Aqueous Solubility−Molecular Size Relationships: A Mechanistic Case Study Using C_{10}- to C_{19}-Alkanes

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Saturated hydrocarbons are important constituents of petroleum products. Their behavior in water, the most prevalent environmental solvent, is of relevance with regard to environmental partitioning. Due to their negligible attractive interactions with water, they are suitable compounds for a mechanism-based validation of the relationship between molecular size and the solubility in water. To that end, we measured the aqueous solubility of aliphatic and alicyclic hydrocarbons with 10 to 19 carbon atoms employing the slow-stirring experiment. Moreover, we compiled data on molecular weight and molar volume at the boiling point as macroscopic size parameters and calculated quantum-chemical molecular size parameters. The aqueous solubility data span a range from 6×10^{-6} M to 4×10^{-11} M with coefficients of variation of less than 15% except for 2,6,10,14-tetramethylpentadecane (39%). The relationships of the experimentally determined solubility values with the macroscopic reflected the general trend of decreasing solubility with increasing molecular size, but discriminated between *n*- and branched alkanes. This indicates that these parameters do not reflect the solute−solvent interactions at the microscopic level. Interpretation of the experimentally observed solubility data based on theoretical considerations of the conformation and the constitution of alkanes is consistent with the following overall picture: For a given *n*-alkane in aqueous solution, the all-trans conformation is preferred over folded geometries. Within alkanes, molecular size is the primary determinant of their solubility in water, and increasing molecular size results in a decrease in water solubility mainly due to the increased free energy penalty for cavity formation in water. The solvent-accessible molecular volume and surface area appeared to be valid reflections of the molecular size.

Introduction

Saturated hydrocarbons are naturally occurring compounds that are produced during the diagenesis of organic material of plant and animal origin.[6] Their electron structure is relatively simple since only two types of bonds (C−H and C−C single bond) are present in these molecules. Due to the small difference in electronegativity between the C- and the H-atom, these bonds are only slightly polarized. Taft and co-workers[12−14] and Ruelle and co-workers[30,31] have proposed linear free energy relationships, which quantitatively account for the interactions involved in solubilization of organic liquids in water. Analysis of the aqueous solubility of *n*-alkanes in terms of these linear free energy relationships demonstrates that the molecular size dominates over solute−solvent interactions in determining aqueous solubility. On a macroscopic level this is reflected in correlations between molecular size parameters and solubility. Such relationships have been reported for polycyclic aromatic hydrocarbons,[1,9] (poly)chlorinated benzenes and biphenyls,[24] and *n*-alcohols.[34] However, these correlations are compound class specific[24,34] indicating that, besides reflecting the fundamental influence of molecular size, these relationships also represent solute−solute and solute−solvent interactions that are specific for the compound classes. Therefore, these relationships are not instructive with regard to the process on the molecular level.

On that level, saturated hydrocarbon molecules that are dissolved in water experience only a weak energy gain due to attractive dispersion forces. It is outweighed by far by the expenditure of the energy required to accommodate the apolar hydrocarbon molecules in the hydrogen-bonding network of the water molecules. Both energetic contributions increase with molecular size, and since the electron density distribution in saturated hydrocarbon molecules is relatively homogeneous, the aqueous solubility of solutes is expected to decrease with increasing size of nonpolar moieties. Therefore, saturated hydrocarbons are suitable model compounds for evaluation of our mechanistic understanding of the influence of molecular size on dissolution of nonpolar chemicals in water as the most prevalent environmental solvent.

