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Salting-Out Effect in Aqueous NaCl Solutions: Trends with Size and Polarity of Solute Molecules

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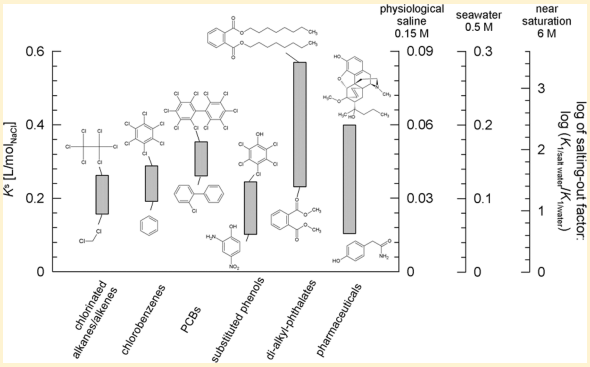
Supporting Information

ABSTRACT: Salting-out in aqueous NaCl solutions is relevant for the environmental behavior of organic contaminants. In this study, Setschenow (or salting-out) coefficients (K^s [M^{-1}]) for 43 diverse neutral compounds in NaCl solutions were measured using a shared headspace passive dosing method and a negligible depletion solid phase microextraction technique. The results were used to calibrate and evaluate estimation models for K^s. The molar volume of the solute correlated only moderately with K^s (R^2 = 0.49, SD = 0.052). The polyparameter linear free energy relationship (pp-LFER) model that uses five compound descriptors resulted in a more accurate fit to our data (R^2 = 0.83, SD = 0.031). The pp-LFER analysis revealed that Na^+ and Cl^- in aqueous solutions increase the cavity formation energy cost and the polar interaction energies toward neutral organic solutes. Accordingly, the salting-out effect increases with the size and decreases with the polarity of the solute molecule. COSMO-RS, a quantum mechanics-based fully predictive model, generally overpredicted the experimental K^s, but the predicted values were moderately correlated with the experimental values (R^2 = 0.66, SD = 0.042). Literature data (n = 93) were predicted by the calibrated pp-LFER and COSMO-RS models with root mean squared errors of 0.047 and 0.050, respectively. This study offers prediction models to estimate K^s, allowing implementation of the salting-out effect in contaminant fate models, linkage of various partition coefficients (such as air−water, sediment−water, and extraction phase−water partition coefficients) measured for fresh water and seawater, and estimation of enhancement of extraction efficiency in analytical procedures.



INTRODUCTION

Partitioning of organic chemicals between water and other phases such as air, organic matter, polymers, and biological tissues is influenced by the salt content in the aqueous phase. Structure-making salts such as NaCl and other salts consisting of small ions enhance the structuring of aqueous phases and thus the cohesive energy in water due to their strong interactions with water dipoles. The increase of structure has various effects on properties of the aqueous phase such as an increase in viscosity.[1] Another example of the effects of the salt content is a shift of the partition equilibrium of neutral organic solutes toward nonaqueous phases. This effect is referred to as the salting-out effect and can be relevant for environmental contaminant dynamics, for example, for the partitioning of contaminants from/to seawater or for the formation of secondary aerosols.[2] Moreover, the salting-out effect is deliberately used to maximize the extraction efficiency in analytical procedures by adding salt to water samples.[3]

A quantitative description of the salting-out effect on neutral organic solutes is provided by the Setschenow relationship:[4]

$$\log(K_{1/\text{salt water}}/K_{1/\text{water}}) = K^s[\text{salt}] \quad (1)$$

Here, $K_{1/\text{salt water}}$ is the partition coefficient of a given neutral solute between phase 1 and a salt water phase, $K_{1/\text{water}}$ is the partition coefficient of the solute between phase 1 and pure water, [salt] is the salt concentration in mol/L, and K^s is the Setschenow coefficient (M^{-1}), an empirical number that depends on the type of organic solute as well as on the type of salt involved. The existing database for Setschenow coefficients is, however, very limited even for the most relevant salt, NaCl.[4] Moreover, in some cases there is a substantial deviation between values from different sources reported for the same solute.[5] Furthermore, previous work[4] noted that the K^s values for aldehydes reported in ref 6 are exceptionally high compared to other classes of compounds and warrant further experimental validation. The relatively small number of tabulated Setschenow coefficients and high uncertainties in the data stress the need for establishing a reliable data basis which can then be used to derive a reliable predictive model.

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In early work, Xie et al.[5] reviewed reported K^s values and found a moderate correlation between K^s for NaCl and the molar volume of the solute. This relationship can be reasonably explained by an increased cohesive energy of the aqueous solution due to the dissolved NaCl. An increase in the cohesive energy of the aqueous solution leads to an increase in the cavity formation energy cost when a solute molecule is transferred to the aqueous solution. The increase in the cavity formation energy cost causes lower solute partitioning into the aqueous solution, thus a salting-out effect. The salting-out effect is large for solutes with a large molecular size, as they are more sensitive to the increase in cohesive energy. Despite the correlation between K^s and the molar volume, Xie et al.[5] suggested a constant salting-out factor of 1.36 to use in fate modeling to take into account differences in partition coefficients between fresh and seawater of any compound (i.e., K^s = 0.27; [NaCl] = 0.5 M), seemingly because the observed data scatter was large and the correlation with the molar volume was not strong. Later, Schwarzenbach et al.[4] reviewed the literature data and mentioned that both size and polarity of the solute may have contributions to K^s. Jochmann et al.[7] measured K^s for aliphatic alcohols in NaCl solutions and found similar K^s values across alcohols with different alkyl chain lengths. Recently, Jonker and Muijs[8] determined K^s for a series of polycyclic aromatic hydrocarbons (PAHs) in artificial seawater, which exhibited no size-dependence of K^s. Apparently, a general agreement is lacking in the literature with regard to the factor(s) that determine the extent of salting-out effects. In particular, influences of polar interactions on the salting-out effects have not been discussed in detail.

