Steroid absorption - use of the substituent constant π'

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The use of the substituent or hydrophobic bonding constant π in the correlation of drug absorption and biological activity with chemical constitution is well established (Hansch & Steward, 1964; Fujita, Iwasa & Hansch, 1964; Dearden & Tomlinson, 1971). Substituent constants have also been used in the prediction of partition coefficients (Currie, Lough & others, 1966; Flynn, 1971) and chromatographic retention times (Knights & Thomas, 1962; Dearden, Patel & Tubby, 1974). π has been derived from systems at equilibrium by application of the free-energy relation

$$\pi = \log K_p - \log K_d \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where K_p is the partition coefficient of the parent molecule and K_d that of the derivative.

The present report is on the derivation and use of π in a dynamic system, that of steroid absorption from the mouth. The initial absorptive process is regarded as an equilibrium between aqueous (oral cavity) and lipid (buccal mucosa) environments (Beckett & Pickup, 1975) such that the free-energy equations 2 and 3 can be applied:

$$\pi'_x = \log B_1 - \log B_2 \quad .. \quad .. \quad .. \quad .. \quad (2)$$

where B_1 and B_2 represent the experimentally determined percentage absorbed from the oral cavity in 5 min of compounds 1 and 2 respectively differing by one functional group x.

$$\text{Also } \log B_{pred} = \Sigma\pi' + \log B_p \quad .. \quad .. \quad .. \quad (3)$$

i.e. the percentage absorption in 5 min of any steroid (B_{pred}) can be predicted using the algebraic sum of the π' values of the component groupings of the molecule and the estimated absorption (B_p) of the parent steroid nucleus, i.e. perhydrocyclopentano-phenanthrene.

The preparation of steroid solutions and determination of the percentage absorbed after 5 min contact time in a given subject were as described by Beckett & Pickup (1975). Substituent constants derived using equation 2 are presented in Table 1. Predicted % absorption, an example of which is shown in Fig. 1, is compared with experimentally obtained data in Table 2 and Fig. 2. A highly significant correlation was obtained ($r = 0.976$, $n = 32$).

The estimated substituent constants shown in Table 1 can be compared with those obtained using the n-octanol–water partition system (Hansch & Anderson, 1967; Tute, 1971). For example, in both systems

Table 1. *Calculated π' constants for some steroid substituents (hydrophilic → lipophylic) and number of steroids used in their derivation* (N).

Functional group/s	π'	N
-OH	−0·64	2
= O	−0·60	3
1,3,5(10)-Trien-3-ol	−0·60	4
-O-Si-$(CH_3)_3$	−0·52	2
Cyclic-O-(oxa)	−0·19	4
Double bond extending conjugation	−0·16	2
Second double bond extending conjugation	−0·09	2
Cis A/B ring junction	−0·04	2
Cyclic double bond (unconjugated)	−0·03	2
C, CH_2, CH_3	+0·06	2
-C≡CH	+0·09	2
-O-(ester)	+0·13	2
π' interaction contributions		
17α-OH/17β-α ketol	+0·28	2
17β-α ketol	+0·64	2
4β-OH/3 keto	+0·69	2

$\pi_{OH} < \pi_{=O}$, reflecting the greater hydrogen bonding power of the hydroxyl substituent in an aqueous environment; and introduction of an ester function (-O-) increases the lipophilic/hydrophilic balance, e.g. π CO·CH_3 < π CO·OCH_3 or π O·CO·CH_3. The latter can possibly be explained in terms of increased hydrogen bonding in the 'lipid' phase, as can the apparent affinity of phenolic groups (e.g. 1,3,5(10)trien-3-ol) towards a lipid environment when compared with the corresponding cyclohexanol (Fujita & others, 1964; Hansch & Anderson, 1967). The greater hydrophilic nature of 5β-

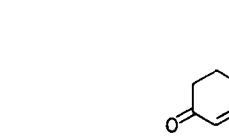

FIG. 1. Example calculation of the predicted percentage absorption in 5 min of ethisterone.