Moreover, saturated hydrocarbons are important constituents of petroleum products. Anthropogenic activity associated with the use of these compounds in chemical industry and in energy generation[6] releases hydrocarbons into the environment. Therefore, the environmental risk associated with the use of aliphatic hydrocarbons has to be assessed. Their behavior in water is of great relevance with regard to environmental transport and partitioning as well as estimation of environmental exposure of aquatic organisms. The aqueous solubility is one of the most important physical-chemical properties governing this behavior

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and can be seen as a measure of hydrophobicity.[2,24] Environmental toxicologists have found hydrophobicity (mostly expressed as the octanol−water partition coefficient) to be correlated with the bioconcentration factor in organisms,[19,25,26,36] toxicity to organisms,[17,20,22] and the tendency to sorb to sediments and soils.[5,15] However, experimental aqueous solubility data are rather scarce for saturated hydrocarbons with 10 or more C-atoms.[37]

It appears likely that the difficulties associated with the experimental determination of the aqueous solubility are the reason for the shortage in data. The first problem encountered is that increasing the number of C-atoms leads to a decrease of the concentrations of the hydrocarbons in the water. As a result, minute amounts of chemicals have to be measured. This causes problems with regard to detection limits of available analytical methods and the reliability of the analytical methods at such low concentrations. Second, even very small amounts of hydrocarbons present in the water as microemulsion can exceed the fraction of dissolved hydrocarbon and lead to erroneous results, as recognized in earlier work.[6,21,27,28]

In the present research we investigated whether the empirical relationships between molecular size and aqueous solubility can be validated on a mechanistic level. To do so we first determined the aqueous solubility for a series of saturated hydrocarbons with 10 to 19 carbon atoms. To that end, we performed slow-stirring experiments, in which water and the neat hydrocarbon are equilibrated without formation of microemulsions.[8] Doing so, we expanded the range in which the relationship between molecular size and aqueous solubility can be investigated. Since for the *n*-alkanes the molecular size is linearly correlated to the number of carbon atoms, we included two cyclic C_{10} hydrocarbons as well as five branched compounds. By not restricting our analysis to one specific homologous series it was considered that the study should give more insight into the actual impact of molecular size on the dissolution process. Second, we assembled a database of macroscopic and molecular level parameters characterizing molecular size and established molecular size−aqueous solubility relationships. To do so, we chose not to establish a variety of empirical relationships with molecular parameters that are correlated with molecular size such as topological indices or the octanol−water partition coefficient but selected parameters that we believe to be reasonable approximations of molecular size. The results are interpreted with regard to the conformation and constitution of the hydrocarbons in aqueous solution and the mechanistic relevance of the size parameters.

Materials and Methods

Materials. *n*-Alkanes, 2,2,4,4,6,8,8-heptamethylnonane, and 2,6,10,14-tetramethylpentadecane were purchased from Sigma (Sigma-Aldrich-Fluka, Zwijndrecht, The Netherlands). Cyclodecane and *cis*-decahydronaphthalene were obtained from Fluka (Sigma-Aldrich-Fluka, Zwijndrecht, The Netherlands) and Merck (Amsterdam, The Netherlands), respectively. 2,2,4,6,6-Pentamethylheptane, 2-methyl-undecane, 2,6-dimethyldecane, and 3,3,6,6-tetramethyloctane were supplied by BP Amoco (Sunbury on Thames, U.K.). All chemicals were used as received. High purity water was prepared using an Elgastat purification system (Elga, Buchs, Switzerland) and filtered through 0.22 μm Teflon filters (Millipore-Waters, Breda, The Netherlands). Hexane (technical grade, Baker-Mallinckrodt, Deventer, The Netherlands) was redistilled prior to use. Solid-phase microextraction fibers were purchased from Supelco (Sigma-Aldrich-Fluka, Zwijndrecht, The Netherlands).

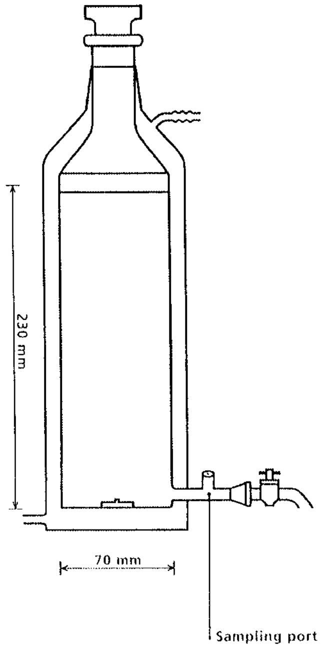

Figure 1. Schematic of the slow-stirring vessels.

