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Structure activity studies on the phenolic substrates in microsomal hydroxylation

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Abstract. Quantitative structure-activity relationships have been developed for three series of phenolic substrates viz. phenols, hydroxyindoles and tyramines in microsomal hydroxylation. The Fujita-Ban group contributions of various substituents have been calculated. Mono-, bi- and tri-substituted phenols have been investigated in the light of the linear free energy related model also.

Keywords. Quantitative structure-activity relationships ; Fujita-Ban group contributions ; Hansch analysis ; phenolic substrates ; microsomal hydroxylation.

1. Introduction

In vivo hydroxylation of simple phenols to catechols is a well established enzymatic reaction (Williams 1964). Other organic compounds containing phenolic groups such as hydroxyindoles, phenolic phenethylamines and many drugs like phenazocine, nalorphine, morphine and levorphanol, etc have been found to be physiologically active substrates for the formation of catechols by microsomal hydroxylation (Daly *et al* 1965 ; Jepson *et al* 1962 ; Mitoma *et al* 1956 ; Posner *et al* 1961). Daly *et al* (1965) have determined the amount of catechol formed for different phenolic substrates during microsomal hydroxylation. They have made use of the enzyme catechol-O-methyltransferase, which methylates catechols formed during the reaction, and a methyl donor S-adenosyl-methioninemethyl-^{14}C for converting catechols into radioactive methylated derivative. The radioactive methylated derivative is in turn extracted into an organic solvent and the radioactivity measured by a liquid scintillation counter.

However, there has been no study on the quantitative structure activity relationships of various substrates for this enzymatic reaction. We have attempted here to correlate the activity of mono-, bi-, and tri-substituted phenols towards catechol formation with σ (Hammett 1940) and π (Hansch 1963) substituent constants. For relatively complex phenolic substrates the contribution of various substituents

in the observed biological activity have been determined on the basis of Fujita-Ban model (Fujita and Ban 1971 ; Kubinyi and Kehrhalm 1976).

2. Calculations

2.1. *Simple phenols*

For mono-, bi- and tri-substituted phenol substrates studied in the present investigations the linear free energy related (LFER) model has been employed to understand the structure-activity (*S–A*) relationships. The substituent constants used are the hydrophobicity constant π due to Hansch *et al* (1963) and the Hammett-σ constant (Hammett 1940). The π values have been calculated according to equation (1)

$$\pi_{\text{substituent}} = \log P_2 - \log P_1, \tag{1}$$

where P is the partition coefficient in octanol-water system and the subscripts 1 and 2 represent the parent and the substituted molecules respectively. For the present study the log P values used are those given by LeO *et al* (1971) and the σ values are those compiled by Martin (1978) unless otherwise mentioned.

2.2. *Complex substrates*

For structure activity studies of hydroxyindoles and substrates related to tyramines the LFER approach could not be applied as experimental values of π and σ were available only for well defined substituents on phenol. Therefore, for these two series of substrates we have used the simple algorithm given by Kubinyi (1977) to construct the normal-equation-matrix and to calculate the Fujita-Ban group contributions of various substituents. This algorithm does not allow contraction in construction of the Fujita-Ban matrices, i.e. two equivalent positions of substituents cannot be combined into one column. The solution of the normal equation matrix obtained from the Fujita-Ban matrix gives directly the calculated values of activity of the reference compound and group contributions of various substituents. In the present study the reference compound has been selected in a way that maximum number of compounds experimentally studied by Daly *et al* (1965) are accounted for by considering a minimum number of independent variables (substituents). All calculations were carried out on the IBM–1620 system at the Department of Mathematics, Panjab University, Chandigarh.

