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MOLECULAR INTERACTIONS IN BIOLOGICAL SYSTEMS. V.[1] THE STRUCTURAL DISTANCE INDUCED BY SD* AND ITS APPLICATION TO THE TASTE CHARACTERISTICS OF ENANTIOMERIC AMINOACIDS.

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Abstract. The Steric Difference method (SD*) induces the structural distance d_{ij} between the bioactive structures S_i and S_j belonging to the same effector series. d_{ij} is used to study the taste characteristics of several enantiomeric aminoacids. The equations thus obtained support the statement (Lehmann, 1978) that the sweetness and, respectively, bitterness taste receptors have enantiomeric active sites.

1. The Structural Distance Induced by SD*

We recall the definition of a metric space (M,d) as a non-empty set of elements, M, to which a non-negative real number d_{ij} is assigned to every pair i,j in M and the following properties hold :

$$d_{ij} \geqslant 0 \tag{1}$$

$$d_{ij} = d_{ji} \tag{2}$$

$$d_{ij} \leqslant d_{ik} + d_{kj} \quad ; \quad i,j,k \in M \tag{3}$$

The bioactive structure S_i belonging to the effector series $S_1, S_2, \ldots, S_i, \ldots, S_n$ is described within the SD*

method[2-4] by the bidimensional vector $\left[SD^{*}_{c,i} , SD^{*}_{w,i} \right] = SD^{*}(S,S_i)$. The vector entries, i.e., $SD^{*}_{c,i}$, $SD^{*}_{w,i}$, are computed within the framework[1] IRS $= \bigcup_1 G_1$, G_1 being the hydrogen-suppressed graphs corresponding to the structures S_1, 1= 1,2, ... , n. The reunion $\bigcup_1$ is performed superimposing the pharmacophoric group of G_1.

It is easily shown[5] that equation

$$d_{ij} = \left[(SD^{*}_{c,i} - SD^{*}_{w,j})^2 + (SD^{*}_{w,i} - SD^{*}_{w,j})^2 \right]^{1/2} \quad (4)$$

satisfies conditions (1) - (3), and, accordingly, (4) defines a structural distance between the compounds S_i and S_j : the larger the structural dissimilarity between S_i and S_j, the larger will be the d_{ij} value.

d_{ij} defined by relation (4) is an useful steric parameter to establish QSAR's for small data series.

2. The Correlation of Sweetness and Bitterness of Enantiomeric Aminoacids with d_{ij}.

The sweetness of D-aminoacids is expressed as the percentage (%) of a sucrose solution with equal sweetness to that of a 0.3% solution of the aminoacid, and the bitterness of L-aminoacids is expressed as the percentage of a caffeine with equal bitterness to that of a 0.3 % solution of the aminoacids.

Table 1 collects the taste (%) and normalized taste (NTS) characteristics[6] of aminoacids, as well as the $SD^{*}(S_o , S_i)$ vectors and the values d_{oi} of the structural distance between S_o (i.e., the standard structure : Trp) and S_i. d_{oi} is computed according to equation :

$$d_{oi} = \left[(SD^{*}_{c,o} - SD^{*}_{c,i})^2 + (SD^{*}_{w,o} - SD^{*}_{w,i})^2 \right]^{1/2} =$$

$$= \left[(10 - SD^{*}_{c,i})^2 + (-SD^{*}_{w,i})^2 \right]^{1/2} \qquad (5)$$

(we note that SD^{*}(Trp, Trp) = $\left[10 ; 0\right]$, and H_2N-CH-COOH is considered as pharmacophoric group.)

Table 1. Taste characteristics, SD^{*} vectors and d_{oi} structural distances.

Aminoacid	%	$Taste_{NTS}$	SD^{*}_{c}	SD^{*}_{w}	d_{oi}
			(Sweetness)		
D-Gly	0.45	1.000	0	0	10.000
D-Leu	1.30	2.889	4	0	6.000
D-Tyr	1.65	3.667	6	2	4.472
D-Phe	2.20	4.889	6	1	4.123
D-Trp	10.50	23.333	10	0	0.000
D-Ala	0.54	1.200	1	0	9.000
D-His	2.23	4.960	6	0	4.000
			(Bitterness)		
L-Gly	0.004	1.000	0	0	10.000
L-Leu	0.011	2.889	4	0	6.000
L-Tyr	0.017	4.464	6	2	4.472
L-Phe	0.069	18.12o	6	1	4.123
L-Trp	0.133	34.93o	10	0	0.000

The following log NTS vs d_{oi} equations were computed :

(sweetness) $\log NTS = 1.268(\pm 0.028) - 0.134(\pm 0.005)\, d_{oi}$ (6)

(44.501) (-29.092)

($R = 0.988$, $S = 0.069$, $F = 85.364$, $EV = 0.973$)

(bitterness) $\log NTS = 1.575(\pm 0.111) - 0.161(\pm 0.019)\, d_{oi}$ (7)

(14.129) (-8.504)

($r = 0.937$, $s = 0.216$, $F = 7.247$, $EV = 0.838$)

The equations (6) and (7), which represent good correlations, support the following conclusions :

i) the molecular shape conditions the taste characteristics, i.e., the above equations are statistically significant.

ii) the taste receptors investigated here have enantiomeric active sites, i.e., equation (6) is, within the experimental error, the same with equation (7) ; eq. (6) was coputed against D-Trp as standard, and eq.(7) against L-Trp as standard ; equation (8), computed by Lehmann[6], supports the same conclusion

$$\log \text{NTS-sweetness} = 0.084 + 0.702 \log \text{NTS-bitterness} \quad (8)$$

$$(r = 0.871,\ n = 4) .$$

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