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The Partition Coefficient of Aminouracil Derivatives[1]

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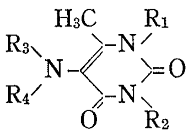
The 1-octanol-water partition coefficient, P, of a number of substituted aminouracil derivatives was determined. The log P values were found to be composed additively from π values, (the increments in log P), attributable to each substituent at various positions. The π values of substituents are position specific and are governed by their hydrophobicity as well as by their electronic effect on the ring system.

Recently, the 1-octanol-water partition coefficient, P, has been widely used as an index of hydrophobic character in structure-activity studies of a variety of drugs.[3-5] One of the most useful features of the partition coefficient is that it is additive and constitutive when expressed on the log scale, as shown in eq. 1.[4] In eq. 1, π is the increment in

$$\log P = \sum\pi + \log P_{\mathrm{H}} \qquad (1)$$

log P attributable to substituents in a molecule and log P_{H} is the value for the unsubstituted parent compound. Sometimes, π values from one reference system can be used to estimate log P of drugs of different systems.[4] However, when the electronic effect of the substituent on the unsubstituted parent molecule differs greatly from those involved in the reference system, the constancy of π values does not hold.[6,7] Examples have been found for heteroaromatic compounds such as substituted quinazolones[8] and triazinones.[7] Furthermore, when specific steric and conformational interactions of the substituents are involved, the additivity fails for predicting the log P value of the molecule;[7,9,10] particularly for aryl[10] and heteroaryl[11] compounds having a long side chain bearing a polarizable functional group.



I

Chart 1

During structure-activity studies of anti-inflammatory aminouracil derivatives (I), we determined their 1-octanol-water partition coefficient and examined the nature of their log P values. We here report that the log P values of this series of compounds are, in fact, additive, but that the π values of substituents are specific to each position and are governed not only by their hydrophobicity but by their electronic effect on the ring system as well.

Experimental

Materials and Methods——The 40 aminouracil derivatives used in this work are shown in Table I, where the figure 1 shows the presence of substituents at the 1, 3 and 5 positions. R_1, R_2 and NR_3R_4, are defined

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[3] C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).

[4] C. Hansch, "Drug Design," Vol. I, ed. by E.J. Ariens, Academic Press, New York, N.Y., 1971, p. 271.

[5] A. Verloop, "Drug Design," Vol. III, ed. by E.J. Ariens, Academic Press, New York, N.Y., 1972, p. 133.

[6] T. Fujita, J. Iwasa and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

[7] A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).

[8] E. Wulfert, P. Bolla and J. Mathieu, *Chim. Therap.*, **4**, 246 (1969).

[9] C. Hansch and S.M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

[10] A. Canas-Rodriguez and M.S. Tute, *Adv. Chem. Ser.*, **114**, 41 (1972).

[11] T. Fujita, *Adv. Chem. Ser.*, **114**, 1 (1972).

in Table II (*vide infra*). Compounds **1**—**34** were kindly supplied by Professor Senda of the Gifu College of Pharmacy. Compounds **35**—**40** were synthesized by us. The syntheses of these derivatives will be published elsewhere. Partition coefficients were measured by shaking 15 ml of 10^{-4}—10^{-5} mole/liter solution (in 0.1 M phosphate buffer, pH, 7.4) with 0.01—5 ml of 1-octanol for 1 hr at 25±2°. The value of P was calculated by eq. 2, where C_i and C_w, the concentration in the aqueous phase before and after equilibrium, respectively, were determined

$$P = \frac{C_i - C_w}{C_w} \times \frac{V_w}{V_o} \qquad (2)$$

spectrophotometrically. V_w and V_o are the volumes of the water and 1-octanol phases, respectively. Since the log K_A value of this series of compounds is located around −4, the P values determined are considered to be those for the neutral form. The log P values listed in Table I are the average of at least 5 determinations. The standard error in these values was estimated as ±0.02.

