ZGODOVINA logP

1872 – porazdelitveni koeficient prvič definiran – Berthelot in Jungfleisch: "On the laws that operate for partitition of a substance between two solvents."

1899 – Meyer porazd. koef. prvič uporabljen za korelacijo in razlago
1901 – Overton učinkovitosti bioaktivnih spojin (narkotiki)

Uporaba porazd. koef. za korelacijo z bioaktivnostjo se zelo razširi: zamudni postopki določanja koncentracije učinkovin (porazdeljevanje – separacija [npr. timol iz oljne faze z destilacijo z vodno paro] – detekcija [titracija ipd.]).

- razvoj UV spektroskopije → za večino spojin (ki absorbirajo svetlobo) – enostavno določanje koncentracije

- določanje P v različnih "kombinacijah" organsko topilo/voda: olivno olje, arašidovo olje, ricinovo olje, laneno olje, kot tudi heptan idr...

- 1964 – začetek "splošne" uporabe logP kot lipofilni faktor:
Hansch uvaja oktanol/voda sistem za določanje logP

- 1971 – Leo, Hansch in Elkins – publicirajo pregledni članek s podatki za logP za skoraj 6000 spojin (z vključno svojimi 800 meritvami) v sistemu okt./voda

PORAZDELITVENI KOEFICIENT

Oznake (kratice): **P, K_p, D**

D – distribution koefficient (P_{nav}, upoštevajte pH)

Definicija: **$P = c_0 / c_w$ (konc. – aktivnost)**

$\gamma = 1$

Termodinamika: **molski ulomki, x_i**

$$(\mu_i)_w = (\mu_i)_0$$

$$\mu_w^0 + RT\ln x_w = \mu_0^0 + RT\ln x_0$$

$$\Delta G^0 = \mu_w^0 - \mu_0^0 = RT\ln \frac{x_0}{x_w} = RT\ln P$$

prehod topljenca iz organske v vodno fazo

Povezava med “obema P”:

molski ulomek: $x_A = \dfrac{n_A}{n}$ **($n = n_A + n_B + \ldots$)**

2 komp.: $x_A = \dfrac{n_A}{n_A + n_B}$ **$n = c \cdot V \rightarrow$** $x_A = \dfrac{c \cdot V}{\underbrace{c \cdot V}_{\text{zanemarimo}} + V / V_m} \rightarrow$

$$x_A \approx c \cdot V_m \Rightarrow P_T = \frac{x_0}{x_w} = \frac{c_0}{x_w} \cdot \frac{\overline{V_0}}{\overline{V_w}} = \underline{\underline{P_c \cdot V_0^0 / V_w^0 = P_c \cdot n_w / n_0}}$$

V_w^0 **= 18 mL → n_w = 55,5 mol/L**

V_{okt}^0 **= 157,5 mL → n_0 = 6,35 mol/L**

Aditivnost logP vrednosti:

Standardni kemijski potencial μ_i^0 se razdeli na lipofilno in hidrofilno komponento (predpostavka)

$$\left(\mu_i^0\right)_w = \left(\mu_L^0\right)_w + n\left(\mu_H^0\right)_w$$

n – št. hidrofilnih skupin

$$\left(\mu_i^0\right)_0 = \left(\mu_L^0\right)_0 + n\left(\mu_H^0\right)_0$$

Kemijski potencial za obe fazi lahko zapišemo: $\mu = \mu^0 +$ RT...

$$\left(\mu_i\right)_w = \left(\mu_L^0\right)_w + n\left(\mu_H^0\right)_w + RT\ln x_w$$

$$\left(\mu_i\right)_0 = \left(\mu_L^0\right)_0 + n\left(\mu_H^0\right)_0 + RT\ln x_0$$

Če uporabimo koncentracije:

$$\left(\mu_i\right)_w = \left(\mu_L^0\right)_w + n\left(\mu_H^0\right)_w + RT\ln c_w + RT\ln V_w^0$$

$$\left(\mu_i\right)_0 = \left(\mu_L^0\right)_0 + n\left(\mu_H^0\right)_0 + RT\ln c_0 + RT\ln V_0^0$$

V RAVNOTEŽJU:

$(\mu_i)_w = (\mu_i)_0$ **; p, T = konst. in ob upoštevanju P = c_0 / c_w :**

$$\mathrm{RT}\ln \mathrm{P} = \left(\mu_L^0\right)_w - \left(\mu_L^0\right)_0 + \left[\left(\mu_H^0\right)_w - \left(\mu_H^0\right)_0\right] + \mathrm{RT}\ln \frac{V_w^0}{V_0^0}$$

$$\ln \mathrm{P} = \frac{\Delta\mu_L^0}{\mathrm{RT}} + \frac{n\Delta\mu_H^0}{\mathrm{RT}} + \ln \frac{V_w^0}{V_0^0}$$

$$\left(\Delta\mu^0 = \left(\mu^0\right)_w - \left(\mu^0\right)_0\right)$$

Potrditev predpostavke:

Če v grafu nanašamo vrednosti lnP za homologno vrsto v odvisnosti od n, dobimo premico; naklon = $\Delta\mu_H^0 / \mathrm{RT}$**, odsek na osi**

$$y = \Delta\mu_L^0 / \mathrm{RT} + \ln\left(V_w^0 / V_0^0\right)$$

DOLOČANJE P (oziroma logP)

a) računsko iz fragmentalnih prispevkov
b) eksperimentalno

Ad a): empirično (baza podatkov)

Hansch: $\log P_{(R-X)} = \log P_{(R-H)} + \pi_{(X)}$

H (vodik) – nima prispevka k lipofilnosti, korekcije

Rekker: $$\log P = \sum_{i}^{n} a_i f_i + k \cdot c_M$$

f_i – hidrofobna fragmentna konstanta za fragment i
a_i – mnogokratnik teh fragmentov v molekuli
$k \cdot c_M$ – dodatni člen, "popravki" – v različnih primerih potrebno korigirati vrednost kot mnogokratnik "magične konstante" (c_M)

Ad b): - konvencionalna (klasična) metoda stresanja – "shake flask method"

- metoda kontinuiranega vzorčenja (modifikacija gornje metode) – "filter probe"

- metoda kontinuiranega spiranja kolone – "regeneration column method": dobimo nasičene raztopine (spiranje topljenca, vezanega na stacionarno fazo v koloni) → gre za razmerje topnosti – neekzaktno!!

