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Solute–Water Interactions in the Organic Phase of a Biphasic System. 1. Structural Influence of Organic Solutes on the "Water-Dragging" Effect

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Abstract: The "water-dragging" effect is characterized by the amount of water "dragged" into a water-insoluble organic solvent by a solute partitioning between water and this solvent.[1] In this study, 62 structurally diverse compounds (*ortho*-, *meta*-, and *para*-substituted phenols, carboxylic acids, alcohols, amines, miscellaneous aprotic solutes, and diastereomeric ephedrines) were investigated. The results were analyzed by an equilibrium model and expressed in terms of the macroscopic stoichiometry of hydrates and an equilibrium constant of hydrate formation. The macroscopic stoichiometry of hydrates being close to one (range 0.5–1.5), a normalized equilibrium constant (log K_w') was calculated for a stoichiometry fixed to a value of one. On this basis, the water-dragging effect was shown to be due primarily to the H-bond-donor acidity of solutes and secondarily to their H-bond-acceptor basicity. In addition, intramolecular effects (e.g., internal H-bonds) and solvent accessibility strongly modulate the water-dragging effect.

Introduction

Water has been shown to exert dramatic influences on the kinetic and thermodynamic properties of solutes in solution.[2] Most remarkable in this context is its determinant role on the conformation and, hence, the function of biological macromolecules such as DNA[3] and proteins.[4] Perhaps the highlight of the important role of water in mediating intermolecular interactions in a biological system is the recent report by Quiocho et al.,[5] using X-ray crystallography, showing that ordered water molecules inside proteins control the binding affinity and specificity of monopyranosides to their transporter protein.

The past years have witnessed enormous and continuous efforts to understand solute–water interactions in aqueous solution. These studies, both experimental and theoretical, concentrated mainly on the hydration energy of solutes and on characterizing the geometries of hydrates.[6,7] In this aspect, while the influence of water on the structural properties (e.g., conformation) of solutes has been extensively investigated, the perturbation/structural influence of solutes on the structure of bulk water has been neglected. This is primarily due to a limited knowledge of the structure of liquid water[8] and to the difficulties of experimental methodologies in detecting perturbation to water structure. A few informative studies using infrared spectroscopy have probed the structural perturbation of solutes on bulk water.[9,10] So far, this approach has been used only for detecting the effects of ionic species and hydrophobic moieties of molecules, the influences of neutral polar groups never being reported.

While hydration of solutes in aqueous solution is of critical importance in understanding solute–water interactions, profound insights into the nature of solute–water interactions can also be gained from studies in the gas phase and organic solvents. On the one hand, a recent experiment in the gas phase has been most thought-provoking in terms of the nature of H-bonding involving π electrons as acceptors, demonstrating as it did the existence of a H-bond between a benzene acceptor and a water donor, in which the OH group of a water molecule is some distance away from and pointing to the center of the benzene plane.[11] On the other hand, studies of solute hydration in organic solvents are scattered in the literature,[12-18] no comparisons of hydration capacity among solutes of different functional groups being made. Such studies focus mainly on the characterization of hydrate species, i.e., the stoichiometry of hydrates, while the influence of different polar groups on the hydration capacity of solutes is completely overlooked.

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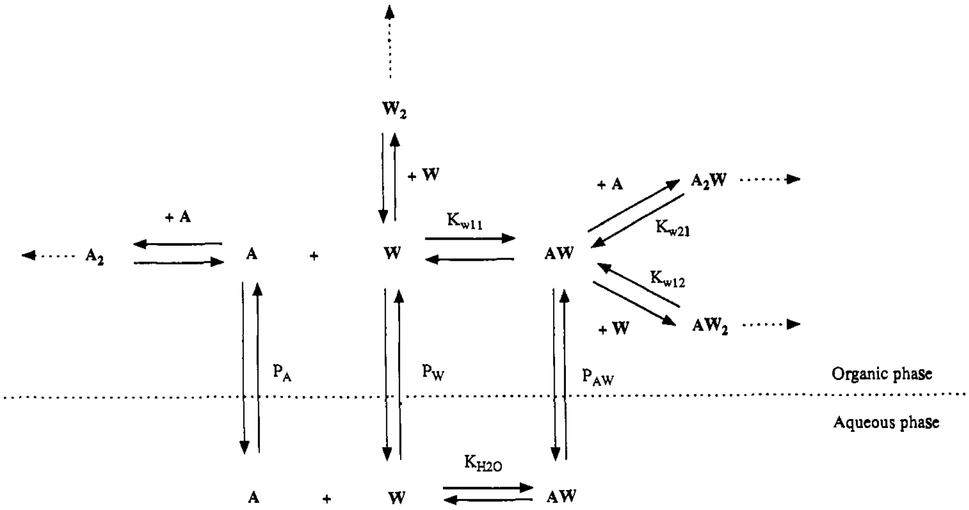

Figure 1. Characterization of the solute–water interactions in a biphasic system. A is a free solute, W a free water molecule, and AW a monomer monohydrate. K_w is the formation constant of hydrates, while P is the partition coefficient of solutes.

