Revue Roumaine de Chimie, **2009**, *54*(8), 671–675

MOLECULAR DESCRIPTORS FOR THE STUDY OF LIPOPHILICITY IN CATECHOLAMINE CLASS

Emilia AMZOIU, [a] * Manuel Ovidiu AMZOIU [b] and Paul Gabriel ANOAICA [a]

[a] Faculty of Pharmacy, University of Medicine and Pharmacy Craiova, 1 Mai 66, Craiova, 200638, Roumania
[b] Scholar Group "I.G. Murgulescu", Brestei 154, Craiova, 200232, Roumania

Received November 12, 2007

The values of the partition coefficient log P (1-octanol/water) for catecholamines has been correlated with molecular shape descriptors CMSA and MV, moments of inertia, their projections (shadow indices) or molecular surfaces where the electrical charged atoms are disposed after forming chemical connections. The knowledge through QSAR technique of the factors that influence the partition coefficients can be useful in the optimization of transport proprieties and maximization of diffusion speed of drugs through biomembranes.

INTRODUCTION

Catecholamines are compounds that appear in a natural way in the human body as hormones or neurotransmitters for sympathetic nervous system.[1-6] These substances prepare the body for cold, fatigue and shock state or physical activity.

Because the activity of catecholamine take place in aqueous environments we try in this paper to correlate the chemical structures of catecholamine represented through different descriptors with the solubility of this substances and, in particular, with the partition coefficient log P, where P represent the partition between two phases, one aqueous and another lipidic.

Indeed, many of the biochemical interactions appear in the aqueous as well as in the lipophilic phases within the biological membranes or at active site of some enzymes or proteins. The nature of this phases can profoundly influence the biological process, like reactivation of ligand-receptor connection or molecular transport through biomembranes.[7-11]

It is know that transport through cellular membranes represents the physico-chemical phenomen on through which the drugs are absorbed by the organism, specially through diffusion. This last process is condition by the solubility of the drugs in the biological membranes and their partition coefficient, which express the differential solubility of the substances in aqueous and organic solvents.[12, 13] The best organic solvent for the study of biological system is 1-octanol, which simulate better the lipidic membrane of cells.[14]

The partition coefficient $log\ P = log \frac{C_1}{C_2}$, where C_1 represents the concentration of substance dissolved in organic solvent and C_2 the concentration of substance dissolved in water, is widely used to predict the pharmacokinetic proprieties like bioavailability, transport and elimination from the human body.

The importance of the partition coefficient for drugs is given by its connection with transport speed through a biological membrane which separate two aqueous compartments.

In drug design is made a optimization of transport speed by increasing the solubility in water for very hydrophobic substances and increasing the solubility in lipides for hydrophilic substances. This thing can be done by introducing in the molecule of a drug substance some hydrophobic groups as alkyl radical, halogens etc. for lipophilic optimization, or through cutting hydrophilic groups as hydroxyl without affecting the biological activity of the substances.[13]

* Corresponding author: emanro2002@yahoo.com

RESULTS AND DISCUSSION

In the present study we try to analyze the electronic, energetic and molecular shape structural factors that are use to the partition coefficient for a series of 17 substances from catecholamine class and analogue compounds, indicated in Figure 1 and Table 1. The experimental values for these substances are reported in literature.[13, 15]

For better understanding of the way these molecular descriptors work we selected from Table 1 two groups of substances with a variable number of -OH groups that influence the experimental values of the partition coefficient in a obviously manner. This substances are presented in Tables 2 and 3.

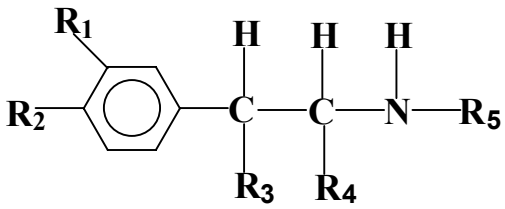

Fig. 1 – Structures of catecholamine derivatives.