- uporaba kromatografskih metod (TLC, HPLC), RPLC; ekstrapolacija, izbor določenega razmerja MeOH : vodna faza; vpliv pH, izbor kolone: nasičena z oktanolom, blokirane silanolne skupine, RP kolone

Omejitve: majhne polarne molekule (vezanje na stacionarno fazo); velike molekule – velikost por

IZBOR ORGANSKEGA TOPILA ZA PORAZDELJEVANJE

n–oktanol - najbolj uporabljan, najpomembnejši

Nepolarna ali delno polarna topila:

cikloheksan, ogljikov tetraklorid, benzen, kloroform

- topljenec prehaja z molekulami vode iz vodne v organsko fazo (hidroksilne spojine, amini, anilini, karboksilne kisline). Tvorba H – vezi.
- asociacija topljencev v organski fazi (karboksilne kisline). Dimerizacija.

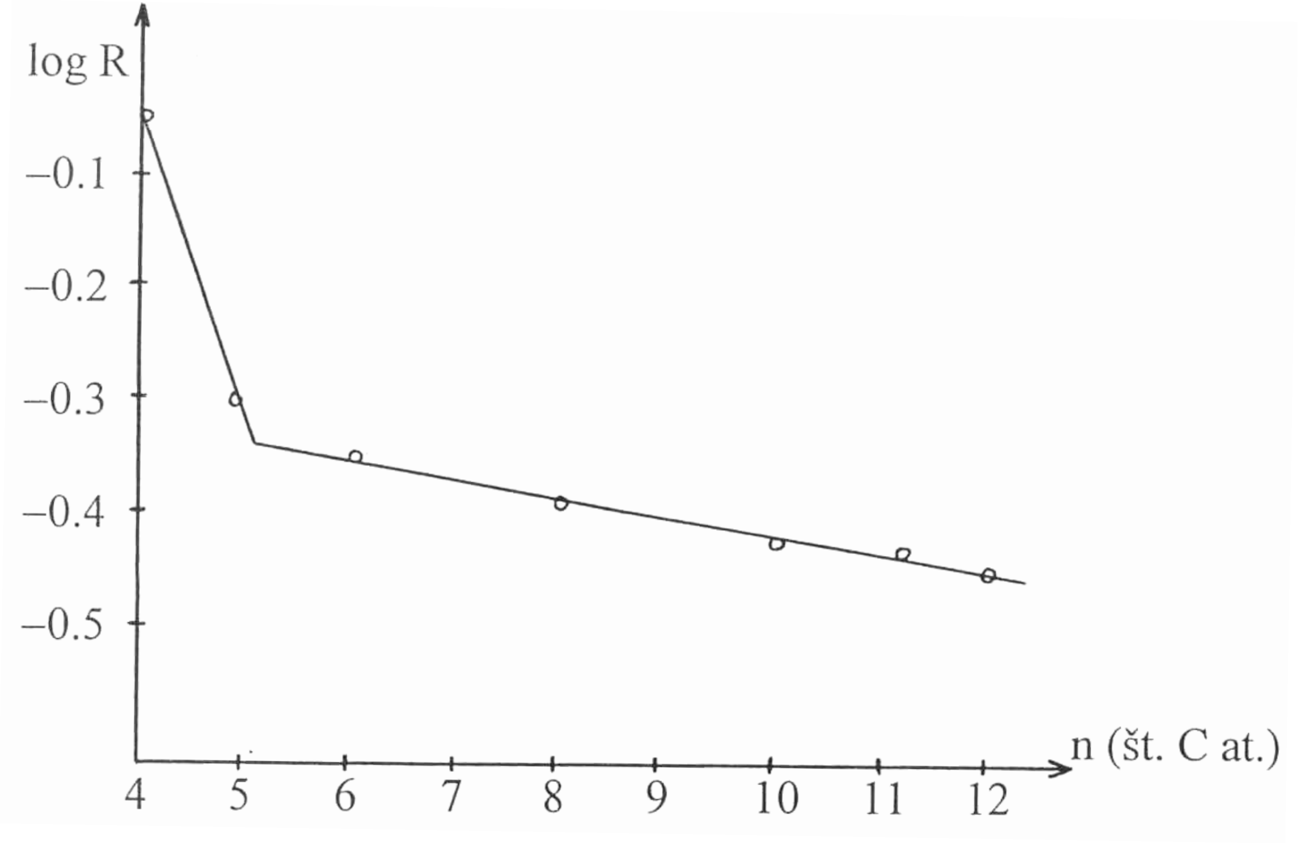
Alkanoli (alkoholi):

- asociirani (linearni, ciklični multimeri)
- mešanje z vodo: do C_3 – mešanje, C_4 in C_5 – močne interakcije z vodo, C_6 – C_{12} – šibkejše interakcije, nad C_{12} – trdne spojine.
- n-heptanol in n-nonanol – podobna n-oktanolu; vsebnost vode različna (2.57 mol/L – heptanol, 2.15 mol/L – oktanol, 1.93 mol/L – nonanol; T = 22 ± 1°C)

- različne teorije o asociatih molekul oktanola in vode: tetraedri (Hahsch) – razmerje W/A v z vodo nasičenem oktanolu = 0,28!?;

novejše teorije – “ clustri”

- oktanol nasičen z vodo (2.3 mola H_2O/L pri 25°C)
- metode preučevanja: NMR raziskave, dielektrična konstanta, viskoznost...NI SPREMEMB V VSEBNOSTI VODE PRI PORAZDELJEVANJU (kot pri nepolarnih topilih)
- n-heptanol, n-nonanol – podobna n-oktanolu, možna alternativa



logR : R = H_2O površina / CH_2 površina; razmerje površin pod trakovoma v NMR spektru za raztopljeno vodo v alkoholu in za protona CH_2 skupine, na katero je pripeta alkoholna OH skupina.

Razmerje W/A > 0.4 pri C_4 in C_5 alkoholih, pri alkoholih C_6 – C_{12}: W/A < 0.4; spremembe strukture niso tako izrazite pri n > 6.
log 0.4 ≈ - 0.4 (- 0.398)

Estri:

največ olivno olje

- problemi: ↑viskoznost, naravna snov → problematična točnost (neenakost) sestave; kvarjenje – oksidacija.
- etilacetat – hidroliza (neprimeren).

