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Relationship Between Lipophilicity, Bitterness and Structure of Phenyl β-D-Glucopyranosides

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ABSTRACT

The relationship between lipophilicity, structure and bitterness of phenyl β-D-glucopyranosides and their methyl ether derivatives was examined quantitatively using lipophilic and STERIMOL parameters, and selected indicator variables to assess position-specific substituent effects. The results indicate that the partial lipophilicity of the methoxyl groups is different for each substituent position of the glucose moiety and that the lipophilicity of a methoxyl group at position 2 is the largest. The results also show that the bitterness of phenyl β-D-glucopyranosides is determined primarily by the presence or absence of the methoxyl group at position 2 of the glucose moiety, not by the lipophilicity of the entire molecule.

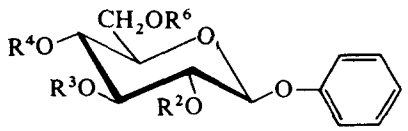
INTRODUCTION

In the course of our studies of the structure of bitter diterpenoids obtained from plants of the *Rabdosia* species (Kubota & Kubo, 1969;

Kubo & Kubota, 1979), we took an interest in the structural requirements for eliciting bitterness. However, the diterpenoids from *Rabdosia* seemed unsuitable for the study of bitter–structure relationships, because they have too many functional groups that could affect their taste. Therefore, we used phenyl β-D-glucopyranosides (1) and their various methyl ether derivatives (2–16) as model materials. The reasons for this choice were as follows. (1) Lipophilicity of a molecule is considered to be a dominant factor of biological activity (Fujita *et al.*, 1964; Hansch, 1971). In the case of phenyl β-D-glucopyranosides, they have both hydrophilic (sugar part) and lipophilic (phenyl group) moieties in each molecule. (2) Quantitative analyses are facilitated due to the ultraviolet absorption common to the phenyl group. (3) All materials probably assume the same $^4C_1$ conformation whereby the bulky aglycone, hydroxyl groups and methoxyl groups are equatorially disposed, thus minimizing stereochemical complications (Table 1).

TABLE 1

Phenyl β-D-Glucopyranosides Methyl Ether Derivatives



Compounds	*Substituents*				*Melting point* (°C)	[α]*D* (*c*, *solv.*)
	R^2	R^3	R^4	R^6		
1	H	H	H	H	178·0 (water)	−90·3 (0·48, water)
2	Me	H	H	H	164·0–165·0 (water)	−56·4 (0·44, water)
3	H	Me	H	H	150·0–151·0 (water)	−70·4 (0·50, water)
4	H	H	Me	H	174·0 (water)	−66·7 (0·59, water)
5	H	H	H	Me	128·5–130·5 (ethyl acetate)	−59·3 (0·54, ethanol)
6	Me	Me	H	H	115·0–116·0 (water)	−70·4 (2·00, chloroform)
7	Me	H	Me	H	170·0–172·0 (water)	−51·6 (0·31, acetone)
8	Me	H	H	Me	111·0–112·0 (ethyl acetate)	−74·3 (0·35, ethanol)
9	H	Me	Me	H	141·0–143·0 (ethyl acetate)	−55·7 (0·52, ethanol)
10	H	Me	H	Me	109·0–110·0 (*c*-hexane)	−62·9 (0·35, ethanol)
11	H	H	Me	Me	130·0 (ethyl acetate)	−61·5 (0·50, chloroform)
12	Me	Me	Me	H	105·0 (water)	−48·5 (0·33, chloroform)
13	Me	Me	H	Me	43·0–44·0 (*c*-hexane/*n*-hexane)	−62·2 (0·37, chloroform)
14	Me	H	Me	Me	107·0–108·0 (*p*-ether)	−33·3 (0·27, chloroform)
15	H	Me	Me	Me	87·0–87·5 (benzene/*p*-ether)	−37·3 (0·54, chloroform)
16	Me	Me	Me	Me	78·0 (*n*-pentane)	−43·0 (0·50, chloroform)

Several studies (Birch & Lee, 1976; Gardner, 1978, 1979) suggest that lipophilicity plays an important rôle in the bitter taste of certain carbohydrates. However, and as far as we are aware, no attempt has been made to quantitatively relate bitter potency with lipophilicity. Hence, we examined the bitter potency of phenyl β-D-glucopyranosides by the QSAR (quantitative structure–activity relationships) analysis (Fujita *et al.*, 1964) using three groups of parameters which could affect bitterness.

