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ON THE STERIC DIFFERENCE (SD) METHOD BASIS FOR ORDERING OF BIOACTIVE STRUCTURES

I. Moţoc and R. Vâlceanu

Chemistry Research Centre
Bul. Mihai Viteazu 24, 1900 Timişoara
Romania

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Content. The paper shows that our steric difference (SD) method defines a partial ordering of bioactive structures. Grid diagrams are built up for two series of hapten - antibody interactions.

1. Introduction

The ordering of structures is a very important problem, and it has been considered both from a mathematical (Muirhead[1], Karamata[2]) and a chemical viewpoint (Ruch[3], Randić and Wilkins[4,5], Randić[6-8]). Because ordering implies comparison, one characterizes the structures by numbers or sequences of numbers and one compares these attached numbers or sequences of numbers.

Any good structure-reactivity or chemical structure-biological activity correlation defines an ordering of the considered structures. For examples, Taft-type equations (i.e. E_S, E_S', E_S^c, E_S^o, E_S^e and ν - for a review see ref. 12) induce the following ordering : the substituent X is bulkier than the substituent Y if $E_{S,X} < E_{S,Y}$ (or $E'_{S,X} < E'_{S,Y}$, ... , $E^e_{S,X} < E^e_{S,Y}$, $\nu_X > \nu_Y$). We note that the mentioned correlations define partial ordering, namely an ordering of a subset of structures. The restricting factors are the geometry of the transition state[10, 11] the conformational rigidity of the parent structure[9] (for LFER's) and the nature of the investigated biological receptor (for QSAR's).

Once an established hyerarchical order is available, a grid diagram may be used to estimate qualitatively missing data. Or, better, one may use the numbers or sequences of numbers characterizing the studied structures as independent variables in correlational equations, which allow quantitative predictions.

2. The Steric Difference (SD) Method

We developed[13,14] the steric difference (SD) method in order to account quantitatively for the steric effects in effector - receptor interactions. The method applies both to congener and non-congener series of bioactive molecules. We are interested to compare the shape of the receptor cavity with the shape of the considered effectors. Toward this end we define the SD function as :

$$SD : \{S\} \times \{S_i\}_{i=1,2,\ldots,n} \longrightarrow N \times N$$

where S is a structure complementary to the receptor cavity, S_i is the structure of the effector and N stands for the set of natural numbers. The n considered effectors elicit the biological response BR interacting with the same biological receptor, via the same mechanism. Thus, $SD(S,S_i)$ results in a pair of natural numbers, namely $[SD_c ; SD_w]$.

The SD function has the following properties : $SD(S, S) = [0 ; 0]$, and, in general, $SD(S, S_i) \neq SD(S_i, S)$.

The values of the SD function are computed according to the following algorithm :

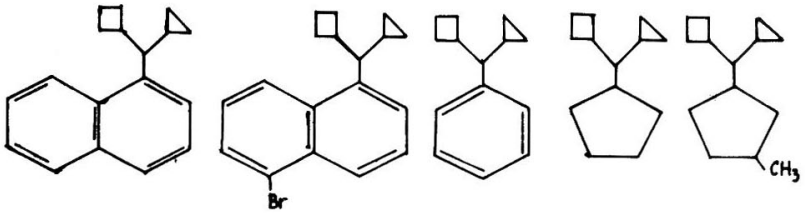
1) If other alternatives are not available, the structure of the most potent drug from the studied series is considered complementary to the receptor cavity. This structure, denoted by S, is termed standard.

2) Superimpose S_i over S. The hydrogen atoms are neglected and the superposition is performed according to the rule that one superimposes the pharmacon of S and S_i. We note that the superposition of the pharmacons implies that the effectors bind the receptor in the same way. In order to obtain a method easy to use for performing the geometrical congruences, one may neglect differences lower than $\pm 0,2$ Å and $\pm 20^{\circ}$ in the bond lengths and bond angles of the effectors.

3) Count the number of unsuperposable non-hydrogen atoms of S over S_i. This number is denoted by SD_c (c for cavity) and it expresses the non-occupancy of the receptor cavity.

