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Ultrasonic detection of hydrophobic interactions: a quantitative approach

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Kinetic effects of sonication on ester hydrolysis and *tert*-butyl chloride solvolysis, studied in ethanol–water binary solvent, are discussed in terms of quantitative relationships between their magnitude and the hydrophobicity of reagents. A number of conclusions were drawn from the observed linear free-energy (LFE) relationships. Independent of reaction mechanism, the decrease in reaction rates with increasing ethanol content in the solvent is mainly due to hydrophobic stabilization of the ground state. While hydrophobic species can be hidden in the ethanol clusters present in the region $X_{EtOH} > 0.15$, at lower ethanol contents hydrophobic reagents are weakly solvated and the hydrophobic stabilization can be easily overcome by sonication. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

Hydrophobic effects play an important role in many chemical processes in aqueous solutions. Two phenomena can be distinguished: hydrophobic hydration and hydrophobic interaction (HI). Hydrophobic hydration denotes how apolar solutes affect the organization of water molecules in their immediate vicinity. The HI is the tendency of apolar species to aggregate in aqueous solutions to reduce their contact surface with water. HI can lead to pairwise interactions, known as encounter complexes, to well-defined host–guest complexes, to the formation of small clusters of molecules, or to large aggregates.[1–5]

HI between apolar molecules or apolar parts of molecules in water are important noncovalent driving forces for inter- and intramolecular binding and assembly processes, taking place in aqueous chemistry and biochemistry.[1–5] In aqueous systems these interactions can strongly influence chemical equilibria and reaction rates.[3–9] For example, in the hydrolysis of esters, HIs (the formation of hydrophobically stabilized encounter complexes or clusters with co-solutes) make the ester less reactive.[10–14] On the other hand, the Diels–Alder reaction[15] and the benzoin condensation[16] are dramatically accelerated when carried out in water rather than in organic solvents. Such rate enhancements mostly result from the packing of hydrophobic surfaces of these reagents in the transition state, whose energy is lowered as hydrocarbon–water contacts are minimized.[2–5]

Although HI can be studied by a large variety of experimental and computational techniques, the determination of chemical reactivity has a special position among them.[4,5,17,18] Indeed, rate constants can usually be determined with so high a precision, that small hydrophobic effects can thus be detected.

Our contribution to HI studies consists in applying power ultrasound to kinetic investigation of polar (ionic) homogeneous reactions in solutions, mainly in ethanol–water binary mixtures.[19–23]

Ultrasonic acceleration effects on chemical processes are widely exploited both in the laboratory and industrial practice.[24–26] Sonication mostly affects reaction rates, yields, and in some cases the ratios of reaction products. Besides bringing about mechanical effects, cavitation induced by sonication can promote many homogeneous and heterogeneous reactions by generating free radicals which give rise to chain reactions in solution.

Sonication studies of solvolysis/hydrolysis reactions in aqueous–organic binary solvents have brought to light specific solute–solvent interactions and hydrophobic effects that are not manifested in conventional kinetic investigations.[19–23,27–29] It was concluded that in these cases the sonochemical effects may be related to the perturbation of the molecular structure of the solvent and, more critically, to the destruction of hydrophobic solute–solvent interactions.

However, conclusions drawn so far have been merely qualitative deductions based on observed sonication effects in reaction kinetics. In this paper, we show that a quantitative correlation of kinetic sonication effects with substrate hydrophobicity reveals novel details of solvation phenomena and HI in solutions.

RESULTS AND DISCUSSION

A comprehensive investigation of sonication effects on polar homogeneous reactions was first performed by Mason's group.[27,28] An unexpectedly complicated dependence of the effect (k_{son}/k) on the composition of ethanol–water binary solvent was found for the solvolysis reaction of *tert*-butyl chloride. The authors concluded that the application of ultrasound to the reaction disrupted the binary solvent structure, thus permitting a

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better solvation of the substrate and resulting in enhanced reaction rates.