Biphasic systems contain water and immiscible organic solvents and are often used to simulate the partitioning of solutes from aqueous to lipophilic media such as lipidic membranes and binding sites of receptors.[19] Here, solute–water interactions both in the aqueous phase and in the organic phase must be considered in order to gain a proper understanding of their nature. In addition, the organic phase often contains significant, even if minute, amounts of water at saturation. Indeed, the partitioning behavior of solutes has been suggested to be influenced by their hydration in both phases.[20] Furthermore, the excess water solubility in relatively nonpolar organic solvents such as carbon tetrachloride or benzene has been shown to be enhanced in the presence of polar solutes.[21-24] A preliminary study by some of us,[1] using Karl Fisher titrimetry to determine the excess water in the organic phase, has indicated that (a) polar solutes upon partitioning can "drag" water molecules into the organic phase and (b) the H-bond-donating capacity of solutes plays a predominant role in this process. In the present study, the "water-dragging" effect is investigated using structurally diverse compounds including phenols with substituents of different electronic and steric properties at *ortho*, *meta*, and *para* positions, carboxylic acids, alcohols, amines, and some miscellaneous aprotic solutes, covering a wide range of polarity and H-bonding capacity. Our first goal in this study is thus to investigate the structural influences of nonionic organic solutes on the excess water in the organic phase of a biphasic system. Di-*n*-butyl ether was chosen as the organic phase because it is a good solvent for most solutes of different lipophilicity and also because of its marginal water content at saturation (0.06 M), a prerequisite for sensitive measurements of excess water solubility in the organic phase.[23] Moreover, a new theoretical treatment taking into account the solute hydrate stoichiometry and quantifying the hydration capacity of solutes in the organic phase has been developed and applied to characterize the macroscopic hydration features of solutes. Such an approach should allow solute–water interactions in a biphasic system to be quantitatively and comparatively evaluated in terms of the physicochemical and structural properties of solutes.

Theoretical Section

A previous study by some of us,[1] determining the average number of water molecules dragged into the organic phase by 1000 molecules of solute (Δf_w), showed that the parameter Δf_w is primarily correlated with the H-bond-donating capacity of solutes ($\log K_A{}^H$):

$$\log K_A{}^H = 3.09(\pm 0.36) \log \Delta f_w - 6.02(\pm 0.85) \qquad (1)$$

$$n = 20,\ r^2 = 0.95,\ s = 0.26$$

where n is the number of compounds used in the correlation, r^2 is the squared correlation constant, and s is the standard deviation of the regression (95% confidence limits in parentheses). This simple treatment, while being useful to extract the molecular determinants of solutes controlling the excess water in the organic phase, may overlook the complex solute–water interactions in a biphasic system. Indeed, solute–water interactions in a biphasic system can be schematized as shown in Figure 1. At least three species can partition between the two phases, namely free solutes (A), free water molecules (W), and solute monohydrates (AW).

In addition to the self-association of solutes and water molecules in the form of a dimer (A_2 and W_2), a trimer, or a tetramer, a higher order of complexation between solutes and water molecules yielding hydrates such as A_2W and AW_2 may also occur. Depending upon the nature of the solutes and the organic phase, the equilibria may be shifted to either solute self-association or solute–water complexation. For example, the monomer monohydrate (AW) and the trimer monohydrate (A_3W) of phenol have been shown to be the major hydrated species present in the organic phase of a CCl_4/water system, when solute concentration is less than 0.15 M.[14] At higher concentrations of phenol, more than one water molecule is attached to the aggregates of phenol molecules. The stoichiometry of each of the solute hydrates can thus be different, allowing no comparisons among solutes in terms of their hydration capacity in the organic phase. Furthermore, to determine all the equilibrium constants as shown in Figure 1 is not straightforward and necessitates a variety of experimental techniques.

From a macroscopic viewpoint, a simplified model can be sketched to represent solute–water interactions in a biphasic system using the partition coefficients of solutes P_A and water molecules P_W and the macroscopic (observed) complexation constant K_w as shown in Figure 2. In fact, the macroscopic complexation constant can be calculated according to the equilibrium:

$$xA + W \rightleftarrows A_xW \qquad (2)$$

where x may be < 1, $= 1$, > 1, an integer, or not and represents the number of solutes needed to form a hydrate with a molecule

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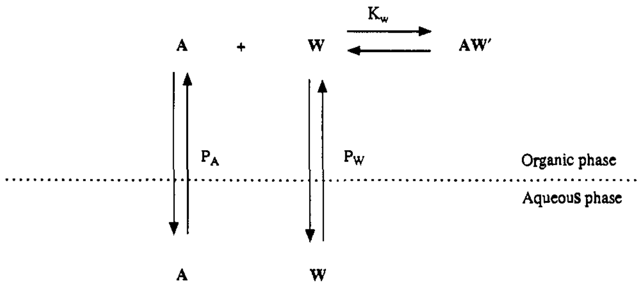

Figure 2. A simplified model of the solute–water interactions in a biphasic system. AW′ is the macroscopic hydrate species, which might be a resultant of the hydrates AW, A_2W, and AW_2, etc.

of water. The K_w can thus be obtained:

$$K_w = \frac{[A_xW]}{[A]^x[W]} \quad (3)$$

or

$$\log[A_xW] = x\log[A] + \log[W] + \log K_w \quad (4)$$

where $[A_xW]$ is the concentration of solute hydrates. [A] and [W] are the concentrations of free solutes and free water molecules, respectively (here, free means that they are not H-bonded to each other but may be H-bonded to the organic solvent). Admittedly, the interactions of solutes and water with the organic phase are neglected in Figures 1 and 2 in order to simplify the treatment. The effects of the organic phase will be discussed separately in a following article. Nevertheless, in contrast to highly structured organic phases such as the amphiprotic 1-octanol, the free water molecules in the aprotic solvent di-*n*-butyl ether are not tightly bound to it and do not form an extensive H-bonding network with the organic solvent molecules, as manifested by the low water content of water-saturated di-*n*-butyl ether (0.06 M).[23] When the free solute molecules interact with the free water molecules, the equilibrium of water partitioning between the two phases would cause the free water concentration to remain constant. [W] can then be obtained experimentally from the water solubility in the absence of solutes (i.e., the blank) and is determined separately for each compound, $[A_xW]$ being equal to the measured excess water in the presence of solutes. [A] can be obtained from the knowledge of the partition coefficient of solutes (P_A) and the concentration of hydrated solutes. Equation 4 thus implies that a plot of log(excess water) against log(free solute concentrations in the organic phase) can yield x and $\log K_w$ from the slope and the intercept of linear regression. Since different solutes may not have the same stoichiometry, their $\log K_w$ values thus have different units and cannot be used to compare their hydration capacity. However, it will be clear later in the Results and Discussion section that the calculated stoichiometries fall in the range between 0.5 and 1.5, meaning that macroscopically monosolute monohydrates are the predominant hydrate species. This allows a comparison of the complexation constants among solutes by forcing a slope of 1 (i.e., a stoichiometry of unity) in the linear regression of $\log[A_xW]$ against $\log[A]$ to yield a normalized complexation constant, designated as $\log K_w'$. The $\log K_w'$ values can then be regarded as a measure of the hydration capacity of the solutes in the organic phase and used in further analyses of structure–hydration relationships.

