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Physico-chemical properties of barbituric acid derivatives. II: Partition coefficients of 5,5-disubstituted barbituric acids at 25°C

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Summary

The partition coefficients between 0.001 M HCl and octan-1-ol at 25°C are reported for seventeen 5,5-disubstituted 2-oxobarbituric acids (**1**). The mean deviation for duplicate values of the partition coefficients was ±0.56% (largest deviation ±0.008 log units). Both phases were analyzed and the mean calculated recovery was 99.2%. Most recoveries were in the range 97.5–102.5%. Increased α-branching at the C1′ carbon of a side chain (by successive replacement of hydrogen atoms with methyl groups) did not produce a constant increment in the log P value. Log P values for derivatives with one highly branched substituent, such as *t*-butyl, should be used with care in estimating a π value for the other substituent. Methylene group contributions to partitioning were determined to be very close to those determined in other studies. Calculated log P values (using the additive-constitutive principle of Hansch) for derivatives with two electron-withdrawing (−I) substituents did not agree with the measured values, even after adjustment of some of the hydrophobic substituent constants. Intramolecular interactions between the two substituents are advanced as an explanation for these discrepancies. The NMR spectra of 5,5-diphenylbarbituric acid and 5,5-diphenylhydantoin are discussed in terms of the conformations of the geminal phenyl groups.

Introduction

The role of the oil-water partition coefficient in the transport of organic compounds across biological membranes was demonstrated by Collander (1954). He showed that the rate of transport of many compounds through *Nitella mucronata* membranes is related to the logarithm of the partition coefficient (log P). Octan-1-ol has been favored as a reference solvent for partitioning experiments (Hansch, 1967; Rytting et al., 1972), mainly for practical reasons. A range of partition coefficients of 10 orders of magnitude may be spanned with octan-1-ol/water systems and thus the greatest quantity of partitioning data available is for this system (Hansch and Leo, 1979a). This extensive data base has led to predictive methods for estimating partition coefficients, or other biologically relevant parameters (using additive-constitutive relationships).

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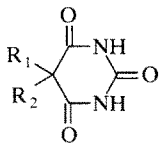
Only a few measured partition coefficients have been recorded in the literature for barbituric acid derivatives (**1**). Thus, the applicability of the Hansch equation to barbituric acid log *P* values has not been tested rigorously. Published reports on correlations of the pharmacological activity (Hansch et al., 1967) or physical properties (Pinal and Yalkowsky, 1987) of barbituric acid deriva-

TABLE 1

Partition coefficients between octan-1-ol and 0.001 M HCl at 25°C for 5,5-disubstituted barbituric acids



(1)

No.	R_1	R_2	Partition coefficient (*P*)	log *P*	log *P* (lit.)	Recovery (%)	Analytical method
1 [a]	CH_3	CH_3	0.363 ± 0.004	−0.440 ± 0.005		102.3 ± 1.0	iii
2 [a]	CH_3	CH_3CH_2	1.21 ± 0.01	0.0808 ± 0.004		93.3 ± 0.2	iv
3 [b]	CH_3	$H_2C{=}CHCH_2$	2.306 ± 0.001	0.363 ± 0.000		95.9 ± 0.5	iv
4 [a]	CH_3	C_6H_5	8.15 ± 0.02	0.911 ± 0.001		99.6 ± 0.1	iv
5 [c]	CH_3	$(CH_3)_2C{=}CHCH_2$	14.81 ± 0.002	1.171 ± 0.000		100.1 ± 0.1	ii
6 [a]	CH_3CH_2	CH_3CH_2	4.64 ± 0.01	0.666 ± 0.001	0.65 [f] 0.66 [g]	99.5 ± 0.0	ii
7 [a]	CH_3CH_2	$(CH_3)_2CH$	12.65 ± 0.07	1.102 ± 0.002	0.97 [g]	97.8 ± 0.4	ii
8 [d]	CH_3CH_2	$H_2C{=}CHCH_2$	7.36 ± 0.03	0.867 ± 0.002	0.93 [g]	98.5 ± 0.1	i
9 [a]	CH_3CH_2	C_6H_5	27.2 ± 0.5	1.434 ± 0.008	1.42 [h] 1.39 [g]	101.0 ± 1.3	i
10 [c]	CH_3CH_2	$(CH_3)_2C{=}CHCH_2$	53.1 ± 0.3	1.725 ± 0.002		99.8 ± 0.1	ii
11 [a]	C_6H_5	C_6H_5	90.5 ± 0.4	1.957 ± 0.002		103.8 ± 0.6	iii
12 [c]	$(CH_3)_2CH$	$(CH_3)_2CH$	43.1 ± 0.3	1.634 ± 0.003	1.56 [e]	99.7 ± 0.1	ii
13 [a]	$(CH_3)_2CH$	$H_2C{=}CHCH_2$	23.20 ± 0.06	1.366 ± 0.001		99.3 ± 0.1	ii
14 [c]	$(CH_3)_2CH$	$(CH_3)_2C{=}CHCH_2$	171.3 ± 0.05	2.234 ± 0.000		99.0 ± 0.2	ii
15 [c]	$(CH_3)_3C$	$(CH_3)_2C{=}CHCH_2$	365.9 ± 2.5	2.563 ± 0.003		99.0 ± 1.8 [i]	ii
16 [a]	$H_2C{=}CHCH_2$	$H_2C{=}CHCH_2$	14.00 ± 0.08	1.146 ± 0.002	1.19 [g]	99.3 ± 0.3	i
17 [d]	$H_2C{=}CHCH_2$	C_6H_5	49.2 ± 0.5	1.692 ± 0.004		97.7 ± 0.1	i