4) Count the number of unsuperposable non-hydrogen atoms of S_i over S. This number is denoted by SD_w (w for wall) and it accounts for the number of atoms which would fall into the cavity walls, deforming them.

Illustratively, for the series of compounds :



S_1(S) S_2 S_3 S_4 S_5

( denotes the pharmacon ; the number of atoms of the pharmacon may be neglected) the SD function has the following values:

S_i	$SD(S,S_i) = [SD_c ; SD_w]$
S_1	0 ; 0
S_2	0 ; 1
S_3	4 ; 0
S_4	5 ; 0
S_5	5 ; 1

For further discussions and applications of the SD method see refs. 13 - 17.

3. The SD Method Basis for Ordering Bioactive Structures

Using the SD method we can characterize each structure of a series of effectors by the pair of natural numbers $[SD_c ; SD_w]$ which modelates the steric effects in effector/receptor interactions. Accordingly, all the structures can be represented as points on a grid. The rule for ordering specifies that two structures (denoted by 1 and 2) can be compared if $SD_{c,1} \leq SD_{c,2}$ and $SD_{w,1} \leq SD_{w,2}$. If this condition holds, we connect the corresponding points on the grid ; the structure 1 dominates the structure 2.

For the haptens collected in Table 1 the SD values were computed according to the described algorithm, with compound 16 as standard (the pharmacon here considered is the nitrogen atom of the heterocycle).

The grid pattern with points corresponding to the seven-

teen substituted pyridine haptens is shown in Figure 1.

For the haptens collected in Table 2 the SD values were computed against p-(p'-azophenylazo)benzoate ion as standard (it is known that the antibody active site copies the shape of the antigenic part of the immunogen[17]). The superpositions were performed considering the carboxyl group as pharmacon. The relative equilibrum constants, K_{rel}, are taken from ref. 17.

The grid for K_{rel} is shown in Figure 2.

Concerning the usefulness of the grid diagrams we must note that it is restricted to cases where the entries of the sequences of numbers (i.e. the coordinate axis of the grid, in our case SD_c and SD_w) have about the same weight in conditioning the relevant property of the considered structures. This problem was omitted by Randić in his discussion on the grid diagrams[4-8]. Thus in our opinion, the correlation equations remain the most important tool in the present context. This statement is argued by the correlation equation computed with the data collected in Table 2 :

$$\log K_{rel} = 2.189 - 0,187\ SD_c - 0,170\ SD_w$$

$$(r = 0,940,\ s = 0,248,\ F = 35.210,\ EV = 0,867,$$
$$r(SD_c,\ SD_w) = -0,142)$$

Obviously, this equation contains more informations than the grid diagram depicted in Figure 2.

4. Conclusions

i) The steric difference method introduced the $SD = [SD_c;\ SD_w]$ steric parameters. They are easily accesible and may be computed both for congener and non-congener effector series.

ii) The steric difference method represents a basis for ordering the bioactive structures via grid diagrams or correlation equations.

iii) The SD and MSD (see ref. 19) methods have in common the first point of the computing procedure, Because the physical significance of the MSD parameter is ambigous, the usefulness of the MSD parameter is limited. The MTD version[20] of the MSD method adds new difficulties : as Motoc has proved[21], the optimization procedure[20] optimizes the correlation coefficient of the BR vs MTD equation and it does not optimize the standard structure, as it had been claimed[20].

Acknowledgement

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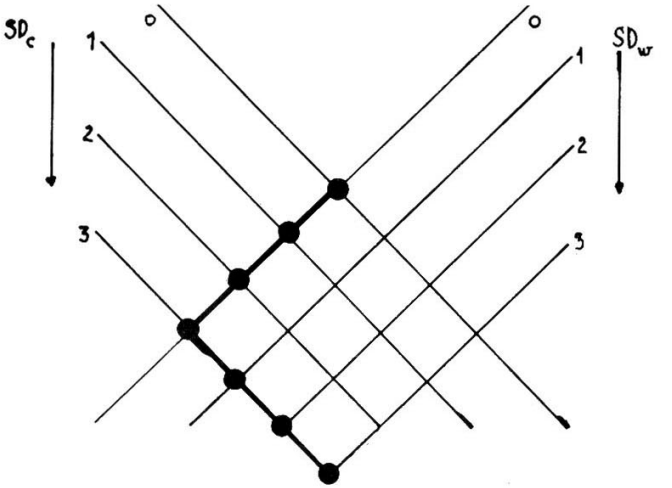


Fig.1. Grid illustrating the hyerarchical relationship and the associated partial order for the haptens collected in Table.1.