COLLANDER-ove ENAČBE

$\log P_2 = a \cdot \log P_1 + b$ pomemben a→1; b – ni pomemben

EKSTRATERMODINAMSKA ZVEZA (Hansch to že ugotovi)

$\log P_{\text{izo-pentanol}} = 1.17 \log P_{\text{izo-butanol}} - 0.17$

$\log P_{\text{n-oktanol}} = 1.24 \log P_{\text{n-butanol}} - 0.42$

Topnost H_2O v n-butanolu: 9.53 mola H_2O/L

0,977 mol/L – topnost n-butanola v H_2O

Ostale zveze: CH_3Cl/H_2O, $CHCl_4/H_2O$, ksilen/H_2O, benzen/ H_2O idr.

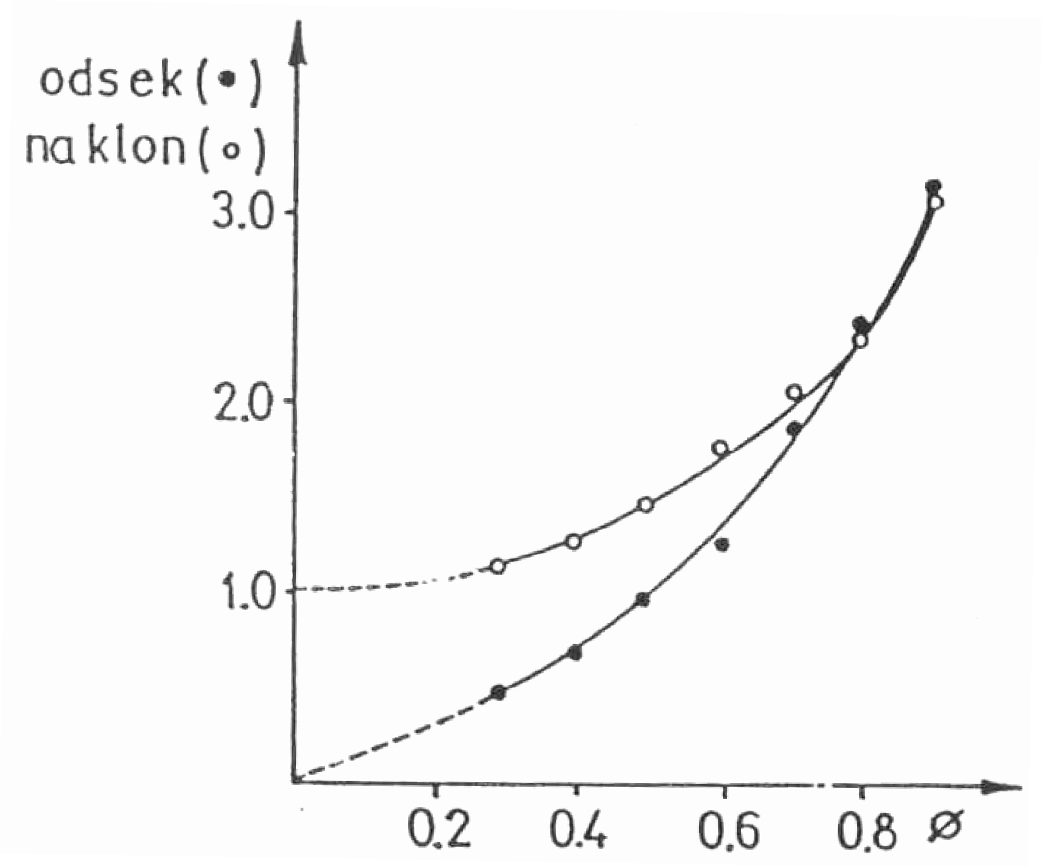
Uporabnost logP:

- predvidevanje biološke aktivnosti (npr. prehod preko membran; QSAR)
- določevanje asociatov v vodni oziroma organski fazi
- predvidevanje vodotopnosti (Yalkowsky)
- določanje pK_a

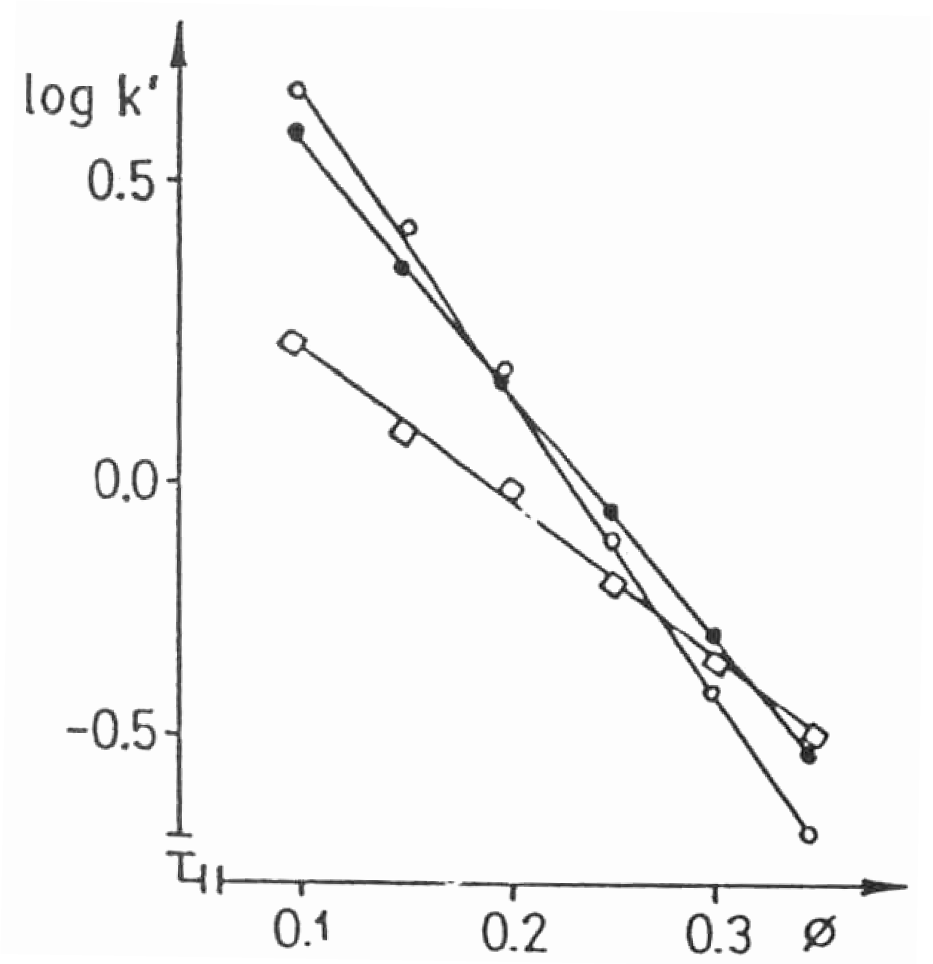
Vpliv medsebojnega (delnega) mešanja vode in oktanola;

$P \neq S_0/S_w$

Slika 1: Odvisnost odseka na ordinati (●) in naklona (○) Collanderove enačbe od volumskega deleža metanola v mobilni fazi (ø).