That pioneering work inspired us to extend the investigation to a mechanistically different reaction, *viz.* to the hydrolysis of esters. For the acid-catalyzed hydrolysis of ethyl acetate we observed a similar dependence of the sonication effect on solvent composition.[19,20] These results initially led us to think that sonication effects were merely related to a perturbation of the solvent system. However, on replacing ethyl acetate with more hydrophobic esters, we observed a dramatic change in the dependence of the sonication effect on solvent composition, which obliged us to revise our early point of view. Solute–solvent interactions in these complicated systems proved to be particularly important in clarifying the matter.[20,23]

Recent spectroscopic, X-ray diffraction, and mass spectrometric investigations have shed light on the structure of ethanol–water solutions.[30–32] It has been concluded that small additions of ethanol in the range of $0 < X_E < 0.08$ (X_E being the ethanol molar ratio) exert a strong structure-making effect accompanied by an increase in the self-association of water. Further addition of alcohol begins to prevent water from organizing into 3D structures. Observations suggested that an ethanol polymer structure evolves and the bulk water structure breaks down at $X_E > 0.1$. In mixtures at $X_E > 0.15$ a large number of ethanol–water hydrogen bonds are formed at the expense of water–water bonds. The resulting structure is described by a cluster model, envisaging a stacked ethanol core and a thin water shell.[30–32]

This model allowed a straightforward interpretation of our results: a hydrophobic reagent could be hidden inside the clusters and thus made unavailable for the reaction. If ultrasound is capable of breaking the reagent's interaction with the hydrophobic interior of the cluster, it will accelerate the reaction.

Ethyl, *n*-propyl, and *n*-butyl acetates were used as probes of the postulated inclusion of a reagent within clusters. Indeed, sonication effects measured in the region $0.2 < X_E < 0.3$ matched in reverse order the hydrophobicity of the esters. *n*-Butyl acetate should be the most powerfully held by clusters, and sonication was found to be least efficient in this case.

To obtain quantitative proof of the above conclusions we related the sonication effects (Table 1, comprising experimental data from References [20,21,27,33]) to the Hansch–Leo hydrophobicity parameter log *P*, where *P* is the partition coefficient of the substrate between 1-octanol and water.[34,35]

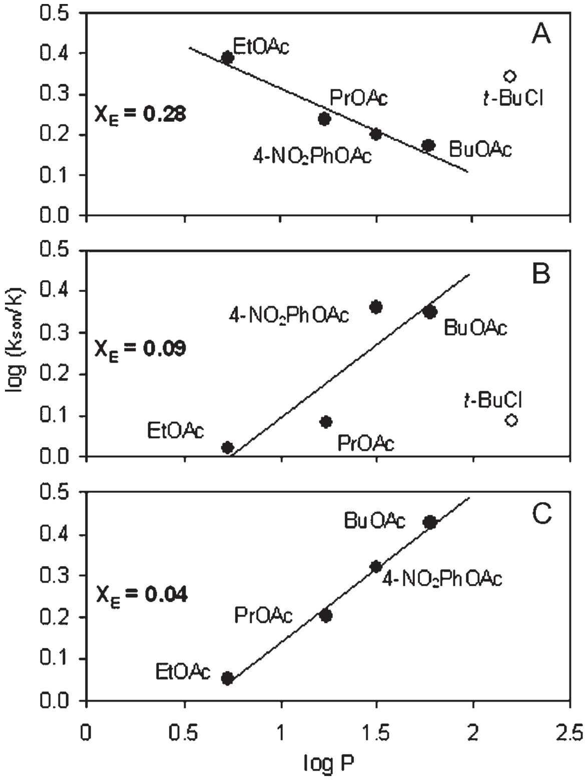

Figure 1. Linear free-energy relationships between sonication effects for ester hydrolyses and the hydrophobicity parameter log *P*. (A) $XE = 0.28$, (B) $XE = 0.09$, and (C) $XE = 0.04$.