Slow-Stirring Experiments−Principle. The aqueous solubility was determined in “slow-stirring”[8] experiments. In these experiments a layer of neat hydrocarbons floated on the water phase. This two-phase system is gently s’tirred. In that manner, the mass transfer between the phases is accelerated while the interface between water and the organic liquid remains laminar and formation of microdroplets of hydrocarbon is minimized. The experiments are carried out in water-jacketed reaction vessels (Figure 1) of 0.5 or 1 L (Utrecht University workplace) that were kept at 25 °C during the experiments. The vessels have a tap that allows for sampling from the flask. A septum-sealed sampling port was added to the glass tube leading to the tap for airtight sampling of water.

Procedure. A slow-stirring experiment was initiated by filling purified and filtered (0.22 μm Teflon filter, Millipore) water into the slow-stirring bottles. The neat hydrocarbon was put as a thin layer on top of the water phase while preventing turbulent mixing of the liquids. To that end, the organic liquid was allowed to flow along the glass wall. The water phase was stirred with a magnetic stir bar. The stirring rate was adjusted such that the vortex depth did not exceed 2 cm. Prior to sampling of the water phase, the tap was opened to drain the stagnant volume of water in the tap. Thereafter, the water in the tap was representative of the bulk solution.

Sampling. The aqueous samples were withdrawn from the vessel via the septum-sealed sampling port using an airtight syringe. For headspace SPME analysis of the more soluble compounds 25 to 500 μL of water were transferred to a precrimped glass vial. In case of the less soluble test compounds, 25 to 200 mL of water sample were transferred to a three-neck bottle of a Euroglass 6/100 (Delft, The Netherlands) purge and trap system closed with a septum. In both cases care was taken to prevent analyte losses due to evaporation. Sampling was started no earlier than 8 days after initiation of the experiment and continued until the concentration in the water samples were consistent. The average concentration ($n = 4$ to 6) represents the aqueous solubility of the test compound.

Chemical Analysis. The concentrations of the test compounds in the water were determined employing gas chromatography after extracting the water samples by headspace solid-phase

TABLE 1: The Test Compounds and Their Properties: Number of C-Atoms (n_C), Molecular Weight (MW), the Density at 293 K, the Boiling Point (BP), the Molar Volume at the Boiling Point (MV_{BP}) (estimated employing Grain's method)[18], and the Solvent Accessible Volume (SAVOL, in Å^3)

	systematic name	MW (g/mol)	density ($T = 293$ K)	BP (K)	MV_{BP} (mL/mol)	SAVOL (A^3)
n-alkanes	octane	114	0.699	398.8	184.1	633
	nonane	128	0.718	424	205.4	691.1
	decane	142	0.730	447.3	226.8	754.6
	undecane	156	0.740	469.1	248.4	812.9
	dodecane	170	0.749	489.5	269.9	876.4
	tridecane	184	0.756	508.6	291.1	934.4
	pentadecane	212	0.769	543.8	334.1	1061.1
branched alkanes	2-methylundecane	170	0.746	483.4	270.2	858.4
	3,3,6,6-tetramethyloctane	170	0.757	462.9	263.9	797.5
	2,2,4,6,6-pentamethylheptane	170	0.764	447.2	259.6	789.6
	2,2,4,4,6,8,8-heptamethylnonane	226	0.793	513.2	341.7	982.9
	2,6,10,14-tetramethylpentadecane	269	0.785	569.2	416.4	1250.4
cycloalkanes	decahydronaphthalene	138	0.791	428.7	201.5	613
	cyclodecane	140	0.858	474.2	192.8	635.7