[a] McKeown, R.H., *J. Chem. Soc. Perkin* II (1980) 504–514. [b] Ngan, H.G., Final Year B. Pharm. Research Project, University of Otago (1974). [c] Present work. [d] Baird, D.R., M. Pharm. Thesis, University of Otago (1979). [e] Wong, O., M. Pharm. Thesis, University of Otago (1979). [f] Hansch, C. and Leo, A., *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979, Appendix II, No. 6482. [g] Kakemi et al. (1967). [h] Footnote (f), No. 9772. [i] Additional barbituric acid derivative (12.61 and 12.34 mg) was added to the partitioning systems to give aqueous phase concentrations that were high enough to be accurately determined.

tives mainly rely upon log P values calculated from assumed additive relationships.

This study is part of a program aimed at (i) providing carefully measured physico-chemical data for the barbiturates and (ii) the use of that data in predictive linear-free energy based equations relating structure to physico-chemical properties and to biological activity. In the present study, 17 barbituric acid derivatives were chosen with systematic alterations in one or both of the C5 side-chains. Partition coefficients between 0.001 M HCl and octan-1-ol at 25.0°C were determined on the molar scale from measured concentrations of the derivatives in each phase of the partitioning system. The partitioning data was used: (i) in examining the effect of increasing α-branching in the side-chain; (ii) in determining methylene group contributions to partitioning; and (iii) for examining the Hansch relationship in predicting log P values for barbituric acids.

Experimental

Materials

The source of each compound used in this study is given in the footnotes to Table 1. All structures were confirmed by standard physical, spectroscopic and microanalytical methods. Synthetic details for compounds made in this study will be published elsewhere.

Instrumental techniques

High-performance liquid chromatography (HPLC) was performed on Waters Associates Liquid Chromatographs using ODS (C18) packings in stainless steel or radially compressed columns (Waters 8C1810 Radial Pak Cartridge) and filtered (Millipore 0.45 μm), degassed aqueous methanol (20–80% v/v) was the mobile phase. Detection was by UV at 210 or 214 nm. UV absorbance measurements were made in 10 or 20 mm Spectrosil (far UV) cuvettes with either a Hilger and Watts Uvispek H700 Mk IX single beam spectrophotometer or a Shimadzu UV 240 Recording Spectrophotometer. Both instruments were equipped with temperature-controlled cuvette holders which were maintained at 25.00 ± 0.02°C. Temperatures were monitored with thermometers calibrated to an accuracy of ±0.02°C (Physics and Engineering Laboratory, Department of Scientific and Industrial Research, Gracefield, New Zealand) and emergent stem corrections were employed where necessary (Prankerd and McKeown, 1990). Fourier transform ^{1}H-NMR spectra were recorded at 300 MHz for solutions in hexadeuteriodimethylsulphoxide (d_6-DMSO), using tetramethylsilane (TMS) as the internal standard on a Varian VXR-300 spectrometer.

Determination of partition coefficients

Partition coefficients were determined between octan-1-ol and 0.001 M HCl. Octan-1-ol (Koch-Light) was washed with dilute H_2SO_4, dilute NaOH, and then water. It was then distilled under partial reflux using a distillation column (1300 mm × 38 mm) packed for 1150 mm of its length with Raschig rings (7 × 7 mm). The distillate was rejected until it gave a single peak on GC. All partition experiments were performed with a single batch of purified octan-1-ol with the following properties:

b.p., 192°C; n_D^{20}, 1.4289; d_4^{25}, 0.8223

literature: b.p., 194–195°C (Weast, 1968); n_D^{20}, 1.4293 (Weast, 1968); d_4^{25}, 0.8221–0.8224 (Dorough et al., 1941; Driesbach and Martin, 1949).

Water was double distilled, the second distillation being from alkaline potassium permanganate in the above still. It was used to prepare 0.001 M HCl by dilution of standard HCl. Standard solutions of the barbituric acid derivatives in 0.001 M HCl were prepared in flasks calibrated at 25°C. Where solubility was a limitation, solutions were prepared at near saturation concentrations. Aliquots of the standard solution of the barbituric acid and of octan-1-ol were transferred at 25°C to duplicate screw-capped vials (using pipettes calibrated for each phase), then the two phases were stirred for at least 24 h at 25.00 ± 0.02°C using magnetic stirrers and glass or teflon-coated stirring bars. Volumes of the aqueous and octan-1-ol phases were chosen so that, as far as possible, about half of the barbituric acid was in each phase at equilibrium. Control experi-

ments showed that equilibrium, both for mutual phase saturation and for barbituric acid distribution, was achieved in less than 24 h. After equilibration, the octan-1-ol phase was removed with a pasteur pipette and the two phases were analysed for the barbituric acid by one of the following methods:

(i) An aliquot of the aqueous phase was diluted with borax or glycine buffer (pH 10.0–10.6) and the absorbance at 240 nm compared with standards prepared from the barbituric acid solution used for the partitioning experiment. An aliquot of the octan-1-ol phase was extracted repeatedly with the same aqueous buffer, this extract was made up to volume with more buffer, then the absorbance determined as for the aqueous phase.