Slika 2: Odvisnost logk’ od volumskega deleža metanola v mobilni fazi (ø); □ - adenin, ● - adenozin, ○ - adenozin 3’, 5’ – monofosfat.



Hydrolipophilic anomalies of some guanine derivatives

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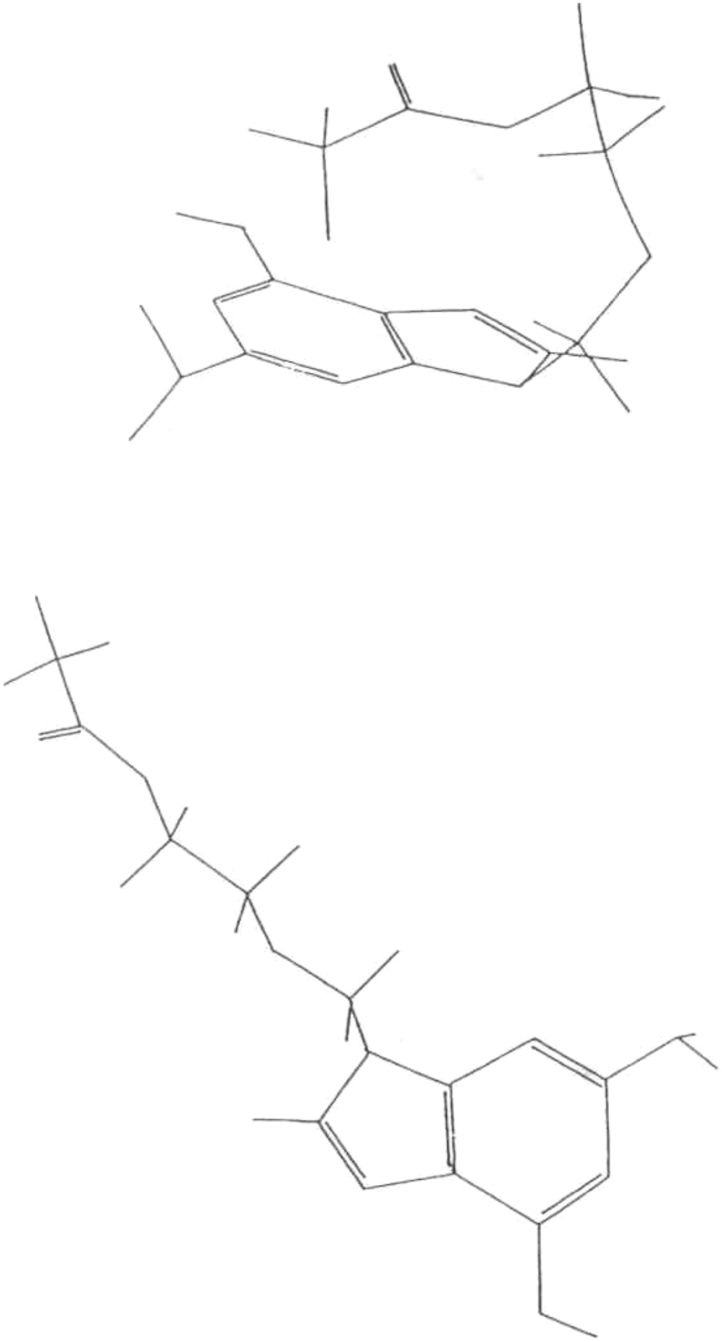
Table I. Log*P* values determined experimentally in *n*-octanol/water and calculated by Rekker's method and differences between these values.

Compound	*LogP (exp)*	*Δ*	*LogP (calc)*	*Δ'*	*Δ' – Δ*
ACV	−1.56	–	−1.55	–	–
NAcACV	−1.30	0.26	−1.26	0.29	0.03
OAcACV	−1.08	0.48	−0.58	0.97	0.49
diAcACV	−0.83	0.73	−0.29	1.26	0.53
DCV	−1.08	–	−1.05	–	–
NAcDCV	−1.33	−0.25	−0.76	0.29	0.54
OAcDCV	−0.61	0.47	−0.08	0.97	0.50
diAcDCV	−1.05	0.03	0.21	1.29	1.23

Δ: the difference between experimentally determined log*P* values = log*P* (acetylated ACV or DCV derivatives) – log*P* of parent molecule (ACV or DCV); Δ': the difference between calculated log*P* values = log*P* (acetylated ACV or DCV derivatives) – log*P* of parent molecule (ACV or DCV); Δ' – Δ: the difference between calculated and experimentally determined log*P* values.

Figure 3:
Molecule of OAcACV in extended and folded conformations.