In Fig. 1 the LFE relationships[36] show how kinetic sonication effects are related to the HI of reagents with the solvent system. Plot 1A represents the relationship at $X_E = 0.28$ in the region of ethanol clusters, providing a convincing quantitative proof of the conclusions made intuitively. Plots of sonication effects at $X_E = 0.04$ and $X_E = 0.09$ against hydrophobicity parameters (Fig. 1B, C) also reveal linear relationships. Statistical characteristics of the correlations are collected in Table 2.

The observed sonication effect for the hydrolysis of 4-nitrophenyl acetate appeared to be systematically smaller compared to those for the alkyl ester hydrolyses due to the lower

Table 1. Sonication effects (k_{son}/k) for the substrates at various molar fractions of ethanol, and the hydrophobicity parameters

	k_{son}/k				
Substrates	0.04 (10)[a]	0.09 (20)[a]	0.25 (45)[a]	Reference	log *P*[b]
EtOAc	1.13[c]	1.05[c]	2.43	[20]	0.73
PrOAc	1.59	1.21	1.73	[33]	1.24
BuOAc	2.67	2.24	1.38	[20]	1.78
4-NO_2-PhOAc	1.43	1.61	1.09	[21]	1.50
tert-BuCl	—	1.22	2.50	[27]	2.20

[a] Molar fraction of ethanol in ethanol–water binary mixture. In parentheses w/w% of ethanol.
[b] Experimental values from Reference [35].
[c] Interpolated values.

Table 2. Statistical characteristics of correlations between sonication effects for ester hydrolysis, $\log(k_{son}/k)$, and hydrophobicity parameters, log *P*

X_E[a]	Regression coefficient	Correlation coefficient, R^2	Standard error
0.04	0.357 ± 0.025	0.995	0.019
0.09	0.356 ± 0.123	0.807	0.095
0.28	-0.209 ± 0.034	0.951	0.026

[a] Molar fraction of ethanol in ethanol–water binary mixture.

sonication intensity used in kinetic measurements (as shown in the Experimental Section). As we have experimentally found for the ethanol–water solvent system[20] that the calorimetric sonication effect depends insignificantly on the solvent composition, the equal deviations at different X_E values can be definitely assigned to the difference in the applied sonication intensity. Indeed, when points for 4-nitrophenyl acetate were shifted upward by 0.16 log units, they laid equally well on the correlation lines in all panels of Fig. 1. Some important conclusions follow from the LFE relationships presented in Fig. 1.

Proceeding from the fact that the points for 4-nitrophenyl acetate and the alkyl acetates lay on common lines in Fig. 1, the formal LFE test asserts that the mechanism of the sonication effect is the same for the esters independent of the hydrolysis reaction mechanism (base-catalyzed *vs*. acid-catalyzed reactions). It is certain that sonochemical effects cannot be caused by direct impact of the acoustic field on the reacting molecules or on the transition states of reactions since the energy of ultrasound is too low to alter their electronic, vibrational, or rotational states.[24,25] However, as discussed above, ultrasonication can readily disturb weak solvent–solute interactions, including the hydrophobic stabilization of reagents. Thus, in light of the sonication effects one can admit now that independent of the reaction mechanism, the esters interact similarly with the solvent system. Furthermore, one can conclude that the regular decrease in the rate of ester hydrolysis with increasing alcohol content of aqueous binary solvents is mainly caused by the ground-state hydrophobic stabilization by the solvent system. In the region $X_E < 0.15$ (Fig. 1 B, C) sonication effects vary linearly with the hydrophobicity parameters; the order of the dependence, however, is the reverse of that found for the cluster region. This unexpected finding can be attributed to the weak solvation of esters in this region. While greater hydrophobicity leads to stronger ground-state stabilization, hence to a greater reactivity decrease, ultrasound breaks down HIs almost entirely, resulting in larger sonication effects for more hydrophobic esters.

Our recent experimental data[28] corroborate this conclusion straightforwardly. We have began investigating hydrophobic effects of small amounts of aliphatic alcohols on ester hydrolysis in water, and started with the neutral hydrolysis of 4-nitrophenyl chloroacetate, using the spectrophotometric method. This enabled us to work with a very low ester concentration (10^{-5} M) and to avoid resorting to the internal standard used in the GLC method (*cf.* References [19,20]).