(ii) The aqueous phase was determined as for method (i). The octan-1-ol phase was diluted with either methanol or 95% ethanol (BDH AnalaR) and the absorbance at 210–215 nm compared with standards prepared from the stock solution and containing an equal concentration of octan-1-ol.

(iii) An aliquot of the aqueous phase was added to a volume of 5,5-diethylbarbituric acid (internal standard) solution, diluted with 0.001 M HCl, and then the concentration of the barbituric acid was determined by HPLC. The octanol phase was analysed similarly, except that it was diluted with methanol. Standards prepared for each phase were also chromatographed and the method of peak height ratios used to determine the concentrations of the barbituric acid in each phase.

(iv) Aliquots of the aqueous and octan-1-ol phases were diluted respectively with 0.001 M HCl and either methanol or ethanol, then the absorbance was determined at 205–210 nm and compared with standards prepared in the same way.

As listed in Table 1, methods (i) and (ii) were used for 5-methyl-5-(3-methylbut-2-enyl)barbituric acid and for all derivatives in which both substituents were larger than methyl and are thus hydrolysed very slowly at room temperature in alkaline aqueous solution. Method (iii) was used for 5,5-dimethylbarbituric acid and for 5,5-diphenylbarbituric acid, due to the very low solubility of this derivative in water. Method (iv) was used for the remaining 5-methylbarbituric acid derivatives.

Beer's law or HPLC calibration plots were obtained for all derivatives. Data for the plots were fitted to straight lines by the method of linear least squares. The concentration of the derivative in each phase was calculated from the derived linear equation, using appropriate dilution factors, then the partition coefficient (P) was calculated from:

$$P = \frac{\text{molar concentration in the octan-1-ol phase}}{\text{molar concentration in the aqueous phase}}$$

The quantity of the barbituric acid in each phase at equilibrium was calculated and the total recovered calculated as a percentage of the quantity originally added to the system (usually in the range 5–100 μmol). Partition coefficients and recoveries are reported in Table 1.

Results and Discussion

For the spectrophotometric analyses, correlation coefficients for Beer's law plots were ≥ 0.999 and all plots passed through the origin. Errors given in Table 1 are the deviations of the mean values of the partition coefficients (P) and recoveries from duplicated measurements. In all cases, the reproducibility of the partition coefficient determinations was very good. The average deviation for duplicate values of the partition coefficients was $\pm 0.56\%$ of the mean value for P and less than $\pm 2\%$ in the worst case (Table 1). This corresponds to a maximum deviation in the precision of the log P value of ± 0.008 unit.

Partition coefficients

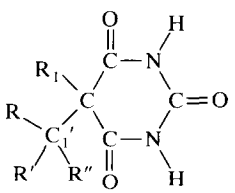
Partition coefficients (P) found for two derivatives in the present work (nos 6 and 9) are in very

good agreement with values previously reported in the literature (Hansch and Leo, 1979b), indicating that the methods used for phase analysis were satisfactory (Table 1). For three other compounds (nos 7, 8 and 16) there were small, but experimentally significant differences. The present values are preferred as both phases were analysed and recoveries were within the acceptable range (97.5–102.5%). The value previously reported for 5,5-diisopropylbarbituric acid (no. 12), log $P = 1.56$ (Wong and McKeown, 1988) is lower than that found in the present work (log $P = 1.634$). The present value is preferred as the recovery ($99.7 \pm 0.1\%$) was excellent, while in the previous report, only the aqueous phase was analyzed and recoveries could not be calculated as the octanol phase concentrations were estimated by difference.

The recoveries for 5-methyl-5-ethyl- (no. 2), 5-methyl-5-allyl- (no. 3) and 5,5-diphenyl- (no. 11) barbituric acids were outside the range set as acceptable. It is possible that the low recoveries for nos 2 and 3 resulted from hydrolysis of these compounds in the acidic solutions used for partitioning. Although acid hydrolysis is not normally seen in barbituric acid derivatives where both of the substituents are ethyl or larger, 5-methyl-substituted derivatives have not been extensively examined. It has been shown that 5-methyl-substituted derivatives are far more susceptible to alkaline hydrolysis than are corresponding 5-ethyl-substituted compounds (McKeown, 1976). It is therefore possible that 5-methyl derivatives are similarly more susceptible to acid-catalyzed hydrolysis, or to spontaneous water attack. Compound no. 11 was very limited in solubility and the quantities of partitioned material were very small (1.8 μmol). The slightly higher recovery (103.8%) probably reflects larger associated analytical errors. Where derivatives were stable to