$\log P(\mathrm{ACV}) < \log P(\mathrm{NAcDCV}) \approx \log P(\mathrm{NAcACV}) <$
$\log P(\mathrm{OAcACV}) \approx \log P(\mathrm{DCV}) \approx \log P(\mathrm{diAcDCV}) <$
$\log P(\mathrm{diAcACV}) < \log P(\mathrm{OAcDCV})$

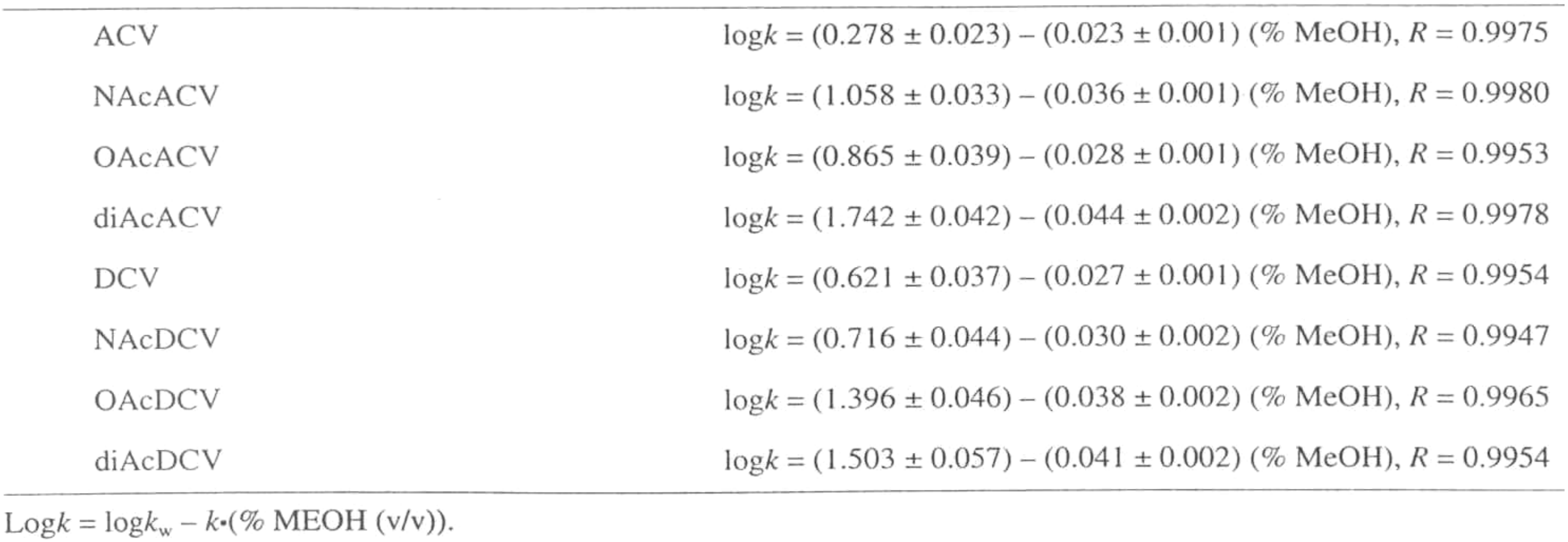
and

$\log k_w(\mathrm{ACV}) < \log k_w(\mathrm{DCV}) < \log k_w(\mathrm{NAcDCV}) <$
$\log k_w(\mathrm{OAcACV}) < \log k_w(\mathrm{NAcACV}) <$
$\log k_w(\mathrm{OAcDCV}) < \log k_w(\mathrm{diAcDCV}) < \log k_w(\mathrm{diAcACV})$

Table 1: Calculated log*k* values for tested guanine derivatives at different methanol concentrations (v/v) in mobile phase.

	Percentage MeOH (%)					
	15	*20*	*25*	*30*	*35*	*40*
ACV	–0.071 ± 0.006	–0.184 ± 0.012	–0.309 ± 0.021	–0.410 ± 0.023	–0.565 ± 0.034	–0.638 ± 0.028
NAcACV	0.521 ± 0.033	0.375 ± 0.025	0.132 ± 0.010	–0.021 ± 0.001	–0.191 ± 0.015	–0.359 ± 0.021
AcACV	0.442 ± 0.021	0.330 ± 0.016	0.143 ± 0.009	–0.022 ± 0.002	–0.103 ± 0.008	–0.253 ± 0.013
diAcACV	1.074 ± 0.062	0.889 ± 0.052	0.598 ± 0.039	0.383 ± 0.014	0.195 ± 0.011	–0.027 ± 0.002
DCV	0.217 ± 0.007	0.114 ± 0.006	–0.085 ± 0.005	–0.186 ± 0.007	–0.338 ± 0.014	–0.432 ± 0.021
NAcDCV	0.269 ± 0.008	0.158 ± 0.005	–0.067 ± 0.002	–0.176 ± 0.004	–0.348 ± 0.017	–0.447 ± 0.017
AcDCV	0.823 ± 0.034	0.663 ± 0.034	0.392 ± 0.012	0.261 ± 0.008	0.034 ± 0.002	–0.133 ± 0.004
diAcDCV	0.887 ± 0.029	0.725 ± 0.025	0.427 ± 0.013	0.266 ± 0.009	0.030 ± 0.001	–0.104 ± 0.006

