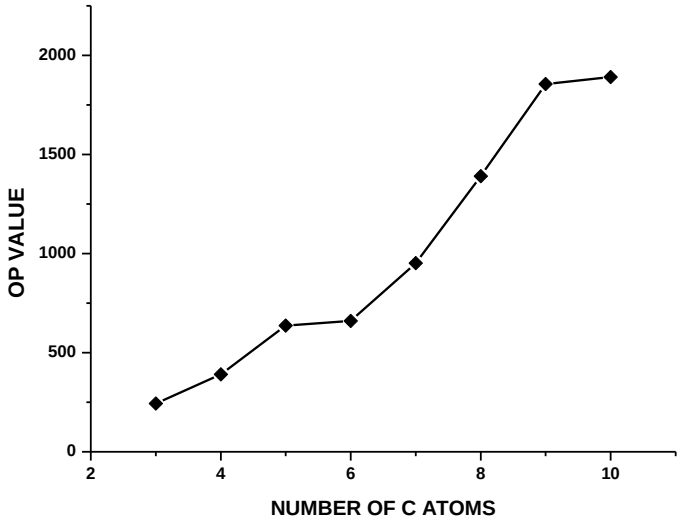

Figure 6: Plot of the number of carbon atoms *vs.* OP value for cycloalkanes with a single ring.

Here we can see that there is no a direct relationship between the number of carbon atoms and the OP values. The reason is the growing number of possible conformations for large cycloalkanes. Probably it would be possible to generate OP values for large cycloalkane that led to a good polynomial fit. The values provided here can be used for a first and fast screening of a set of molecules. For the case of large substituents, it is preferable to select a specific conformation and calculate the specific OP value. As an example of a specific choice, Fig. 7 shows the results of a molecular mechanics optimization of *n*-pentyl phenyl surrounded by water molecules.

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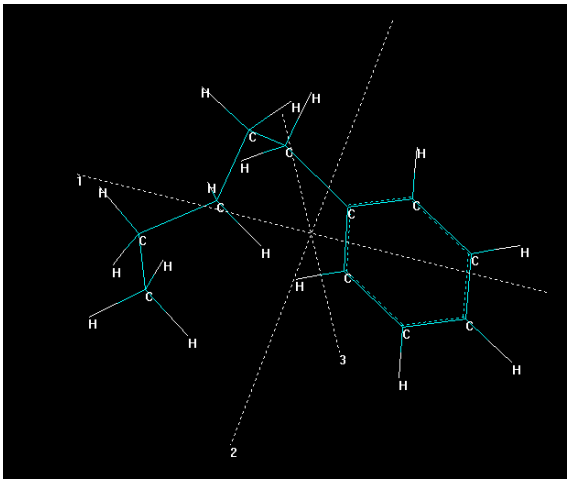

Figure 7: A possible *n*-pentyl phenyl conformation.

The OP value for this conformation is 1057.87 (compare with Table 2). Let us consider another example. A statistically significant equation has been obtained and from it we observe that a given substituent must have a small OP value for better activity. If the substituent is small we may use the OP values of the Tables. Nevertheless, there is another fact that must be considered. Despite the fact that the orientational parameters have a purely geometrical meaning, they also influence the electronic structure of the molecules. Then, if in our series an ethyl substituent (OP value = 138.96, Table 2) has the smallest OP value we may suggest that a methyl substituent (OP value = 41.59) should be used because it has a smaller OP value. But it is not correct to replace the ethyl group by, for example, a fluorine atom (OP value = 40.00, Table 1), because the electronic effects of the later are different. Here, the chemical criterion must be employed.

If you are interested in calculating specific OP values for a given substituent you may contact the author for a free executable copy of the STERIC software together with a short manual.

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