TABLE 2

Measured log P differences for 5,5-disubstituted barbituric acids



No.	R_1	R	R′	R″	Log P	Δ log P
2	Et	H	H	H	0.08 [a]	0.59
6	Et	H	H	Me	0.67 [a]	0.43
7	Et	H	Me	Me	1.10 [a]	0.28
–	Et	Me	Me	Me	1.38 [b]	
3	allyl	H	H	H	0.36 [a]	0.51
8	allyl	H	H	Me	0.87 [a]	0.50
13	allyl	H	Me	Me	1.37 [a]	0.27
–	allyl	Me	Me	Me	1.64 [b]	
5	3MBE [c]	H	H	H	1.17 [a]	0.54
10	3MBE	H	H	Me	1.73 [a]	0.51
14	3MBE	H	Me	Me	2.23 [a]	0.33
15	3MBE	Me	Me	Me	2.56 [a]	

[a] Present work.
[b] Wong and McKeown (1988).
[c] 3MBE, 3-methylbut-2-enyl.

the partitioning conditions and were sufficiently soluble to be determined by the UV method, recoveries were excellent (99–101%).

The importance of pre-saturation of aqueous and organic phases prior to partitioning a solute has previously been stressed, especially with solvents which are miscible to some degree with water. Mutual phase pre-saturation is crucial when analysis of only one phase is performed (Purcell et al., 1973). In the present work, pre-saturation of the phases was not performed, as both phases were analysed. Control experiments showed that mutual phase saturation was achieved within the time span of the partitioning experiments. Thus, the log P values obtained are for systems in which each phase is completely saturated with the other. The excellent recoveries for compounds with no complicating factors indicated that the volume changes occurring on mutual phase saturation, from non-ideality, were too small to have any significant effect. Gentle stirring of the aqueous and octan-1-ol phases, as in the present work, meant that centrifugation of the phases (Purcell et al., 1973; Prankerd, 1977; Wong, 1979; Janini and Attari, 1983) was obviated and allowed rapid separation of the phases. In addition, partition coefficients for highly lipophilic compounds are subject to large errors if 'non-centrifugable microdroplets of octanol' form in the aqueous phase (Hammers et al., 1982), using more common shake-flask equilibration methods. The stirring technique used in the present work completely circumvents this possibility. The partition coefficents reported in Table 1 may be regarded as being at concentrations for which solute-solute interactions are negligible (Davis et al., 1972).

Effect on log P of side-chain methylation

The effect of increasing side chain 1′-methylation (α-branching) can be seen by comparing the differences between log P values for nos 5, 10, 14 and 15, for which R_1 remains constant and R_2 varies (Table 2). The addition of a methyl group to the 5-methyl substituent of no. 5 to form the 5-ethyl substituent of no. 10 increases log P by 0.54 (Table 2). Additional methyl groups on C1′ to give no. 14 (5-isopropyl) and no. 25 (5-t-butyl) produce further increments in log P of 0.51 and 0.33, respectively. The same trend (Table 2) is seen in comparing data from the present study (nos 2, 3, 6–8 and 13) with those for 5-t-butyl-barbituric acid derivatives from other work (Wong and McKeown, 1988).

In all cases, the increment in hydrophobicity on going from 5-ethyl to 5-isopropyl is slightly less than on going from 5-methyl to 5-ethyl. An even smaller increment is seen on going from 5-isopropyl to 5-t-butyl. C1′-methylation increases log P: (i) by increasing the hydrocarbon content of the molecule, which might be expected to be a constant effect; and (ii) by steric hindrance to hydration of the barbituric acid nucleus. The smaller increment in log P on methylation of the isopropyl substituent to give the t-butyl substituent suggests that hindrance to hydration is approaching a limit. A similar limitation on steric hindrance to hydration has been previously discussed in relation to studies of very precisely determined ionization constants (Ives and Marsden, 1965). Thermodynamic functions for ionization of barbituric acid derivatives (Manov et al., 1952; Prankerd, 1977; Wong, 1984) have also been interpreted as demonstrating such a limitation (McKeown et al., 1986). These comparisons strongly suggest that log P values for derivatives with one highly branched substituent, such as t-butyl, should be used cautiously in estimating a π value for the other substituent.

Methylene group contributions

Aliphatic methylene group contributions (MGCs) to partition coefficients have been reviewed (Davis et al., 1974) but were not listed in an otherwise very thorough compilation of substituent constants (Hansch and Leo, 1979b). In aliphatic open chain compounds, the MGC was thought to be the same as that for the methyl group ($\pi = 0.50$) (Tute, 1971). Davis (1973) has since shown that this assumption was not valid and that the additional hydrogen atom in the methyl group contributes significantly to the hydrophobicity of the group. The review by Davis et al. (1974) gives log $F(CH_2)$ (equivalent to $\pi(CH_2)$) a value of 0.52. The compilation by Hansch and Leo (1979a) gives a value for

TABLE 3

Aliphatic methylene group contributions

Nos	Log P_1	$-$Log P_2 =	Δ log P	$\pi(CH_2)$ = (Δ log P/ no. of methylenes)
6 and 1	0.666	−0.440	1.106	0.553
6 and 2	0.666	0.0808	0.585	0.585
8 and 3	0.867	0.363	0.504	0.504
9 and 4	1.434	0.911	0.523	0.523
10 and 5	1.725	1.171	0.554	0.554

Mean $\pi(CH_2) = 0.544$; S.D. = 0.031.

