Free Energy of Transfer of a Solute and Its Relation to the Partition Constant

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There is an ongoing debate in the literature about the correct relationship between the free energy of transfer of a molecule i between two phases 1 and 2, ΔG°_{i12}, and the corresponding partition constant, K^c_{i12}. This work presents experimental evidence, based on data from the literature, indicating that the unit molar concentration scale is close to the correct standard state. However, a discrepancy remains that appears to be related to the free volume in the liquid phase, as has been postulated before by Vitha and Carr. This discrepancy can be quantified by an empirical linear regression with the surface tension of the respective liquid phase. Other approaches that account for an additional entropy contribution arising from differences in the molar volume of the solvents are disproved by these data. This finding has consequences for Raoult's law convention and the Flory–Huggins theory.

Introduction

The free energy of transfer, ΔG°_{i12}, of an infinitely dilute solute i between two immiscible phases 1 and 2 corresponds to the work needed to transfer one mole of i from a fixed position in phase 1 to a fixed position in phase 2. This free energy depends on the interactions between the solute molecule i and the solvent molecules of the phases 1 and 2. It is related to the equilibrium partition constant K^c_{i12}, which describes the equilibrium concentrations (in moles per volume) of solute *i* in phases 1 and 2. However, there is an ongoing debate in the literature[1] about the exact relationship between these two entities.

According to Ben-Naim,[2] this relationship should simply be (R = universal gas constant, T = absolute temperature):

$$\Delta G^\circ_{i12} = -RT \ln K^c_{i12} \tag{1}$$

Others have argued that eq 1 must be extended by an entropy contribution that accounts for differences in the molar volumes of phases 1 and 2. For partitioning between two liquid phases one often finds the following equation:

$$\Delta G^\circ_{i12} = -RT \ln K^c_{i12} - RT \ln(V_2/V_1) = -RT \ln K^x_{i12} \tag{2}$$

where V_1 and V_2 are the molar volumes of phase 1 and 2 and K^x_{i12} is the partition constant based on mole fraction concentrations. On the basis of the Flory–Huggins theory, other corrections for differences in the molar volumes of phases 1 and 2 have been suggested.[3,4] In contrast to that, Vitha and Carr[1] have concluded in a theoretical discussion based on idealized assumptions that a correction term is needed in eq 1 that accounts for the free volume available in the liquid solvents. However, they did not suggest a quantitative term for this correction.

The question of the correct relationship between K^c_{i12} and ΔG°_{i12} becomes relevant whenever K^c_{i12} is calculated from ΔG°_{i12}, which in turn has been calculated from quantum chemical methods or estimated from other models of intermolecular interactions. However, it appears that currently these methods lack the accuracy that would be needed to use them for a validation of eq 1 or 2. Hence, an experimental determination of ΔG°_{i12} is required to decide which, if any, of these equations gives the correct relationship between K^c_{i12} and ΔG°_{i12}. The goal of this paper is to use an existing set of experimental partition data of *n*-alkanes in 69 different solvents to shed some new light on the question of the correct relationship between K^c_{i12} and ΔG°_{i12}.

Theory

Obviously, ΔG°_{i12} of a compound *i* cannot be determined unambiguously from one of the above equations because the exact form of the relationship is under debate. However, the equations can be used for an unambiguous determination of the free energy of transfer for a methylene group (CH$_2$), $\Delta G^\circ_{CH_2 12}$. This increment can be calculated from the partition coefficients K^c_{i12} or K^x_{i12} of two nonbranched, consecutive members of a homologous series of compounds (e.g., *n*-hexane and *n*-heptane or *n*-heptanol and *n*-octanol). In this case both equations, (1) and (2), give the same expression for $\Delta G^\circ_{CH_2 12}$:

$$\Delta G^\circ_{CH_2 12} = -RT \ln K_{C_{n+1}12} - (-RT \ln K_{C_n 12}) \tag{3}$$

