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Octanol−Water Partition Coefficients of Cyclic C-7 Hydrocarbons and Selected Derivatives

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Partition coefficients between 1-octanol and water, K_{ow}, of 16 C-7 cyclic hydrocarbons were measured using the classic shake-flask method or the more recent slow-stir method. For eight compounds, both methods were used and the results are summarized by log K_{ow}(shake flask) = m log K_{ow}(slow stir), where m is 0.998 ± 0.003 (±SD). The compounds include quadricyclane, bicyclohepta-2,5-diene, norbornylene, norborane, and commercially available derivatives containing oxygen or halogen atoms. The rapid hydrolysis of three halogenated derivatives prevented direct measurements; estimates for these were calculated from retention times measured with a C-18 reverse-phase column. The compounds are hydrophilic to moderately hydrophobic; the values of log K_{ow} range from −0.42 to 3.78.

Introduction

The development of accurate prediction methods for hydrophobicity depends on the availability of measurements on compounds with unique fragments (Mannhold et al., 1998). Direct measurements of the octanol−water partition coefficients, K_{ow}, have not been widely reported for compounds containing fragments derived from tricyclo[2.2.1.0^{2,6}]heptane, quadricylane (quadricyclo[2.2.1.0^{2,6}.0^{3,5}]heptane), and norbornane. Nevertheless, discussions of the chemistry and the use of such compounds are widespread in the literature. A single example is provided by toxaphene, which comprises a mixture of highly chlorinated bornanes; this mixture has been used as a pesticide (Montgomery, 1996), and its persistence in the environment is a matter of concern.

Octanol−water partition coefficients were measured using three methods. The retention-time method was used to obtain initial estimates. The shake-flask and slow-stir methods were used to obtain more accurate values. A summary of the retention-time and shake-flask methods may be found in the comprehensive treatise of Hansch and co-workers (1995). The use of the slow-stir method for very hydrophobic compounds (Brooke et al., 1986, 1990; de Bruijn et al., 1989) has been widespread in recent years; it is thought to minimize the production of micelles and thereby lead to more accurate values of the partition coefficient. In this work both methods are evaluated on a suite of compounds that are not very hydrophobic (log K_{ow} < 4). Significant differences are not expected; the discrepancies between various methods are believed to become important when log K_{ow} > 5.5 (Chessells et al., 1991). The measurements are reported for 19 C-7 cyclic hydrocarbons, whose structures are shown in Figure 1; the names, sources, and CAS registry numbers are given in Table 1.

Experimental Section

Chemicals. ACS spectrophotometric grade 1-octanol from Aldrich was used for the direct measurements. The solvents, acetonitrile and methanol, were HPLC grade from Fisher Scientific. The suppliers and purity of the chemicals are given in Table 1; the chemicals were used without further purification. The concentrations of the chemicals in octanol were in the range 1−200 mg/g; the same stock of octanol solution was used for both shake-flask and slow-stir experiments. The sample of 5-norbornen-2-ol was a mixture of the exo and endo isomers, which were clearly resolved under the chromatographic conditions used. No attempt to separate these isomers was made for the shake-flask and slow-stir methods. However, a sample was separated on a silica gel column to confirm by NMR that the endo isomer eluted before the exo isomer under our chromatographic conditions.

Chemical Analysis. All analyses were made with an HP1090 liquid chromatograph fitted internally with a UV−visible detector and coupled externally to an RI detector (HP1047A). The liquid chromatograph was connected to a chromatography server (VG Data Systems Ltd) and a personal computer (the acquisition and analysis software was Xchrom from LabSystems). All the measurements were made on a reverse-phase C-18 column (Hypersil ODS 5 μm, 100 mm × 4.6 mm) fitted with a guard column (Hypersil ODS 5 μm, 2.0 mm × 4 mm) and held in an oven set at 40 °C. The mobile phases were prepared from ultrapure water (from a Barnstead II unit) and acetonitrile. The HPLC was operated with no change in the composition of the mobile phase during a run (isocratically) at the flow rate of 1 mL/min.