One is a lipophilic parameter estimated from 1-octanol/water partition coefficients (P).

The second is STERIMOL parameters (L, W_l, W_r, W_u, W_d) developed by Verloop *et al.* (1976), employed for an evaluation of the steric dimensions of the molecules. The L parameter in phenyl β-D-glucopyranosides is taken as the longest length of molecule along an axis which connects the glycosidic oxygen and C-4 of the glucose moiety, as shown in Fig. 1. The W_l, W_r, W_u and W_d parameters are the molecular

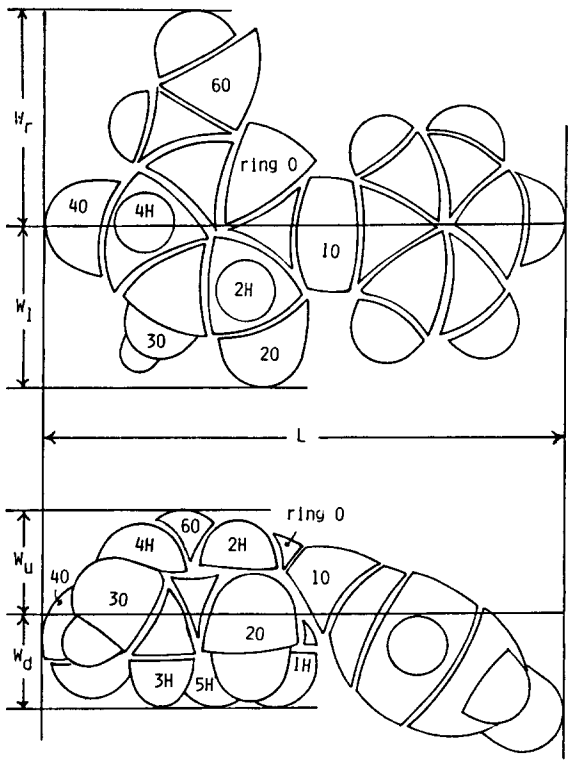


Fig. 1. Schematic representation of STERIMOL parameters L, W_l, W_r, W_u and W_d.

width in the directions perpendicular to the L axis and rectangular to each other. W_l is the width in the direction to which the C-2 or C-3 substituent extends. W_r is the width in the direction opposite to W_l. The W_u and W_d parameters are the vertical width upward and downward, respectively, of the molecule in its favoured conformation, when the molecule is laterally along the L axis.

The third is indicator variables (I_i) (Inoue *et al.*, 1974) to express some position-specific effects of the substituents of phenyl β-D-glucopyranosides. They are assigned the value 1 (one) when the methoxyl group is at the i position of the glucose moiety and 0 (zero) when the hydroxyl group is at the i position, as defined in Table 2.

Values for the STERIMOL parameters and indicator variables are listed in Table 2. From Table 2 it is evident that: (1) the W_u parameter is constant (= 2·38) for all compounds; (2) the L and W_r parameters are linearly dependent on I_4 and I_6, respectively, i.e. relations $L = 12{\cdot}39 + 0{\cdot}62\ I_4$ and $W_r = 4{\cdot}88 + 0{\cdot}44\ I_6$ hold and (3) the W_d parameter is almost linearly dependent on I_6. In fact, the correlation coefficient between W_d and I_6 is greater than 0·999.