$\pi(CH_2) = 0.53$, calculated from 1/11 of the difference between log P for dodecanol (log P = 5.13) and for methanol (log $P = -0.66$). However, it may also be seen that the difference between log P for dodecanol and for ethanol gives a value for the MGC of 0.544 (from $[5.13 - (-0.31)]/10 = 0.544$).

The log P values determined for open chain barbituric acid derivatives in the present work may not be useful for calculation of MGCs having wide applicability, as the chain lengths cannot be considered long enough for the additional methylene groups to be sufficiently remote from the hydrophilic, polar barbituric acid nucleus. However, these values may be used to estimate a MGC where a methylene group is inserted into the α-position of an active methylene compound (Table 3).

The mean contribution to the introduction of an additional methylene group ($\pi(CH_2) = 0.54$) is very close to that given by Davis et al. (1974) and Hansch and Leo (1979a). An earlier study on barbituric acid derivative partition coefficients using vigorous shaking and analysis of only one phase (Yih and Van Rossum, 1977) included compounds with suitable substituent chain lengths for determination of open chain MGCs, but calculations from their log P values gave widely varying results ($\pi(CH_2) = 0.21 - 0.85$). Table 3

TABLE 4

Calculated partition coefficients for 5,5-disubstituted barbituric acids using unadjusted substituent constants and their deviations from observed log P values

Log P(calc) = $-1.35 + \pi_{R_1} + \pi_{R_2}$

No.	R_1	R_2	π_{R_1}	π_{R_2}	Log P (calc)	Log P (obs)	Δ (calc) − (obs)
1	Me	Me	0.50	0.50	−0.35	−0.44	0.09
2	Me	Et	0.50	1.02	0.17	0.081	0.089
3	Me	allyl	0.50	1.10	0.25	0.363	−0.113
4	Me	phenyl	0.50	1.77 [a]	0.92	0.911	0.009
5	Me	3MBE [b]	0.50	2.10 [c]	1.25	1.171	0.079
6	Et	Et	1.02	1.02	0.69	0.666	0.024
7	Et	i-Pr	1.02	1.53	1.20	1.102	0.098
8	Et	allyl	1.02	1.10	0.77	0.867	−0.097
9	Et	phenyl	1.02	1.77 [a]	1.44	1.434	0.006
10	Et	3MBE [b]	1.02	2.10 [c]	1.77	1.725	0.045
11	phenyl	phenyl	1.77 [a]	1.77 [a]	2.19	1.957	0.233
12	i-Pr	i-Pr	1.53	1.53	1.71	1.634	0.076
13	i-Pr	allyl	1.53	1.10	1.28	1.366	−0.086
14	i-Pr	3MBE [b]	1.53	2.10 [c]	2.28	2.234	0.046
15	*t*-Bu	3MBE [b]	1.98	2.10 [c]	2.73	2.563	0.167
16	allyl	allyl	1.10	1.10	0.85	1.146	−0.296
17	allyl	phenyl	1.10	1.77 [a]	1.52	1.692	−0.172

[a] Defined from log P for no. 9 (Hansch et al., 1967).

[b] 3MBE, 3-methylbut-2-enyl.

[c] Calculated from π(allyl) + 2[π(methyl)] = 1.10 ± 2(0.50).

shows that with the more precise experimental data of the present work, reasonably constant values for the MGC are obtained. In a very recent study, a closely similar value was found for the MGC (Wong and McKeown, 1988). Careful attention must always be paid when log P values are calculated (rather than measured) for use in correlations (Kim and Martin, 1986).

Calculated log P values for barbituric acids

Calculated partition coefficients for the derivatives examined in the present work were based on the additivity rules proposed by Hansch and Leo (1979a), according to Eqn 1:

$$\log P_x = \log P_H + A \sum_1^i \pi_x \qquad (1)$$

where A is a constant which normally has a value of unity. The calculated values are given in Table 4 and are compared with those determined experimentally. Substituent constants (π_x values) were taken from the literature (Hansch and Leo, 1979b), except where noted, and log P_H was taken as -1.35 (Hansch et al., 1967).

Calculation of the mean of the deviations (Δ) between calculated and observed values in Table 4 (after exclusion of nos 11 and 15–17) gave a value of 0.021. The standard deviation of this mean was found to be 0.0745. Therefore, the arithmetic mean of the deviations is not significantly different from zero and indicates that the value of -1.35 for log P for the barbituric acid nucleus may be relied upon. The deviations between the calculated and observed log P values for nos. 11 and 15–17 are regarded as excessive, in view of the precision with which the observed values were obtained (Table 4). An explanation for these deviations is needed.