microextraction (SPME)[29,39] for the C_{10} to C_{13}-*n*-alkanes, the cycloalkanes, and the branched dodecane isomers. The headspace extraction makes use of the high Henry's Law constants of the saturated hydrocarbons (>2000 Pa m^3 mol^{-1}) which result in high volatilization of the compounds from water to the gas phase.[37] Vortexing of the sample for 30 s appeared to be sufficient to accelerate evaporation of the alkanes from the water phase into the headspace. Subsequently, the sample was extracted by inserting a PDMS coated (film thickness: 100 μm) glass fiber into the headspace of the sample vial. Extraction was found to be complete after 5 min. The fiber was thermally desorbed in the GC-injector for 4 min at 250 °C. Upon repeating the headspace SPME extraction no hydrocarbon could be detected in the samples indicating that the first extraction had been quantitative.

For the less soluble compounds pentadecane, 2,6,10,14-tetramethylpentadecane, 2,2,4,4,6,8,8-heptamethylnonane, purge and trap/thermal desorption was the method of choice since the amounts of chemical sampled by SPME were too small to be detected. The closed three-neck bottle of the purge and trap system was mounted to a cooler with a glass tube (6 mm i.d.). This tube is the outlet of the system, contains 0.1 g to 0.2 g of TENAX (mesh 60 to 80) and constitutes the trap. The analytes were purged from the water at 95 °C for 30 min using highly pure nitrogen. The temperature was controlled by a thermocouple. The gas stream was dried by cooling to 8 °C in a cooler. The analytes were trapped then on the TENAX trap. Transfer of the analytes from the TENAX trap to the GC-column was achieved using a Gerstel TD/CIS thermal desorption apparatus (Analytical Applications, Brielle, The Netherlands) coupled to a temperature-controlled injector fitted to a Gerstel Controller 505 (Analytical Applications, Brielle, The Netherlands). The analytes were thermally desorbed from the TENAX trap for 8 min at 300 °C. Within the TD/CIS system they are focused in the temperature-controlled injector at -110 °C. Injection into the gas chromatograph occurs by heating the injector to 300 °C at a rate of 12 °C/s.

All gas chromatographic analyses were performed by GC-FID fitted with a DB-5 column (25m, 0.35 mm i.d., 0.25 μm film thickness, Bester, The Netherlands). A Carlo Erba 5300 gas chromatograph (Interscience, Breda, The Netherlands) fitted with a Gerstel TD/CIS system (Analytical Applications, Brielle, The Netherlands) and a Varian Cx 3400 gas chromatograph (Varian, Houten, The Netherlands) equipped with an autosampler for solid-phase microextraction were used. Both instruments were calibrated by liquid injection of standard solutions containing analyte concentrations in the range of the concentrations that were expected in the samples. All analyses were performed within the linear range of the detector. Linearity of the detector response was checked at least once per week. The limits of detection and quantitation were defined as the concentration that is necessary to cause a signal three and 10 times as high as the noise of the baseline in the retention time interval of the compound of interest.

Recovery. Recovery experiments consisted of addition of known amounts of analytes dissolved in acetone or methanol to water samples. After sample treatment, the amount of analyte recovered was determined by GC-analysis employing the methods described above. The analytical recovery specifies what percentage of the analyte added initially could be recovered in the sample after sample treatment. The analytical recovery was determined for all methods described above using all compounds for which that method was appropriate. The analytical recovery always exceeded 60% and was employed to correct for losses occurring during sample preparation in all samples.