where $K_{C_{n+1}12}$ and $K_{C_n 12}$ denote the partition constant between phases 1 and 2 for two consecutive members of a homologous series of compounds having *n* and (*n* + 1) carbon atoms in their molecules. The important thing about eq 3 is that the resulting value for $\Delta G^\circ_{CH_2 12}$ is independent of any possibly occurring influence of the molecular volume of the phases because the term $RT \ln(V_1/V_2)$ cancels out in the difference formed in eq 3. Hence, eq 3 allows an unambiguous determination of the free energy of transfer of a methylene group between phases 1 and 2 from measured partition constants. Such methylene increments, $\Delta G^\circ_{CH_2 12}$, are constant for a given solvent as can be seen in many data collections of partition constants for C$_4$ to C$_{10}$ *n*-alkanes.[1,5–11] Therefore it should be possible to determine the free energy of transfer of *n*-nonane for example

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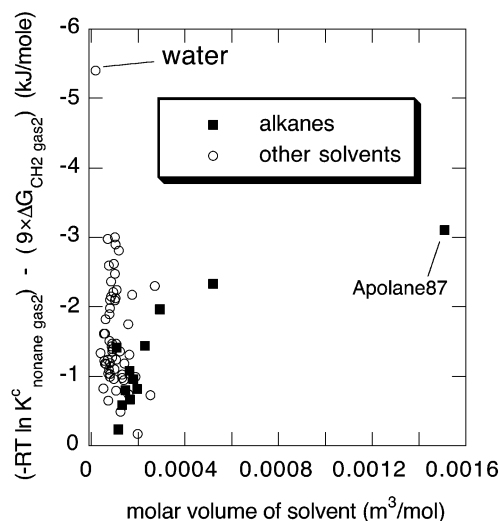
Figure 1. Difference between $(-RT \ln K^c_{\text{nonane gas2}})$ and $9\Delta G°_{\text{CH}_2\text{gas2}}$ plotted versus molar volume of 69 solvents.
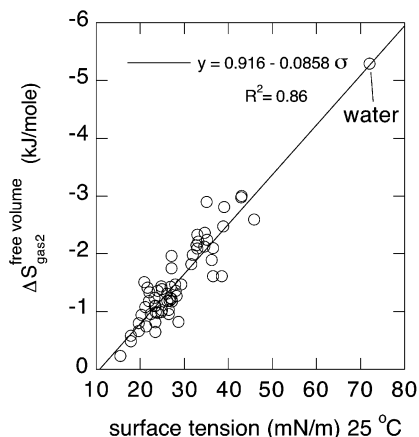

Figure 2. $\Delta S^{\text{free volume}}_{\text{gas2}}$ $(=(-RT \ln K^c_{\text{i gas2}}) - \Delta G°_{\text{i gas2}})$ plotted versus surface tension, σ_2, for 61 solvents (surface tension data at 25 °C taken from.[22−26] For eight solvents no surface tension data could be found in the literature).

as 9 times the free energy of a methylene increment.[12] This procedure yields an unambiguous value of $\Delta G°_{\text{i12}}$ for the partitioning of *n*-nonane that can be compared to the respective free energy calculated with eq 1. Performing this comparison for an alkane in a large number of various solvents will provide a good idea about the validity of eqs 1 and 2.