TABLE I. Observed and Calculated log P Values of 40 Aminouracils

Compd. No.	R_1								R_2									NR_3R_4									μ	log P	
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z		Obsd.	Calcd.
1	1																1	1									1	3.02	2.98
2	1								1									1									1	0.99	1.00
3	1									1								1									1	1.30	1.31
4	1									1									1								1	2.11	1.91
5	1									1										1							1	1.20	1.29
6	1									1											1						1	1.69	1.69
7		1							1									1									1	1.19	1.63
8	1										1							1									1	2.47	2.47
9			1						1									1									1	2.94	2.68
10		1										1						1									1	1.40	1.44
11			1									1						1									1	2.53	2.49
12	1												1					1									1	2.65	2.65
13	1									1												1					1	1.48	1.62
14		1							1											1							1	1.70	1.61
15	1									1													1				1	2.76	2.64
16	1									1														1			1	0.69	0.80
17		1							1														1				1	3.21	2.97
18		1							1																1		1	2.68	2.59
19	1									1															1		1	2.26	2.27
20			1						1														1				1	3.68	4.01
21			1						1															1			1	2.39	2.16
22			1						1																1		1	3.55	3.63
23				1						1								1									1	1.44	1.44
24		1							1																	1	1	2.59	2.59
25					1				1									1									1	2.32	2.32
26						1			1									1									1	1.96	1.96
27		1												1				1									1	1.98	1.98
28		1							1										1								1	2.19	2.23
29		1													1			1									1	2.29	2.23
30							1			1								1									1	1.30	1.70
31		1													1				1								1	2.78	2.84
32							1			1									1								1	2.20	2.30
33		1														1		1									1	1.12	1.12
34								1		1								1									1	0.85	0.85
35		1															1							1			1	3.05	3.09
36			1							1												1					1	3.27	3.29
37		1								1														1			1	1.44	1.42
38			1							1														1			1	2.37	2.47
39		1								1													1				1	3.24	3.27
40		1								1												1					1	2.40	2.24

restriction equations

R_1; $12A+15B+7C+D+E+F+2G+H=0$

R_2; $13I+17J+K+2L+M+N+2O+P+2Q=0$

NR_3R_4; $17R+4S+2T+U+3V+4W+5X+3Y+Z=0$

Table II. Contributions to log P of Substituents at Various Positions

	Substituents		π_{ref}	σ^*[a]	π_i		
					Calcd. from eq.5	$\Delta\pi_i$	Calcd.[b]
R_1	A	CH_3	0.56[c]	0.0	−0.596	0.0	−0.563
	B	phenyl	1.96[c]	0.60	0.031	0.627	0.159
	C	cyclohexyl	2.26[d]	−0.15	1.076	1.672	0.927
	D	$CH_2CH=CH_2$	1.10[c]	0.13[e]	−0.464	0.132	−0.214
	E	*p*-Cl-phenyl	2.67[f]	0.75[g]	0.720	1.316	0.634
	F	*p*-CH_3O-phenyl	1.94[f]	0.36[g]	0.360	0.956	0.311
	G	CH_2CH_3	1.02[c]	−0.10	−0.205	0.391	−0.119
	H	CH_2CH_2OH	−0.14[h]	0.19[i]	−1.054	−0.458	−1.267
R_2	I	CH_3	0.56[c]	0.00	−0.322	0.0	−0.018
	J	phenyl	1.96[c]	0.60	−0.018	0.304	0.364
	K	benzyl	2.01[c]	0.22	1.144	1.466	0.836
	L	H	0.0	0.49	−0.511	−0.189	−1.004
	M	cyclopentyl	1.85[d]	−0.20	1.324	1.646	1.194
	N	$CH_2CH=CH_2$	1.10[c]	0.13[e]	0.027	0.349	0.245
	O	CH_2CH_3	1.02[c]	−0.10	0.281	0.603	0.447
	P	CH_2CH_2OH	−0.14[h]	0.19[i]	−0.833	−0.511	−0.768
	Q	cyclohexyl	2.26[d]	−0.15	1.652	1.974	1.449
NR_3R_4	R	$N(CH_3)_2$	1.00[j]	0.00	−0.257		−0.128
	S	$N(CH_2CH_3)_2$	2.00[j]	−0.20	0.345		0.720
	T	$NHCH_2CH_2CH_3$	1.50[j]	0.37	−0.277		−0.111
	U	$NH(CH_2)_3CH_3$	2.00[j]	0.36	0.125		0.235
	V	$NHCH_2CH(CH_3)_2$	1.80[j]	0.36	0.052		0.100
	W	piperidino	2.05[j]	−0.14[k]	1.078		0.701
	X	morpholino	0.66[j]	0.67[k]	−0.770		−0.937
	Y	pyrrolidino	1.64[j]	−0.26[k]	0.701		0.529
	Z	$N(CH_2CH=CH_2)_2$	2.40[j]	0.26	0.702		0.591
	μ	skeleton			2.179		