3. Results and discussion

The linear correlations of activities, expressed in terms of log $(1/C)$, of various mono-, bi- and tri-substituted phenol substrates are found to be extremely poor when only the parameter π is used as the independent variable in LFER study of these molecules. However, when π^2 terms and σ terms are included the correlation is very good (equation (2)).

$$\begin{aligned}\log(1/C) = {} & 7{\cdot}4132\ (\pm 0{\cdot}0776) + 0{\cdot}1935\ (\pm 0{\cdot}0337)\,\pi^2 \\ & - 0{\cdot}3513\ (\pm 0{\cdot}0919)\,\pi - 0{\cdot}1953\ (\pm 0{\cdot}1935)\,\sigma, \qquad (2)\end{aligned}$$

$$n = 28,\ r = 0{\cdot}897,\ S = 0{\cdot}2053,\ F = 33{\cdot}06.$$

Here C represents activity in $m\mu$ moles per gram of the liver (Daly *et al* 1965). The quantities within brackets are the limits at 95% confidence level and n, r, S and F stand for the sample size, correlation coefficient, standard error and F-ratio respectively for the regression.

The meta- and para-substituted phenols are generally found to give relatively higher yields of catechol than that from corresponding ortho-substituted substrate. When m- and p-substituted phenols are treated separately (equation (3)) and o-substituted separately (equation (4)) the correlation is comparatively better.

$$\log (1/C) = 7{\cdot}4130\ (\pm 0{\cdot}1159) + 0{\cdot}1573\ (\pm 0{\cdot}1117)\pi^2 - 0{\cdot}3829\ (\pm 0{\cdot}1032)\pi - 0{\cdot}2685\ (\pm 0{\cdot}2615)\sigma$$
$$n = 20,\ r = 0{\cdot}904,\ S = 0{\cdot}1954,\ F = 23{\cdot}83, \tag{3}$$

$$\log (1/C) = 7{\cdot}6262\ (\pm 0{\cdot}3484) + 0{\cdot}1954\ (\pm 0{\cdot}1026)\pi^2 - 0{\cdot}4840\ (\pm 0{\cdot}4604)\pi + 0{\cdot}0809\ (\pm 0{\cdot}6045)\sigma$$
$$n = 11,\ r = 0{\cdot}937,\ S = 0{\cdot}2058,\ F = 12{\cdot}02. \tag{4}$$

The π, σ and C values used to obtain these correlations are given in table 1. The derivatives for which no catechol formation has been reported have not been considered in generating these correlations. The calculated values of log $(1/C)$ according to equations (2), (3) and (4) are compared with the observed values in table 1. The calculated and observed values are in such a good agreement that standard deviation in no case is greater than 0·2 and correlation coefficients in all cases are of the order of 0·9.

For hydroxyindoles and tyramines the observed activities and Fujita-Ban matrices are given in tables 2 and 3 respectively. The corresponding normal-equation-matrices are Matrix 1 and Matrix 2. The calculated group contributions are given in table 4. The $-\log C$ values calculated on the basis of these group contributions are compared with the observed values in table 4. The agreement is fairly good except in case of tyramines which have –OH substituent at the X_1 position (see table 3). The statistics of these two series, however, cannot be discussed because the degree of freedom is only one in both these cases.

Fujita-Ban studies are carried out for some selected substituted phenols as well. The derivatives are selected in a way that maximum of the compounds listed in table 1 are accounted for with minimum number of independent group substituents (variables). Selection of –Cl and $-CH_3$ groups at o–, m– and p– positions in phenol account for 12 phenol substrates in table 1 with 5 degrees of freedom. The Fujita-Ban matrix corresponding to the seven initial compounds (phenol, o–, p– and m– Cl– and $-CH_3$ phenol) is given in table 5 and the corresponding normal equation matrix is Matrix 3. The group contributions thus calculated (table 4) lead to a fair agreement between calculated and observed $-\log C$ values.