Results

Castells et al.[13] have measured the partition constants of three to five *n*-alkanes (from C_5 to C_9) between air and 67 different organic solvents at 25 °C and infinite dilute conditions. This large and accurate[14] data set is perfectly suited for the intended investigation. In addition, data for two more solvents, water, and Apolane-87 ($C_{87}H_{176}$), have been included into the analysis. First, the performance of eq 1 for the partitioning of *n*-nonane between the gas phase and various solvents is studied (note that eq 2 cannot be applied to gas phase partitioning.) The results in Table 1 show that the free energy of transfer of nonane calculated from eq 1 gives values that are rather close (mostly within 10%) to the values of $9\Delta G°_{\text{CH}_2\text{gas2}}$. However, a significant difference remains. A plot of this observed difference against the molar volume of the solvent phases (Figure 1) reveals no relationship. For the alkane phases alone, a positive correlation can be seen for small carbon numbers, but this relationship levels
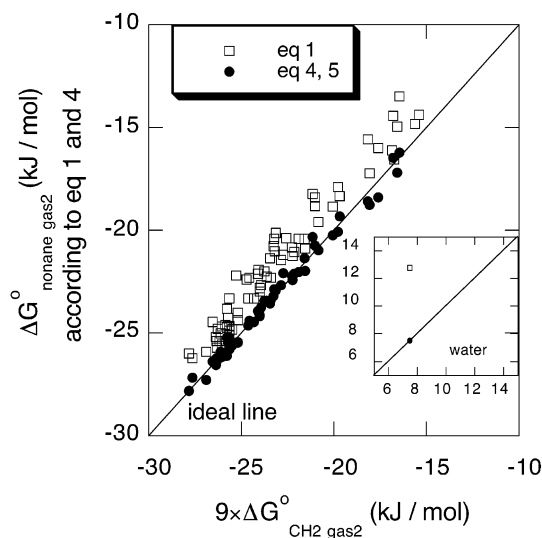
Figure 3. Comparison of the free energy of transfer of *n*-nonane between the gas phase and various solvents calculated as $9\Delta G°_{\text{CH}_2\text{sw}}$ and calculated with eq 1 and combined eqs 4 and 5. The inset shows the values for the gas water partitioning of nonane.

off at higher carbon numbers. Examination of an additional experimental data set for the partitioning of *n*-alkanes in $C_{28}H_{58}$, $C_{32}H_{66}$, $C_{36}H_{74}$, and various aliphatic polymers (at 100 °C) gives further support to the conclusion that there is no relationship between the observed discrepancy between $(-RT \ln K^c_{\text{i gas2}})$ and $\Delta G°_{\text{i gas2}}$ and the molar volume of the solvent phase 2 (see Table 2). Vitha and Carr[1] argued that eq 1 has to be extended for an entropic contribution to account for the difference in the free volume available to the solute within a phase. Obviously, the free volume in a condensed phase must be smaller than in a dilute gas phase. Hence, the partitioning from a gas phase into the liquid phase should be less favorable than one would expect from the interaction free energy $\Delta G°_{\text{i12}}$. This is indeed the case for all solvents in Table 1. Following the argumentation of Vitha and Carr, we may therefore interpret the observed difference between $(-RT \ln K^c_{\text{i gas2}})$ and $\Delta G°_{\text{i gas2}}$ as an entropy difference, $\Delta S^{\text{free volume}}_{\text{gas2}}$, that arises from the difference in the accessible free volume of the solvent as compared to its saturated vapor phase.

Interestingly, $\Delta S^{\text{free volume}}_{\text{gas2}}$ shows a very good linear relationship to the surface tension, σ_2, of the respective solvents (Figure 2). Surface tension is a measure of the cohesive free energy within a solvent. The stronger the cohesive energy between molecules in a solvent the smaller should be the free volume that is accessible for a solute molecule. Hence, this finding also supports the above interpretation. In summary, the data suggest that eq 1 needs to be extended by a small correction term accounting for the available free volume.

$$\Delta G°_{\text{i gas2}} = -RT \ln K^c_{\text{i gas2}} + \Delta S^{\text{free volume}}_{\text{gas2}} \qquad (4)$$

This correction term, $\Delta S^{\text{free volume}}_{\text{gas2}}$, can be quantified by a linear regression with the surface tension of the solvents, σ_2:

$$\Delta S^{\text{free volume}}_{\text{gas2}} = 916\ (\text{J mol}^{-1}) - 85.8\ (\text{J m mol}^{-1}\ \text{mN}^{-1}) \times$$
$$\sigma_2\ (\text{mN m}^{-1})\ (5)$$

In Figure 3 the interaction free energy of *n*-nonane, $\Delta G°_{\text{i gas2}}$, calculated from the methylene increments is plotted versus the results of eq 1 and combined eqs 4 and 5. The results of eqs 4 and 5 fit the ideal line extremely well.