A contributing reason for the missing consensus is that the experimental variability is relatively large for K^s. Experiments are often conducted up to the salt concentration in seawater (i.e., [NaCl] = ca. 0.5 M). For a solute with a K^s value of say 0.3, the difference between partition coefficients in fresh water and seawater is only 0.15 log units, or 40%. In this case, even highly reproducible measurements with an error range of ±5% in both fresh and salt waters could result in a determined K^s value of 0.21−0.39. The error range could be even larger for compounds with low aqueous solubilities, such as high molecular weight PAHs, due to the experimental difficulty associated with low aqueous phase concentrations. Thus, to investigate the factors that influence the value of K^s and establish predictive models, it is important to assemble highly accurate data of K^s.

The goal of this work is 3-fold: (i) to measure a data set of K^s that is diverse and consistent; (ii) to test experimentally some of the reported K^s values that appear exceptionally high; and (iii) to develop predictive models for estimating K^s for NaCl.

MATERIAL AND METHODS

K^s values were determined for a series of alkanals, 2-alkanones, 1-nitroalkanes, and *n*-alkylbenzenes, with increasing alkyl chain length, to assess the influence of molecular size on K^s in a systematic manner. These compounds were measured with a shared headspace method as detailed below. In addition, four highly fluorinated alcohols (2,2,2-trifluoroethanol, 1,1,1,3,3,3-hexafluoro-2-propanol, and C4:2 and C6:2 fluorotelomer alcohols (FTOHs)) were measured using the shared headspace method, because highly fluorinated compounds fall in a different chemical domain compared to hydrocarbon-based compounds and often show characteristic partitioning behavior.[9] Moreover, K^s values of 22 additional compounds with various polar functional groups were determined using a negligible-depletion solid phase microextraction (SPME) technique. Finally, to cross-validate the two methods used, 2-alkanones were also measured with the negligible-depletion SPME method.

Materials. Chemicals used as organic solutes were purchased from different providers. Ethyl acetate (SupraSolv), isohexane (SupraSolv; a mixture of isomers), methanol (LiChrosolv), *n*-hexadecane (synthetic grade), and NaCl (analytical grade) were obtained from Merck. Olive oil was obtained from a local grocery store. Water was treated with a Milli-Q Gradient A10 system (Millipore, Billerica, MA). Poly(dimethylsiloxane) (PDMS; 30 μm coating thickness, 13.2 μL/m coating volume) and polyacrylate (PA; 36 μm coating thickness, 16.5 μL/m coating volume) microfibers were produced by Polymicro Technologies (Phoenix, AZ).

Shared Headspace Method. This method uses a spiked nonvolatile organic solvent as a donor phase of the solutes to aqueous phases (i.e., water and salt water) (Figure 1). The

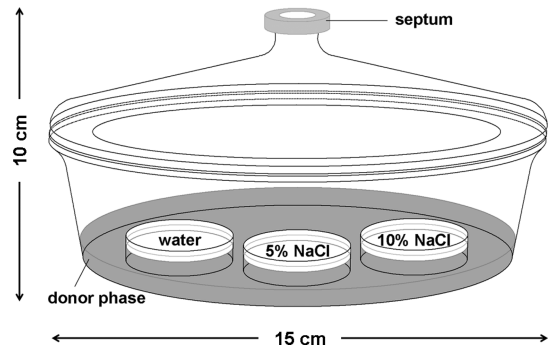

Figure 1. Experimental setup for the shared headspace method.

method principle is based on the passive dosing approach proposed by Jahnke and Mayer.[10] The transfer of chemicals from the organic solvent to the aqueous phases takes place via the headspace which is shared by all individual liquid phases in a closed container. After equilibration, all aqueous solutions are at equilibrium with a single common phase (i.e., headspace), thus the relative concentrations of the test solute in the aqueous solutions reflect the degree of salting-out. In this method, any loss (e.g., volatilization from the container, adsorption to glass wall or the septum, degradation) of solutes does not influence experimental results, because the donor phase serves as a continuous source of solutes and maintains the headspace concentration at a constant level. This robustness is an advantage compared to methods that rely on the mass balance, in particular for relatively volatile compounds (e.g., alkylbenzenes) and for compounds that tend to adsorb to interfaces (e.g., highly fluorinated compounds).