While the hydrolysis rate, measured in the presence of 1 mol% of aliphatic alcohols, decreased with increasing hydrophobicity of the co-solvent, reaction rates under ultrasound were almost the same, thus providing a dependence of apparent sonication effects similar to those shown in Fig. 1 B, C. In other words, ultrasound appeared to destroy the ester–co-solvent encounter complexes regardless of the hydrophobicity of these compounds.

For the solvolysis of *tert*-butyl chloride the points fall away from the line in both A and B panels of Fig. 1 (For $X_E = 0.04$ no experimental data are available). Although relative sonication intensities applied in the experiments cannot be estimated, it is evident that, in comparison with the hydrolysis reactions, at $X_E = 0.28$ solvolysis is largely susceptible to sonication, while at $X_E = 0.09$ its rate is little affected by ultrasound.

In a recent paper[23] we extensively discussed the effects of sonication on the solvolysis reaction in the ethanol–water binary solvent. We concluded that in this system ethanol causes an effective hydrophobic stabilization of the ground state of *tert*-butyl chloride, leading to a dramatic decrease in the reaction rate. Sonication effects[27,28] are large and increase with increasing ethanol content in the binary solvent. However, the reaction rate observed under ultrasound is only slightly dependent on solvent composition. This indicates that sonication suppresses the prevalent hydrophobic ground-state stabilization, leaving little room for speculation about other medium effects. Extrapolation of these data to pure water resulted in an almost negligible sonication effect, in accordance with the highly destabilized ground state of *tert*-butyl chloride in water.[37]

According to our LEF tests, the mechanism of ultrasound interaction with the reacting system might be different for the solvolysis of *tert*-butyl chloride and the ester hydrolysis. This can be inferred from the observed sonication effects for *tert*-butyl chloride solvolysis incompatible with the hydrophobicity of the reagent in terms of the Hansch–Leo parameter.[35] However, if to question the tabulated log *P* value for *tert*-butyl chloride, equal shifts of the points in panels A and B of Fig. 1 place them well on the correlation lines and the same reduced log *P* value provides a reasonable sonication effect from the line in panel C.

In Fig. 2 data for an ester hydrolysis and for the solvolysis of *tert*-butyl chloride are presented. For the base-catalyzed hydrolysis of esters, sonication data for 4-nitrophenyl acetate[21] are plotted together with the activation enthalpy for the reaction of structurally similar ethyl 4-hydroxybenzoate.

In the case of the highly hydrophobic esters under consideration here, the plot of the sonication effect *versus* solvent composition shows a reversed trend by comparison with the corresponding curve of the activation enthalpy. Relatively great sonication effects and lower values of the activation enthalpy indicate a weak interaction of the esters with the solvent framework in the region $0.04 < X_E < 0.15$. Further additions of ethanol ($X_E > 0.15$) lead to formation of clusters,[32] that are capable of holding ester molecules more effectively; that leads to