Table I. Macroscopic Complexation Constants of Solute–Water Interactions in the Organic Phase of a Di-*n*-Butyl Ether/Water System

no.	compound	x[a]	$\log K_w$[b]	$\log K_w'$[c]
1	phenol	1.2	1.3	1.1
2	2-nitrophenol	1.1	–0.3	–0.4
3	3-nitrophenol	1.2	1.6	1.4
4	4-nitrophenol	1.1	1.8	1.7
5	2-hydroxybenzaldehyde	*d*	*d*	ca. –0.2
6	3-hydroxybenzaldehyde	1.2	1.2	1.0
7	4-hydroxybenzaldehyde	*d*	*d*	ca. 1.1
8	2-methoxyphenol	0.8	0.0	0.2
9	3-methoxyphenol	1.1	0.9	0.8
10	4-methoxyphenol	1.2	0.9	0.7
11	2-cyanophenol	1.4	1.5	1.1
12	3-cyanophenol	1.0	1.2	1.2
13	4-cyanophenol	1.2	1.4	1.2
14	2-methylphenol	1.2	1.0	0.8
15	3-methylphenol	0.8	0.7	0.9
16	4-methylphenol	0.8	0.7	0.8
17	2-fluorophenol	1.5	0.9	0.5
18	3-fluorophenol	1.2	1.0	0.9
19	4-fluorophenol	1.1	0.9	0.9
20	2-chlorophenol	1.4	1.0	0.7
21	3-chlorophenol	1.1	1.0	0.9
22	4-chlorophenol	1.1	1.0	0.9
23	2-bromophenol	1.0	0.7	0.7
24	3-bromophenol	1.1	1.0	0.9
25	4-bromophenol	0.9	0.8	0.9
26	2-iodophenol	1.2	0.9	0.8
27	3-iodophenol	1.0	0.8	0.8
28	4-iodophenol	1.4	1.1	0.8
29	1-naphthol	0.8	0.8	0.9
30	2-naphthol	0.9	0.9	1.0
31	thiophenol	1.0	1.5	1.5
32	benzoic acid	0.8	0.7	0.9
33	phenylacetic acid	1.0	0.8	0.8
34	chloroacetic acid	0.8	0.8	1.0
35	benzyl alcohol	1.0	0.4	0.4
36	2-phenylethanol	0.9	0.4	0.5
37	3-phenylpropanol	1.4	0.7	0.4
38	4-phenylbutanol	1.2	0.6	0.5
39	5-phenylpentanol	1.0	0.6	0.6
40	aniline	1.0	0.2	0.2
41	*N*-methylaniline	0.6	–0.2	0.1
42	*N*,*N*-dimethylaniline	*d*	*d*	ca. –0.5
43	2-nitroaniline	0.9	0.3	0.4
44	2-phenylethylamine	*d*	*d*	ca. 0.2
45	amphetamine	*d*	*d*	ca. 0.3
46	pyridine	*d*	*d*	ca. 0.1
47	benzaldehyde	0.6	–0.1	0.2
48	acetophenone	0.8	0.1	0.3
49	anisole	0.7	–0.3	–0.1
50	thioanisole	*e*	*e*	*e*
51	nitrobenzene	0.6	–0.2	–0.1
52	methyl phenyl sulfoxide	1.3	0.5	0.1
53	catechol	1.0	0.9	1.0
54	resorcinol	1.2	1.4	1.1
55	2-hydroxybenzoic acid	0.9	0.8	0.8
56	2-hydroxybenzyl alcohol	0.6	0.5	1.0

[a] Stoichiometry of solute hydrates as calculated according to eq 4, the standard errors being within 0.1 [b] Solute–water complexation constants in the organic phase as calculated according to eq 4, the standard errors being within 0.1. [c] Normalized solute–water complexation constants in the organic phase as calculated according to eq 4 and by forcing $x = 1$. [d] The linear regression based on eq 4 does not yield a good correlation constant ($r^2 < 0.8$), and hence, neither x nor $\log K_w$ can be generated. [e] The excess water in the organic phase is negligible.