Free Energy of Transfer of a Solute

J. Phys. Chem. B, Vol. 107, No. 50, 2003 **14027**

TABLE 1: Free Energies of Transfer between Air and Various Solvents at 25 °C for a Methylene Increment and for *n*-Nonane

solvent	$\Delta G°_{CH_2gas2}$,[a] kJ/mol (sd < 2%)	$9\Delta G°_{CH_2gas2}$, kJ/mol (sd < 2%)	$-RT \ln K^c_{nonane\ gas2}$, kJ/mol	Δ,[b] kJ/mol
n-pentane	−2.87	−25.87	−25.63	−0.23
n-hexane	−2.92	−26.31	−25.73	−0.58
n-heptane	−2.91	−26.18	−25.38	−0.80
n-octane	−2.90	−26.11	−25.03	−1.08
n-nonane	−2.85	−25.64	−24.68	−0.96
n-decane	−2.80	−25.20	−24.39	−0.81
n-dodecane	−2.86	−25.71	−24.27	−1.44
n-hexadecane	−2.86	−25.78	−23.81	−1.96
cyclohexane	−3.07	−27.65	−26.24	−1.41
squalane	−2.85	−25.64	−23.32	−2.33
2,2,4-trimethylpentane	−2.83	−25.49	−24.83	−0.66
methanol	−2.19	−19.69	−18.36	−1.33
ethanol	−2.40	−21.58	−20.41	−1.18
propan-1-ol	−2.46	−22.14	−21.05	−1.09
butan-1-ol	−2.54	−22.86	−21.46	−1.39
octan-1-ol	−2.64	−23.77	−22.02	−1.75
propan-2-ol	−2.52	−22.72	−21.21	−1.51
hex-1-ene	−2.89	−26.04	−25.55	−0.49
oct-1-ene	−2.85	−25.64	−24.90	−0.74
dec-1-ene	−2.85	−25.64	−24.66	−0.99
acetone	−2.39	−21.54	−20.89	−0.65
butanone	−2.63	−23.64	−22.27	−1.36
pentan-2-one	−2.66	−23.93	−22.69	−1.24
heptan-2-one	−2.67	−23.99	−22.81	−1.18
acetonitrile	−2.01	−18.06	−17.24	−0.82
propionitrile	−2.32	−20.85	−19.61	−1.24
butyronitrile	−2.47	−22.25	−20.83	−1.43
pentadecanenitrile	−2.75	−24.71	−22.40	−2.30
methyl acetate	−2.47	−22.23	−21.24	−0.99
ethyl acetate	−2.60	−23.41	−22.31	−1.10
butyl acetate	−2.67	−23.99	−22.98	−1.02
hexyl acetate	−2.74	−24.64	−23.32	−1.31
ethyl butyrate	−2.70	−24.30	−23.33	−0.97
benzene	−2.87	−25.87	−24.60	−1.27
toluene	−2.92	−26.27	−24.80	−1.47
p-xylene	−2.89	−26.04	−24.68	−1.36
benzyl alcohol	−2.35	−21.14	−18.24	−2.90
nitrobenzene	−2.57	−23.15	−20.14	−3.00
anisole	−2.73	−24.55	−22.31	−2.24
benzonitrile	−2.58	−23.26	−20.79	−2.47
acetophenone	−2.58	−23.23	−20.42	−2.81
chlorobenzene	−2.95	−26.56	−24.47	−2.09
N-methylformamide	−1.96	−17.62	−16.01	−1.61
dimethylformamide	−2.20	−19.78	−17.89	−1.89
dimethylacetamide	−2.34	−21.03	−18.82	−2.21
N-methylpyrrolidone	−2.34	−21.03	−18.41	−2.62
dimethyl sulfoxide	−1.83	−16.46	−13.48	−2.98
acetic acid	−2.23	−20.07	−18.85	−1.22
methylene chloride	−2.80	−25.20	−24.03	−1.17
chloroform	−2.93	−26.38	−25.19	−1.19
carbon tetrachloride	−2.99	−26.89	−25.93	−0.96
1,2-dichloroethane	−2.68	−24.10	−22.12	−1.98
tetrahydrofuran	−2.86	−25.78	−24.75	−1.03
1,4-dioxane	−2.58	−23.19	−21.04	−2.15
triethylamine	−2.93	−26.33	−25.40	−0.94
γ-butyrolactone	−2.02	−18.17	−15.58	−2.59
hexamethylphosphoramide	−2.51	−22.57	−20.40	−2.17
trifluoroethanol	−1.71	−15.41	−14.37	−1.04
hexafluoro-2-propanol	−1.73	−15.61	−14.82	−0.79
perfluorohexane	−1.86	−16.72	−16.55	−0.17
perfluorooctane	−1.87	−16.86	−16.13	−0.73
nitromethane	−1.84	−16.59	−14.98	−1.61
nitropropane	−2.43	−21.90	−20.43	−1.47
carbon disulfide	−3.09	−27.83	−26.01	−1.82
cyclohexanone	−2.67	−24.06	−21.94	−2.12
propylene carbonate	−1.87	−16.79	−14.43	−2.36
pyridine	−2.61	−23.46	−21.36	−2.10
Apolane87	−2.81	−25.29	−22.19	−3.10
water[c]	0.83	7.47	12.759	−5.3