Olive oil served as the donor phase solvent except for FTOHs, for which hexadecane was used. Hexadecane has an advantage over olive oil for H-bond donor compounds such as FTOHs in that hexadecane does not have an H-bond acceptor property and thus results in higher solute concentrations in the aqueous phases. Solutes were dissolved directly in olive oil. FTOHs were dissolved in hexadecane via a small amount of acetone. Concentrations in the donor phase were adjusted so that equilibrium aqueous phase concentrations would be measurable. The donor phase (180 mL) spiked with several test chemicals was poured in a glass container. Pure water, and

5% (w/v) and 10% (w/v) NaCl solutions (25 mL each) were prepared in glass Petri dishes and put in the container. We prepared only three NaCl concentrations, because the linear relationship between the log of the salting-out factor and the NaCl concentration (i.e., eq 1) has been shown to hold for a range of compounds.[4] What is important for reducing errors in K^s is to have a large difference between the highest and lowest NaCl concentrations (here: 1.7 and 0 M, respectively). The container was closed with a glass lid. Equilibration was performed in a temperature-controlled room (25 ± 2 °C). No additional effort was made to control the temperature because the temperature dependence of K^s for NaCl has been shown to be negligibly small.[11,12] The aqueous phases were stirred using magnetic stirrers to accelerate equilibration. An equilibration time of 24 h or longer was given; preliminary experiments showed that this was long enough for equilibrium to be reached. The concentrations in the donor phase were not expected to be depleted because of sufficiently high donor phase-water and donor phase-air partition coefficients for the measured compounds (as estimated from polyparameter linear free energy relationships (pp-LFERs)). Note that, even if any depletion occurred, this would not influence the results at equilibrium. For all compounds but the fluorinated ones, the aqueous solutions (500 μL × 4 replicates) were sampled through a septum using a gastight syringe. These samples were liquid−liquid extracted with 500 μL isohexane, and the extracts were subjected to GC/MS analysis. This extraction with isohexane is an exhaustive extraction (estimated to have 98% or higher efficiency, based on the pp-LFER model for the hexane-water partition coefficients),[13] and thus this extraction is not influenced by the salt concentration. For analysis of FTOHs, 1000 μL aqueous solutions were sampled and extracted with 250 μL isohexane to enrich the compounds. The two small fluorinated alcohols (2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoro-2-propanol) are hydrophilic and difficult to extract; thus, 10 μL aqueous solutions were sampled and mixed in 1000 μL acetone and analyzed with a GC/MS. Using GC peak areas, K^s was determined through eq 2,

$$\log A_{[\mathrm{NaCl}]} = -K^s[\mathrm{NaCl}] + \log A_0 \quad (2)$$

where $A_{[\mathrm{NaCl}]}$ is the measured peak area for a given NaCl concentration, and K^s and log A_0 serve as the slope and intercept, respectively, of the linear regression. If an injection internal standard was added to extracts, the peak area of the solute was normalized to that of the internal standard before regression analysis with eq 2 (chemicals used as injection internal standards are given in SI-1 in the Supporting Information). The regression analysis was typically performed using 12 measured peak areas (four replicates × three NaCl concentrations). The standard error of the slope was calculated to indicate the error in determined K^s.

Negligible-Depletion SPME Method. In this SPME method, pure water and salt solutions of the same volume receive a constant amount of the test solute and a short piece of SPME fiber. If the SPME fiber absorbs only a negligible amount of the solute, aqueous concentrations of the solute remain constant across the solutions with varying NaCl concentrations. In this nondepletion case, the relative fiber phase concentrations directly reflect the extent of salting-out effects.

Pure water and 5% (w/v) and 10% (w/v) NaCl solutions of the same volume were pipetted into vials and received a piece of SPME fiber and a 10 μL methanol mixture of 3−5 solutes. The solution volumes and the fiber types and lengths were chosen to avoid significant solute depletion in the solutions (see Supporting Information SI-2 for the solution volumes and the fibers used). Depletion was estimated to be <1% in pure water, based on measured and estimated PDMS-water[14] and PA-water[15] partition coefficients. Depletion in the NaCl solutions should be larger due to the salting-out effect, but it was estimated to be <4% later using the experimentally determined K_s. A depletion of 4% in 10% NaCl causes only an error of 0.01 in K_s. Four replicates were made for each salt concentration. The vials were shaken horizontally for 24 h at room temperature (25 ± 2 °C). An equilibration time of 24 h is sufficient for our test compounds, as tested previously.[15] Fibers were retrieved, wiped with dry tissue, and extracted with 500 μL ethyl acetate. The extracts were analyzed with GC/MS. In nondepletion cases, K^s can be determined from linear regression analysis,

$$\log A_{[\mathrm{NaCl}]} = K^s[\mathrm{NaCl}] + \log A_0 \quad (3)$$

as analogues to the shared headspace method described above. In contrast to eq 2, K^s in eq 3 does not carry a negative sign. This difference comes from the following reason: in the headspace method, the concentration in the nonaqueous phase (i.e., headspace) is constant and the aqueous phase concentration is measured, whereas in the SPME method, the aqueous phase concentration is constant and the nonaqueous phase (i.e., fiber) is measured.

The aqueous solutions were unbuffered, and the pH values in NaCl solutions were 5.5−6.2, as measured with a pH electrode (LE438, Mettler Toledo). The pH value of pure water could not be measured because of low ionic strength, but it is expected to be slightly acidic because of CO_2 from air. The acidic solutes measured here have the pK_a values >9.21, and the basic solutes have the pK_b < 4.35 (see Supporting Information SI-3 for a list of pK_a). Thus, all solutes were predominantly in their neutral form in the solutions.