Results and Discussion

(A) Structural Influence of Solutes on Their Hydration in the Organic Phase. For the 56 compounds investigated here, the calculated stoichiometries x and the complexation constants $\log K_w$ of solute–water interactions in the organic phase of a di-*n*-butyl ether/water system using eq 4 are compiled in Table I. For a number of representative compounds, the amounts of excess water in the organic phase in the presence of different concentrations of solutes are demonstrated in Table II. Indeed, as described in the Theoretical Section, this was rendered possible because a linear relationship was observed, at least in the concentration range studied (<1 M), between the logarithm of excess water ($\log[A_xW]$) and that of equilibrium free solute concentrations in the organic phase ($\log[A]$), thus demonstrating a constant macroscopic stoichiometry of the hydrates. This is the case for phenols (Figure 3) and the other chemical classes of

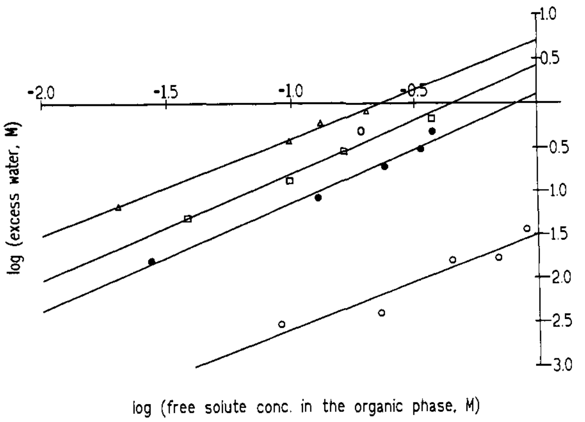

Figure 3. Linear relationship between log(excess water in the organic phase, M) and log(free solute concentration in the organic phase, M) for phenol (filled circle), 2-nitrophenol (empty circle), 3-nitrophenol (empty square), and 4-nitrophenol (empty triangle).

Table II. The Amounts of Excess Water in the Organic Phase in the Presence of Different Concentrations of Solutes

no.	compound	solute conc in the organic phase (M)	excess water in the organic phase (M)
1	phenol	0.043	0.016
		0.211	0.084
		0.431	0.192
		0.643	0.308
		0.857	0.482
2	2-nitrophenol	0.092	0.003
		0.231	0.004
		0.459	0.016
		0.700	0.017
		0.935	0.036
3	3-nitrophenol	0.087	0.049
		0.230	0.132
		0.454	0.291
		0.683	0.491
		1.041	0.670
4	4-nitrophenol	0.087	0.067
		0.091	0.079
		0.232	0.210
		0.472	0.374
		0.730	0.599
		1.018	0.816
35	benzyl alcohol	0.081	0.011
		0.223	0.031
		0.225	0.032
		0.425	0.059
		0.428	0.059
38	4-phenylbutanol	0.095	0.016
		0.237	0.039
		0.238	0.041
		0.477	0.098
		0.479	0.100
40	aniline	0.080	0.010
		0.197	0.020
		0.404	0.042
		0.630	0.065
		0.830	0.102
43	2-nitroaniline	0.045	0.007
		0.092	0.015
		0.137	0.018
		0.188	0.029
		0.238	0.036
51	nitrobenzene	0.095	0.009
		0.229	0.012
		0.439	0.018
		0.659	0.027
		0.926	0.034

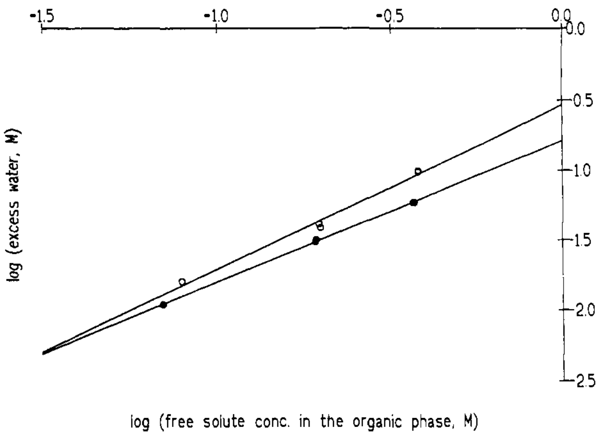

Figure 4. Linear relationship between log(excess water in the organic phase, M) and log(free solute concentration in the organic phase, M) for benzyl alcohol (filled circle) and 4-phenylbutanol (empty circle).

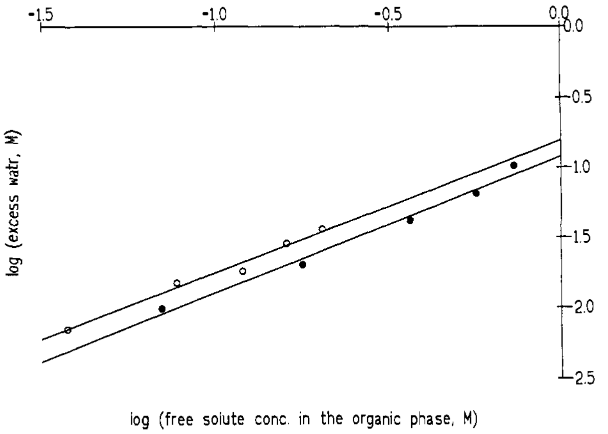

Figure 5. Linear relationship between log(excess water in the organic phase, M) and log(free solute concentration in the organic phase, M) for aniline (filled circle) and 2-nitroaniline (empty circle).

solutes investigated, e.g., phenyl alcohols (Figure 4) and anilines (Figure 5). Noteworthy in Table I is that of the 49 solutes for which x could be calculated, most have a hydrate stoichiometry near unity (38 in the range 0.7–1.2) and none are outside the range 0.5–1.5. This justifies the calculations of the normalized complexation constant log K_w', which is obtained by assuming a hydrate stoichiometry of unity for all compounds, allowing a comparison of water-complexation capacity in the organic phase among the solutes. In so doing, it should be noted that a microscopic complexation phenomenon such as a higher order of association as depicted in Figure 1 is beyond the description of our calculation method. An observed unitary stoichiometry could imply that the hydrate complexes are in reality a combination of types AW, A_2W, and AW_2 but are seen macroscopically as AW. Aside from the negligible hydration capacity of thioanisole (**50**), the log K_w' values thus calculated are in the range –0.50 (*N,N*-dimethylaniline, **42**) to 1.7 (4-nitrophenyl, **4**), the latter corresponding to a free energy change ($\Delta G°$) of ca. –3.4 kcal/mol. Such modest interaction energies would imply a competition between the solute–water interactions in the organic phase and the solvation of solutes by the organic solvent, since solvation energies are in the order of –10 kcal/mol.[25]