[a] Calculated according to eq 3 from data in ref 13; data for apolane from refs 17 and 18; for water see footnote *c*. [b] Difference between the two previous columns. [c] Gas/water partition coefficient from data collection by Shaw.[19] $\Delta G°_{CH_2}$ vlaues for gas/water partitioning show a large scatter (but no systematic trend). The value of 0.83 (sd 38%) kJ/mol is the average of 67 values calculated for C_4–C_9 homologues of the following compound classes collected in ref 6: *n*-alkanes, *n*-alk-1-ynes, 1-chloroalkanes, 1-bromoalkanes, 1-iodoalkanes, *n*-alkanals, 2-alkanones, *n*-alkyl acetates, *n*-alkylamines, *n*-alkan-1-ols, and *n*-alkylbenzenes.

TABLE 2: Free Energies of Transfer between Air and Various Solvents and Polymers at 100 °C for a Methylene Increment and for *n*-Nonane

solvent	MW	T_g,[a] °C	$\Delta G^\circ_{CH_2gas2}$,[b] kJ/mol (sd <3%)	$9\Delta G^\circ_{CH_2gas2}$, kJ/mol (sd <3%)	$-RT \ln K^c_{nonane\,gas2}$, kJ/mol	Δ,[d] kJ/mol
C$_{28}$H$_{58}$	395		−2.39	−21.51	−18.31	−3.20
C$_{32}$H$_{66}$	451		−2.38	−21.42	−18.19	−3.23
C$_{36}$H$_{74}$	507		−2.37	−21.33	−18.03	−3.30
polypropylene 1		−26	−2.30	−20.70	−16.92	−3.78
polypropylene 2	2000	−26	−2.30	−20.70	−17.12	−3.58
polyethylethylene		−26	−2.24	−20.16	−16.60	−3.56
polypropylene		−4	−2.29	−20.61	−16.65	−3.96
polyisobutylene		−68	−2.27	−20.43	−15.90	−4.53
polyvinylethylene		−30	−2.23	−20.07	−16.56	−3.51

[a] Glass transition temperature. [b] Calculated according to eq 3 from partition data of *n*-pentane to *n*-nonane.[20] [c] Data from ref 20. [d] Difference between the previous two columns.

There is another interesting feature of the data in Table 1 that is noteworthy. The value of $\Delta S^{free\;volume}_{gas2}$ is close to zero for *n*-alkane and *n*-alkene solvents with low carbon numbers. If one extrapolates these data, one finds that it equals zero for a *n*-alkane or *n*-alkene-solvent whose boiling point lies just at the experimental temperature of 25 °C. In other words, at their boiling temperature these solvents have the same free accessible volume in their liquid phase as in their saturated vapor phase.

So far it has not been considered that $\Delta S^{free\;volume}_{gas2}$ may also depend on the type of solute that is considered. This effect would occur if the free volume is distributed such that not all of it would be accessible for a solute of a finite size.[1] As a consequence, one would expect that the available free volume of a solvent would decrease for solutes whose size is above a certain threshold. An analysis of the partitioning of *n*-pentane in the same way as has been done for *n*-nonane did not reveal any change in the available free volume (see Table A in Supporting Information). The fact that there is no systematic trend in the values of $\Delta G^\circ_{CH_212}$ between pentane and nonane also indicates that at least all alkanes smaller than nonane encounter the same free volume in a solvent. It remains unclear though whether there is an upper limit for the solute-size-independence of the "free volume" term of a solvent.