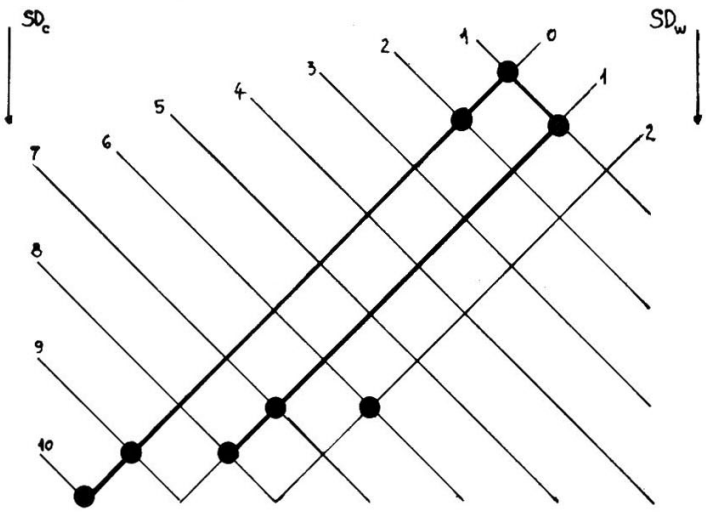


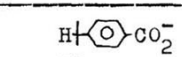
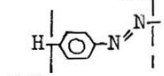
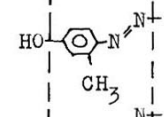
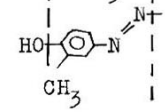
Fig.2. Grid illustrating the hyerarchical relationship and the associated partial order for the haptens collected in Table 2.

Table 1. Combination of X - Substituted Pyridines in Anti-3-Azo-pyridine System.

No.	X	$-\Delta F^{o}_{rel}$	SD_c	SD_w
1.	H	0,00	3	0
2.	2-NH_2	-0,98	3	1
3.	3-NH_2	-0,16	2	0
4.	4-NH_2	-2,02	3	1
5.	2-CH_3	-0,26	3	1
6.	3-CH_3	0,66	2	0
7.	4-CH_3	-0,49	3	1
8.	2-CN	-1,09	3	2
9.	3-CN	0,05	1	0
10.	4-CN	-1,09	3	2
11.	3-CH_2OH	0,05	1	0
12.	4-CH_2OH	-1,46	3	2
13.	2-Cl	-0,56	3	1
14.	2-Br	-0,53	3	1
15.	3-Br	0,48	2	0
16.	3-Acetyl	0,69	0	0
17.	2,4,6-tri-CH_3	-1,09	3	3

($-\Delta F^{o}_{rel}$ values are taken from ref. 18)

Table 2. Combination of Para-Substituted Benzoates in Anti-p-(p'-azophenylazo)benzoate System.

No.	Hapten	K_{rel}	SD_c	SD_w
1.		1.0	10	0
2.	F–	3.6	9	0
3.	Cl–	5.3	9	0
4.	H_2C–	1.8	9	0
5.	Br–	5.4	9	0
6.	J–	9.0	9	0
7.	H_2N–	2.1	9	0
8.	HO–	4.7	9	0
9.	O_2N–	1.8	8	1
10.	^-O_2C–	5.3	8	1
11.	$H_3CC(O)HN$–	1.6	7	1
12.	Ph–	6.8	6	2
13.		67	2	0
14.	H_2N–	70	1	0
15.	H_3C–	65	1	0
16.	HO–	111	1	0
17.		81	1	1
18.		125	1	1

(K_{rel} values are taken from ref. 17)