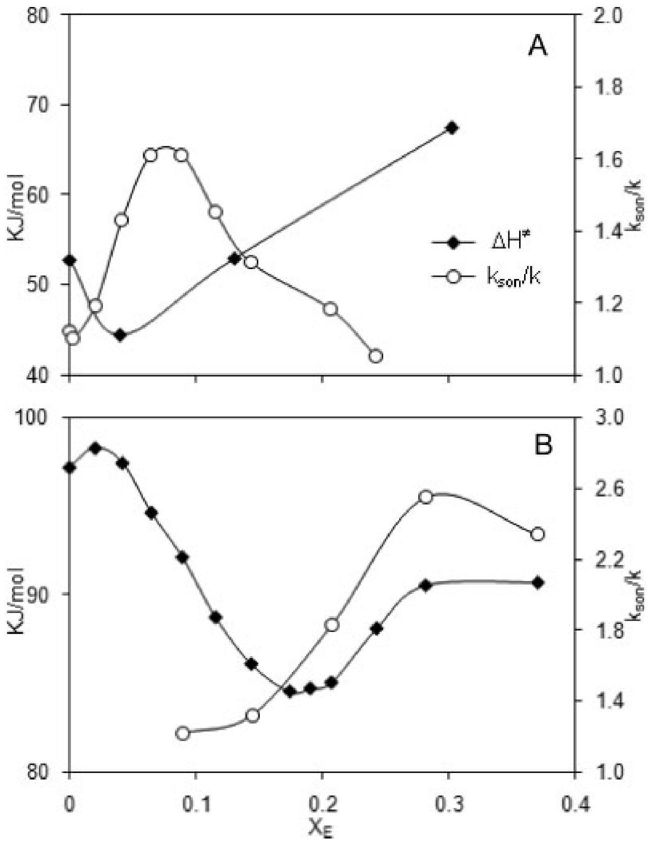

Figure 2. Sonication effects (k_{son}/k) and activation enthalpies ($\Delta H^{\neq}$) in ethanol–water binary solvents. (A) Base-catalyzed hydrolysis of ethyl 4-hydroxybenzoate (data from Reference [38], sonication data for 4-nitrophenyl acetate from Reference [21]); (B) solvolysis of *tert*-butylchloride (data from Reference [39], sonication data from Reference [27]).

decreasing sonication effects and increasing activation enthalpies. However, in the case of weakly hydrophobic esters the sonication effect increases in this region[19,20] (*cf.* Table 1).

The sonication effect for *tert*-butyl chloride increases with the increase in ethanol content. The increase in sonication effect reverse to that for highly hydrophobic esters and a parallelism with the activation enthalpy are obvious for the solvolysis of *tert*-butyl chloride providing additional support for discrediting the log *P* value of this compound.

CONCLUSIONS

Ultrasonic irradiation has become a useful tool for physicochemical investigations. It can reveal subtle HIs that remain hidden in conventional kinetic studies. Relation of kinetic sonication effects to the quantitative measure of substrate hydrophobicity, log *P*, has shed light on details of the solvation of reagents in the ethanol–water binary solvent.

An analysis of sonication data showed that independent of the reaction mechanism, the decrease in reaction rates with increasing ethanol content in the solvent system is mainly due to ground-state stabilization, which is largely of hydrophobic origin. While hydrophobic species can be hidden in the ethanol clusters present in the region of $X_E > 0.15$, at lower ethanol contents hydrophobic reagents are weakly solvated and hydrophobic stabilization can be readily suppressed by sonication.

Correlation of kinetic sonication effects with quantitative hydrophobicity parameters not only affords a better understanding of sonication effects on homogeneous polar reactions, but also opens perspectives for broader investigation into these solvation phenomena and reaction mechanisms.

EXPERIMENTAL

Data for sonication effects published in former papers were used in this work. For experimental details corresponding articles should be addressed. The most important features are the following:

Alkyl acetates.[19,20] Acid-catalyzed hydrolysis of esters was followed by gas–liquid chromatography determinations of the ester concentration in 1 M HCl solutions at 18.3 °C (at 20 °C for propyl acetate[33]). Sonication was performed with an immersed titanium horn at 22 kHz. Sonication intensity was 55 W/80 ml.

4-nitrophenyl acetate.[21] Base catalyzed hydrolysis at pH = 8.0 was followed spectrophotometrically at 20 °C. Sonication was performed with an immersed quartz horn at 21.1 kHz. Sonication intensity was 9.4 W/100 ml.

4-nitrophenyl chloroacetate.[33] Neutral hydrolysis of the ester in water and in the presence of 1 mol% amounts of alcohols was followed spectrophotometrically at 20 °C. Sonication was performed with a cleaning bath at 25 kHz. The sonication intensity in the reaction cell was 8.1 W/100 ml.

tert-Butyl chloride.[27,28] The solvolysis was followed conductometrically at different temperatures. Data for 20 °C are used in this work. Sonication was carried out in a cup horn reactor operating at 20 kHz with an acoustic intensity of ~1 W cm^{-2}. The authors believe they worked in the region of stable cavitation.[28]

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