Molecular Size Descriptors. The macroscopic descriptors employed are the molecular weight and the molar volume. Given that the molar volume at room temperature also reflects intermolecular interactions, we chose for the molar volume at the boiling point, since at the boiling point intermolecular interactions are disrupted. Therefore, the molar volume at the boiling point can be expected to be a better approximation of molecular size. We calculated it according to Grain's method [18] using the most recent entries on density, boiling point, and molecular weight reported in the Beilstein's Handbook of Organic Chemistry.[3] The data are compiled in Table 1. For the quantum-chemical computations of the molecular volumes and surface areas, the 3-dimensional geometries of the compounds were optimized at the AM1 level of theory using the MOPAC package.[4] Two different geometries, the all-trans and a helical configuration, were computed for the *n*-alkanes. Subsequently, molecular volumes and surface areas were calculated with MOLSV[35] employing van der Waals radii as presented recently for the COSMO-RS model.[16] Two different kinds of molecular surfaces and corresponding volumes were calculated. While the surface area (SA) represents the area of the van der Waals surface of the molecule, the solvent-accessible surface area (SASA) is defined as the locus of the center of a solvent sphere, which is rolled over the van der Waals surface of the solute. The molecular volume (VOL) and solvent-accessible volume (SAVOL) are defined correspondingly. For the calculation of SASA and SAVOL, an effective radius of 1.5 Å for the solvent molecule (H_2O) was assumed. The data are available as Supporting Information.

TABLE 2: Values of the Aqueous Solubility (*S*) in μg/L and in M of the Hydrocarbon Compounds As Determined in the Present Project with Water and Headspace Volumes of 0.5 and 1.5 mL, Respectively

	compound	*S* (μg/L)	CV[b] (%)	*S* (M)	S (M) literature
n-alkanes	octane	660		5.8E−06	
	nonane	171		1.3E−06	
	decane	46	8	3.2E−07	1.4E−07
	undecane	9	4	5.8E−08	2.8E−08
	dodecane	1	15	5.9E−09	2.1E−08
	tridecane	0.4	10	2.2E−09	1.8E−09
	pentadecane	0.04	7	1.9E−10	
branched alkanes	2-methylundecane	2	2	1.2E−08	
	3,3,6,6-tetramethyloctane	21	8	1.2E−07	
	2,2,4,6,6-pentamethylheptane	25	3	1.5E−07	
	2,2,4,4,6,8,8-heptamethylnonane	0.31	6	1.4E−09	
	2,6,10,14-tetramethylpentadecane	0.01	39	3.7E−11	
cycloalkanes	decahydronaphthalene	850	2	6.1E−06	6.4E−6
	cyclodecane	330	1	2.4E−06	

[a] Incomplete recovery is corrected for. [b] CV specifies the coefficient of variation.

Data Treatment. The arithmetic mean of the concentrations measured in the water samples ($n > 5$) is the aqueous solubility of the test compounds. Linear regression of the experimental solubility data to the descriptors was employed to evaluate the goodness of the fit, as indicated by the r^2-value.

Results and Discussion

Experimental Setup. A number of different experimental approaches were evaluated in order to determine the aqueous solubility of alkanes using *n*-decane as a model compound. Initially, we evaluated two saturation approaches using decane as reference compound. In the first, air was saturated by leading it over glasswool that had been immersed in the test compound. The concentrations measured were very variable (0 to 100 μg/L) and often higher than the reported solubility value of 52 μg/L reported by McAuliffe.[21] Similarly, draining water by gravity through a column containing a sorbent that is coated with test compound yielded highly variable results (30 to 600 μg/L). The latter approach was refined by controlling the column temperature and the water flow rate (by using an HPLC-pump and a well packed column). This resulted in reproducible concentrations of decane somewhat below the values reported by Coates et al.[6] Equilibration of an aqueous solution with the neat hydrocarbon via the headspace was the next attempt. After an equilibration time of more than 3 weeks this resulted in a concentration of 20 μg/L, quite similar to the values reported in the literature. In contrast, the slow-stirring method allows for equilibrating water and the neat hydrocarbon in about 50 h. The average of the decane concentrations measured between day 3 and 18 was taken as the aqueous solubility (45.5 μg/L). The time to equilibrium was similar for the other compounds (results not shown). The between day variation was used to calculate the standard deviation (3.5 μg/L) and the coefficient of variation (8%). These data demonstrate that the overall approach yields highly reproducible results. Therefore, the slow-stirring experiment was the approach of choice for the determination of the aqueous solubility in the present study.