4. Conclusions

It would be interesting to explore equation (2) to select the most active substrates. Partial differentiation of (2) with respect to π gives

$$\partial\ [\log (1/C)]/\partial\pi = 0{\cdot}3870\,\pi - 0{\cdot}3513.$$

Table 1. Enzymatic hydroxylation of substituted phenols

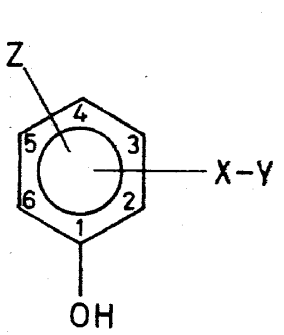
No.	Substituent	π	σ	log (1/C) Observed	Equation (2)	Equation (3)	Equation (4)
1.	..	0	0	7·5436	7·4132	7·4130	7·6262
2.	4-CHO	−0·38	0·42	7·4056	7·4926	7·4685	
3.	4-NO_2	0·45	0·78	7·2097	7·1419	7·0631	
4.	4-Cl	0·98	0·23	7·2636	7·2098	7·1271	..
5.	4-CH_3	−0·46	−0·17	7·3625	7·3257	7·3158	..
6.	4-OCH_3	−0·12	−0·27	7·3768	7·5108	7·5337	..
7.	4-OH	−0·96	−0·37	8·0915	8·0010	8·0250	..
8.	4-$COCH_3$	−0·11	0·50	7·1537	7·3565	7·3228	..
9.	4-C $(CH_3)_3$	1·85	−0·20	7·2161	7·4646	7·2968	..
10.	3-CHO	−0·19	0·35	7·4881	7·4185	7·3975	..
11.	3-NO_2	0·54	0·71	7·1457	7·1412	7·0614	..
12.	3-Cl	1·01	0·37	7·1367	7·1835	7·0874	..
13.	3-CH_3	0·55	−0·07	7·1612	7·2921	7·2688	..
14.	3-OCH_3	0·12	0·12	7·2204	7·3503	7·3371	..
15.	3-OH	−0·66	0·12	7·9508	7·7059	7·7021	..
16.	3-$COCH_3$	−0·07	0·38	7·1864	7·3645	7·3389	..
17.	4-NH_2	−1·42	−0·66	8·7959	8·4311	8·4513	..
18.	3-NH_2	−1·29	−0·16	7·7496	8·2196	8·2118	..
19.	3, 5 $(CH_3)_2$	1·10	−0·14	7·3098	7·2882	7·2198	..
20.	3, 4 $(CH_3)_2$	1·01	−0·24	7·1261	7·3026	7·2512	..
21.	2-Cl	0·69	0·21	7·3605	7·2219	..	7·4022
22.	2-CH_3	0·49	−0·14	7·6990	7·3148	..	7·4246
23.	2, 3 $(CH_3)_2$	1·04	−0·21	7·4145	7·2981	..	7·3171
24.	2, 4 $(CH_3)_2$	0·95	−0·31	7·1198	7·3146	..	7·3176
25.	2, 5 $(Cl)_2$	1·70	0·58	7·4248	7·2619	..	7·4149
26.	2, 4 $(Cl)_2$	1·67	0·44	7·1857	7·2802	..	7·3984
27.	2, 4, 6 $(Cl)_3$	2·36	0·65	7·8069	7·5349	..	7·6247
28.	2, 4, 6 $(I)_3$	3·83	0·84*	8·6778	8·7421	..	8·7065

* (Posner *et al* 1961).

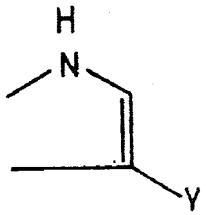
Matrix. 1. Normal equations matrix for hydroxyindoles and related compounds.

$$\begin{vmatrix} 11 & 1 & 5 & 3 & 1 & 1 & 1 & 1 & 1 & 2 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 5 & 0 & 5 & 0 & 0 & 1 & 0 & 1 & 1 & 1 \\ 3 & 0 & 0 & 3 & 0 & 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 2 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 2 \end{vmatrix} = \begin{vmatrix} 90{\cdot}0948 \\ 8{\cdot}4437 \\ 41{\cdot}4188 \\ 24{\cdot}8125 \\ 7{\cdot}8762 \\ 8{\cdot}2007 \\ 7{\cdot}8125 \\ 8{\cdot}4559 \\ 7{\cdot}8996 \\ 18{\cdot}2518 \end{vmatrix}$$

Table 2. Activities in catechol formation of hydroxyindoles and related compounds.