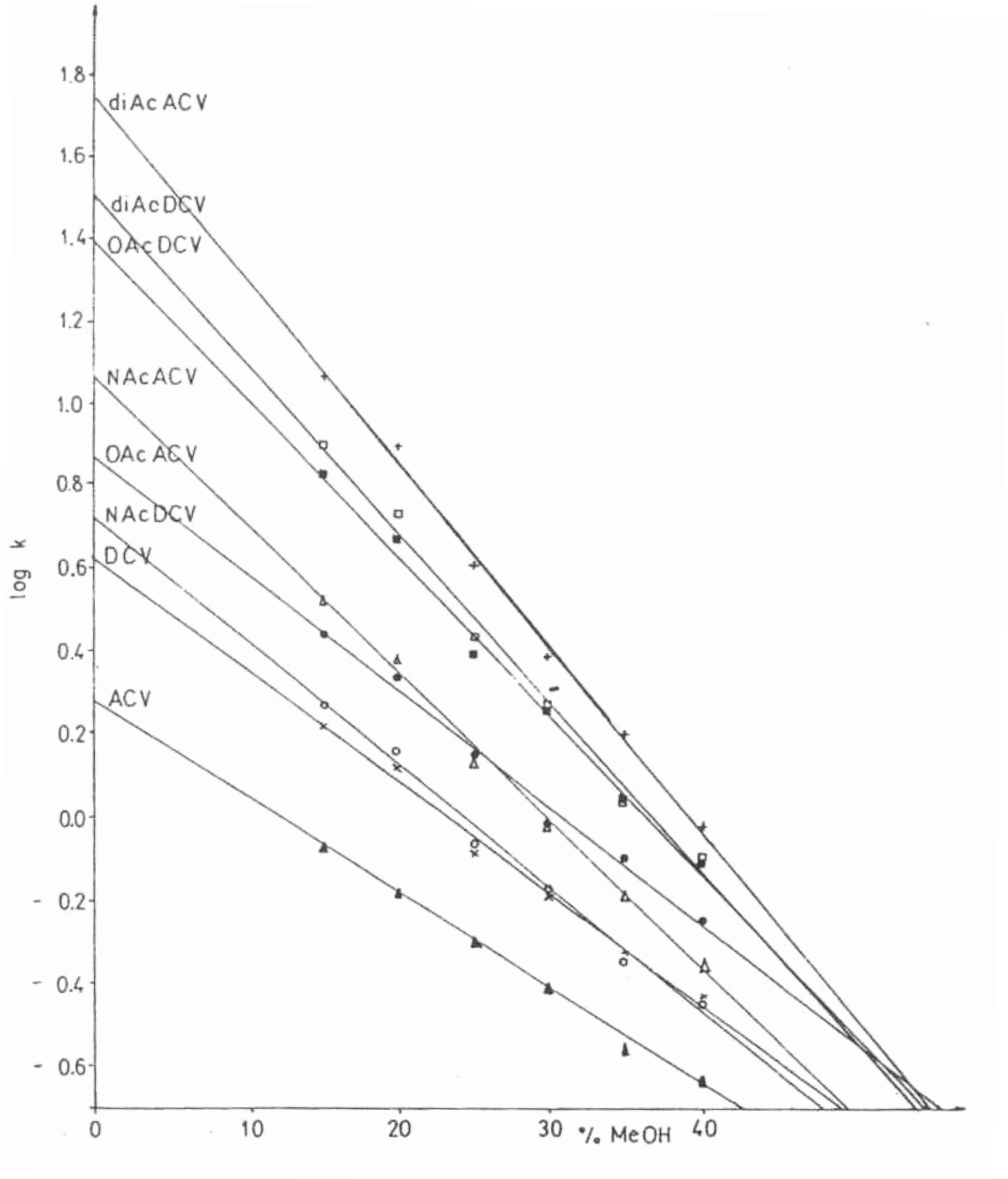
Table 2: The equations for log*k* values of tested guanine derivatives versus percentage MeOH (v/v) in mobile phase obtained by the least-squares linear regression method (using data from Table 1) with Pearsons coefficients of correlation (R).

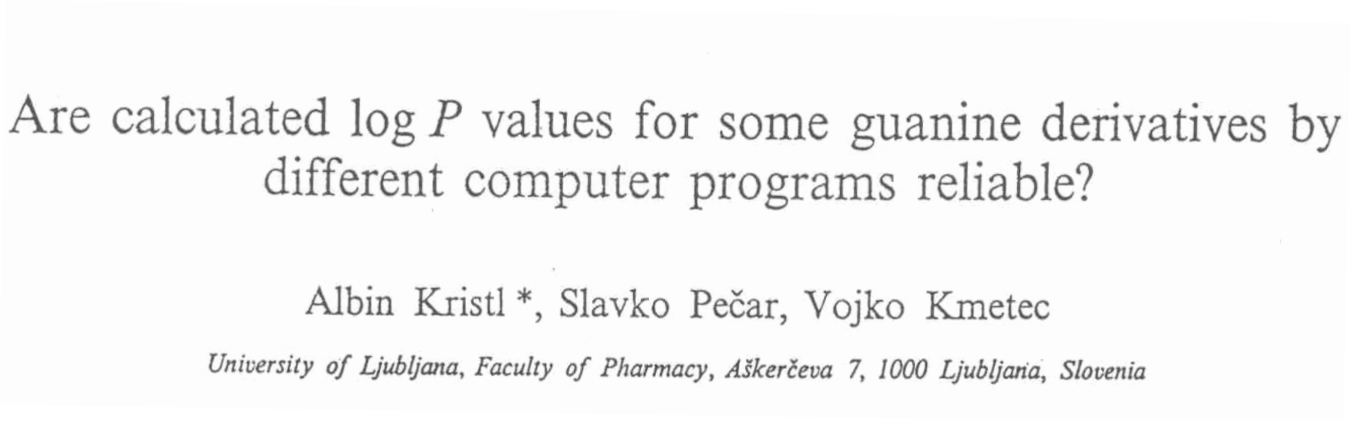


ACV	$\log k = (0.278 \pm 0.023) - (0.023 \pm 0.001)$ (% MeOH), $R = 0.9975$
NAcACV	$\log k = (1.058 \pm 0.033) - (0.036 \pm 0.001)$ (% MeOH), $R = 0.9980$
OAcACV	$\log k = (0.865 \pm 0.039) - (0.028 \pm 0.001)$ (% MeOH), $R = 0.9953$
diAcACV	$\log k = (1.742 \pm 0.042) - (0.044 \pm 0.002)$ (% MeOH), $R = 0.9978$
DCV	$\log k = (0.621 \pm 0.037) - (0.027 \pm 0.001)$ (% MeOH), $R = 0.9954$
NAcDCV	$\log k = (0.716 \pm 0.044) - (0.030 \pm 0.002)$ (% MeOH), $R = 0.9947$
OAcDCV	$\log k = (1.396 \pm 0.046) - (0.038 \pm 0.002)$ (% MeOH), $R = 0.9965$
diAcDCV	$\log k = (1.503 \pm 0.057) - (0.041 \pm 0.002)$ (% MeOH), $R = 0.9954$

$\text{Log}k = \log k_w - k \cdot (\%\ \text{MEOH (v/v)})$.

Figure 4: Relationship between log*k* values of tested substances and methanol concentration (v/v%) in the mobile phase. The points represent experimentally determined values, the lines are obtained by the least squares linear regression method. The equations are given in Table 2. ▲ ACV; Δ NAcACV; ● OAcACV; + diAcACV; x DCV; ○ NAcDCV; ■ OAcDCV; □ diAcDCV.





Are calculated log P values for some guanine derivatives by different computer programs reliable?