[a] R.W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 3120 (1952); **75**, 4231 (1953).
[b] A-H from eq. 7, I-Q from eq. 8, R-Z from eq. 9
[c] values for subst. benzenes[6,7]
[d] estimated according to the additivity rule using Table XVI in ref. 7
[e] the value for crotyl
[f] estimated as π(phenyl)+π(Cl or CH_3O); π-values are for subst. benzenes[6,7]
[g] Y. Nagai, H. Matsumoto, T. Nakano and H. Watanabe, *Bull. Chem. Soc. Japan* **45**, 2560 (1972).
[h] estimated as $\pi(CH_3CH_2)+\pi$(OH, aliphatic)[7]
[i] estimated from $\sigma^*(CH_2OH)$ and the transmission coefficient as $0.55\times0.34=0.19$
[j] values for N-substituents; estimated as in footnote b
[k] J.K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

Result and Discussion

First, partition coefficients of the 40 aminouracil derivatives were analyzed in terms of the sum of their $\pi_{\text{ref.}}$ values which were derived in other reference systems. As reference π values for R_1 and R_2, those obtained in substituted benzenes were used unless otherwise noted. For NR_3R_4, the summation of $\pi_{(\text{alkyl})}$ values for two substituents was employed. The $\pi_{\text{ref.}}$ values are shown in Table II. As shown in eq. 3, the correlation is very poor, indicating that the π values of other reference systems are not applicable as such to the log P values of

$$\log P = 0.565\sum\pi_{\text{ref.}} - 0.162 \qquad (3)$$

$$n=40,\ r=0.614,\ s=0.620,\ F=22.938$$

this series of compounds. In eq. 3 and the following equations, n is the total number of compounds used in the correlation, r is the correlation coefficient, s is the standard deviation and F is the value of the F-ratio.

If we add the electronic term of the substituent at each position, the correlation is much improved as shown in eq. 4 where σ^* is the Taft electronic parameter of the substituents as listed in Table II. For substituents at the 5 position, the sum of the σ^* values for two *N*-

$$\log P = 0.726\sum\pi_{\text{ref.}} - 0.927\sigma_1{}^* - 1.521\sigma_2{}^* - 0.599\sum\sigma^*_{5\text{N}} - 0.144 \qquad (4)$$
$$n=40,\ r=0.895,\ s=0.365,\ F=35.170$$

substituents was used. Conceivably not only hydrophobicity but the electronic effect of substituents on the ring system and the side chain amino nitrogen, as well, plays a role in the partitioning of this series of compounds. If we added the electronic terms $\sum\sigma^*$ together for the 1-, 3- and 5*N*-substituents to eq. 3, the correlation was improved but was much poorer than that of eq. 4. Since the situations where these substituents are attached to the heterocyclic system differ greatly from each other, they should contribute to the total log *P* value specifically from each position.

To separate the position specific contribution of the substituents, we applied the Free–Wilson technique.[12] Assuming that the contribution of a certain substituent to the total log *P* value is additive but constant only at a certain position, we can derive a linear equation similar to eq. 2 for each compound in the form of eq. 5. In eq. 5, π_i is the log *P* increment attributable to the *i*-th substituent and X_i is 1 or 0 depending upon the presence or

$$\log P = \mu + \sum\pi_i X_i \qquad (5)$$

absence of the *i*-th substituent. Since the log *P* value of the unsubstituted aminouracil itself is not available, we took the constant contribution from the parent skeleton, μ, as the overall average of the log *P* values of the 40 compounds.[12,13] The X_i values for each compound are shown in Table I. The restriction equations where substituent contributions at each position are summed for a whole set of compounds and set to zero are also included in Table I. Application of these restriction equations reduces the number of unknowns, including μ, from **27** to **24**. Then, **40** simultaneous equations with **24** unknowns were solved by the method of least squares. The calculated contribution, π_i, of each substituent at each position and the value of μ are shown in Table II. The correlation between the observed and calculated log *P* values is very good as judged from $r=0.986$, $s=0.205$, and $F_{23,16}=23.59$ ($F_{23,16,0.005}=3.6$). The calculated log *P* values are shown in Table I. Thus, the additivity model is valid for the log *P* values of these compounds. The observed and calculated log *P* values are identical for several compounds. This is necessarily so for compounds **6**, **8**, **12**, **23**—**27**, **33**, and **34**, because these compounds have a substituent which is only observed once. It should be noted that the π_i values cannot be compared on the same basis for substituents at different positions, since π_i values are normalized at each position. Taking $\pi_{i(\text{CH}_3)}$ as the standard, we can compare $\Delta\pi_i$ values for the R_1 and R_2 substituents. As shown in Table II, the sequence in the magnitude of the $\Delta\pi_i$ values for phenyl, allyl and ethyl groups at the 1-position is not the same as that for the same groups at the 3-position. Thus, the constancy of π does not hold even in the same molecule. This must be due to differences in the electronic environment at various positions.