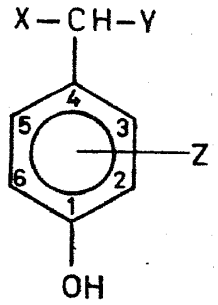
X-Y:



X	*Z*	*Y*
X_1 : 2, 3	Z_1 : 6-OCH_3	Y_1 : $CH_2CH_2NHCH_3$
X_2 : 3, 4	Z_2 : 2-OCH_3	Y_2 : $CH_2CH_2NHCOCH_3$
X_3 : 4, 5		Y_3 : $CH_2CH_2N(CH_3)_2$
X_4 : 5, 6		

No.	Structures *Z*	*X*	*Y*	Compound	X_1	X_2	X_3	X_4	Z_1	Z_2	Y_1	Y_2	Y_3	log (1/*C*) (Obsd.)
40	H	H		Phenol										7·5436
41	H	2–3–CH=CH–NH–		4-hydroxyindole	1									8·4437
42	H	3–4–CH=CH–NH–		5-hydroxyindole		1								7·7077
43	H	4–5–CH=CH–NH–		6-hydroxyindole			1							7·9031
44	H	5–6–CH=CH–NH–		7-hydroxyindole				1						7·8762
45	6–OCH_3	3–4–CH=CH–NH–		5-hydroxy-6-methoxyindole	1				1					8·2007
46	2–OCH_3	4–5–CH=CH–NH–		6-hydroxy-5-methoxyindole		1				1				7·8125
47	H	3–4–CH=CH–NH–	$-CH_2CH_2NHCH_3$	N-Methyl-serotonin	1						1			8·4559
48	H	3–4–CH=CH–NH–	$-CH_2CH_2NHCOCH_3$	Acetyl serotonine	1							1		7·8996
49	H	4–5–CH=CH–NH–	$-CH_2CH_2N(CH_3)_2$	6-hydroxy N, N dimethyl tryptamine		1							1	9·0969
50	H	3–4–CH=CH–NH–	$-CH_2CH_2N(CH_3)_2$	Bufotenine	1								1	9·1549

Table 3. Activities in catechol formation of tyramines and related phenols.



X_1 : OH
Y_1 : $-CH_2NH_2$
Y_2 : $-CH_2NHCH_3$
Y_3 : $-CH_2N(CH_3)_2$
Y_4 : $-CH_2NHCOCH_3$
Y_5 : $-CH(CH_3)NH_2$
Y_6 : $-CH(CH_3)NHCH_3$
Y_7 : $-CH_2OH$
Z_1 : 3-OCH_3

Compound No.	Structure X	Structure Y	Structure Z	Compound	X_1	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Z_1	log (1/C) (Obsd.)
29	H	$-CH_2NH_2$	H	*p*-tyramine		1								7·7852
30	H	$-CH_2NHCH_3$	H	*N*-methyl tyramine			1							7·5751
31	H	$-CH_2N(CH_3)_2$	H	Hordenine				1						7·2993
32	H	$-CH_2NHCOCH_3$	H	*n*-acetyl tyramine					1					7·2815
33	H	$-CH(CH_3)NH_2$	H	*p*-hydroxy amphetamine						1				7·7747
34	OH	$-CH(CH_3)NHCH_3$	H	*p*-hydroxy ephidrone	1						1			7·8539
35	H	$-CH_2OH$	H	tyrosol								1		7·4389
36	OH	$-CH_2NH_2$	H	*p*-octopamine	1	1								7·4145
37	OH	$-CH_2NHCH_3$	H	synephrin	1		1							9·6990
38	H	$-CH_2OH$	3-OCH_3	*m*-methoxy tyrosol								1	1	7·9788
39	H	H	H	*p*-cresol										7·3625
					3	2	2	1	1	1	1	2	1	85·4634