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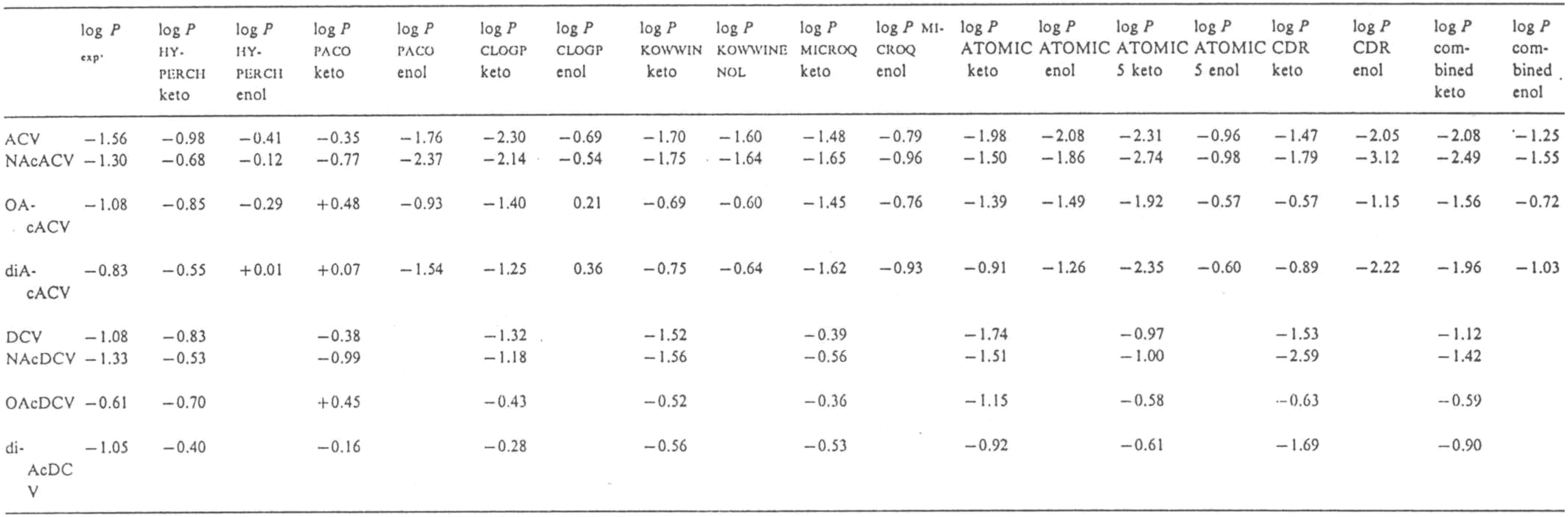
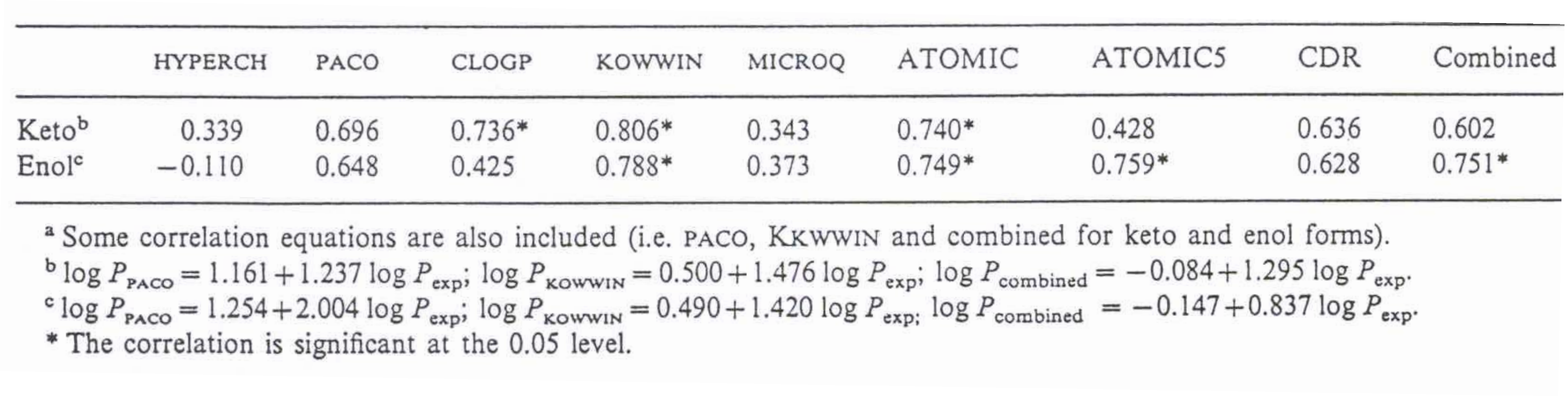
Table 3: Experimental and calculated log$P$ values by different programs (HYPERCHEM, PACO, CLOGP, KOWWIN, MICROQUSAR and PROLOGP: ATOMIC, ATOMIC5, CDR and combined)



	log P exp.	log P HYPERCH keto	log P HYPERCH enol	log P PACO keto	log P PACO enol	log P CLOGP keto	log P CLOGP enol	log P KOWWIN keto	log P KOWWINENOL	log P MICROQ keto	log P MICROQ enol	log P ATOMIC keto	log P ATOMIC enol	log P ATOMIC 5 keto	log P ATOMIC 5 enol	log P CDR keto	log P CDR enol	log P combined keto	log P combined enol
ACV	−1.56	−0.98	−0.41	−0.35	−1.76	−2.30	−0.69	−1.70	−1.60	−1.48	−0.79	−1.98	−2.08	−2.31	−0.96	−1.47	−2.05	−2.08	−1.25
NAcACV	−1.30	−0.68	−0.12	−0.77	−2.37	−2.14	−0.54	−1.75	−1.64	−1.65	−0.96	−1.50	−1.86	−2.74	−0.98	−1.79	−3.12	−2.49	−1.55
OAcACV	−1.08	−0.85	−0.29	+0.48	−0.93	−1.40	0.21	−0.69	−0.60	−1.45	−0.76	−1.39	−1.49	−1.92	−0.57	−0.57	−1.15	−1.56	−0.72
diAcACV	−0.83	−0.55	+0.01	+0.07	−1.54	−1.25	0.36	−0.75	−0.64	−1.62	−0.93	−0.91	−1.26	−2.35	−0.60	−0.89	−2.22	−1.96	−1.03
DCV	−1.08	−0.83		−0.38		−1.32		−1.52		−0.39		−1.74		−0.97		−1.53		−1.12	
NAcDCV	−1.33	−0.53		−0.99		−1.18		−1.56		−0.56		−1.51		−1.00		−2.59		−1.42	
OAcDCV	−0.61	−0.70		+0.45		−0.43		−0.52		−0.36		−1.15		−0.58		−0.63		−0.59	
diAcDCV	−1.05	−0.40		−0.16		−0.28		−0.56		−0.53		−0.92		−0.61		−1.69		−0.90	

Table 4: The Pearson correlation coefficients obtained by the least-squares linear regression method for experimentally determined log*P* values and those calculated[a].



