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Thermodynamics of Liquid-Liquid Partition and Hydration of Aliphatic Ethers

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Interaction between water and ethers in dilute aqueous solutions was investigated by water-heptane partition of twelve linear aliphatic ethers containing various number of carbon atoms (from 2 to 8), and one branched homologue. Standard free energy (Gibbs) and enthalpy of partition were calculated from partition constants and from their temperature dependence. The differences in the free energy and entropy result from different hydrophobic hydration of these amphiphilic solutes in the aqueous phase. The position of the oxygen atom in an ether molecule affects the hydrophilic-hydrophobic properties of the molecule. The methylene groups in the α and β positions in respect to the oxygen atom are distinctly less hydrophobic than those more distant, therefore, different are their hydrophobic contributions into standard thermodynamic functions of hydration. The commonly accepted group contribution models, which assume equal contributions from the same fragments irrespectively of their position (additivity principle), should be revised.

Key words: amphiphiles, aqueous solution, aliphatic ethers, homologous series, hydration, thermodynamics, group contribution models, additivity principle

Hydration of amphiphilic molecules was studied by numerous authors [1–5]. Such molecules, containing hydrophilic functions (*e.g.* oxygen atoms) and hydrophobic groups (hydrocarbon chains), interact with water in two ways: by hydrogen bonding through the hydrophilic functions [1], and by promoting liquid water structure around the hydrocarbon chains (hydrophobic hydration) [2]. The latter includes the formation of a cavity in the solvent, able to accommodate the guest molecule. Aliphatic ethers may be regarded as the simplest amphiphilic molecules. In order to study the interactions between the ethers and water, we investigated liquid-liquid partition of these compounds in the water/heptane system as a function of the ethers structure. Assuming that the heptane solutions of ethers do not significantly deviate from ideal [6], we were able to attribute the experimental differences in the standard thermodynamic functions of partition to the differences in hydration of ether molecules in the aqueous phase. Following a group-contribution model [4], we could distinguish in each ether molecule a number of hydrophobic groups (methyl, methylene, *etc.*) and the hydrophilic function (ethereal oxygen), and expect the additivity of their contributions to the thermodynamic functions related to partition, hydration, *etc.*, in particular the equal contributions from the same groups. However, this “additivity principle” commonly used *e.g.* to evaluate quantitative relationships between structure and activity of amphiphilic molecules and/or the solubility of amphiphiles in water [7], is an oversimplification. Already Cabani concluded that the hydrophobic properties of methylene groups depend on their position in the molecule [5]. It has also been recognised that the contributions from polar groups "are not additive in most instances" [8].

The aim of this work was to explain how the number of CH_2 groups and the position of the oxygen atom in an ether molecule affect the balance between its hydrophobic and hydrophilic properties, and to conclude whether the contributions from these fragments in the standard thermodynamic functions of hydration of the molecule are additive or not.

EXPERIMENTAL

Materials: The ethers: diethyl, dipropyl, dibutyl, methylbutyl, ethylbutyl and diisopropyl were commercial products (POCh, Fluka, Aldrich, > 99%). The other ethers: ethylmethyl, methylpropyl, methylpentyl, hexylmethyl, ethylpropyl and butylpropyl have been synthesized [9,10] at the Institute of Organic Chemistry in Warsaw, and dimethyl ether [11] – in this laboratory. The purity of the ethers was checked by GLC, and in the case of dimethyl and ethylmethyl ethers additionally by GLC-MS. Heptane was the commercial product (Merck, > 99%). Twice distilled water was used throughout.

Measurements: Gas Chromatograph Unicam Series 610 was used, with FID and packed columns. The solid support was Gas Chrom Q (100–80 mesh) and the stationary phases were Squalane, Carbowax 20 M, SE-30 and Silar 10C. Their different polarities allowed us to find proper conditions for determination of all the species studied.