GC/MS Analysis. The instrument used was (i) A 7890A GC with a 5975C MS detector equipped with a split/splitless injector (Agilent Technologies, Wilmington, DE) and an autosampler (CombiPAL, CTC Analysis, Zwingen, Switzerland), or (ii) a 7890A GC with a 5975C MS triple-axis detector (Agilent Technologies) equipped with a programmable temperature vaporizing injector (Cooled Injection System 4, Gerstel, Mülheim a.d. Ruhr, Germany) and an autosampler (MultiPurpose Sampler, Gerstel). Helium was used as the carrier gas. The columns used were HP-5 ms-UI (30 m × 0.25 mm i.d., 0.25 μm film thickness, Agilent Technologies), DB-1701 (30 m × 0.25 mm i.d., 0.25 μm film thickness, Agilent Technologies), and Rtx-VMS (30 m × 0.25 mm i.d., 1.4 μm film thickness, Restek). The oven temperature program varied across analytes. Extracts (1 μL) were injected into the GC in the splitless mode, and chromatograms were recorded in the SIM mode for quantification. More details have been described elsewhere.[15]

Modeling. Following the approach by Xie et al.,[5] we first compared K^s with the molecular size. The molar volume of all solutes was calculated from McGowan's approach, which is a simple incremental method.[16] Note that the increment value for a fluorine atom needs correction, as was discussed before.[17] The molecular surface area was calculated with the software TURBOMOLE (version 6.0, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989−

2007, TURBOMOLE GmbH, since 2007 available from www.turbomole.com) as an alternative descriptor for the molecular size.

To take molecular interaction properties of compounds into consideration, polyparameter linear free energy relationships (pp-LFERs) developed by Abraham[13,18] were used.

$$K^s = c + eE + sS + aA + bB + vV \quad (4)$$

The notations used are as following: E, excess molar refraction; S, dipolarity/polarizability parameter; A, overall solute H-bond acidity; B, overall solute H-bond basicity; V, McGowan's molar volume divided by 100 (i.e., in the unit of $(cm^3/mol)/100$). This division for the V descriptor is simply to scale down the V descriptor to make its values comparable to the other descriptors. The descriptor values used are presented in Supporting Information SI-4 and SI-5. The pp-LFERs have been applied and validated for modeling of numerous types of partition coefficients.[13] In theory, the pp-LFER should be able to describe the salting-out too, because K^s is formally equivalent to the log of the partition coefficient between the 1 M NaCl solution and pure water, as can be deduced from eq 1.

In previous studies, the a priori predictive model COSMO-RS has been demonstrated to give a good agreement between experimental and calculated K^s values for a few compounds.[19,20] COSMO-RS has the advantage of requiring only the molecular structure of the solute as input without additional empirical descriptors. A more comprehensive validation of this computational approach is desirable. In this work, COSMO*thermX* (version C21_0111, COSMO*logic* GmbH & Co. KG, Leverkusen, Germany 2010) was used to perform the COSMO-RS calculations. The calculations were started with a search for low energy conformations (performed with COSMO*conf*, v.2.1). This was followed by BP-TZVP gas phase and COSMO calculations with the TURBOMOLE program for the complete set of conformations with full geometry optimization in the conductor reference state (COSMO). The COSMO files of the solutes that resulted from the TURBOMOLE calculations were then used in the COSMO*thermX* software for calculating the free energies of partitioning between pure water and 0.5 M NaCl solution based on statistical thermodynamics. The results were evaluated through eq 1 to give the predicted values of K^s.

RESULTS AND DISCUSSION

Experimental Data. Table 1 shows the K^s values for NaCl measured in this study using the shared headspace and the SPME method. In both methods, we obtained low standard errors (SE) in K^s, in the range of 0.004−0.025. Note that K^s is a log value (see eq 1), thus the absolute error (as shown in Table 1) instead of the relative error is a proper measure of uncertainty in the salting out effect. The SE indicates somewhat less precise results for alkylbenzenes than for the others, which could be due to the relatively high volatility (i.e., high air−water partition coefficients) of alkylbenzenes. Although volatilization loss from the system does not cause errors in the results as explained above, the loss during the sampling of aqueous solutions using a syringe may generate errors. We performed two individual experimental runs for 2-ketones and FTOHs with the headspace method. While the two runs provided nearly identical values for 2-ketones, the duplicate measurements for FTOHs resulted in K^s values that differ by 0.03−0.05 (Table 1). This relatively large difference for FTOHs may also be explained by relatively high volatility of these chemicals.