	HYPERCH	PACO	CLOGP	KOWWIN	MICROQ	ATOMIC	ATOMIC5	CDR	Combined
Keto[b]	0.339	0.696	0.736*	0.806*	0.343	0.740*	0.428	0.636	0.602
Enol[c]	−0.110	0.648	0.425	0.788*	0.373	0.749*	0.759*	0.628	0.751*

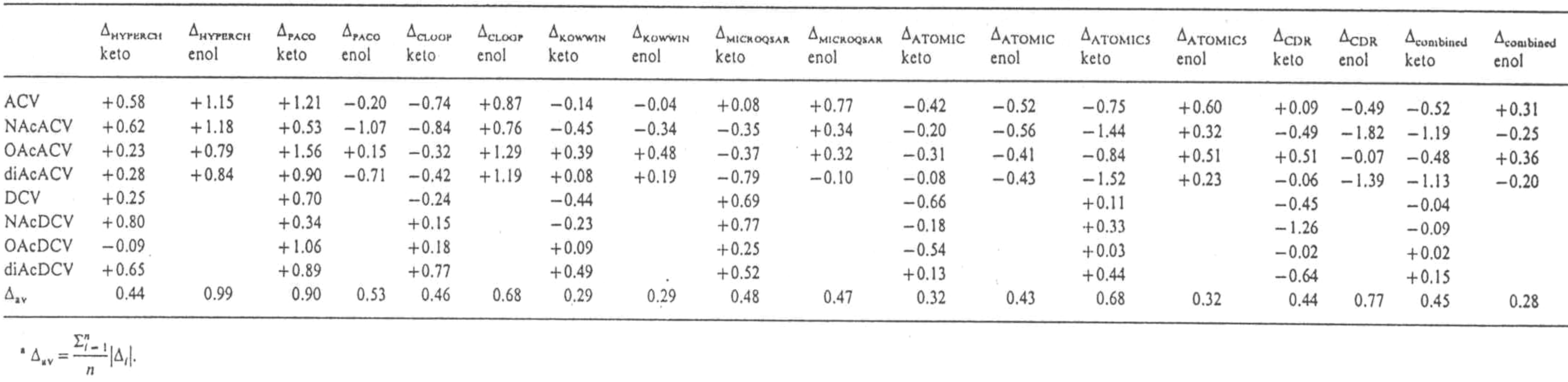
[a] Some correlation equations are also included (i.e. PACO, KKWWIN and combined for keto and enol forms).

[b] $\log P_{\mathrm{PACO}} = 1.161 + 1.237 \log P_{\mathrm{exp}}$; $\log P_{\mathrm{KOWWIN}} = 0.500 + 1.476 \log P_{\mathrm{exp}}$; $\log P_{\mathrm{combined}} = -0.084 + 1.295 \log P_{\mathrm{exp}}$.

[c] $\log P_{\mathrm{PACO}} = 1.254 + 2.004 \log P_{\mathrm{exp}}$; $\log P_{\mathrm{KOWWIN}} = 0.490 + 1.420 \log P_{\mathrm{exp}}$; $\log P_{\mathrm{combined}} = -0.147 + 0.837 \log P_{\mathrm{exp}}$.

* The correlation is significant at the 0.05 level.

Table 5: The differences between calculated and experimentally determined data ($\Delta = \mathrm{logP}_{calc} - \mathrm{logP}_{exp}$) with averages of their absolute values (n = 8), are given[a]).



	$\Delta_{HYPERCH}$ keto	$\Delta_{HYPERCH}$ enol	Δ_{PACO} keto	Δ_{PACO} enol	Δ_{CLOGP} keto	Δ_{CLOGP} enol	Δ_{KOWWIN} keto	Δ_{KOWWIN} enol	$\Delta_{MICROQSAR}$ keto	$\Delta_{MICROQSAR}$ enol	Δ_{ATOMIC} keto	Δ_{ATOMIC} enol	$\Delta_{ATOMICS}$ keto	$\Delta_{ATOMICS}$ enol	Δ_{CDR} keto	Δ_{CDR} enol	$\Delta_{combined}$ keto	$\Delta_{combined}$ enol
ACV	+0.58	+1.15	+1.21	−0.20	−0.74	+0.87	−0.14	−0.04	+0.08	+0.77	−0.42	−0.52	−0.75	+0.60	+0.09	−0.49	−0.52	+0.31
NAcACV	+0.62	+1.18	+0.53	−1.07	−0.84	+0.76	−0.45	−0.34	−0.35	+0.34	−0.20	−0.56	−1.44	+0.32	−0.49	−1.82	−1.19	−0.25
OAcACV	+0.23	+0.79	+1.56	+0.15	−0.32	+1.29	+0.39	+0.48	−0.37	+0.32	−0.31	−0.41	−0.84	+0.51	+0.51	−0.07	−0.48	+0.36
diAcACV	+0.28	+0.84	+0.90	−0.71	−0.42	+1.19	+0.08	+0.19	−0.79	−0.10	−0.08	−0.43	−1.52	+0.23	−0.06	−1.39	−1.13	−0.20
DCV	+0.25		+0.70		−0.24		−0.44		+0.69		−0.66		+0.11		−0.45		−0.04	
NAcDCV	+0.80		+0.34		+0.15		−0.23		+0.77		−0.18		+0.33		−1.26		−0.09	
OAcDCV	−0.09		+1.06		+0.18		+0.09		+0.25		−0.54		+0.03		−0.02		+0.02	
diAcDCV	+0.65		+0.89		+0.77		+0.49		+0.52		+0.13		+0.44		−0.64		+0.15	
Δ_{av}	0.44	0.99	0.90	0.53	0.46	0.68	0.29	0.29	0.48	0.47	0.32	0.43	0.68	0.32	0.44	0.77	0.45	0.28

[a] $\Delta_{av} = \frac{\Sigma_{i=1}^{n}}{n}|\Delta_i|$.

Figure 5: The dependance of log*P* calculated by different programs on logP_{exp} is given. The solid line represents the values where logP_{exp} = logP_{calc}, while the dotted lines represent the area of (0.3 log*P* units).