5,5-Diphenylbarbituric acid For the 5-phenyl-substituted derivatives, only 5,5-diphenylbarbituric acid (no. 11) gives a calculated log P value which is significantly different from the observed value. The 5-alkyl-5-phenyl-substituted derivatives were expected to give good agreement, as the literature value for π(phenyl) was originally derived from log P for no. 9 (Table 4, footnote a). The deviation for no. 11 must therefore result from the combination of two phenyl substituents (*gem*-diphenyl). Deviations between calculated and observed log P values for compounds analogous to no. 11 have been reported previously (Gould, 1972). Particularly large deviations were observed for diphenylacetic acid, diphenylmethanol and related compounds, although this was partly due to the fact that π(phenyl) was taken as 2.13 (the normal value calculated from monosubstituted benzenes), in place of the value used in the present work, π(phenyl) = 1.77 (derived from the log P value for 5-ethyl-5-phenylbarbituric acid). It was proposed that hydrophobic interactions between the two phenyl rings led to the formation of an intramolecular hydrophobic bond (Gould, 1972). This might be envisaged in terms of the 'inner' phenyl ring faces being too close to each other to allow them to exert their full lipophilic effect.

In the present series of compounds, the same explanation might apply to no. 11. Neither X-ray crystal structure studies, molecular orbital calculations, nor solution conformational studies are available to indicate the relative orientation of the phenyl rings in 5,5-diphenylbarbituric acid. However, the structure for an analogous *gem*-diphenyl derivative, 5,5-diphenylhydantoin (DPH), has been elucidated by single-crystal X-ray diffractometry (Camerman and Camerman, 1971). It was shown that the two phenyl rings were neither coplanar nor directly facing each other in the solid state. These results have been confirmed for the isolated molecule by theoretical calculations (Lloyd and Andrews, 1986; Wong et al., 1986).

Due to the similarity in structures with DPH (*gem*-diphenyl), it might be expected that the phenyl rings in 5,5-diphenylbarbituric acid (no. 11) would be similarly restricted in rotation. This expectation was supported by Catalin (space-filling) molecular models, which indicated that in the half-chair conformation (McKeown, 1980) of the barbituric acid nucleus, neither phenyl ring can rotate freely around the phenyl-C5 bond axis. Rotation of one ring (equatorial) was restricted by interactions between the *ortho* hydrogen orbitals and the carbonyl oxygens of the nucleus

and rotation of the other (axial) was restricted by interactions between its *ortho* hydrogen and carbon atoms and those of the first ring. Further support for this model was obtained from ^{1}H-NMR spectra in hexadeuteriodimethylsulphoxide solution (Fig. 1a). The resonance signals for the aromatic ring protons for no. 11 are in two groups of multiplets when irradiated at 300 MHz. The first group has signals with chemical shifts ranging from 7.12 to 7.15 ppm (integration 4H) and the second has chemical shifts of 7.37–7.43 ppm (integration = 6H). The group of signals at chemical shifts less than 7.27 ppm (the normal chemical shift for benzene or alkylbenzenes) indicates that shielding occurred to some extent for four of the hydrogen atoms. This might result if two of the hydrogen atoms of each ring were located in the shielding zone above the plane of the other ring, as is suggested by the X-ray crystallographic and potential energy studies for DPH. Shielding would also be expected for hydrogen atoms located in the shielding cones of the 4- and 6-carbonyl groups, as suggested by the Catalin molecular model.

In view of the structural similarities between no. 11 and DPH (*gem*-diphenyl), it is rather curious that their ^{1}H-NMR spectra are different (Fig. 1). The resonance signals for the aromatic ring protons for DPH are very similar to those reported for primidone (Florey, 1973) and for phe-