At the end of shake-flask and slow-stir experiments, both the aqueous and octanol phases were analyzed. For the chemicals containing double bonds, UV detection was used; for all other compounds RI detection was used. The injection volume (5, 20, 50 or 100 μL) was selected to optimize response, and a mobile phase composition that gave a retention time < 6 min was selected. Calibration standards were used to establish the linear region of the

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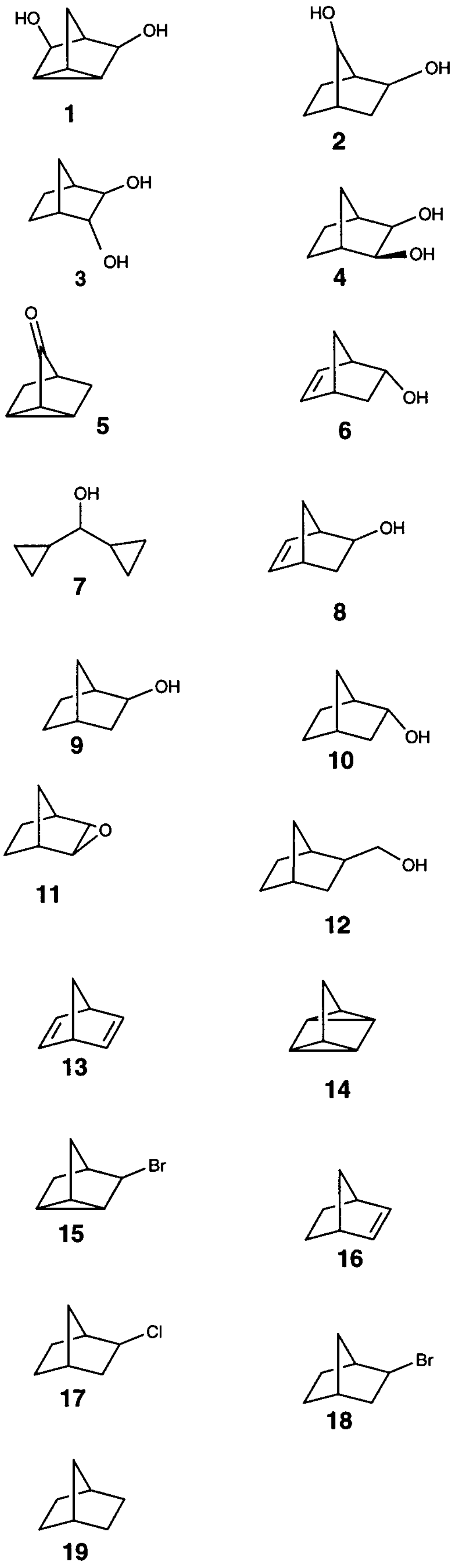

Figure 1. Structures of the C-7 compounds.

detector response. For dilutions of the octanol and aqueous samples, a stock mobile phase was used, and the dilutions were selected so that the resultant peak areas were in the linear region of response and were close together in magnitude. The partition coefficients were calculated from

$$K_{ow} = \text{(concentration in octanol)/(concentration in water)} = \frac{\text{(peak area} \times \text{dilution factor) of the octanol sample}}{\text{(peak area} \times \text{dilution factor) of the aqueous sample}} \qquad (1)$$

Samples from the shake-flask and slow-stir experiments on the same chemical were analyzed concurrently, thereby minimizing influences of the analytical errors.

Retention-Time Method. Solutions of the calibration compounds, listed in Table 2, and of the chemicals were prepared in methanol. The mobile phase composition was 50 vol % acetonitrile in water, and the injection volume was 5 μL. The retention times were those recorded on the RI detector.

Shake-Flask Experiments. The shake-flask experiments were performed in 15-mL capped disposable glass centrifuge tubes (Kimble 73785) using 10 mL of ultrapure water and 1.5−2.0 mL of the octanol solution of the chemical. For shaking the contents of each tube, a vortex mixer (Fisher Genie 2) was used on its highest setting for 1 min. Then each tube was centrifuged for at least 15 min at 900*g* in a refrigerated centrifuge (Fisher Marathon 22KBR), whose temperature was set at 25 °C. For chemical analysis, an aqueous sample was withdrawn using an HPLC syringe; the needle was wiped with tissue moistened with mobile phase to remove any droplets of octanol solution. This sample was promptly injected into the HPLC. The sequence of shaking, centrifugation, and chemical analysis of the aqueous phase was repeated another two times. Thereby, it was demonstrated that equilibrium is attained after the second sequence. Tubes were kept in the centrifuge until the final analyses of the octanol and aqueous phases.