Procedure: Partition of the ethers between heptane and water was studied by using two methods, as described in [12]. The first one based on shaking water and heptane with small amount of ether in stoppered glass test tubes at a constant temperature for a few minutes, which was enough to reach the equilibrium. The phases were then separated and the equilibrium concentrations of the ethers in both solvents were determined. Partition constants (P), defined as the ratio of molar concentrations of a given ether in the infinitely dilute organic and aqueous phases at equilibrium, were determined by measuring (GLC) the ether concentrations in heptane (initial and at equilibrium) and/or in the gas phase in equilibrium with the organic and aqueous ether solutions, separately. The P values obtained were independent of the ether concentration in the whole range studied (10^{-2}÷10^{-1} mol dm^{-3}). The volume ratio of organic and aqueous phases was kept 1:1 for ethers with $P < 10$, while in the case of higher P values it was equal to 10:1. The second method (used in the case of the highest P values) based on measuring the concentration of ethers in the saturated gas phase over the organic and aqueous solutions [12]. Both methods were always used when possible. The P values determined by both methods did not differ from each other within the experimental error of about 3%. The temperature dependence of P for the ethers (except for dibutyl ether) was studied in the range of 5÷40°C. In the case of dibutyl ether its concentration in the gas phase over the heptane solution at lower temperatures was too small to be reliably determined. All experimental details are given in [13].

RESULTS AND DISCUSSION

The results of the experiments are given in Table 1 and Figures 1 and 2. Standard thermodynamic functions of partition: Gibbs free energy (ΔG_p^o), enthalpy (ΔH_p^o) and entropy (ΔS_p^o) were calculated using the formulae:

$$\Delta G_p^o = -RT\ln P \qquad (1)$$

$$\Delta H_p^o = -R\frac{\partial \ln P}{\partial T^{-1}} = -RT\ln P \qquad (2)$$

$$\Delta S_p^o = \frac{\Delta H_p^o - \Delta G_p^o}{T} = -RT\ln P \qquad (3)$$

respectively, where T denotes temperature, K. The least square method was used to calculate the error of P. The uncertainties reported in Table 1 were calculated by error propagation of the P values. Table 1 presents the dependence of P (at 25°C) on the number, *n*, of carbon atoms in the molecule. It is known that in the homologous series of aliphatic hydrocarbons and their derivatives, the hydrophobic hydration increases the log P values by about 0.65 per each CH_2 group [3]. The same relationship follows from our results for the ethers studied. Figure 1 shows the temperature dependence of log P for the monoethers. Figure 2 shows that ΔG_p^o calculated using (1) is a linear function of *n* with the slope of -3.7 ± 0.5 kJ mol^{-1}, similar to that observed in the homologous series of various organic compounds. Using (2) and (3) we have calculated the ΔH_p^o and ΔS_p^o values.

Table 1. Partition constants (based on molarities) and standard thermodynamic functions of partition of the ethers in the water/heptane system at 25°C. The uncertainties are equal to two standard deviations, 2σ.

Ether	n	P	ΔG_p^o kJ mol^{-1}	ΔH_p^o kJ mol^{-1}	ΔS_p^o J mol^{-1} K^{-1}
CH_3OCH_3	2	0.9 ± 0.2	0.4 ± 0.4	20.8 ± 1.9	68.4 ± 6.4
$CH_3OC_2H_5$	3	2.9 ± 0.4	–3.0 ± 0.4	11.9 ± 1.0	50.0 ± 3.4
$CH_3OC_3H_7$	4	7.8 ± 0.8	–5.1 ± 0.2	10.4 ± 0.4	52.0 ± 1.5
$CH_3OC_4H_9$	5	40.9 ± 0.6	–9.2 ± 0.3	10.3 ± 0.8	65.4 ± 2.9
$CH_3OC_5H_{11}$	6	182 ± 7	–12.9 ± 0.3	10.2 ± 0.7	77.5 ± 2.6
$CH_3OC_6H_{13}$	7	776 ± 14	–16.5 ± 0.2	10.9 ± 0.6	91.9 ± 2.1
$C_2H_5OC_2H_5$	4	6.7 ± 0.5	–4.7 ± 0.3	9.9 ± 0.6	49.0 ± 2.2
$C_2H_5OC_3H_7$	5	29.6 ± 0.7	–8.4 ± 0.2	9.9 ± 0.5	61.4 ± 1.8
$C_2H_5OC_4H_9$	6	161 ± 5	–12.6 ± 0.3	10.6 ± 0.7	77.8 ± 2.6
$C_3H_7OC_3H_7$	6	117 ± 6	–11.8 ± 0.4	9.7 ± 0.9	72.0 ± 3.3
$C_3H_7OC_4H_9$	7	407 ± 12	–14.9 ± 0.3	10.1 ± 0.7	83.8 ± 2.6
$C_4H_9OC_4H_9$	8	1420 ± 31	–18.0 ± 0.4	–	–
$(CH_3)_2CHOCH(CH_3)_2$	6	37.7 ± 0.8	–9.0 ± 0.7	10.0 ± 0.9	63.7 ± 3.3