TABLE 2

Lipophilicities, Bitter Taste Thresholds, Physico-chemical Parameters and Indicator Variables of Phenyl β-D-glucopyranosides

No.	*Obsd. log P*[a]	*Obsd. log 1/C*	*STERIMOL parameters*					*Indicator variables*			
			L	W_1	W_r	W_u	W_d	I_2	I_3	I_4	I_6
1	−0·50 (0·04)	3·0	12·39	4·03	4·88	2·38	3·11	0	0	0	0
2	0·08 (0·03)	4·2	12·39	5·74	4·88	2·38	3·11	1	0	0	0
3	−0·19 (0·05)	3·0	12·39	4·94	4·88	2·38	3·12	0	1	0	0
4	−0·23 (0·03)	2·4	13·01	4·03	4·88	2·38	3·11	0	0	1	0
5	−0·16 (0·05)	2·1	12·39	4·03	5·32	2·38	4·02	0	0	0	1
6	0·76 (0·03)	3·6	12·39	5·74	4·88	2·38	3·12	1	1	0	0
7	0·58 (0·04)	3·0	13·01	5·74	4·88	2·38	3·11	1	0	1	0
8	0·60 (0·03)	3·0	12·39	5·74	5·32	2·38	4·02	1	0	0	1
9	0·44 (0·02)	3·3	13·01	4·94	4·88	2·38	3·12	0	1	1	0
10	0·30 (0·03)	2·7	12·39	4·94	5·32	2·38	4·02	0	1	0	1
11	0·35 (0·02)	3·0	13·01	4·03	5·32	2·38	4·02	0	0	1	1
12	1·41 (0·05)	3·6	13·01	5·74	4·88	2·38	3·12	1	1	1	0
13	1·29 (0·04)	3·9	12·39	5·74	5·32	2·38	4·02	1	1	0	1
14	1·11 (0·02)	3·3	13·01	5·74	5·32	2·38	4·02	1	0	1	1
15	0·95 (0·01)	2·7	13·01	4·94	5·32	2·38	4·02	0	1	1	1
16	2·00 (0·03)	4·2	13·01	5·74	5·32	2·38	4·02	1	1	1	1

[a] Figures in parentheses are the standard deviation of log P.

TABLE 3
Correlation Matrix for Variables and Parameters Used in Derivation of Equations (1), (2), (3) and (4)

	log 1/C	*log P*	W_1	I_2	I_3	I_4	I_6
log *P*	0·60	1·00					
W_1	0·72	0·70	1·00				
I_2	0·71	0·65	0·89	1·00			
I_3	0·32	0·48	0·32	0·00	1·00		
I_4	0·00	0·42	0·00	0·00	0·00	1·00	
I_6	−0·13	0·39	0·00	0·00	0·00	0·00	1·00

Therefore, we excluded the L, W_r, W_u and W_d parameters from the group of explanatory variables. The degree of independence of the variables in our analysis is listed in Table 3.

METHOD

Phenyl β-D-glucopyranosides (1) and their methyl ether derivatives (2–16) were synthesized and purified by standard methods so that their physical and spectral data agreed with published values (Table 1) (Nanasi & Liptac, 1974).

Relative lipophilicity was estimated from 1-octanol/water partition coefficients (P): 0·1 mmol of each compound was dissolved in water saturated with 1-octanol (50 ml) and 1-octanol saturated with water (50 ml). The solutions were vigorously shaken for an hour and then left to stand overnight at 25°C. The concentrations of the compounds in the organic and water layers were determined by measuring ultraviolet absorption at 256 nm (λ_{max}). The partition coefficient was calculated from the expression $P = [C_{1-octanol}]/[C_{water}]$. The mean value of four replications and the standard deviation of the logarithm of P are listed in Table 2.

The bitter threshold (C) of the compounds was determined according to the method of Fisher *et al.* (1963) using ten panelists selected from Kinki University personnel on a basis of ability to recognize the bitter taste of a phenylthiourea solution at a concentration of 5·08 mg/litre. The logarithms of $1/C$ which are directly related to bitterness are listed in Table 2.

STERIMOL parameters were calculated using Corey–Pauling–Koltun (CPK) atomic models according to the method developed by Verloop *et al.* (1976).