We assumed that the π_i values of the substituents at each position can be further analyzed in terms of the reference π value and Taft's σ^* in the form of eq. 6.

$$\pi_i = a\pi_{\text{ref.}} + \rho^*\sigma^* + c \qquad (6)$$

a, ρ^* and c are the constants which can be calculated by the method of least squares. For the substituents, R_1, R_2, and $-NR_3R_4$, eq. 7, 8 and 9 were derived, respectively.
For R_1:

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[12] S.M. Free, Jr. and J.W. Wilson, *J. Med. Chem.*, 7, 395 (1964).
[13] T. Fujita and T. Ban, *J. Med. Chem.*, **14**, 148 (1971).

$$\pi_i = 0.815(\pm 0.212)\pi_{\text{ref.}} - 0.698(\pm 0.616)\sigma^* - 1.020(\pm 0.312) \tag{7}$$
$$n=8,\ r=0.976,\ s=0.182,\ F=51.00$$

For R_2:

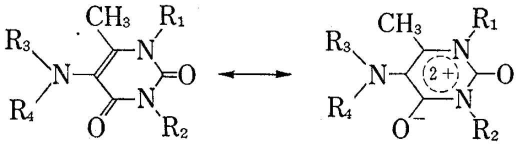
$$\pi_i = 0.762(\pm 0.342)\pi_{\text{ref.}} - 1.142(\pm 1.103)\sigma^* - 0.445(\pm 0.538) \tag{8}$$
$$n=9,\ r=0.940,\ s=0.345,\ F=22.60$$

For NR_3R_4

$$\pi_i = 0.674(\pm 0.441)\pi_{\text{ref.}} - 0.866(\pm 0.758)\sigma^* - 0.801(\pm 0.817) \tag{9}$$
$$n=9,\ r=0.921,\ s=0.262,\ F=16.71$$

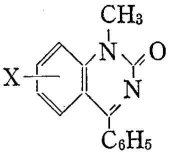
The correlations obtained with both parameters were much improved over single parameter equations. Figures in parentheses are the 95% confidence intervals of the susceptibility constants. The F-test shows that the σ^* term in eq. 7, 8 and 9 is justified at better than the 95% confidence level (for eq. 7: $F_{1,5}=8.49$, for eq. 8: $F_{1,6}=6.42$, for eq. 9: $F_{1,6}=7.81$, $F_{1,5,0.05}=6.61$, $F_{1,6,0.05}=5.59$).

These results indicate that the free energy difference in the partitioning process is separable to those attributed to each substituent which, in turn, are a function of the hydrophobicity and electronic effect on the ring system. The greater the hydrophobic and electron donating characters of the substituents at any position, the larger the 1-octanol-H_2O partition coefficient in spite of differences in susceptibility. This may be due to the fact that the electron donating character of the substituents stabilizes the resonance canonical form (II) in varying degrees at different positions. 1-Octanol is much weaker as a hydrogen bond doner than is water.



I II

Chart 2



III

Chart 3

Thus, while form (I) would favor solvation with water, form (II), being charge-separated, could undergo solvation with 1-octanol to a certain extent. Although solubility in the water phase may increase with the increasing contribution of the charge-separated form (II), 1-octanol would compete more effectively to increase the relative solubility in its phase. This situation is quite similar to the log P values of substituted quinazolones (III), where eq. 10 was found by Wulfert and his co-workers.[8] Here, the electron releasing effect of the

$$\pi_{\text{exp}} = 1.09\pi_{\text{POA}} - 1.03\sigma + 0.10 \tag{10}$$
$$n=9,\ r=0.97$$

aromatic substituent, X, also favors partition into the 1-octanol phase.

This report shows that, for structure-activity studies of heteroaromatic compounds, experimentally determined log P values can be recommended for use as the "hydrophobic" parameters. The log P values of substituted heteroaromatic compounds are quite complex in composition. However, if they are separable into contributions from the substituents at each position, they can be further analyzed in terms of the intrinsic physicochemical parameters of the substituents. It is desirable that examples, such as those shown in this work, should be accumulated so that one can generalize the nature of the log P of heteroaromatic compounds.