Solubility Data. Tables 2 and 3 give an overview of the results obtained for the compounds studied. The solubilities span a range from 6×10^{-6} M for decahydronaphthalene to 4×10^{-11} M for tetramethylpentadecane. The coefficient of variation for all compounds is less than 15% indicating that aqueous solubility was determined with high precision. 2,6,10,14-Tetramethylpentadecane is an exception with a CV of 40%, presumably due to the measurements being performed close to the limit of quantitation of the analytical method. Comparison to critically reviewed solubility data (Table 2) demonstrates that the values determined in the present study differ by less than a factor of 3 from data selected to be reliable in a recent literature review. This supports the validity of the experimental approach taken in the present study.

TABLE 3: Synopsis of Aqueous Solubility (*S*), Vapor Pressure (p^0_{298K}), and Henry's Law (*H*) Constants of Selected Long Chain Saturated Hydrocarbons[a,b]

compound	*S* (M)[c]	*P* (Pa)[d]	*H* (Pa m^{-3} mol^{-1})	*H*′ [e]
n-decane	3.2E−07	183.0	5.7E+05	228
n-undecane	5.8E−08	57.2	9.9E+05	401
n-dodecane	5.9E−09	17.6	3.0E+06	1210
n-tridecane	2.2E−09	5.3	2.4E+06	984
decahydronaphthalene	6.1E−06	147.0	2.4E+04	10

[a] Only compounds for which data for *S* and p^0_{298K} are available are included. [b] *H* was calculated as p^0_{298K}/S. [c] Data from this study. [d] Data collected in Verbruggen et al.[37] [e] *H*′ is the dimensionless Henry's Law constant.

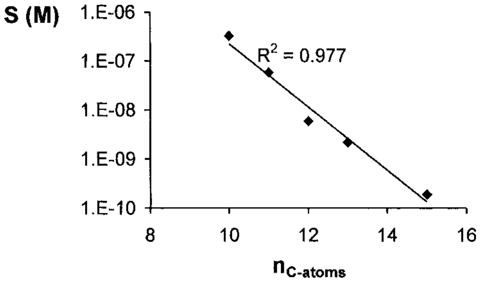

Figure 2. Plot of the logarithm of the aqueous solubility (log *S*) of the *n*-alkanes tested in the present study against the molecular weight.

Structure−Solubility Relationships. *Bulk-Related Size Descriptors.* From Table 2 different trends become apparent. Aqueous solubility decreases with increasing number of carbon atoms as can be observed in the series of *n*-alkanes and branched alkanes. Solubility decreases by 3 orders of magnitude going from *n*-decane (3.2×10^{-7} M) to *n*-pentadecane (1.9×10^{-10} M). The linear relationship between the solubility of the *n*-alkanes and the molecular weight (Figure 2) indicates that the solubility of the *n*-alkanes decreased by a constant increment for each additional CH_2-unit.

Within the dodecane isomers, a trend of increasing solubility with increasing degree of branching can be observed. Comparison of the data for *n*-decane (3.2×10^{-7} M) to the results obtained for the monocyclic compound cyclodecane (2.4×10^{-6} M) and the bicyclic compound decahydronaphthalene (6.1 ×

10^{-6} M) demonstrates that a small variation in molecular weight results in a pronounced increase of aqueous solubility. Therefore, the molecular weight is not a suitable descriptor of the molecular size for the selected compounds. Likewise, the molar volume at the boiling point does not appear to be appropriate, since we found that the *n*-alkanes and the multiply branched alkanes (2-methylundecane excluded), display significantly ($P < 0.01$, analysis of covariance [23]) different relationships between molar volume at the boiling point and aqueous solubility.

