DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS

61

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IMPACT OF ULTRASOUND ON HYDROPHOBIC INTERACTIONS IN SOLUTIONS

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Dissertation is accepted for the commencement of the degree of Doctor of Philosophy in Chemistry on December 18, 2006, by the Doctoral Committee of the Department of Chemistry, University of Tartu.

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Commencement:	March 20, 2007, 18 Ülikooli Str.

ISSN 1406–0299
ISBN 978–9949–11–550–1 (trükis)
ISBN 978–9949–11–551–8 (PDF)

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimuse nr. 48

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I. Hagu, H., Salmar, S., Tuulmets, A. Ultrasonic acceleration of ester hydrolysis in ethanol-water and 1,4-dioxane-water binary solvents. *Proc. Estonian Acad. Sci. Chem.* **2002**, 51, 235–239.

II. Tuulmets, A., Salmar, S., Hagu, H. Effect of ultrasound on ester hydrolysis in binary solvents. *J. Phys. Chem.*, *B* **2003**, 107, 12891–12896. doi: 10.1021/jp035714l

III. Hagu, H., Salmar, S., Tuulmets, A. Impact of ultrasound on hydrophobic interactions in solutions: ultrasonic retardation of benzoin condensation. *Ultrason. Sonochem.* **2007**, accepted. doi: 10.1016/j.ultsonch.2006.09.012

IV. Tuulmets, A., Hagu, H., Salmar, S., Cravotto, G., Järv, J. Ultrasonic evidence of hydrophobic interactions. Effect of ultrasound on benzoin condensation and some other reactions in aqueous ethanol. *J. Phys. Chem.*, *B* **2007**, accepted 02.02.2007. jp0682199

Author's contribution

Paper I: Responsible for around half of the performed experiments and calculations. Participation in manuscript preparation.

Paper II: Responsible for around half of the performed experiments and calculations. Participation in manuscript preparation.

Paper III: Responsible for all experimental work and calculations. Significant participation in manuscript preparation.

Paper IV: Responsible for all experimental work and most of calculations. Significant participation in manuscript preparation.

ABBREVIATIONS

HI	hydrophobic interaction
BuOAc	butyl acetate
t-BuCl	*tert*-butyl chloride
EtOAc	ethyl acetate
dioxane	1,4-dioxane
GLC	gas-liquid chromatography
HPLC	high-pressure liquid chromatography
NMR	nuclear magnetic resonance
4-NPA	4-nitrophenyl acetate
PrOAc	propyl acetate
X	molar ratio
X_{E}	molar ratio of ethanol
X_{dioxane}	molar ratio of 1,4-dioxane
$\Delta H^{\neq}$	standard molar enthalpy of activation
$\Delta S^{\neq}$	standard molar entropy of activation
$\Delta G^{\neq}$	standard molar Gibbs energy of activation

1. INTRODUCTION

Studies of kinetic medium effects in different solvents and solvent mixtures provide important information about intermolecular interactions that play a decisive role in controlling the rates of chemical reactions. Aqueous binary solvent mixtures are of particular interest. The properties of water are dominated by hydrogen bond interactions. Furthermore, polar and apolar groups of dissolved molecules interact with water and organic solvent in distinctive ways. These features make chemical reactivity in mixed aqueous media a challenging topic.

Hydrophobic interactions (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 [1–4]. In aqueous systems they can have a strong influence on chemical equilibriums and reaction rates [3–8]. For example, in hydrolysis reaction of esters the formation of hydrophobically stabilized encounter complexes or clusters with co-solutes may make the ester less reactive [9–11]. On the other hand, the Diels-Alder reaction [12] and the benzoin condensation [13] are dramatically accelerated when carried out in water rather than in organic solvents. These rate enhancements mostly result from the packing of hydrophobic surfaces of the reagents in the transition state, energy it lowers by minimizing hydrocarbon-water contacts [2–4].

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 [3, 4]. For example, the rate constants can usually be determined with high precision, so that small hydrophobic effects can be detected.

Solvolysis and hydrolysis reactions in aqueous-organic binary solvents have brought to light specific solute-solvent interactions and hydrophobic effects that do not manifest in conventional reaction kinetics [14–16]. It was concluded that in these cases the sonochemical acceleration may be related to the perturbation of the molecular structure of the binary solvent and, more critically, with the destruction of hydrophobic solute-solvent interactions.