Table 1

The values of the partition coefficient for catecholamine derivatives

Nr.	Substance	R_1	R_2	R_3	R_4	R_5	log P
1	Amphetamine	H	H	H	CH_3	H	1.41
2	Fenylethylamine	H	H	H	H	H	1,07
3	Fenylephrine	OH	H	OH	H	CH_3	-0.03
4	Metaraminol	OH	H	OH	CH_3	H	-0.09
5	Tiramine	H	OH	H	H	H	-0.24
6	o-Metyldopamine	OCH_3	OH	H	H	H	-0.29
7	Isoprenaline	OH	OH	OH	H	$CH(CH_3)_2$	-0.52
8	Sinephrine	H	OH	OH	H	CH_3	-0.59
9	o-Metyladrenaline	OCH_3	OH	OH	H	CH_3	-0.64
10	Octopamine	H	OH	OH	H	H	-0.99
11	Dopamine	OH	OH	H	H	H	-0.99
12	o-Metylnoradrenaline	OCH_3	OH	OH	H	H	-1.04
13	Adrenaline	OH	OH	OH	H	CH_3	-1.34
14	α-Metylnoradrenaline	OH	OH	OH	CH_3	H	-1.40
15	Noradrenaline	OH	OH	OH	H	H	-1.74
16	Tyrosine	H	OH	H	COOH	H	-1.79
17	3,4-Dihydroxyphenyilalanine	OH	OH	H	COOH	H	-2.54

Table 2

Catecholamines with a variable number of -OH groups

Group A	R_1	R_2	R_3	R_4	R_5	log P
Fenylethylamine	H	H	H	H	H	1,07
Tiramine	H	OH	H	H	H	-0,24
Dopamine	OH	OH	H	H	H	-0,99
Noradrenaline	OH	OH	OH	H	H	-1,74

Table 3

Catecholamines with -OH and CH_3 groups

Group B	R_1	R_2	R_3	R_4	R_5	log P
Fenylethylamine	H	H	H	H	H	1,07
Fenylephrine	OH	H	OH	H	CH_3	-0,03
Sinephrine	H	OH	OH	H	CH_3	-0,59
Adrenaline	OH	OH	OH	H	CH_3	-1,34

As we can notice the progressive introduction of hydroxyl groups causes a decrease of lyophilicity and an increase of hydrophilicity expressed here through negative values of log P.

The QSAR/QSPR technique, to correlate a propriety, here the partition coefficient, with structural and molecular descriptors show the dependence of lipophilicity with Connolly molecular surface area (CMSA), with molecular volume (MV) and, especially, with the electronic factor FNSA-3 that is fractional atomic charge weighted partial negative surface area.

The results of linear regression are indicated in Tables 4 and 5:

Table 4

Molecular shape descriptors and electrical charged descriptors (Group A)

Substance / **R^2**	**CMSA (Å^2)** **0.9872**	**MV(Å^3)** **0.9737**	**FNSA-3** **0.9977**	**log P**
Fenylethylamine	315,44	470,58	-0,0286	1,07
Tiramine	326,50	491,47	-0,0481	-0,24
Dopamine	335,96	511,73	-0,0585	-0,99
Noradrenaline	346,86	530,67	-0,0720	-1,74

Table 5

Molecular shape descriptors and electrical charged descriptors (Group B)

Substance / **R^2**	**CMSA (Å^2)** **0.9598**	**MV(Å^3)** **0.8598**	**FNSA-3** **0.9609**	**log P**
Fenylethylamine	315,44	470,58	-0,0286	1,07
Fenylephrine	370,25	569,58	-0,0503	-0,24
Sinephrine	371,17	570,20	-0,0535	-0,99
Adrenaline	380,14	587,07	-0,0628	-1,74

CMSA – Connolly molecular surface area
MV – molecular volume
FNSA-3 – fractional atomic charge weighted partial negative surface area
log P – partition coefficient

As we can see in Table 4, the decrease of lipophilicity (negative values for log P) is caused by the increase of the molecular surface area or the molecular volume of substances (correlation coefficients 0.9872, respectively 0.9737). The increase of the molecular surface area or the molecular volume is given by the progressive introduction of hydroxylic groups into the molecule.

The electronic factor that would essentially give an increase of hydrophilicity is FNSA-3, with the partition coefficient closest to the unity (0.9977). This descriptor is, actually, the part of molecular surface negatively charged reported to the all molecular surface. Is assume that this electrostatic descriptor condition the hydrophilic interaction of the studied molecules.