Because solute–water interactions in the organic phase have been shown to be mainly polar in nature,[1,12] a number of structural descriptors such as the H-bonding capacity of solutes and their dipolarity/polarizability were used to unravel the structural properties underlying this type of interaction. The parameters listed in Table III including the H-bond-donating capacity of solutes (log $K_A{}^H$ from Abraham et al.[26] and α from Kamlet et

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Table III. Physicochemical and Structural Descriptors of Solutes

no.	compound	log K_A^H [a]	log K_B^H [b]	α[c]	β[d]	π^* [e]	ΔG_H[f]	σ[g]
1	phenol	1.665	−0.080	0.61	0.33	0.72	−6.63	0
2	2-nitrophenol	−1.1		0.00	0.35	1.11		1.40
3	3-nitrophenol	2.541		0.82	0.40	0.90	−9.65	0.78
4	4-nitrophenol	2.719		0.92	0.40	1.17	−10.67	1.24
5	2-hydroxybenzaldehyde							0.75
6	3-hydroxybenzaldehyde						−9.48	0.35
7	4-hydroxybenzaldehyde						−10.43	1.03
8	2-methoxyphenol	0.109						0.00
9	3-methoxyphenol	1.641						−0.12
10	4-methoxyphenol	1.557						−0.11
11	2-cyanophenol	2.323					−9.63	1.32
12	3-cyanophenol	2.480						0.69
13	4-cyanophenol	2.547		0.88	0.37		−10.19	0.88
14	2-methylphenol	1.304		0.56	0.34	0.69		−0.13
15	3-methylphenol	1.550	0.013	0.58	0.34	0.68		−0.07
16	4-methylphenol	1.538	0.013	0.58	0.34	0.68		−0.17
17	2-fluorophenol							0.54
18	3-fluorophenol	2.035		0.69	0.23	0.77		0.37
19	4-fluorophenol	1.818	−0.126	0.67	0.23	0.72		0.07
20	2-chlorophenol	1.914						0.68
21	3-chlorophenol	2.112		0.69	0.23	0.77		0.37
22	4-chlorophenol	2.007		0.67	0.23	0.72		0.30
23	2-bromophenol							0.70
24	3-bromophenol	2.139		0.69	0.23	0.84		0.39
25	4-bromophenol	2.023		0.67	0.30	0.79	−7.11	0.23
26	2-iodophenol							0.63
27	3-iodophenol							0.36
28	4-iodophenol	2.048						0.23
29	1-naphthol	1.720		0.61	0.33	0.82		
30	2-naphthol	1.739		0.61	0.33	0.82		
31	thiophenol	−0.756					−2.54	
32	benzoic acid	1.626		0.59	0.40	0.74		
33	phenylacetic acid	1.500						
34	chloroacetic acid	2.690			0.41			
35	benzyl alcohol	0.715	0.847	0.39	0.52	0.99		
36	2-phenylethanol		0.986	0.33	0.55	0.99		
37	3-phenylpropanol			0.33	0.55	0.97		
38	4-phenylbutanol			0.33	0.55	0.95		
39	5-phenylpentanol			0.33	0.55	0.95		
40	aniline	0.122	0.651	0.26	0.50	0.73		
41	*N*-methylaniline	−0.296		0.17	0.47	0.82		
42	*N*,*N*-dimethylaniline		0.527	0.00	0.43	0.90		
43	2-nitroaniline	0.604		0.22	0.46	0.99		
44	2-phenylethylamine							
45	amphetamine							
46	pyridine		1.797	0.00	0.42	0.87	−4.71	
47	benzaldehyde	−1.1	0.847	0.00	0.44	0.92	−4.03	
48	acetophenone		1.268	0.00	0.49	0.90	−4.59	
49	anisole	−1.1	0.105	0.00	0.32	0.73	−1.03	
50	thioanisole						−2.72	
51	nitrobenzene	−1.1	0.482	0.00	0.30	1.01	−4.10	
52	methyl phenyl sulfoxide			0.00				
53	catechol							
54	resorcinol							
55	2-hydroxybenzoic acid							
56	2-hydroxybenzyl alcohol							

[a] A measure of solute H-bond-donating capacity according to Abraham et al.[26] [b] A measure of solute H-bond-accepting capacity according to Abraham et al.[28] [c] A measure of solute H-bond-donating capacity according to Kamlet et al.[27] [d] A measure of solute H-bond-accepting capacity according to Kamlet et al.[27] [e] A measure of solute dipolarity/polarizability according to Kamlet et al.[27] [f] Hydration free energy change in kcal/mol taken from ref 6. [g] Hammett substituent electronic constant taken from ref 29.

al.[27]), the H-bond-accepting capacity of solutes (log K_B^H from Abraham et al.[28] and β from Kamlet et al.[27]), and the dipolarity/polarizability (π^* from Kamlet et al.[27]) were employed in quantitative structure-complexation analyses. It was found that log K_w' correlates globally with the H-bond-donating capacity (log K_A^H and α, eqs 5 and 6) but not with the H-bond-accepting capacity (log K_B^H and β) nor with π^*(eq not shown):

$$\log K_w' = 0.37(\pm 0.05) \log K_A^H + 0.23(\pm 0.09) \tag{5}$$

$$n = 36, r^2 = 0.87, s = 0.16$$

$$\log K_w' = 1.60(\pm 0.21)\alpha - 0.08(\pm 0.11) \tag{6}$$

$$n = 32, r^2 = 0.89, s = 0.17$$

Note that thiophenol is an outlier in these correlations and is not included in eqs 5 and 6. The unexpected and remarkable hydration behavior of thiophenol in the organic phase should not be regarded as unreasonable: the log K_A^H or α is derived from intermolecular H-bonding interactions using other organic compounds rather than water as a reference H-bond acceptor, and the hydration of thiophenol might involve other subtle intermolecular interactions with water molecules. Equations 5 and 6 thus suggest that a high H-bond-donor acidity of solutes can enhance their complexation capacity with water in a hydrophobic environment. These