Table 1. Setschenow coefficients (K^s) measured in this study

	K^s [M^{-1}]	SE[a]	R^{2a}
shared headspace method			
2,2,2-trifluoroethanol	0.125	0.008	0.962
1,1,1,3,3,3-hexafluoro-2-propanol	0.222	0.018	0.945
4:2 FTOH	0.290	0.006	0.995
	0.257	0.012	0.982
6:2 FTOH	0.404	0.005	0.998
	0.353	0.013	0.987
1-nitropentane	0.203	0.009	0.982
1-nitrohexane	0.236	0.010	0.984
2-heptanone	0.235	0.018	0.949
	0.237	0.023	0.915
2-octanone	0.281	0.015	0.976
	0.271	0.020	0.949
2-nonanone	0.296	0.017	0.970
	0.303	0.021	0.954
2-decanone	0.299	0.013	0.984
	0.320	0.020	0.962
2-undecanone	0.362	0.018	0.978
	0.366	0.021	0.969
heptanal	0.237	0.013	0.965
octanal	0.265	0.021	0.924
decanal	0.283	0.019	0.943
benzene	0.190	0.023	0.868
toluene	0.221	0.024	0.891
ethylbenzene	0.238	0.025	0.904
n-propylbenzene	0.262	0.025	0.919
n-butylbenzene	0.285	0.024	0.931
n-pentylbenzene	0.300	0.024	0.939
SPME method			
2-hexanone	0.198	0.004	0.997
2-heptanone	0.228	0.003	0.999
2-octanone	0.267	0.003	0.999
2-nonanone	0.306	0.003	0.999
2-decanone	0.321	0.009	0.994
1-hexanol	0.221	0.004	0.997
4-ethyl-3-hexanol	0.291	0.004	0.998
4-fluorophenol	0.168	0.004	0.995
4-nitroaniline	0.099	0.007	0.961
4-iodophenol	0.162	0.003	0.997
bisphenol A	0.174	0.010	0.971
1-naphthol	0.182	0.009	0.978
2-phenylphenol	0.274	0.011	0.984
4-aminobiphenyl	0.208	0.009	0.982
carbazole	0.232	0.006	0.994
2-butoxyethanol	0.211	0.009	0.984
2,5-dimethylpyrazine	0.209	0.007	0.988
acetanilide	0.197	0.005	0.994
methyl phenyl sulfoxide	0.166	0.006	0.990
caffeine	0.114	0.007	0.959
4-nitroanisole	0.126	0.012	0.926
valerophenone	0.271	0.012	0.982
benzophenone	0.262	0.005	0.997
di-*n*-propyl phthalate	0.374	0.005	0.999
tri-*n*-butyl phosphate	0.428	0.006	0.998
atrazine	0.274	0.005	0.997
metolachlor	0.296	0.005	0.997

[a]SE and R^2 are the standard error in K^s and the coefficient of determination, respectively, as obtained from the linear regression through eq 2 or 3.

Nevertheless, these errors are still much smaller than data variability in the literature. K^s values for 2-heptanone, 2-octanone, 2-nonanone, and 2-decanone were measured with both shared headspace and SPME methods. The difference was 0.02 in the worst case and mostly <0.01, indicating high comparability of measured values from these two methods. Table 1 also shows high R^2 of the regressions in general, which could indicate a high linearity, but this interpretation is conditional, as only three NaCl concentrations were evaluated here.

The data measured here for aldehydes are much smaller than those reported in ref 6 (e.g., 0.237 for heptanal in this work as compared to 0.5 in ref 6; 0.283 for decanal in this work as compared to ~1.0 in ref 6). Because our data fit well into the general trend of the whole data set, as shown below, the values for aldehydes from ref 6 are likely too high.

Correlation with Molecular Size. Figure 2 shows a positive correlation between McGowan's molar volume (V_x)

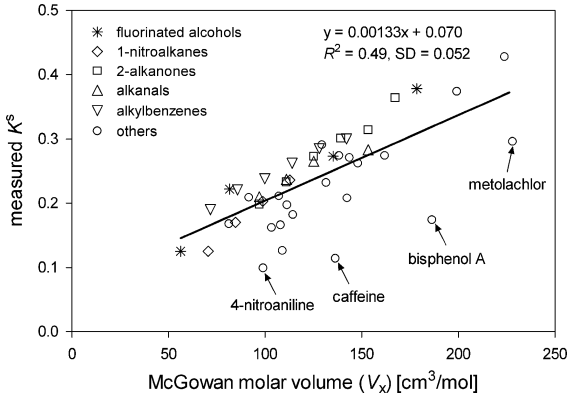

Figure 2. Correlation between the Setschenow coefficient (K^s) for NaCl in M^{-1} and the McGowan molar volume (V_x). The data shown are from this study. The line indicates the linear regression for all data plotted.

and K^s. From the linear regression analysis, we obtained,

$$K^s = (0.00133 \pm 0.00021)V_x + (0.070 \pm 0.028) \quad (5)$$

$$n = 43,\ R^2 = 0.49,\ \mathrm{SD} = 0.52$$

For compounds with more than one measured value in Table 1, a mean value was used. Within each class of compounds with differing alkyl chain lengths (e.g., *n*-alkylbenzenes, alkanals), there is a highly linear relationship between K^s and V_x. In addition, the slopes for these chemical classes are similar. Because an increase in the alkyl chain length only increases the molecular size but not the polar interaction properties of the compound, the linear increase of K^s along with V_x confirms that the molecular size is linearly related to the salting out effect. Figure 2 also shows that aliphatic compounds with one functional group, that is, 1-nitroalkanes, 2-alkanones, *n*-alkylbenzenes, alkanals, and tri-*n*-butyl phosphate, fall well on a single correlation. However, many of the other compounds exhibit lower K^s than expected from this correlation. Notable examples are 4-nitroaniline, caffeine, bisphenol A, and metolachlor. As these are multifunctional polar compounds, the results may be explained by strong polar interactions that negatively contribute to the salting out effect. The influences of polar interactions on K^s will be discussed below based on the pp-LFER model.

For most compounds the McGowan volume and the molecular surface area are correlated to a high degree (Figure S1 in Supporting Information SI-6). Thus, use of the molecular surface area as predictor variable would lead to the same results. However, it has been argued by various authors that the surface area should actually be the more relevant parameter to describe the cavity formation energy (ref 21 and literature cited therein). Thus, the correlation with the surface area might give better results for very bulky molecules such as highly branched aliphatic compounds, which are not included in the test set here.