Matrix 2. Normal equations matrix for tyramines and related phenols.

$$\begin{vmatrix} 11 & 3 & 2 & 2 & 1 & 1 & 1 & 1 & 2 & 1 \\ 3 & 3 & 1 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 2 & 1 & 2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 2 & 1 & 0 & 2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 2 & 1 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 \end{vmatrix} = \begin{vmatrix} 85{\cdot}4634 \\ 24{\cdot}9674 \\ 15{\cdot}1997 \\ 17{\cdot}2741 \\ 7{\cdot}2993 \\ 7{\cdot}2815 \\ 7{\cdot}7747 \\ 7{\cdot}8539 \\ 15{\cdot}4177 \\ 7{\cdot}9788 \end{vmatrix}$$

Table 4. Fujita-Ban group contributions, comparison of observed and calculated activities and statistics of correlations.

Phenols			
Group No.	Group	Contribution	Standard error
X_1	2–Cl	−0·0120	±0·3659
X_2	3–Cl	−0·2029	±0·4395
X_3	4–Cl	−0·2590	±0·4395
X_4	2–CH_3	+0·0685	±0·3516
X_5	3–CH_3	−0·1974	±0·3516
X_6	4–CH_3	−0·2440	±0·3516

Compound No.	log (1/*C*) observed	log (1/*C*) Calculated	Δ log (1/*C*)
1.	7·3605	7·4776	0·1171
2.	7·1367	7·2868	0·1501
3.	7·2636	7·2307	−0·0329
4.	7·6980	7·5582	−0·1408
5.	7·1612	7·2924	0·1312
6.	7·3625	7·2457	−0·1268
7.	7·4145	7·3609	−0·0536
8.	7·1198	7·3142	0·1944
9.	7·1261	7·0485	−0·0776
10.	7·4248	7·2747	−0·1501
11.	7·1857	7·2186	0·0329
12.	7·5436	7·4897	−0·0539
Totals	87·7980	87·7980	$\Sigma\,\Delta^2 = 0{\cdot}1636$

$n = 12$ $r = 0{\cdot}750$ $s = 0{\cdot}181$

Table 4 (*Contd.*)

Tyramines

Group No.	Group structure	Contribution
X_1	$-OH$	0·8766
Y_1	$-CH_2NH_2$	−0·2009
Y_2	$-CH_2NHCH_3$	0·8362
Y_3	$-CH_2N(CH_3)_2$	−0·0632
Y_4	$-CH_2NHCOCH_3$	−0·0810
Y_5	$-CH(CH_3)NH_2$	0·4122
Y_6	$-CH(CH_3)NHCH_3$	−0·3852
Y_7	$-CH_2OH$	0·0764
Z_1	$3-OCH_3$	0·5399

Compound No.	Log (1/*C*) Observed	log (1/*C*) Calculated	Δ log (1/*C*)
1.	7·7852	7·1616	−0·6236
2.	7·5751	8·1987	0·6236
3.	7·2993	7·2993	0·0000
4.	7·2815	7·2815	0·0000
5.	7·7747	7·7747	0·0000
6.	7·8539	7·8539	0·0000
7.	7·4389	7·4389	0·0000
8.	7·4145	8·0382	0·6237
9.	9·6990	9·0753	−0·6237
10.	7·9788	7·9788	0·0000
11.	7·3625	7·3625	0·0000
Totals	85·4634	85·4634	$\Sigma\Delta^2 = 1·556$

$n = 11$ $r = 0·817$ $s = 1·248$

Hydroxyindoles

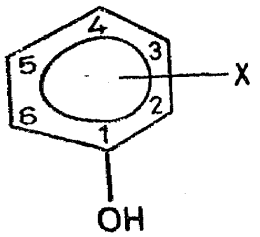
Group No.	Group structure	Contribution
X_1	$2-3-CH=CH-NH-$	0·8998
X_2	$3-4-CH=CH-NH-$	0·2269
X_3	$4-5-CH=CH-NH-$	0·2958
X_4	$5-6-CH=CH-NH-$	0·3323
Z_1	$6-OCH_3$	0·4299
Z_2	$2-OCH_3$	−0·0272
Y_1	$-CH_2CH_2NHCH_3$	0·6851
Y_2	$-CH_2CH_2NHCOCH_3$	0·1288
Y_3	$-CH_2CH_2N(CH_3)_2$	1·3207