We have shown that the enthalpy of partition substantially decreases at the beginning of the series, *i.e.* from dimethyl ether through ethylmethyl ether, and then (from $n = 4$) it remains fairly constant, equal to 10.0 ± 0.5 kJ mol^{-1}, therefore, the differences between ΔG_p^o along the series ($n \geq 4$) are of entropic nature (Fig. 2). Because the enthalpies of solution in water of homomorphic aliphatic hydrocarbons are close to zero [14], the positive ΔH_p^o values observed for the ethers reflect the hydrogen bond breaking between water and ether molecules, which accompanies the transfer of the ethers from water to heptane. The constancy of the ΔH_p^o values along the series seems to indicate that the claimed effect of slight strengthening of the hydrogen bond with increasing aliphatic chain [1] is rather small.

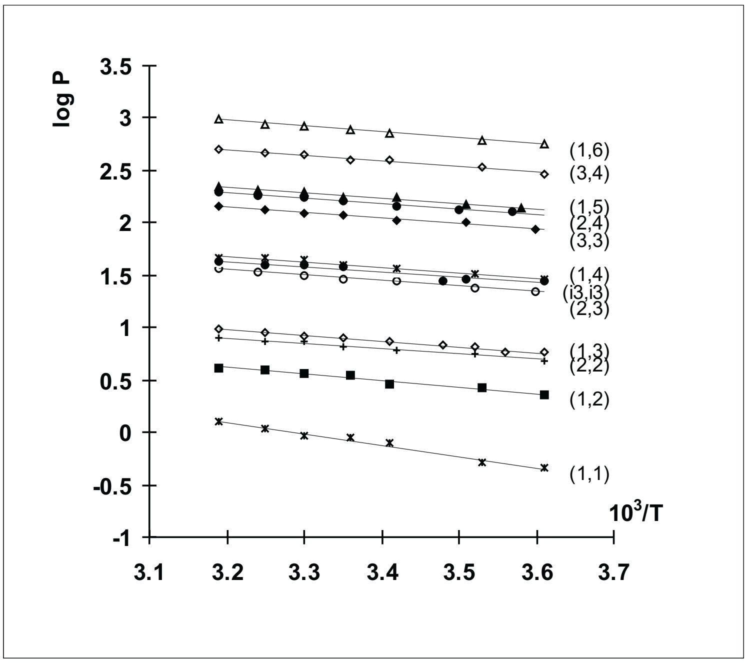

Figure 1. Temperature dependence of partition constant of aliphatic ethers in the water/heptane system. The numbers in parenthesis denote the number of carbon atoms in each linear or branched (i3, i3) alkyl group.

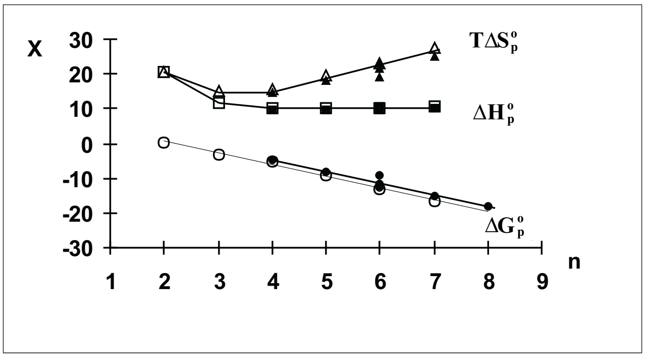

Figure 2. The dependence of standard thermodynamic functions of partition (x, kJ mol^{-1}) of aliphatic ethers on the number of carbon atoms (*n*) in the molecule in the water/heptane system at 298 K; $X = \Delta G_p^o$ (circles), $X = \Delta H_p^o$ (squares) and $X = T\Delta S_p^o$ (triangles). The large open symbols denote the methylalkyl ethers and the small closed ones – the more symmetrical isomers.