Ni and Yalkowsky[22] claimed that the log of the octanol–water partition coefficients (K_{ow}) is a better descriptor than the molar volume. However, the correlation of K^s measured here with log K_{ow} is not better (R^2 = 0.50, Figure S2 in Supporting Information SI-7) than with the molar volume.

In Figure S3 in the Supporting Information, 93 literature K^s data for NaCl are compared with predictions from eq 5. The literature data used are those selected by Xie et al.[5] and more recent data from others.[3,7,8] Note that more than one data point is plotted for some compounds in Figure S3. The literature data cited include those measured with NaCl solutions and natural and artificial seawater. The comparability of NaCl solutions and seawater has been shown before.[5] The predictions with eq 5 for the literature data resulted in a root mean squared error (RMSE) of 0.055. As in Figure 2, relatively strong polar compounds (i.e., nitrophenols, benzoic acids, phenylurea) tend to be overestimated by eq 5. However, systematic deviations for polar compounds are far less clear than in Figure 2, most likely because data uncertainties are higher in the literature data.

Pp-LFERs. The resulting equation and statistics of the pp-LFER model are as follows:

$$K^s = 0.112(\pm 0.021) - 0.020(\pm 0.013)E - 0.042(\pm 0.020)S - 0.047(\pm 0.018)A - 0.060(\pm 0.022)B + 0.171(\pm 0.017)V \quad (6)$$

$$n = 43,\ R^2 = 0.83,\ \mathrm{SD} = 0.031$$

The combination of these five descriptors performed statistically better than any combination of fewer descriptors, as judged from the Akaike Information Criterion.[23,24] Experimental and calculated K^s values are compared in Figure 3. The standard deviation of estimates (0.031) is comparable to the experimental errors in K^s as discussed above. Also, standard errors for the regression coefficients are notably small (0.01–0.02).

The coefficient for V in eq 6 is positive, which indicates a positive influence of the molecular size on K^s, agreeing with our interpretations above. The coefficients of the polar interactions terms (i.e., *s*, *a*, *b*) are negative and are different from 0 by >2 SE. Thus, polar interactions negatively contribute to K^s, mitigating the salting out effect driven by the increased cavity formation energy. However, the absolute values of *s*, *a*, and *b* are relatively small. This explains that monofunctional compounds (generally low in *S*, *A*, and *B*) do not show significant deviations from the general correlation between K^s and V_x in Figure 2, whereas multifunctional polar compounds (generally high in *S*, *A*, and *B*) do deviate from the correlation.

The slightly but significantly increased polar interactions in salt solutions prove that Na^+ and Cl^- increase the polar

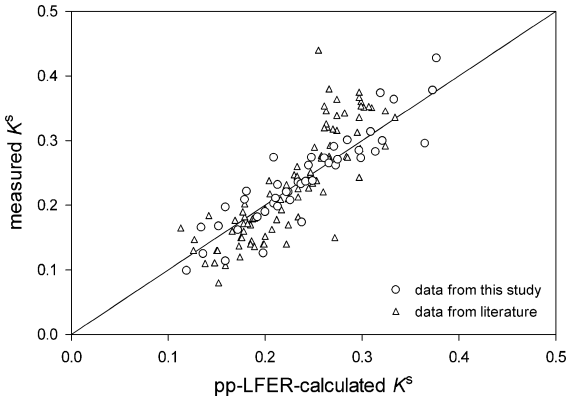

Figure 3. Fitting of the pp-LFER model to the data from this study, and prediction for the literature data. The statistics and coefficients are presented in the text (see eq 6). The line indicates the 1:1 fit.

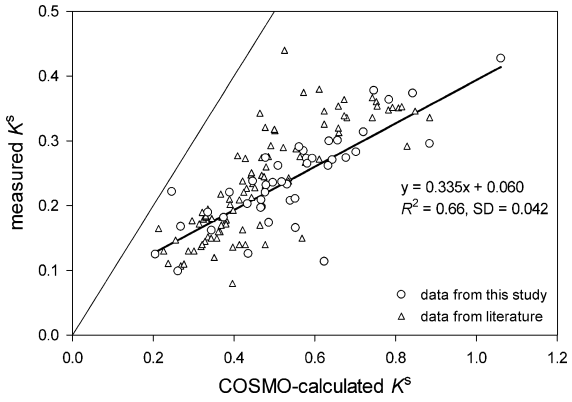

Figure 4. Measured vs COSMO*thermX*-predicted K^s values for NaCl. The thin line indicates the 1:1 agreement, and the bold line is the linear regression for the data from this study.

interactions of the aqueous solution toward neutral organic solutes. The pp-LFER model offers a way to estimate the enhanced polar interactions in NaCl solution compared to pure water.