Table 4 (*Contd.*)

Compound No.	log (1/C) Observed	log (1/C) Calculated	Δ log (1/C)
1.	7·5436	7·5439	0·0003
2.	8·4437	8·4437	0·0000
3.	7·7707	7·7708	0·0001
4.	7·9031	7·8397	−0·0634
5.	7·8762	7·8762	0·0000
6.	8·2007	8·2007	0·0000
7.	7·8125	7·8125	0·0000
8.	8·4559	8·4559	0·0000
9.	7·8996	7·8996	0·0000
10.	9·0969	9·1604	0·0635
11.	9·1549	9·0915	−0·0634
Totals	90·0948	90·0319	$\Sigma \Delta^2 = 0·0121$

$n = 11$ $r = 0·998$ $s = 0·110$

Table 5. Activities in catechol formation of simple substituted phenols.



X_1 : 2–Cl X_4 : 2–CH_3
X_2 : 3–Cl X_5 : 3–CH_3
X_3 : 4–Cl X_6 : 4–CH_3

Compound No.	Structure X	Compound	X_1	X_2	X_3	X_4	X_5	X_6	log (1/C) (Obsd)
21	2–Cl	*o*-chlorophenol	1						7·3605
12	3–Cl	*m*-chlorophenol		1					7·1367
4	4–Cl	*p*-chlorophenol			1				7·2636
22	2–CH_3	*o*-methylphenol				1			7·6990
13	3–CH_3	*m*-cresol					1		7·1612
5	4–CH_3	*p*-cresol						1	7·3625
23	2, 3 $(CH_3)_2$	2, 3–dimethylphenol				1	1		7·4145
24	2, 4 $(CH_3)_2$	2, 4-dimethylphenol				1		1	7·1198
20	3, 4 $(CH_3)_2$	3, 4-dimethylphenol					1	1	7·1261
25	2, 5 $(Cl)_2$	2, 5-dichlorophenol	1	1					7·4248
26	2, 4 $(Cl)_2$	2, 4-dichlorophenol	1		1				7·1857
1	H	phenol							7·7436
			3	2	2	3	3	3	87·7980

Matrix 3. Normal equations matrix for simple substituted phenols.

$$\begin{bmatrix} 12 & 3 & 2 & 2 & 3 & 3 & 3 \\ 3 & 3 & 1 & 1 & 0 & 0 & 0 \\ 2 & 1 & 2 & 0 & 0 & 0 & 0 \\ 2 & 1 & 0 & 2 & 0 & 0 & 0 \\ 3 & 0 & 0 & 0 & 3 & 1 & 1 \\ 3 & 0 & 0 & 0 & 1 & 3 & 1 \\ 3 & 0 & 0 & 0 & 1 & 1 & 3 \end{bmatrix} = \begin{bmatrix} 87{\cdot}7980 \\ 21{\cdot}9710 \\ 14{\cdot}5615 \\ 14{\cdot}4493 \\ 22{\cdot}2333 \\ 21{\cdot}7018 \\ 21{\cdot}6084 \end{bmatrix}$$

Therefore, it is evident that log $(1/C)$ would be maximum when $\pi = 0{\cdot}3513/0{\cdot}3870$, i.e. ≈ 1. So far as the dependence on σ is concerned the amount of catechol formed will be less for the substituent which has lower value of σ provided π values of the substituents are similar.

It can be concluded therefore that the optimum conditions for catechol formation require a higher value of σ and $\pi \approx 1$ (compare 3-Cl-phenol and 4-Cl-phenol). Here we have not considered steric factor.

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