Molecular size as the parameter determining the energy penalty of cavity formation as well as the energy gain of dispersion interactions is correlated to the bulk-related parameters molecular weight and molar volume at the boiling point. The observed relationships between molecular weight (Figure 2, for *n*-alkanes) and, for a highly aggregate set of hydrocarbon data for molar volume at the boiling point[18] are thus no mechanistic relationships. Rather, they reflect the correlation between the pivotal parameter on the molecular level and the bulk related size descriptors.

Conformation. When considering solubility at the molecular level, it has to be noted, that solubility is also affected by the conformation of the molecules, and that the macroscopic solubility would in principle reflect a Boltzmann-weighted conformational distribution of the compound in solution. According to free-energy simulations based on force-field calculations of n-dodecane[38] and of some smaller alkanes,[11] the solvation free energy of folded *n*-alkanes is less unfavorable than the one of all-trans conformations, which can be traced back to a decrease in the cavity size and the respective formation energy. At the same time, the all-trans conformation of *n*-alkanes is still significantly more stable in aqueous solution than substantially folded structures, which was shown for n-dodecane[38] and also checked for the present set of *n*-alkanes by SM2[7] calculations.

For the seven *n*-alkanes as listed in Table 2, the all-trans conformations are preferred to helical structures by −15.1 kJ/mol (octane) to −36.3 kJ/mol (pentadecane) according to SM2, while the corresponding unfavorable solvation free energy is calculated to increase from 11.2 kJ/mol (octane) to 18.7 kJ/mol (pentadecane). Recall that solvation free energies refer to Henry's law constant and thus the free energy difference between the gas phase and the aqueous phase,[33] while the water solubility of solids and liquids represents the free energy difference between the chemical in its pure phase and the chemical as solute in water.[32] Interestingly, the helical structures yield slightly less unfavorable solvation free energies, which cannot compensate their significantly less favorable formation energies in the gas phase as calculated by AM1. It follows that the substantial preference for all-trans conformations of *n*-alkanes in aqueous solution is due to the fact that they are intrinsically more stable than helical (or otherwise folded) structures as reflected by gas-phase calculations. Hence, the all-trans conformations may be taken as fairly good representatives of the *n*-alkanes in aqueous solution.

Quantum Chemical Molecular Size Parameters. As outlined above, the all-trans conformation of *n*-alkanes is the energetically most favorable conformation both in the gas phase and in aqueous solution. The latter is confirmed by the present analysis of the solubility-size relationship employing molecular volume (VOL) and molecular surface area (SA) calculated for the helical and all-trans conformations of the alkanes using the semiempirical quantum chemical AM1 scheme. With the helical structures, linear regression of log S_w on SA and VOL yields r^2 values of 0.87 and 0.86, respectively, while the corresponding regression equations with the all-trans conformers have r^2 values of 0.96 (SA) and 0.90 (VOL), respectively. Replacement of SA and VOL by their solvent-accessible counterparts finally leads to an r^2 value of 0.96 for both SASA (solvent-accessible surface area) and SAVOL (solvent-accessible volume). Inspection of the data distributions reveals further, that the previous separation between *n*-alkanes, branched isomers and cyclic counterparts is overcome when referring to the molecuar size rather than to molecular weight or molar volume at the boiling point, which is shown for the log S_w-SAVOL relationship in Figure 3b.