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(27) Kamlet, M. J.; Doherty, R. M.; Abraham, M. H.; Marcus, Y.; Taft, R. W. *J. Phys. Chem.* **1988**, *92*, 5244 and references therein.

equations, however, do not exclude the role of H-bond acceptors because, first, all solutes with H-bond donors are equally H-bond acceptors and, second, most of the aprotic solutes (**44**–**52**) indeed have non-negligible complexation constants. This conclusion is further supported by a better correlation between log K_w' and the H-bond-donor acidity when excluding some strong H-bond-acceptor solutes in the regressions. Thus, removing benzaldehyde (**47**) from eq 5 yields:

$$\log K_w' = 0.40(\pm 0.05) \log K_A^H + 0.18(\pm 0.08) \qquad (7)$$

$$n = 35,\ r^2 = 0.89,\ s = 0.14$$

Removing benzaldehyde (**47**), acetophenone (**48**), and *N,N*-dimethylaniline (**42**) from eq 6 yields:

$$\log K_w' = 1.65(\pm 0.19)\alpha - 0.17(\pm 0.10) \qquad (8)$$

$$n = 29,\ r^2 = 0.92,\ s = 0.14$$

A good correlation was also found between the complexation constant log K_w' and the hydration energy in aqueous solution[6] (ΔG_h, see Table III):

$$\log K_w' = -0.18(\pm 0.05)\Delta G_h - 0.46(\pm 0.35) \qquad (9)$$

$$n = 15,\ r^2 = 0.84,\ s = 0.18$$

Here again, the thiophenol with a relatively modest ΔG_h value (−2.5 kcal/mol) appeared as an outlier and was excluded in the correlation. Equation 9 suggests that the solutes well-hydrated in the aqueous phase are also those that drag more water into the organic solvent.

(B) Hydration Capacity in the Organic Phase of Different Chemical Classes of Solutes. In the following discussion, different chemical classes of solutes will be discussed separately since each of them may have a different pattern of interactions with water in the organic phase.

Phenols. The self-association and the hydration of phenol in CCl_4, benzene, 1,1,2,2-tetrachloroethane, and 1,2-dichloroethane were studied by Johnson et al.[14] It was concluded that AW and A_3W are the major hydrated species in CCl_4, while cyclic aggregates A_2W and AW_2 are predominant in the other three solvents. The study also suggested the important role of the amphiprotic nature of phenol forming in hydrates. Interestingly, our results (Table I) suggest a macroscopic hydrate of the type AW for most of the phenols studied. However, this may well be a resultant of, e.g., the three different hydrates AW, A_2W, and AW_2. While a global correlation between log K_w' and the H-bond-donor acidity exists for the phenols (results not shown), the lower log K_w' values of all *m*- and *p*-halophenols in comparison to that of phenol, despite their relatively higher log K_A^H values, are not straightforward enough to explain and suggest that other factors may be involved. Indeed, a modest correlation between log K_w and H-bond-donating capacity is obtained if only *meta*- and *para*-substituted phenols are considered in the regression:

$$\log K_w' = 0.57(\pm 0.23) \log K_A^H - 0.17(\pm 0.49) \qquad (10)$$

$$n = 15,\ r^2 = 0.68,\ s = 0.16$$

$$\log K_w' = 2.25(\pm 0.90)\alpha - 0.56(\pm 0.65) \qquad (11)$$

$$n = 11,\ r^2 = 0.78,\ s = 0.14$$

It is interesting to note that including the H-bond-accepting capacity parameter β in the regression improves the correlation significantly:

$$\log K_w' = 0.46(\pm 0.23) \log K_A^H + 1.82(\pm 1.18)\beta - 0.45(\pm 0.47) \qquad (12)$$

$$n = 11,\ r^2 = 0.88,\ s = 0.11$$

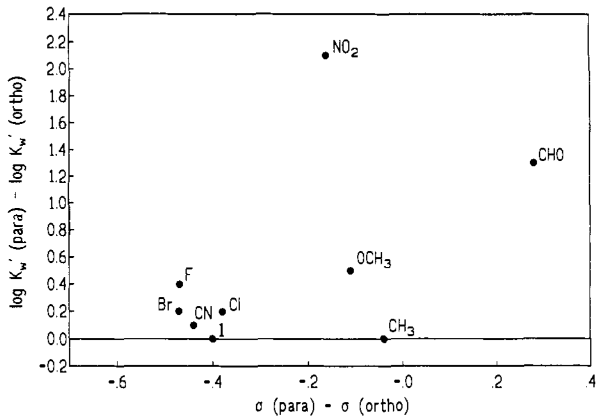

Figure 6. Plot of the differences in log K_w' values between the *para*- and *ortho*-substituted phenols against their differences in the Hammet substituent electronic constant σ to quantify the influence of the ortho effect on hydration capacity. The horizontal line passing through the origin is considered as a standard line, while the distance from the standard line was taken as a measure of the ortho effect.

$$\log K_w' = 1.71(\pm 0.86)\alpha + 1.43(\pm 1.28)\beta - 0.60(\pm 0.52) \qquad (13)$$

$$n = 11,\ r^2 = 0.88,\ s = 0.11$$

Equations 12 and 13 suggest that the H-bond-accepting capacity of phenols is of critical importance, although to a lesser extent than their H-bond-donating capacity, for the hydration capacity of solutes. Hence, the reduced complexation constants of *m*- and *p*-halophenols must be due, at least in part, to a decrease of their H-bond-accepting capacity as compared to that of phenol (see Table III).