The results of our experiments indicate that we cannot describe physicochemical properties of amphiphilic molecules without taking into account their structure. On the basis of significant differences between the log P values observed for the isomers ($n = 4 \div 7$), and of the differences in the structure of these molecules, we can divide the linear ethers studied, R-O-R, into two groups: these with both aliphatic chains larger than methyl (*i.e.* R = C_2H_5 to C_4H_9) and those with at least one methyl group bonded to the oxygen atom (CH_3-O-R). The latter ethers appear to be more hydrophobic (by about 0.5 to 1.8 kJ mol^{-1}) than their more symmetrical isomers (Fig. 2). This observation can be explained in terms of the effect of the ethereal oxygen which breaks the ordered structure of liquid water around its neighbouring CH_2 groups and reduces in this way the hydrophobic hydration of the CH_2 groups not only in the α [5] but also in the β position. The lack of influence of the ethereal oxygen atom on hydrophobicity of the CH_2 groups can be observed practically beginning from the γ position.

The less hydrophobic hydration of the methylene group in the β position in respect to oxygen atom (what has been neglected in earlier papers [5,15]) explains why di-n-propyl ether is much more hydrophobic than diisopropyl ether (Table 1). Comparing this difference with those in the solubility in water of their homomorphs: heptane and 2,4-dimethylpentane [16] and of other isomeric aliphatic hydrocarbons, we can see that the hydrocarbons with branched chains are more soluble (more hydrophilic) than their linear isomers, but the differences are much smaller than that observed for the isomeric ethers studied. In our opinion, the much more hydrophilic character of diisopropyl ether is the result not only of the branched alkyl group, but also of the presence of a greater number of methylene (methyl) groups in the β position in the branched chains (four) than that in the linear molecule (two). Because of less hydrophobic properties of these groups (β position), the whole diisopropyl ether molecule is less hydrophobic. Taking into account the less hydrophobic properties of methylene groups in the β position, we assume the calculated [15] energies of hydrogen bond formed by different ethers to be incorrect; they should be equal [17].

Relatively high ΔH_p^o and ΔS_p^o values for dimethyl ether (and rather high values for ethylmethyl ether) can be interpreted in terms of formation of a quasi-clathrate structure in the aqueous solution. The small dimethyl ether molecules can locate in the bigger cavities formed in the tetrahedral structure of liquid water. Assuming that the cavity size makes possible free rotation of the small guest molecule, we can expect that the molecule can be orientated in such a way that it forms a hydrogen bond with one of the host water molecules without disordering the liquid water structure (*i.e.* without disturbing hydrophobic hydration). Therefore, there is no (or little) contribution from the structure breaking (positive ΔH_p^o and ΔS^o) in the negative enthalpy and entropy of hydrogen bonding, which results in high positive ΔH_p^o and ΔS_p^o values. Beginning from the ethers with $n = 4$, formation of hydrogen bond is accompanied by significant effects of the water structure breaking.

CONCLUSION

The commonly accepted group contribution models, which describe hydrophilic–hydrophobic properties of amphiphilic molecules in aqueous solution in terms of additive contributions from small fragments, are oversimplified. It results from our data that in evaluating hydration of amphiphilic molecules, one cannot neglect the effect of their structure. The methylene groups in the α and β positions in respect to the oxygen atom are less hydrophobic than those more distant. Therefore, different are the hydrophobic contributions into standard thermodynamic functions of hydration from methylene groups in different positions in the molecule. They become equal to one another beginning from the methylene groups in the γ position only. In view of that, we can expect that the ethereal oxygen atom has the same hydrophilic properties, independently of the length and of possible branching of the alkyl groups, what we have also shown in NMR experiments [17].

Basing on the demonstrated influence of the ethereal oxygen atom on the hydrophobicity of neighbouring (α and β) methylene groups, we propose a new division of the ether molecules into the hydrophilic and hydrophobic fragments, the contributions of which to standard thermodynamic functions of hydration would be additive. The hydrophilic fragment would be either the whole group H_4C_2-O-C_2H_4, or – when that is not possible – the H_2C-O-CH_2 group at least. Only the remaining parts of the hydrocarbon chains may be considered as fully hydrophobic fragments.

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