RESULTS AND DISCUSSION

Of the various combinations of the variables studied, eqn (1) gave the best correlation between structure and lipophilicity:

$$\log P = 0{\cdot}86(\pm 0{\cdot}13)\, I_2 + 0{\cdot}64(\pm 0{\cdot}13)\, I_3 + 0{\cdot}55(\pm 0{\cdot}13)\, I_4 + 0{\cdot}51(\pm 0{\cdot}13)\, I_6 - 0{\cdot}73\ (\pm 0{\cdot}14) \quad (1)$$

$$n = 16,\ R = 0{\cdot}990,\ s = 0{\cdot}114,\ F = 132{\cdot}8$$

In eqn (1) and subsequent equations, n is the number of compounds included in each analysis, R is the multiple correlation coefficient, s is the standard deviation and F is the ratio of variance. The figures in parentheses are the 95% confidence level.

Table 4 shows the development of eqn (1) and Table 5 the deviation of the calculated values from those observed.

In Table 5, the deviation of eqn (1) for compound 1 is larger than for the other compounds. In fact, the t value for this deviation is significantly large ($t = 3{\cdot}53$). Therefore, we investigated another case whereby compound 1 is omitted, and obtained eqn (2):

$$\log P = 0{\cdot}90(\pm 0{\cdot}09)\, I_2 + 0{\cdot}68(\pm 0{\cdot}09)\, I_3 + 0{\cdot}60(\pm 0{\cdot}09)\, I_4 + 0{\cdot}55(\pm 0{\cdot}09)\, I_6 - 0{\cdot}84(\pm 0{\cdot}12) \quad (2)$$

$$n = 15,\ R = 0{\cdot}995,\ s = 0{\cdot}080,\ F = 228{\cdot}4$$

Tables 4 and 5 show the development and the deviation of eqn (2).

The excellent correlation coefficient obtained in eqn (2) suggests that log P has an additive–constitutive property that can be expressed as follows:

$$\log P = c_2 I_2 + c_3 I_3 + c_4 I_4 + c_6 I_6 + c$$

for all compounds except compound 1. From the values of the coefficient attached to I_1, it is clear that the partial lipophilicities of the methoxyl groups are different for each glucopyranosyl position and that the lipophilicity of the methoxyl group at position 2 of phenyl β-D-glucopyranosides is larger than the others.

TABLE 4
Development of Equations (1) and (2)[a]

Constant	I_2	I_3	I_4	I_6	r	s	F
(0·12	0·86				0·65	0·54	10·2
(0·21)	(0·77)				(0·62)	(0·53)	(8·0)
−0·20	0·86	0·64			0·81	0·43	12·3
(−0·13)	(0·81)	(0·60)			(0·78)	(0·44)	(9·2)
−0·48	0·86	0·64	0·55		0·91	0·31	19·6
(−0·47)	(0·86)	(0·64)	(0·55)		(0·89)	(0·33)	(14·4)
−0·73	0·86	0·64	0·55	0·51	0·99	0·11	132·8
(−0·84)	(0·90)	(0·68)	(0·60)	(0·55)	(0·99)	(0·08)	(228·4)

[a] Figures in parentheses are the development of eqn (2).

TABLE 5
Deviation of Calculated Values from Observed log P

No.	*Observed log P*	*Calculated by eqn (1)*		*Calculated by eqn (2)*	
		log P	*Δ log P*	*log P*	*Δ log P*
1	−0·50	−0·73	0·22	—	—
2	0·08	0·13	−0·05	0·06	0·02
3	−0·19	−0·09	−0·10	−0·16	−0·03
4	−0·23	−0·18	−0·05	−0·24	0·01
5	−0·16	−0·22	0·06	−0·29	0·13
6	0·76	0·77	0·01	0·75	0·01
7	0·58	0·69	−0·10	0·66	−0·08
8	0·60	0·63	−0·04	0·62	−0·02
9	0·44	0·46	−0·02	0·44	−0·00
10	0·30	0·42	−0·12	0·40	−0·10
11	0·35	0·33	0·02	0·31	0·04
12	1·41	1·32	0·09	1·34	0·07
13	1·29	1·28	0·01	1·30	−0·01
14	1·11	1·19	−0·08	1·21	−0·10
15	0·95	0·97	−0·02	0·99	−0·04
16	2·00	1·83	0·17	1·90	0·10