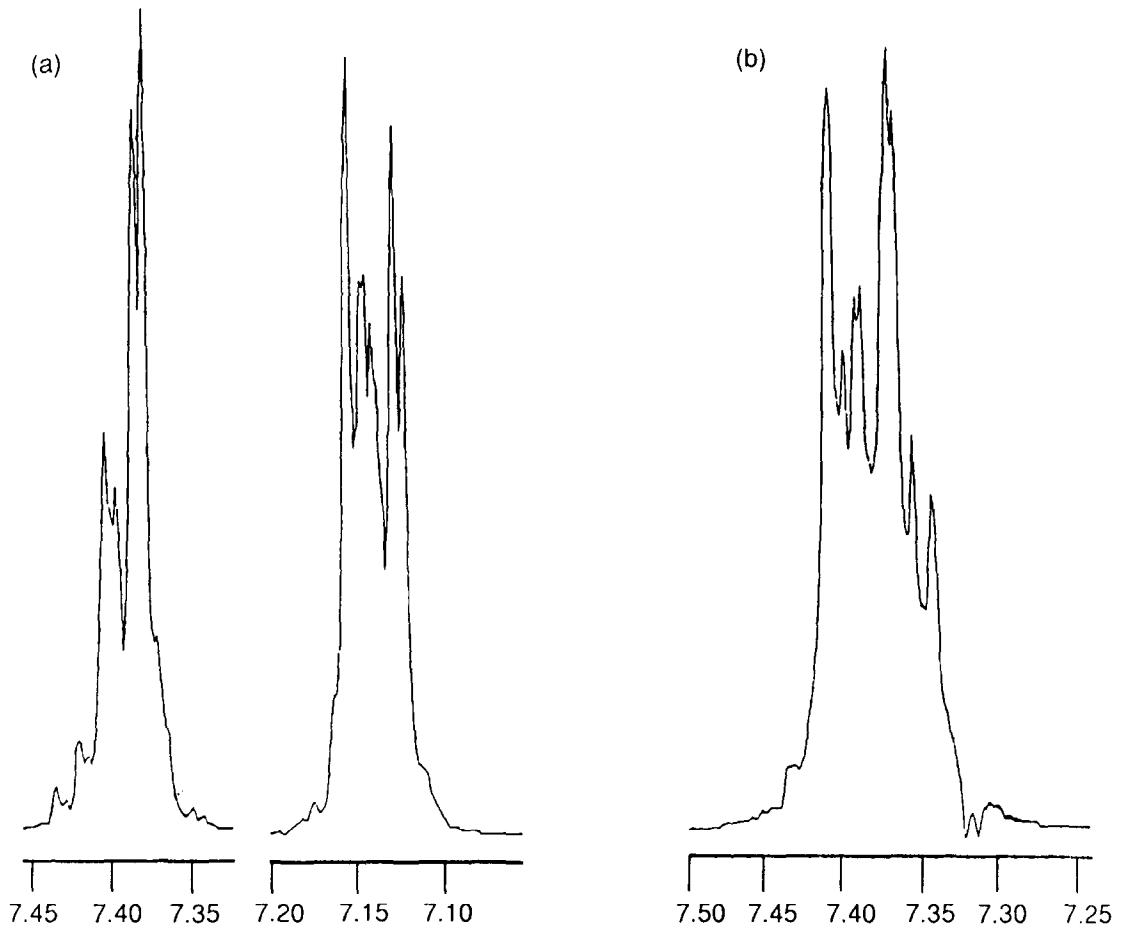


Fig. 1. 300 MHz ^{1}H FT-NMR spectra of (a) 5,5-diphenylbarbituric acid and (b) 5,5-diphenylhydantoin. Chemical shifts (δ) are in parts per million (ppm) from TMS. Both compounds were at a concentration of 20 mM in d_6-DMSO.

nobarbitone (Florey, 1978). At 300 MHz, signal multiplicity is apparent for DPH, but all of the resonance signals are confined to the region δ = 7.34–7.41 ppm (Fig. 1b). This group of multiplets seems to correspond to the second of the two multiplet groups of no. 11 (Fig. 1a). The additional carbonyl group of the barbituric acid nucleus has a considerable effect on the complexity of the NMR spectrum, and on the electronic environment of four of the ring hydrogen atoms (probably the *ortho* hydrogens). The cause of these differences at the molecular level is not clear, but it is likely that the aromatic rings in no. 11 are even more restricted in rotation about the phenyl-C5 bond axes than those of DPH.

Allyl and 3-methylbut-2-enyl derivatives Introduction of a double bond into an alkyl chain decreases log P, as may be seen from the π values for the allyl (π = 1.10) and *n*-propyl (π = 1.55) groups (Hansch and Leo, 1979b). In Table 4, all of the allyl derivatives have calculated log P values which are less than the observed values, especially nos 16 and 17. These two compounds are distinguished from the other allyl-substituted barbituric acids (which have observed and calculated log P values in reasonable agreement) by having a second electron-withdrawing (−I) substituent. The deviations may be due to an interaction between the two substituents. For nos 16 and 17, interaction between the π-electron systems may reduce the effectiveness of the allyl groups in causing the derivatives to be more hydrophilic. This situation is opposite to that observed for no. 11, in which the calculated value is much larger than that observed. A Catalin molecular model suggests that for the two allyl groups of no. 16 to interact, the substituents must be directed completely away from the hydrophilic nucleus. However, in this conformation, it might be expected that the partition coefficient would decrease, due to the greater degree of hydration of the nucleus as discussed above (see section entitled Effect on log P of side-chain methylation).

An alternative explanation for the deviations is that π(allyl) may be too low by about 0.1 log unit, as the remaining 5-allyl derivatives have calculated log P values which are low by this amount. Recalculation of the log P values for all 5-allyl derivatives with π(allyl) = 1.20 gives log P values for which the deviations (Δ) are not more than ±0.1 log unit for all derivatives. The literature value for π(allyl) = 1.10 was derived from the difference between log P for benzene (log P = 2.13) and allylbenzene (log P = 3.23) (Hansch and Leo, 1979c; nos 3003 and 7048). Calculation of π(allyl) from other pairs of log P values in the compilation of Hansch and Leo (1979c) gives a range of values which tend to be even lower than 1.10, although a value as high as 1.35 was recently suggested (Wong and McKeown, 1988).