As group B of catecholamine is concerned, in Table 5 we can see, as in the case of first group, the increase of hydrophilicity with the increase of the molecular surface area and the molecular volume, variation explained by progressive introduction of hydroxyl groups into the molecule. The fact that the hydrophilicity depends on the number of hydroxyl groups is obvious, the correlation coefficients being for the molecular surface area 0.9598 and for molecular volume 0.8958.

As in the first group of catecholamine, the descriptor FNSA-3 (the correlated coefficient is 0.9609) is conditioning the electrostatic type interactions that would lead to the increase of hydrophilicity.

Being obvious that the three descriptors selected by QSAR technique are conditioned by the shape and size of the molecule and its access to the solvent (Connolly surface), we considers necessary the study of lipophilicity for all catecholamines represented in Table 1. To this purpose, we made the modelling of all molecular structures from Table 1 in the same way as for those from Tables 2 and 3.

Using the semiempirical quantomolecular procedure MOPAC 7[16] (RHF, PM3) and CODESSA 2.64 program[17] for QSAR type correlations between different molecular descriptors that can be

regressionaly calculated from output MOPAC type files, we obtain the next results concerning the correlation coefficients (noted in the CODESSA program with R2, Table 6):

Table 6

The multiliniar regression analysis log P = $a_0+a_1X_1+a_2X_2+\ldots$, X_i = descriptors

4 descriptors: best correlation R2 = 0.9202 (4 descriptors) 25 216 211 152	*descriptors involved:* 25 - Final heat of formation 216 – Principal moment of inertia C / # of atom 211 - Principal moment of inertia A 152 - Max electron-nuclear attraction for a C-C bond
2 descriptors: best correlation R2 = 0.8317 (2 descriptors) 83 160	*descriptors involved:* 83 - FNSA-3 Fractional PNSA (PNSA-3/TMSA) /MOPAC PC/ 160 - Max resonance energy for a C-H bond
1 descriptor: best correlation 1. R2 = 0.7595 (1 descriptors) 210 2: R2 = 0.7558 (1 descriptors) 28 3: R2 = 0.7498 (1 descriptors) 83 4: R2 = 0.7371 (1 descriptors) 80 5: R2 = 0.7305 (1 descriptors) 101 6: R2 = 0.7193 (1 descriptors) 100 7: R2 = 0.7086 (1 descriptors) 206 8: R2 = 0.6901 (1 descriptors) 123 9: R2 = 0.6822 (1 descriptors) 97 10: R2 = 0.6639 (1 descriptors) 79	*descriptors involved:* 210 - Total molecular electrostatic interaction /# of atoms 28 - No. of occupied electronic levels / # of atoms 83 - FNSA-3 Fractional PNSA (PNSA-3/TMSA) /MOPAC PC/ 80 - PNSA-3 Atomic charge weighted PNSA /MOPAC PC/ 101 - FHBCA Fractional H-bonding charged surface area 100 - HBCA H-bonding charged surface area /MOPAC PC/ 206 - Total molecular two-center resonance energy / # of atoms 123 - Average valency of a H atom 97 - FHDCA Fractional H-donors charged surface area 79 - PPSA-3 Atomic charge weighted PPSA /MOPAC PC/

As we can notice, molecular shape descriptors are important in the partition process between the aqueous and the lipidic phases (1-octanol). Indeed, the values of moments of inertia depend of molecular shape, that being the reason why the moments of inertia and their components projection on different planes (shadow indices), are considered descriptors in QSAR technique. This become even more obvious when there are considered fewer descriptors. In this case, the correlations show that this coefficient values depend on the positive and negative electrical charges repartition on atoms, but also on the spatial arrangement of these molecules (the descriptors 83, 80, 101, 100, 97 and 79 that depend, in the last instance, of spatial shape of each molecule).

The dependence between the partition coefficients and spatial arrangement of electrical charges on the atoms in the molecule is to be expected, because the hydrophilic character of a substance is based, most of the times, on its electrostatic interactions with the solvent.

As a conclusion, we can say that the interaction between ligand and receptor is conditioned by a reduce number of descriptors: molecular shape descriptors (CMSA, MV, R^2 = 0.85 - 0.99), moments of inertia, their projections (shadow indices) or the molecular surfaces where the electrical charged atoms are disposed after forming chemical connections.

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