As it is reported that lipophilicity is an important parameter for bitterness (Birch & Lee, 1976; Gardner, 1978, 1979), a linear relationship (log $1/C = a \log P + b$) was assumed, and eqn (3) was then derived:

$$\log 1/C = 0{\cdot}53(\pm 0{\cdot}40) \log P + 2{\cdot}90(\pm 0{\cdot}40) \quad (3)$$

$$n = 16,\ R = 0{\cdot}60,\ s = 0{\cdot}50,\ F = 7{\cdot}87$$

Figure 2 shows a scatter diagram for log $1/C$ versus log P, and Table 6 the deviations of eqn (3). The agreement between eqn (3) and the observed log $1/C$ is poor.

Using a stepwise procedure applied to the various combinations of variables listed in Table 3, eqn (4) was next obtained:

$$\log 1/C = 0{\cdot}83(\pm 0{\cdot}47)\ I_2 + 2{\cdot}78(\pm 0{\cdot}33) \quad (4)$$

$$n = 16,\ R = 0{\cdot}71,\ s = 0{\cdot}43,\ F = 14{\cdot}4$$

Table 6 shows the deviation of the calculated values from those observed.

It would thus appear that neither lipophilicity nor the STERIMOL parameters of the molecules are important for the bitterness of the phenyl β-D-glucopyranosides. Only the presence or absence of a methoxyl group at position 2 of the glucose moiety determines bitter taste intensity in this set of compounds. This result contradicts that of Gardner (1978, 1979).

It would appear that methylation of the hydroxyl group at position

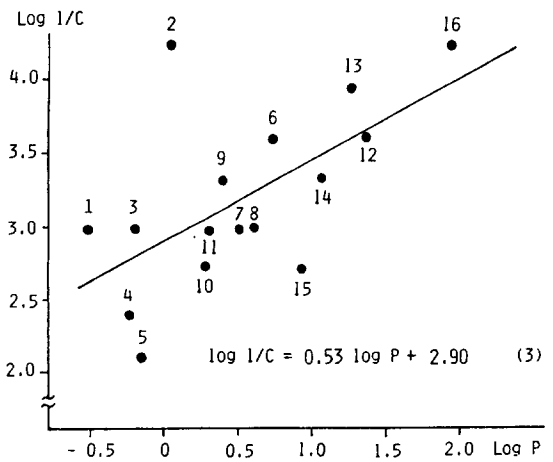


Fig. 2. Scatter diagram for log $1/C$ versus log P.

TABLE 6
Deviation of Calculated Values from Observed log 1/C

No.	*Observed log 1/C*	*Calculated by eqn (3)*		*Calculated by eqn (4)*	
		log 1/C	*Δ log 1/C*	*log 1/C*	*Δ log 1/C*
1	3·0	2·6	0·3	2·8	0·2
2	4·2	2·9	1·3	3·6	0·6
3	3·0	2·8	0·2	2·8	0·2
4	2·4	2·8	−0·4	2·8	−0·4
5	2·1	2·8	−0·7	2·8	−0·7
6	3·6	3·3	0·3	3·6	0·0
7	3·0	3·2	−0·2	3·6	−0·6
8	3·0	3·2	−0·2	3·6	−0·6
9	3·3	3·1	0·2	2·8	0·5
10	2·7	3·1	−0·4	2·8	−0·1
11	3·0	3·1	−0·1	2·8	0·2
12	3·6	3·6	−0·0	3·6	0·0
13	3·9	3·6	0·3	3·6	0·3
14	3·3	3·5	−0·2	3·6	−0·3
15	2·7	3·4	−0·7	2·7	−0·1
16	4·2	3·9	0·3	3·6	0·6

2 (which is nearest to the benzene ring) leads to higher electron density of the molecule toward the direction of, and including, the benzene ring. As opposed to lipophilicity it is the localization of electron density in the molecule that is most important for determining the bitterness of phenyl β-D-glucopyranosides.

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