Equations 4 and 5 should facilitate an improved prediction of partition constants for all methods that are based on a calculation of the free energies of interaction between the solvent and the solute. Hence, the best way to validate eqs 4 and 5 would be their practical application. Abraham and co-workers have set up a system of so-called linear solvation free energy relationships that allows the prediction of partition constants, K^c_{i12} of organic solutes in various solvents based on the relevant interaction free energies.[15,16] As one would expect from the results presented here, these equations only yield a satisfying agreement with experimental data if supplemented by a solvent specific free energy contribution in addition to the calculated interaction free energies. In Abraham's LSER equations this supplemental free energy contribution is simply determined by a fit of the experimental data. For many solvents this solvent specific free energy contribution is rather close to zero similar to what one could expect from Figure 2. Table 3 shows Abraham's solvent specific free energy contributions for those solvents where the contribution is substantially different from zero in comparison to $\Delta S^{free\;volume}_{gas2}$ values predicted by eq 5. The observed agreement between both values nicely supports the validity of eqs 4 and 5 and suggests that they are not limited to the alkane solutes that were used for the derivation of eq 5.

Using the thermodynamic cycle, all above results for the partitioning between a gas phase and a liquid solvent can readily

TABLE 3: Comparison between $\Delta S^{free\;volume}_{12}$ Predicted from Eq 5 and the Respective Terms of Abraham's LSER Equations Obtained from a Fit of Experimental Partition Data for a Diverse Set of Organic Solutes in the Respective Solvent

solvent	$2.3c_{LSER}/RT$,[a] kJ/mol	$\Delta S^{free\;volume}_{gas2}$,[b] kJ/mol
DMSO	−3.36	−2.77
ethylene glycol	−5.33	−3.20
methylene iodide	−4.21	−3.44
water	−6.89	−5.26

[a] c_{LSER} is the constant from Abraham's LSER equations for the prediction of log K^c_{i12} in the various solvents at 25 °C.[16,21] The error of c_{LSER} is not reported in the references. [b] Calculated from eq 5.

be transformed into the partitioning between two solvents 1 and 2. In analogy to eq 4 we have

$$\Delta G^\circ_{i\,12} = -RT \ln K^c_{i\,12} + \Delta S^{free\;volume}_{12} \qquad (6)$$

On average the free energy contribution that arises from $\Delta S^{free\;volume}_{12}$ must of course be smaller for solvent/solvent partitioning than for gas/solvent partitioning. Equation 5 that corrects for the "free volume effect" in liquid phases through the surface tension of the solvent becomes eq 7 for the partitioning between two solvents 1 and 2:

$$\Delta S^{free\;volume}_{12} = 85.8 \;(J\,m\,mol^{-1}\,mN^{-1}) \times$$
$$(\sigma_1 - \sigma_2)\,(mN\,m^{-1})) \quad (7)$$

Table B (Supporting Information) contains the data for the partitioning of *n*-nonane between organic solvents, s, and water, w, calculated from the data in Table 1 assuming zero mutual solubility of the organic solvents with water. The only new aspect that arises from these data is the possibility of directly applying eq 2 and other equations that suggest a correction term for solvent/solvent partitioning based on the molar volumes of the solvents. In Figure 4 the interaction free energy of *n*-nonane calculated from the methylene increments is plotted versus the results of eqs 1, 2, 6, and 8. The latter equation has been suggested by Honig et al.:[3]

$$\Delta G^\circ_{i\,sw} = -RT \ln K^c_{i12} - RT\,V_i(1/V_2 - 1/V_1) \qquad (8)$$

Figure 4 demonstrates that $\Delta G^\circ_{nonae\,sw}$ values from both equations that include the molar volumes of the solvents (eqs 2 and 8) deviate considerably from the values calculated as $9 \times \Delta G^\circ_{CH_2sw}$. The results from eq 1 reveal a better agreement and the results from combined eqd 6 and 7 that contain the "free volume effect" agree extremely well with $9 \times \Delta G^\circ_{CH_2sw}$.