The calculated log P values for the 5-(3-methylbut-2-enyl) (3MBE) derivatives (nos 5, 10, 14 and 15) in Table 4 were derived from π(allyl) = 1.10. If π(allyl) = 1.20 is adopted (to obtain consistency for all log P values for the 5-allyl-substituted barbituric acids), the calculated log P values for nos 5, 10, 14 and 15 are higher than the observed values by 0.15–0.27 log unit. However, a higher value for π(allyl) is not supported by other log P data in the literature for allyl-substituted compounds (Hansch and Leo, 1979b). The relatively high polarity of the barbituric acid nucleus may be better suited to a higher π(allyl) value. There may be an interaction between the allyl substituent and the polar nucleus which reduces hydration of the nucleus to some extent. A solution to this problem is to abandon the use of π(3MBE) = π(allyl) + 2π(methyl) and adopt an average value based on the log P values for nos 5, 10 and 14, π(3MBE) = 2.04 ± 0.02. Compound no. 15 should not be included in such an average as the resulting calculated value (π(3MBE) = 1.93) is significantly different and has already been noted as anomalous (see above, section entitled Effect on log P of side-chain methylation (α-branching)).

The value for π(3MBE) = 2.10, although calculated (as in Table 4), gives good predictability for the other homologues with this substituent (nos 5, 10 and 14), indicating that either π(*t*-Bu) is erroneous, or that special interactions take place to give the discrepancy for no. 15. The literature value for π(*t*-Bu) was calculated from log P values for benzene compounds, as were almost all other π values in Table 4. None of the other benzene-derived π values gave poorly pre-

dicted values for log P (except for nos 16 and 17, both of which have two –I substituents). The more compact structure and the flanking polar 4- and 6-carbonyl groups in the barbituric acid derivative may permit the t-Bu analog to be more hydrated than a corresponding t-Bu-substituted aromatic compound and thus, log P would be expected to be less. With this in view, $\pi(t\text{-Bu}) = 1.98$ has been left unchanged and the log P data in Table 4 were re-evaluated, using revised values for both π(allyl) = 1.20 and π(3MBE) = 2.04 (Table 5). Table 5 shows that the deviations for 5-allyl- and 5-3MBE-substituted compounds are now very small. Little would be gained from further refinement of the π values for Table 5 as larger deviations are now seen for compounds which include 5,5-dialkyl substituents.

Independent contributions of the C5 substituents to log P

The geometry of the half-chair conformers of 5,5-disubstituted barbituric acids in solution tends to have one substituent in the plane of the barbiturate nucleus (equatorial) and the other perpendicular to the plane (axial) (McKeown, 1980b). This geometry suggests that the two substituents might be in different environments. The effects on partitioning of the two substituents could then be considered independently. Multiple regression of the log P values as the dependent variable against the $\pi(R_1)$ and $\pi(R_2)$ values as independent variables led to a regression equation which was highly significant. However, the coefficients for $\pi(R_1)$ and $\pi(R_2)$ were not significantly different and the additivity of the π values for the two substituents could not be challenged. Hence, it is always safer to measure a number of log P values in a series of compounds, especially where substituents could be involved in intramolecular interactions.

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TABLE 5

Calculated partition coefficients for 5,5-disubstituted barbituric acids using adjusted substituent constants (revised π values) and their deviations from observed log P values

Log P(calc) = $-1.35 + \pi_{R_1} + \pi_{R_2}$

No.	R_1	R_2	π_{R_1}	π_{R_2}	Log P (calc)	Log P (obs)	Δ (calc) – (obs)
1	Me	Me	0.50	0.50	–0.35	–0.44	0.09
2	Me	Et	0.50	1.02	0.17	0.081	0.089
3	Me	allyl	0.50	1.20	0.35	0.363	–0.013
4	Me	phenyl	0.50	1.77 [a]	0.92	0.911	0.009
5	Me	3MBE [b]	0.50	2.04 [c]	1.19	1.171	0.019
6	Et	Et	1.02	1.02	0.69	0.666	0.024
7	Et	i-Pr	1.02	1.53	1.20	1.102	0.098
8	Et	allyl	1.02	1.20	0.87	0.867	0.003
9	Et	phenyl	1.02	1.77 [a]	1.44	1.434	0.006
10	Et	3MBE [b]	1.02	2.04 [c]	1.71	1.725	–0.028
11	phenyl	phenyl	1.77 [a]	1.77 [a]	2.19	1.957	0.233
12	i-Pr	i-Pr	1.53	1.53	1.71	1.634	0.076
13	i-Pr	allyl	1.53	1.20	1.38	1.366	0.015
14	i-Pr	3MBE [b]	1.53	2.04 [c]	2.22	2.234	–0.014
15	t-Bu	3MBE [b]	1.98	2.04 [c]	2.67	2.563	0.107
16	allyl	allyl	1.20	1.20	1.05	1.146	–0.096
17	allyl	phenyl	1.20	1.77 [a]	1.62	1.692	–0.072

[a] Defined from log P for no. 9 (Hansch et al., 1967).

[b] 3MBE, 3-methylbut-2-enyl.

[c] Calculated from the mean value for π(3MBE) = log P(5-R_1-5-(3MBE)ba) – (–1.35) – π_{R_1} = 2.04 (see text).

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