$\log B_{pred} = \Sigma\pi' + \log B_p$

Angular methyl groups (×2)	= +0·12
3 Keto	= −0·60
Double bond extending conjugation	= −0·16
17β-OH	= −0·64
17α-Ethynyl	= +0·09
	$\Sigma\pi'$ = −1·19
Steroid nucleus ($\log B_p$)	= +2·86
$\therefore \log B_{pred}$	= +1·67

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Table 2. *Oral mucosal absorption of steroids (5 min contact time).*

Steroid	log % absorbed, B	log predicted % absorbed, B_{pred}
Per hydro cyclopentano phenanthrene	N.D.	2·86* ($\log B_p$)
Testosterone butyrate	1·99	1·99
Stanolone acetate	1·94	2·03
Testosterone propionate	1·91	1·93
Testosterone acetate	1·85	1·87
3α-Hydroxy-5β-pregnan-20-one	1·84	1·82
Ethynyloestradiol	1·81	1·77
Stanolone	1·79	1·74
Dehydroepiandrosterone	1·76	1·71
Trimethylsilyl-testosterone	1·75	1·70
Androsterone	1·74	1·74
Pregnanedione	1·74	1·86
Methandriol	1·73	1·73
Deoxycorticosterone	1·72	1·74
Norethynodrel	1·72	1·74
Ethisterone	1·72	1·67
Oestrone	1·72	1·72
Progesterone	1·72	1·74
Etiocholanolone	1·70	1·70
Oxymesterone	1·70	1·69
Oestradiol-17β	1·68	1·68
Methyltestosterone	1·65	1·64
Epitestosterone	1·63	1·58
Testosterone	1·63	1·58
Norethandrolone	1·61	1·64
Norethisterone	1·61	1·61
Methandienone	1·56	1·55
Oxandrolone	1·56	1·55
Cortexolone	1·36	1·38
Corticosterone	1·18	1·10
Oestriol	1·04	1·04
Cortisone	1·04	0·78
Cortisol	0·60	0·74
Prednisolone	log 0·00	0·65

* Calculated as log B (androsterone)-$\pi'_{OH}-\pi'_{=O}-2\times\pi'_{CH_3}$

N.D. not determined.

steroids relative to 5α (see π' for a Cis A/B ring juncture) is the one example in the present study of the importance of stereochemistry in determining passive absorption characteristics. This phenomenon is best explained in thermodynamic terms: the 'A' ring of a 5β-steroid is directed away from the plane of the molecule as a whole resulting in a less ordered water structure around the molecule and consequently a more favoured state on entropy grounds.

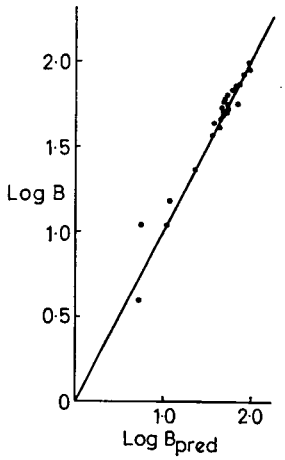

FIG. 2. A comparison of predicted (B_{pred}) and experimental (B) oral mucosal absorption of steroids.

The additivity principle implicit in equation 3 breaks down in certain circumstances (Currie & others, 1966; Tute, 1971) and this has necessitated use of $\pi'_{interaction}$ contributions. For example corticosteroids may be subject to intramolecular bonding *in vivo* between C(20) carbonyl, C(17) and C(21) hydroxyl functions thus rendering the molecule more lipid soluble. The extent of this increased lipid solubility is calculated in terms of the $\pi'_{interaction}$ contribution (Table 1). Intramolecular bonding between the 4β-hydroxyl and 3-keto functions may also explain the greater than expected % absorption of oxymesterone.

The number of steroid groupings examined hitherto has been limited but the present results indicate that these substituent constants may be used to predict the degree of absorption of a steroid across the oral mucosa and may well predict the relative absorption of a series of steroids across any membrane where passive processes only are involved.

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