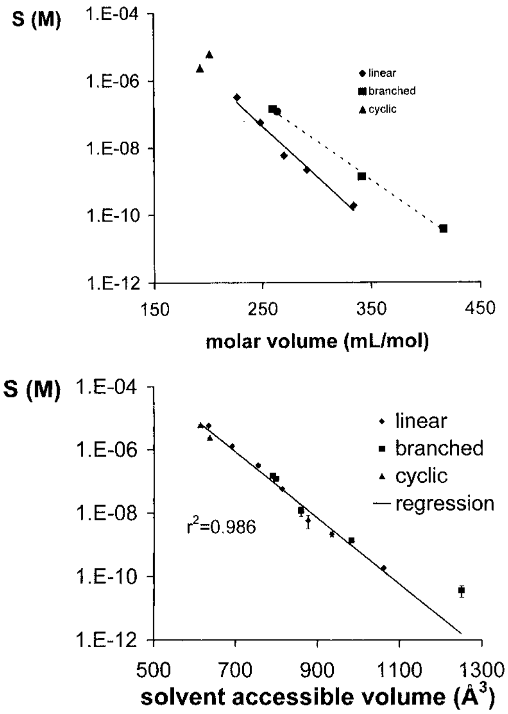

Figure 3. Plot of the logarithm of the aqueous solubility (log *S*) of the test compounds against the molar volume at the boiling point (MV) (a) and the solvent accessible molecular volume (b).

Recall that the molar volume at the boiling point results from solute−solute interactions, while water solubility is driven by solute−water interactions and the free energy penalty to build the cavity around the solute. The latter is energetically unfavorable due to entropy loss of water (because the cavity defines a volume that can no longer be populated by water molecules) and a partial loss of favorable water−water interactions, and in general will increase with increasing molecular size. As a consequence, increasing molecular size tends to decrease water solubility, which in the absence of strong solute−water interactions will dominate the overall trend as in the case of the present set of alkanes. This phenomenon is illustrated by the above-mentioned series of *n*-decane, cyclodecane, and decahydronaphthalene: In this order, SAVOL decreases from 754.6 A^3 to 613.0 A^3, which results in an increase of water solubility by more than 1 order of magnitude.

On the other hand, inceasing molecular size offers an increased molecular surface that can undergo favorable dispersion interactions with the solvent molecules. It follows that the resultant effect of molecular size on water solubility depends on the actual balance between the unfavorable component from cavity formation and the favorable component from dispersion interactions, which is specific for the compound or compound class under investigation. For the alkanes discussed here, the size-solubility relationships based on molecular size parameters such as SASA and SAVOL show that to a first order, the free energy penalty for cavity formation when increasing molecular size is larger than the gain in free energy through dispersion interactions, such that the overall trend is an increase of water solubility with decreasing molecular size. For the above-mentioned set of three C_{10} alkanes it follows specifically that *n*-decane has the lowest water solubility, although it contains the largest number of atoms available for favorable dispersion interactions with water.

To understand the variation of the solubility of alkanes in water, bulk-related descriptors of molecular size (molecular weight and molar volume at the boiling point) are inappropriate. In contrast, the molecular interaction based interpretion of the experimentally observed solubility data employing theoretical considerations of both the conformation and the constitution of alkanes is much more successful for deepening our understanding of the dissolution of hydrocarbons in water. The following overall picture can be drawn: For a given *n*-alkane in aqueous solution, the all-trans conformation is preferred over folded geometries. When comparing different alkanes, molecular size is the primary determinant of their solubility in water, and increasing molecular size results in a decrease in water solubility mainly due to the increased free energy penalty for cavity formation in water.

In light of the above, a comparison of the present data with the solubilities of chlorinated *n*-alkanes[10] is instructive for evaluating the relative influence of molecular size on the aqueous solubility. Both, 1,10-di- and 1,2,9,10-tetrachlorodecane have aqueous solubilities of 1.2×10^{-6} M, while that of the hydrocarbon analogue amounts to 3.2×10^{-7} M. Similarly the solubility of 1,2-dichlorododecane is higher than that of *n*-dodecane (9.4×10^{-8} M versus 5.9×10^{-9} M). Hence the increased apolarity in the chlorinated analogues overcompensates the larger molecular size resulting in increased solubility. With regard to understanding aqueous solubility as the resultant of multiple interactions this suggests that the presence of polar moieties (such as the C−Cl dipole) in hydrophobic neutral molecules effectively counterbalances the effect of molecular weight.

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Supporting Information Available: Supporting Information Available: Values of the molecular surface area and volume calculated employing different configurations of the *n*-alkanes and volumes of the solvent molecule (r_{H_2O}). This material is available free of charge via the Internet at http://pubs.acs.org.

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