Slow-Stir Experiments. Slow-stir experiments were carried out in 10-mL reaction vials (Ace Glass 9591-48); these vials have a capped sidearm. Approximately 10 mL of ultrapure water was dispensed into each vial along with a clean Teflon-coated stirring bar (Fisher 14-511-95C). The octanol solution of the chemical, 1.5−2.0 mL, was placed on top of the water with great care, thereby ensuring that the sidearm was only filled with aqueous phase. The vials were clamped over magnetic stirrers (Fisher Electronic Stirrer 2003) enclosed in a custom-built temperature-controlled enclosure set at 25 °C. The stir bars rotated at 50 rpm. The approach to equilibrium was monitored by withdrawing a sample of aqueous phase from the sidearm using an HPLC syringe and injecting the sample on the HPLC. Forty-eight hours proved sufficient time for equilibrium to be attained.

There was only a small quantity of the 3,5-dihydroxytricyclo[2.2.1.0^{2,6}]heptane (compound **1**, Figure 1) available. So miniature slow-stir experiments were performed with 2-mL HPLC sample vials (HP 5080-8712). From the experience with the other experiments, it was regarded as unnecessary to monitor the approach to equilibrium, so samples of both phases were analyzed after 48 h of equilibration.

Experiments. The number of and the type of experiments run for each chemical are summarized in Table 1. The halogenated compounds hydrolyze too rapidly for slow-stir and shake-flask experiments to be done, so only the retention times for these compounds were measured; their partition coefficients were estimated by interpolation of the data from other compounds.

Table 1. Octanol−Water Partition Coefficients for the C-7 Compounds

compound	structure number[a]	CAS registry number	source	% purity	methods[b]	starting conc in octanol (mg/g)	log K_{ow}	sample standard deviation in log K_{ow}
3,5-dihydroxytricyclo[2.2.1.$0^{2,6}$]heptane	**1**(s)	4054−88−0	Salor (Aldrich)	94−97	SS(3)	32	−0.42	0.05
2,7-norbornanediol	**2**(s)	5888−34−6	Salor (Aldrich)	94−97	SF(4)	12	0.40	0.02
exo-2-*endo*-3-norbornanediol	**3**(s)	14440−78−9	Maybridge (Ryan)		SF(4)	4	0.40	0.06
cis-*exo*-2,3-norbornanediol	**4**(s)	16329−23−0	Aldrich	99	SF(4)	19	0.47	0.01
nortricyclenone-3	**5**(l)	695−05−6	Salor (Aldrich)	94−97	SF(4), SS(3)	1	0.81	0.01
5-norbornen-2-ol (*endo*)	**6**(s)	13080−90−5	Aldrich	99	SF(4), SS(3)	17	0.994	0.004
dicyclopropyl carbinol	**7**(l)	14300−33−5	Salor (Aldrich)	94−97	SF(4)	14	1.07	0.01
5-norbornen-2-ol (*exo*)	**8**(s)	13080−90−5	Aldrich	99	SF(4), SS(3)	17	1.243	0.007
(±/−)-*exo*-norborneol	**9**(s)	497−37−0	Aldrich	98	SF(2), SS(3)	1	1.37	0.06
(±/−)-*endo*-norborneol	**10**(s)	497−36−9	Aldrich	96	SF(4)	18	1.45	0.01
exo-2,3-epoxynorbornane	**11**(s)	3146−39−2	Aldrich	97	SF(2), SS(3)	6	1.578	0.005
2-norbornane methanol (*exo* & *endo*)	**12**(l)	5240−72−2	Aldrich	97	SF(4)	10	1.99	0.01
bicyclohepta-2,5-diene	**13**(l)	121−46−0	Aldrich	99	SF(2), SS(3)	52	2.67	0.01
quadricyclane	**14**(l)	278−06−8	Aldrich	99	SF(8)	71	2.90	0.03
nortricyclyl bromide	**15**(l)	31991−53−4	MTM	practical	RT		3.11	0.08[c]
norbornylene	**16**(s)	498−66−8	Aldrich	99	SF(2), SS(3)	117	3.24	0.01
(±/−)-*exo*-2-chloronorbornane	**17**(l)	67844−27−2	Aldrich	98	RT		3.35	0.08[c]
(±/−)-*exo*-2-bromonorbornane	**18**(l)	2534−77−2	Aldrich	98	RT		3.54	0.08[c]
norbornane	**19**(s)	279−23−2	Aldrich	98	SF(4), SS(3)	201	3.78	0.03

[a] Numbers refer to the structures in Figure 1. The physical state of the compound under ambient conditions is given in parentheses. [b] SS refers to slow-stir method, SF to the shake-flask method, and RT to the retention-time method. The number in parentheses is the number of determinations made by each method. [c] Standard error of the estimate.

Table 2. Calibration Compounds used for the Retention-Time Method[a]

	log K_{ow}
acetonitrile	−0.34
ethyl acrylate	1.32
toluene	2.73
naphthalene	3.30
biphenyl	4.01

[a] Data are taken from *Exploring QSAR* (Hansch et al., 1995).