The influences of *ortho* substituents on the complexation constants are most challenging. A H-bond-accepting group such as NO_2, CHO, OCH_3, or F *ortho* to the phenolic OH should and does considerably reduce the log K_w' values, while the effects of methyl, bromo, and iodo substituents are much less dramatic. To reasonably quantify the "*ortho* effects", a plot of the differences in the log K_w' values between the *para*- and *ortho*-substituted phenols against their differences in the Hammett substituent electronic constant σ[29] (Table III) is shown in Figure 6. The distance from the horizontal line passing through the origin was calculated and used as a standard line, while the deviations from this standard line, designated as Ω, were taken as a measure of the ortho effects. The sequence of Ω values of the substituents is approximated as follows:

$$NO_2\ (2.1) > CHO\ (1.3) > OCH_3\ (0.5) > F\ (0.4) >$$
$$Cl\ (0.3) > Br\ (0.2) > CN\ (0.1) > CH_3\ (0.0) \sim I\ (0.0)$$

The results suggest that electronic rather than steric factors are expressed in the ortho effect of monosubstituted phenols, the bulky iodo substituent having a negligible Ω value. The relatively small Ω value of the cyano substituent seems to suggest the nonexistence of an internal H-bond between –OH and –CN, while the H-bond-acceptor site of the cyano group is uncertain.[30] The interesting ortho effect of 2-fluorophenol (**17**) among the halophenols can be explained by its higher electronegativity, and hence, electrostatic and H-bonding interactions are implied between the phenolic OH and the F atom. In contrast, the absence of an ortho effect in 2-methylphenol must be due to the lack of H-bonding and/or the existence of repulsive electrostatic interactions between –OH and –CH_3. On the whole, the *syn* conformer

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[28] Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 521.

[29] Exner, O. In *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: London, 1972; p 1.

[30] Laurence, C.; Berthelot, M.; Raczynska, E.; Le Questel, J.-Y.; Duguay, G.; Hudhomme, P. *J. Chem. Res. Synop.* **1990**, 250.

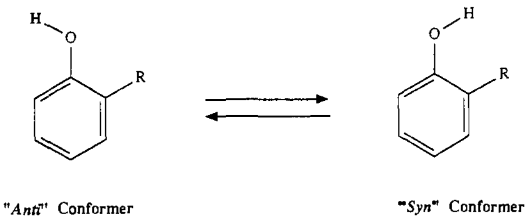

Figure 7. Conformational equilibria of *ortho*-substituted phenols.

Table IV. Influence of Stereochemical Factors on the Hydration Capacity of Ephedrines in the Organic Phase of a Di-*n*-butyl Ether/Water System

no.	compound	log K_w' [a]
57	(1*R*,2*S*)-norephedrine	0.1
58	(1*R*,2*R*)-norpseudoephedrine	0.3
59	(1*R*,2*S*)-ephedrine	0.5
60	(1*S*,2*S*)-pseudoephedrine	0.0
61	(1*R*,2*S*)-*N*-methylephedrine	0.3
62	(1*S*,2*S*)-*N*-methylephedrine	0.0

[a] Normalized solute–water complexation constants in the organic phase as calculated according to eq 4 and by forcing $x = 1$.

is probably the populated one among *ortho*-substituted phenols of higher Ω values, while the *anti* conformer might be more populated among those of lower Ω values (Figure 7). It appears that the ortho effect of monosubstituted phenols which decreases their hydration capacity is mainly due to electronic effects, while intramolecular steric effects may shift the equilibrium to the *anti* conformer and hence increase their hydration capacity. Nevertheless, unfavorable intermolecular steric effects must be invoked to explain the lower log K_w' values of 1-naphthol (**29**) as compared to those of 2-naphthol (**30**), the phenolic group of the former being geometrically less accessible than that of the latter.

Carboxylic Acids and Alcohols. Benzoic acid has been shown to be highly self-associated and hydrated in benzene, the predominant species being A_2, AW, AW_2, and A_2W.[13] Our results with benzoic acid (**32**), phenylacetic acid (**33**), and chloroacetic acid (**34**) demonstrate an observed stoichiometry of near unity in terms of their hydrates. The relatively lower log K_w' value of benzoic acid (0.9) as compared to that of phenol (1.1), the two having a comparable H-bond-donating and H-bond-accepting capacity (Table III), can be due to a dimerization of benzoic acid in the organic phase. The higher log K_w' value of chloroacetic acid among the carboxylic acids can be attributed to the electron-withdrawing inductive effect of the chloro substituent which increases the H-bond-donor acidity of the COOH group and hence its hydration capacity.

The log K_w' values of phenyl alcohols (**34**–**38**), except 3-phenylpropyl alcohol (**36**), increase with increasing number of methylene groups. Since increasing the length of the alkyl chain reduces and enhances the H-bond-donating and H-bond-accepting capacity, respectively, of the OH group,[27] the importance of the H-bond-accepting capacity seems to overwhelm that of the H-bond-donating capacity in terms of the hydration capacity of alcohols.

Amines. Amines are generally good H-bond acceptors but poor H-bond donors. Indeed, all amines examined (**40**–**46**) have relatively modest log K_w' values. The *N*-methylation of anilines leads to a decrease of their H-bond-donating as well as H-bond-accepting capacity (Table III) and hence a decrease of their log K_w' values. The higher log K_w' value of 2-nitroaniline (**43**) compared to that of aniline (**40**) can be explained by the effect of the electron-withdrawing NO_2 group, which increases the H-bond-donating capacity of 2-nitroaniline. The log K_w' values of 2-phenylethylamine (**44**) and amphetamine (i.e., 1-methyl-2-phenylethylamine, **45**) are comparable to that of aniline despite the NH_2 group being aliphatic and aromatic, respectively.