The descriptors for pp-LFER models are available for 91 out of 93 literature data. In Figure 3, these literature K^s data are compared with predicted values from the newly established pp-LFER model (see Supporting Information SI-5 for data and predictions). The pp-LFER predictions agree well with the literature data, with RMSE of 0.047. Considering the relatively large uncertainty in K^s data in general, this agreement is regarded as high. The RMSE does not greatly improve from the simple correlation with the molar volume, but this may be because the data set contains only a limited number of highly polar compounds for which modeling of polar interactions is crucial. Good agreement between data and predictions is exemplified with the data for PAHs. The pp-LFER model predicts a slight increase of K^s values along with the size of compounds, from 0.25 (acenaphthene) up to 0.33 (dibenz[*a*,*h*]anthracene). The literature values selected by Xie et al.[5] for PAHs are 0.24 (acenaphthene) to 0.35 (benz[*a*]anthracene), matching the predictions excellently. Jonker and Muijs[8] measured fairly constant K^s values (0.29−0.38) for PAHs and no increasing trend with the molecular size. Again, considering a typical error range, the agreement is regarded as good. It is encouraging that the established pp-LFER model reasonably predicts the K^s values of PAHs, as our calibration data set does not include such hydrophobic compounds. Similarly, some polar classes of compounds like nitrophenols, and benzoic acids are not in our data set, but the literature data thereof are predicted within ±0.06 log units.

COSMO-RS. The K^s values predicted with the COSMO*thermX* software were generally higher than the measured values (Figure 4; predictions are listed in Supporting Information SI-4 and SI-5). However, there was a moderate correlation between the predictions and the values measured in this study (R^2 = 0.66). This correlation is lower than that with the pp-LFER descriptors, but higher than that with the molar volume alone. This suggests that the COSMO*thermX* modeling captures the increased polarities of salt water to some extent. Caffeine is the strong outlier (deviation >3 SD) for unknown reasons and contributes largely to the relatively poor correlation. Removing this chemical alone would improve the correlation to R^2 = 0.75 and SD = 0.035, which are close to the statistics for the pp-LFER model. An empirical regression equation, K^s = 0.335 K^s(COSMO-calculated) + 0.060 predicts 93 literature data to the accuracy of RMSE = 0.050. The RMSE is just comparable to that of the simple regression with V_x, but as for the pp-LFER model above, this conclusion may be biased because of the limited polar compounds and relatively high uncertainties in the literature data set.

The fact that COSMO-RS provides a better correlation than the molar volume is interesting, because the COSMO-RS model is based on a fundamental approach that was neither calibrated with salting-out data nor was it specifically designed to deal with this task. Based on the experimental data from this study, the COSMO*thermX* calculations in combination with a calibrated regression would look like a useful tool for predicting K^s from molecular structure, if it were not for the outlying value of caffeine. It is not clear whether more outliers like this might exist. Note that COSMO-RS approach is principally also able to compute K^s for other salts and complex mixtures of various salts, such as in aerosols. This feature still warrants evaluation.

Implications. Using the pp-LFER model presented here, salting-out effects can be estimated for a large number of compounds with various functional groups. Calculated salting out effects of some environmentally relevant compounds in physiological saline, seawater, and 6 M NaCl solution (near saturation) are presented in Figure 5. Again, only neutral species of compounds are considered here. Salting out effects in physiological saline are generally small, always <0.1 log unit for the compounds shown in Figure 5. This finding is corroborated by previous studies[15,25] that compare partition coefficients measured in fresh water and physiological saline. In seawater, effects of 0−0.3 log units are calculated. Thus, the relevance of the effect is typically not high, although deviations from fresh water may be detectable for some compounds. Note that the data and models presented here are for 25 °C, whereas the seawater temperature varies widely. May et al.[11] measured K^s of phenanthrene in NaCl solutions from 1.5 to 29.9 °C and showed that the K^s values were 0.25−0.27 without any increasing or decreasing trend. Paul[12] measured K^s of naphthalene in NaCl at 0.1 and 25 °C and found only a 0.027 difference. These data suggest that salting-out in seawater at temperatures other than 25 °C does not substantially differ from that at 25 °C. At 6 M NaCl, an increase of 0.5−3.4 log units from pure water can be expected (Figure 5). Hence, adding NaCl can dramatically improve the extraction efficiency for some compounds. It should be noted here that the data of K^s used to calibrate the pp-LFER model were measured up to