Results and Discussion

Linear regression analysis of the results from the eight compounds that were run by both the shake-flask and slow-stir experiments gives

$$\log K_{ow}(\text{shake flask}) = (0.998 \pm 0.003) \log K_{ow}(\text{slow stir}) \quad r^2 = 0.9998 \quad (2)$$

The intercept was forced to zero, and the uncertainty is the standard deviation (here and throughout). In view of the good agreement and the proximity of the square of the correlation coefficient (r^2) to unity, Table 1 contains the combined results in these cases.

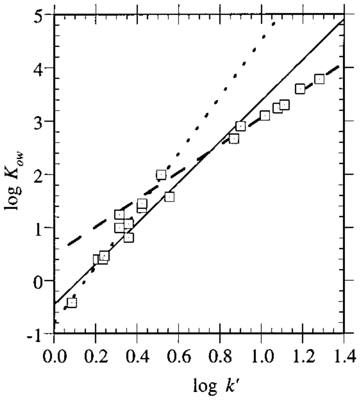

Figure 2. Partition coefficients and capacity factors: (⊡) data; (—) calibration line; (···) group 1; (− − −) group 2.

Initial experimental estimates were obtained from a retention-time method. For the calibration compounds, the retention times and the accepted values (see Table 2) of K_{ow} were fitted to

$$\log K_{ow} = a \log k' + b \quad (3)$$

where a and b are constants and $k' = (t_R - t_0)/t_R$. Here t_R is the retention time of the standard compound and t_0 is the retention time of the unretained solute, or the dead time. Normally, workers (Könemann et al., 1979; Minick et al., 1989; Ritter et al., 1994) select compounds with small values of K_{ow} to act as surrogates for the unretained solute. For this work the data were fitted directly to eq 3, in which t_0 was treated as a fitting parameter. Least-squares analysis of this model (Synergy Software, 1996) gave

$$a = 3.8 \pm 0.1;\ b = -0.5 \pm 0.3;\ t_0 = 0.64 \pm 0.04 \text{ min}, \text{ and } r^2 = 0.9999 \quad (4)$$

This calibration line is plotted in Figure 2; therein, the results of the direct measurements of K_{ow} as a function of k' are also shown.

In general, the retention-time method used here tends to underestimate the partition coefficient for log $K_{ow} < 1.5$, and it tends to overestimate it for log $K_{ow} > 3$. By inspection, it is possible to divide the compounds into two groups through which separate lines may be drawn. Group 1 contains the alcohols and the ketone (structures 1−10 and 12, Figure 1). The best-fit line through the data for this group is

$$\log K_{ow} = (5.3 \pm 0.5) \log k' - (0.8 \pm 0.2) \quad r^2 = 0.94 \quad (5)$$

Group 2 contains the compounds that do not contain oxygen or halogens; the best-fit line through the data for this group is

$$\log K_{ow} = (2.5 \pm 0.2) \log k' + (0.5 \pm 0.2) \quad r^2 = 0.98 \quad (6)$$

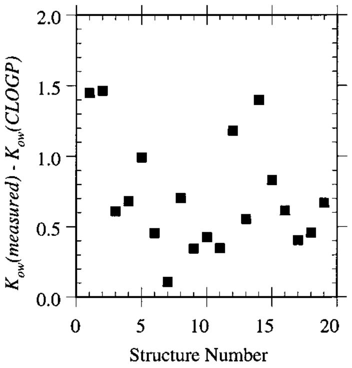

Figure 3. Measurements and predictions. The structure numbers refer to the compounds in Figure 1.

Table 3. Comparison of Substituent Effects[b]

group substituted	into	to give	log K_{ow} decreases by
OH	norbornane	norborneol[a]	2.4
	n-heptane	2-heptanol	2.4
>C=C<	norbornane	norbornylene	0.5
	n-heptane	1-heptene	0.7
Cl	norbornane	exo-2-chloronorbornane	0.4
	n-heptane	1-chloroheptane	0.5
Br	norbornane	exo-2-bromonorbornane	0.2
	n-heptane	1-bromoheptane	0.3
O	norbornane	exo-2,3-epoxynorbornane	2.2
	ethane	ethylene oxide	2.1
	n-propane	propylene oxide	2.3
CH_2OH	norbornane	2-norbornane methanol	1.8
	n-propane	isobutanol	1.6
	n-heptane	1-octanol	1.7
OH	norbornane	2,7-norbornanediol	3.4
OH	propane	1,3-propanediol	3.4
	norbornane	2,3-norbornanediol[a]	3.3
	propane	1,2-propanediol	3.3

[a] Mean log K_{ow} of the two isomers used. [b] Data relating to ethane, propane, and heptane and related compounds were taken from *Exploring QSAR* (Hansch et al., 1995).