Other Miscellaneous Aprotic Solutes. The association of aprotic solutes with water in CCl_4 was characterized by infrared spectroscopy,[17] indicating that monomer monohydrates (AW) are predominant at low solute concentrations, while dimer monohydrates (A_2W) are detectable at high solute concentrations. Thus, the H-bond basicity must be of critical importance in their hydration capacity. Indeed, the higher H-bond-accepting capacity of the carbonyl group of benzaldehyde (**47**) and acetophenone (**48**) as compared to those of the ether function of anisole (**49**), the thio function of thioanisole (**50**), and the nitro function of nitrobenzene (**51**) explains their higher log K_w' values.

Biamphiprotic Solutes. The nonadditivity in hydration capacity of compounds **53**–**56** with two H-bond donors is most interesting. While an internal H-bond of catechol between the neighboring OH groups is possible, its non-H-bonded proton can function as a H-bond donor, explaining the comparable log K_w' values of catechol (1.0) and phenol (1.1). The log K_w' value of resorcinol (i.e., 3-hydroxyphenyl, **54**, log K_w' = 1.1) suggests that the two phenolic OH groups do not have the same hydration capacity. Specifically, once one OH group is hydrated, the hydration capacity of the other is almost nil. In this case, unfavorable entropic changes for the hydration of the second OH should account for the nonadditivity. The somewhat lower log K_w' values of 2-hydroxybenzoic acid (**55**, 0.8) and 2-hydroxybenzyl alcohol (**56**, 1.0) as compared to that of phenol are probaby due to an internal H-bonding between the amphiprotic groups.

(C) Influence of Stereochemical Factors on the Hydration Capacity of Ephedrins. Diastereomers possess different physicochemical properties such as lipophilicity[31] due to the different spatial relations between their atoms. Indeed, the hydration capacity of the *erythro* (**57**, **59**, and **61**) and *threo* (**58**, **60**, and **62**) isomers of ephedrins displays significant, albeit small, differences in their log K_w' values (Table IV). While *erythro* ephedrine (**59**) and *N*-methylephedrine (**61**) show a higher log K_w' value than their isomers, the *erythro* norephedrine (**57**) has a lower log K_w' value (0.1) compared to its *threo* isomer (0.3). Due to rotational hindrance of the ethyl chain, all the *erythro* isomers were shown to exist predominantly as *gauche* rotamers, while the *threo* isomers exist predominantly as *anti* rotamers in solution.[32] However, none of these conformational features can satisfactorily explain the differences in hydration capacity of all three diastereomeric pairs. Here again, only the log K_w' value of (1*R*,2*S*)-ephedrine (0.5) is almost additive in comparison with those of benzyl alcohol (**35**, log K_w' = 0.4) and 2-phenylethylamine (**44**, log K_w' = 0.2). For the other ephedrines studied, their log K_w' values are lower than expected, implying intramolecular interactions unfavorable for hydration.

Conclusion

Two conclusions emerge from this study. First, the water-dragging effect can be expressed in terms of a macroscopic equilibrium constant (log K_w') based on an apparent 1:1 solute–water stoichiometry. Second, log K_w' thus obtained is a function mainly of the H-bond-donor acidity of solutes but also of their H-bond-acceptor basicity. As a result, log K_w' is exquisitely sensitive to structural properties of solutes, e.g., internal H-bond, positional isomerism, and diastereomerism. However, it is not possible, at this stage, to offer a molecular interpretation before the effects of the organic phase are assessed. Our following studies will address this point.

Experimental Section

Materials. All compounds used were of the best available purity and obtained from either Fluka (Buchs, Switzerland) or Aldrich (Steinheim, Germany). Di-*n*-butyl ether was of quality "purissimum" (Fluka) or analytical grade (Aldrich) and used without further purification. The reagents for Karl Fischer titration were purchased from commercial

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sources (Riedel-de Haën AG, Germany). To have only the neutral form of solutes present in solution, phosphate buffers (0.2 M), HCl/NaCl solutions (0.2 M), and glycine/NaOH buffer (0.2 M) covering a pH range from 1 to 12 were used. A preliminary experiment showed that the buffer type did not influence the water content in the organic solvent.

Determination of Excess Water in the Organic Phase Using Karl Fisher Titrimetry. All experiments were performed at ambient temperature (21 ± 1 °C). Aqueous and organic phases were mutually saturated by continuous stirring for more than 6 h and then separated by centrifugation for 5 min at 6000 rpm. The solutes were dissolved at five concentrations (range 0.1–1 M) in 5 mL of the organic phase, and the solution was gently shaken with an equal volume of the aqueous phase for 1 h. After centrifugation for 5 min at 4000 rpm, the two phases were separated and the concentrations of the solutes measured in each phase using a Perkin-Elmer Model 557 UV spectrophotometer.

Both ^{1}H-NMR spectroscopy and Karl Fisher titrimetry were previously employed to quantitate the excess water in the presence of solutes in the organic phase of a biphasic system.[33] The Karl Fisher method proved to be more efficient, more sensitive, and more precise and was thus used in this study. Aliquots of the organic phase form both the blank and the samples were titrated using a Metrohm 652 KF coulometer (Herisau, Switzerland), yielding amounts of water in micrograms. The excess water was then calculated in molarity after subtracting the amounts of the water in the blank.

Multivariate Statistical Analyses. The multivariate regression analysis was performed using the QSAR program[34] run on a VAX 9000 computer.

Acknowledgment. B.T., P.A.C., and N.E.T. are indebted to the Swiss National Science Foundation for support.

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