Free Energy of Transfer of a Solute

J. Phys. Chem. B, Vol. 107, No. 50, 2003 **14029**

TABLE 4: Relative Infinite Dilution Activity Coefficients, γ, of *n*-Pentane at 25 °C in Two Solvents in Which a Methylene Group Exhibits the Same Interaction Free Energy[a]

solv1/solv2	$\Delta G^{\circ}_{CH_2gas\ solv1}/\Delta G^{\circ}_{CH_2gas\ solv2}$	$\gamma^{x}_{pentane\ in\ solv1}/\gamma^{x}_{pentane\ in\ solv2}$	$\gamma^{c}_{pentane\ in\ solv1}/\gamma^{c}_{pentane\ in\ solv2}$
CH$_2$Cl$_2$/Apolane87	0.996	11	0.47
benzene/squalane	1.01	3.6	0.61

[a] Activity coefficients are either based on a mole fraction scale, γ^{x}, or a molar concentration scale, γ^{c}. Calculations are based on data from refs 13, 17, and 18.
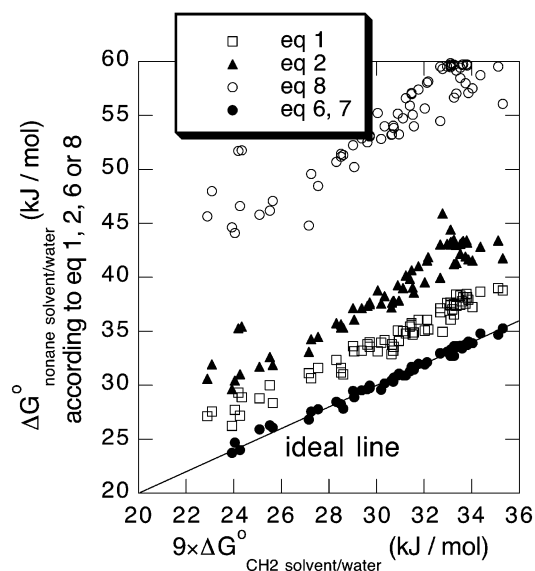
Figure 4. Comparison of the free energy of transfer of *n*-nonane between water and 68 organic solvents calculated as $9 \times \Delta G^{\circ}_{CH_2sw}$ and estimated with eqs 1, 2, and 8 and 6 and 7.

Finally, two interesting consequences arise from the above discussion:

Figure 4 (eq 2) has shown that partition constants based on a mole fraction scale do not give a good picture of the thermodynamic state of a molecule. Therefore, Raoult's law convention, which defines the ideal/nonideal behavior of a solute in a solvent on the basis of a mole fraction scale, may imply results that deviate considerably from the actual thermodynamic situation; i.e., a solute may have a similar free energy of interaction in two solvents although its activity coefficients are quite different and vice versa. In contrast, the activity coefficient of a compound in a solvent based on a molar concentration scale would be much more consistent (see examples in Table 4).

The results in Figure 1 and Table 4 demonstrate that the molecular volume of a condensed phase, be it a solvent or a polymer, appears to have no impact on the partitioning of a solute. Hence, the Flory–Huggins treatment does not seem appropriate. Instead, a correction term that accounts for the free volume in a condensed phase needs to be entered in eq 1. In the data examined here, this correction was smaller than and of opposite sign to the correction terms on the basis of the Flory–Huggins theory. For solvents this correction term can be estimated from the surface tension, as has been done in eq 5 and 7.

The results of this study should help to improve our thermodynamic understanding of partitioning. They are impor-

tant for the prediction of equilibrium partitioning from the respective free energies of interaction as well as for a consistent thermodynamic interpretation of equilibrium partition constants.

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(12) Obviously, this approach assumes that the endstanding methyl groups contribute about the same free energy to the partition process as the methylene groups. This seems reasonable since the cavity energy (which depends on the size of the solute) and the London-dispersive interaction (which depends on the polarizability of the solute) are influenced only little and in opposite direction by an additional H atom.

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