The retention times of the halogenated compounds fall within the range of retention times for the group 2 compounds; so, this best-fit line was used to calculate the partition coefficients of the halogenated compounds.

The epoxynorbornane (structure 11, Figure 1) was not considered a member of either group; its partition coefficient is well predicted by the retention-time method. The demarcation of compounds into two groups indicates different retention mechanisms at work. In comparison to the calibration compounds, the compounds of group 1 are not as strongly retained on the C-18 column, whereas the compounds of group 2 are more strongly retained.

In Figure 3, the difference between our measured values and the predictions of CLOGP (Daylight Chemical Information Systems, 1997) is plotted against the structure number of the compound given in Figure 1. The measured values are all larger than the calculated values; the mean difference in log K_{ow} is 0.7 with the sample standard deviation of 0.4. Dicyclopropyl carbinol (structure 7, Figure 1) is the compound for which the prediction is best. The effects of adding substituents to norbornane, heptane, and other straight-chain hydrocarbons on the partition coefficients are shown in Table 3; the ancillary data were obtained from a standard source (Hansch et al., 1995). From these there appears to be no significant difference in adding a given substituent to norbornane or to a straight-chain hydrocarbon; the decrease in log K_{ow} is essentially the same. This conclusion holds for seven substituents, and this provides confidence in the measurements reported here. The fact that the measured partition coefficients are higher indicates that the basic tricyclo-[2.2.1.0^{2,6}]heptyl, quadricylyl, and norbornyl fragments are more hydrophobic than the aligorithm for calculating log K_{ow}, CLOGP, allows.

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Literature Cited

Brooke, D. N.; Dobbs, A. J.; Williams, N. Octanol/Water Partition Coefficients (P): Measurement Estimation, and Interpretation for Chemicals with P > 10^5. *Ecotoxicol. Environ. Saf.* **1986**, *11*, 251−260.

Brooke, D.; Nielsen, I.; de Bruijn, J.; Hermens, J. An Interlaboratory Evaluation of the Stir-Flask Method for the Determination of Octanol−Water Partition Coefficients (Log P_{ow}). *Chemosphere* **1990**, *21*, 119−133.

Chessells, M.; Hawker, D. W.; Connell, D. W. Critical Evaluation of the Measurement of the 1-Octanol/Water Partition Coefficient of Hydrophobic Compounds. *Chemosphere* **1991**, *22* (12), 1175−1190.

CLOGP; Daylight Chemical Information Systems, Inc.: http://www.daylight.com (accessed August 1997).

de Bruijn, J.; Busser, F.; Seinen, W.; Hermens, J. Determination of Octanol/Water Partition Coefficients for Hydrophobic Organic Chemicals with the "Slow Stirring" Method. *Environ. Toxicol. Chem.* **1989,** *8*, 499−512.

Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR*; American Chemical Society: Washington, DC, 1995.

KaleidaGraph, Ver. 3.09; Synergy Software: Reading, PA, 1996.

Könemann, H.; Zelle, R.; Busser, F. Determination of log P_{oct} values of chloro-substituted benzenes, toluenes and anilines by high-performance liquid chromatography on ODS-silica. *J. Chromatogr.* **1979**, *178*, 559−565.

Mannhold, R.; Rekker, R. J.; Dross, K.; Bijloo, G.; de Vries, G. The lipophilic behavior of organic compounds: 1. An Updating of the Hydrophobic Fragmental Constant Approach. *Quant. Struct.-Act. Relat.* **1998**, *17*, 517−536.

Minick, D. J.; Brent, D. A.; Frenz, J. Modeling Octanol-Water Partition Coefficients by Reversed-Phase Liquid Chromatography. *J. Chromatogr.* **1989**, *461*, 177−191.

Montgomery, J. H. *Groundwater Chemicals Desk Reference*, 2nd ed.; CRC Press: Boca Raton, FL, 1996.

Ritter, S.; Hauthal, W. H.; Maurer, G. Partition Coefficients of Some Environmentally Important Organic Compounds between 1-Octanol and Water from Reversed-Phase High-Performance Liquid Chromatography. *J. Chem. Eng. Data* **1994**, *39*, 414−417.

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