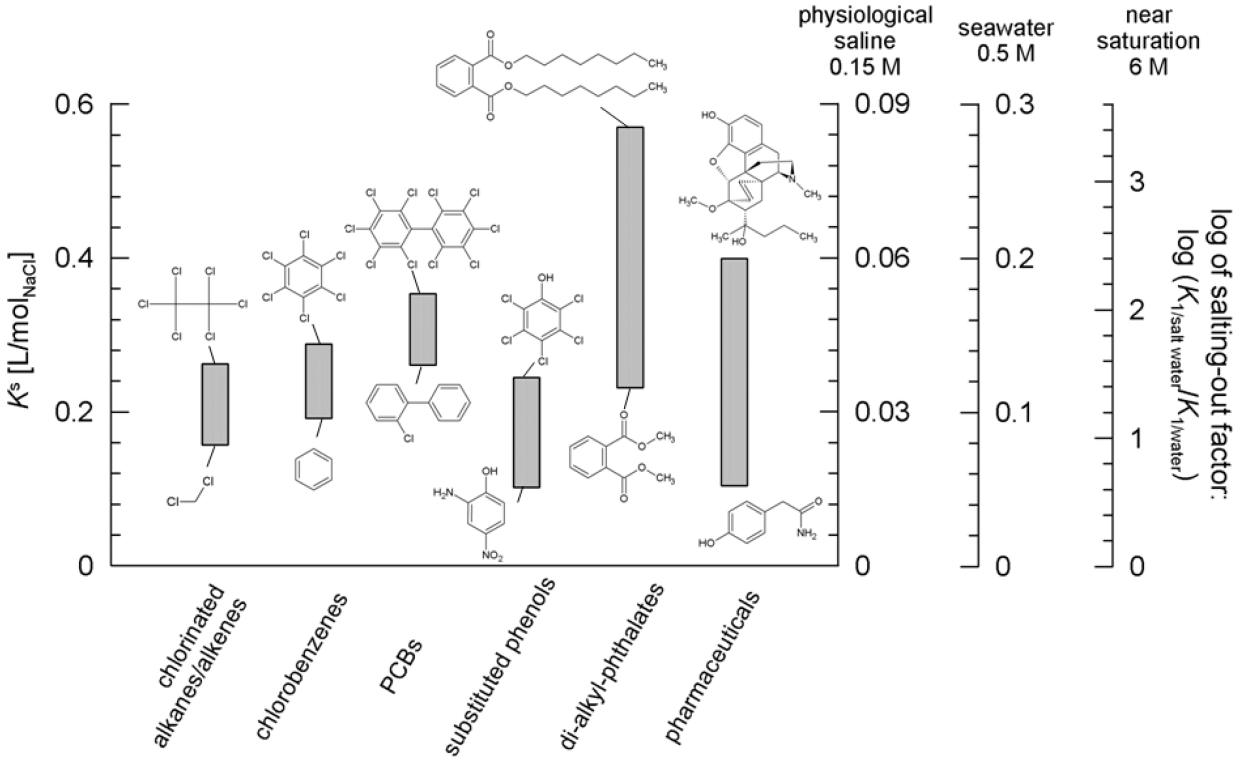

Figure 5. Salting-out effects of some environmentally relevant compounds. K^s values were estimated from the pp-LFER model. Physiological saline and seawater were approximated as 0.15 and 0.5 M NaCl solutions, respectively. For ionizable compounds, only the neutral species were considered. "Pharmaceuticals" are those compounds listed in ref 28. All pp-LFER descriptors used and the calculation results are given in SI-9, Supporting Information.

1.7 M NaCl solution. Thus, the calculation for 6 M NaCl involves upward extrapolations with respect to the NaCl concentration using the Setschenow equation (eq 1). The Setschenow equation has been shown to be valid for benzene up to 4 M NaCl[26] and for four alkylbenzenes up to 5 M NaCl.[27] However, to our knowledge it has not been tested whether this equation holds for a diverse set of nonpolar and polar compounds up to the solubility of NaCl.

Figure 5 also indicates the extent of salting-out effects for specific compound groups. Small, low-polarity compounds such as chlorinated alkanes, alkenes and benzenes undergo relatively small salting-out effects, because their molecule sizes are small. Larger hydrophobic compounds such as hexachlorobenzene, large PAHs, and highly substituted polychlorinated biphenyls (PCBs) are somewhat more influenced by salt than their smaller homologues. However, the influence of salt is still rather limited; for example, K^s is <0.4 even for PCB 209, which corresponds to the salting out effect in seawater being <0.2 log units. These hydrophobic compounds are large in size (e.g., the molar volume of PCB 209 is 220 cm^3/mol (i.e., V = 2.2), according to van Noort et al.),[29] but the S values for these compounds (and also the B values for PAHs) are relatively large and partially compensate the positive influence of the size on K^s. Relatively high K^s is expected for compounds with long alkyl chains, such as dialkyl phthalates. For example, K^s of dioctyl phthalate is calculated to be 0.57 (Figure 5). An alkyl group simply increases the size but not the polarity, thus increasing the chain length generally enhances the salting-out effect. In this respect, it is notable that tri-*n*-butyl phosphate exhibited the highest K^s value of our experimental data set.

Small and multiply polar-functionalized compounds (e.g., polar substituted phenols) undergo only weak salting out effects. These compounds are often difficult to extract into organic solvents or polymeric sorbents due to their strong tendency to partition into water. For these compounds, however, adding NaCl may not improve the extraction efficiency much, as their K^s values are small.

Pharmaceuticals include structurally diverse compounds. Accordingly, the K^s values calculated for these types of compounds cover a wide range. The pharmaceuticals considered here include very large molecules, with a molar volume of 300 cm^3/mol (i.e., V = 3) or higher. Nevertheless, K^s values do not become extremely large for these compounds, as large pharmaceutical compounds are usually highly polar-functionalized (in order to render them sufficiently water-soluble), which negatively contributes to K^s.

Using the measured data and the pp-LFER model, we demonstrated that the salting-out effect in NaCl solutions occurs due to the cavity formation and polar interaction energies that are enhanced by the dissolved salt. The pp-LFER model established here offers a way to implement salting-out in solute transport models for natural or engineered systems, as far as the compound descriptors are available. In addition, estimations of salting-out effects can link various partition coefficients measured for fresh water and seawater, such as air–water, sediment–water, and polymeric passive sampler–water partition coefficients. The presented experimental and modeling approaches are promising for studying the salting-out by other salts as well. Apart from NaCl, ammonium sulfate and nitrate may be of high environmental relevance, as the salting-out by these salts is important for the phase distribution of organic chemicals in aerosol.

■ ASSOCIATED CONTENT

Supporting Information

More information is available for the experimental methods, values of the pp-LFER descriptors used, experimental K^s data collected from the literature, K^s values calculated from the pp-LFER and the COSMO-RS models, and figures for correlations between the molar volume and the surface area and between K^s and log K_{ow}. This material is available free of charge via the Internet at http://pubs.acs.org.

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