In the present work two different solvent systems 1,4-dioxane-water mixtures, and ethanol-water mixtures were studied, expecting that the structuredness of the medium is of great importance in hydrogen bonding solvents. Therefore**,** ultrasonic effect on the acid-catalyzed aliphatic ester hydrolysis reaction was investigated in both solvent systems. In addition, a quantitative relationship between sonication effects and the hydrophobicity of reagents was presented for the first time.

Further, kinetics of KCN-catalyzed benzoin condensation of benzaldehyde was investigated under ultrasound and without sonication in water and in ethanol-water binary mixtures, and a statistically significant decrease of the reaction rate was observed in water. The thermodynamic activation parameters were calculated from the kinetic data for this reaction.

2. HYDROPHOBIC INTERACTIONS IN SOLUTIONS

Hydrophobic effects play an important role in many chemical processes in aqueous solution like protein folding, molecular recognition processes, and aggregation of amphiphilic molecules. In studies of hydrophobic effects, two phenomena are usually distinguished: hydrophobic hydration and hydrophobic interaction. Hydrophobic hydration denotes the way in which apolar solutes affect the organization of the water molecules in their immediate vicinity. The HI describes the tendency of apolar molecules or their parts to stick together in aqueous media [1–4].

HI was first introduced by Kauzmann [17] in the context of protein folding. There are, however, numerous other processes, which depend strongly on HI in aqueous solutions. HI are different from other non-covalent interactions in the liquid phase in the sense that they do not primarily depend on direct attractive intermolecular interactions/forces between the species that are perceived to interact, but are rather driven by the tendency of water molecules to retain their own water-water hydrogen bonding interactions as much as possible.

The precise mechanism of HI has been under debate for many decades and still not all the details are well understood, particularly the thermodynamics of dissolution of apolar molecules in water.

HI can lead to pairwise interactions (encounter complexes), to well defined host-guest complexes, to the formation of small clusters of molecules, or to large aggregates. It is clear that HI depends on the size and shapes of the molecules, on the temperature and pressure, and on the presence of co-solutes. HI can be studied by a large variety of experimental and computational techniques, but we focus our attention on reaction kinetics.

The limited solubility of many organic compounds in water explains why this solvent has traditionally not been a popular solvent among organic chemists. Furthermore, many transformations involve reactive intermediates, which often readily react with water.

Nowadays, many reactions have been successfully performed in water or a highly aqueous solvent mixture [5–8]. Numerous reactions are accelerated in water-rich environments relatively to organic solvents. This is valid for hydrolysis reactions, but also for other organic reactions that are less expected to show rate enhancement in aqueous media, among which the Diels-Alder reaction and the benzoin condensation are the best-known examples [12, 13].

It is easy to rationalize that Diels-Alder reaction benefits from HI: two relatively apolar molecules react to form a single product molecule. This implies that the apolar surface area, which is exposed to water, is reduced during the activation process. In other words, some of the water molecules, which formed the hydrophobic hydration shell surrounding the reactants, are liberated during the reaction, and the release of these water molecules into bulk solvent provides an additional driving force for the process.

It can be suggested that solvent effects in highly aqueous media should reflect the interactions between the reactant(s) and the co-solvent, and between the activated complex and the co-solvent. In diluted solutions the rate effects are mainly caused by pairwise interactions, and the results indicate that the apolar character of the reacting species and the co-solvent governs these interactions. It is remarkable that the low solubility of the reactants enhances their reactivity, whereas complexation or aggregation only renders them less reactive [3].

3. ULTRASOUND EFFECT ON POLAR HOMOGENEOUS REACTIONS

In what way does ultrasound affect chemical reactions? The analysis of numerous experiments has revealed that ultrasound had no effect on chemical pathways, and the reaction rates were often comparable to those for non-sonicated processes. Thus, in many heterogeneous reactions the application of ultrasound has the same effect as a high-speed agitator or a homogenizer in which fluids do not cavitate [18]. Differently, the chemical effects of ultrasound should occur, if an elemental reaction is the sonication-sensitive step, or when the high-energy species released after cavitational collapse do indeed participate as reaction intermediates [19–23]. These possibilities have been suggested long ago, however, without quotation of definite ways of action. Although the sonochemical effects, not directly related to cavitation phenomena, have been beyond the paradigm of the current sonochemistry, the possible role of acoustic waves on stereochemical course of reactions has been increased [23].

If the sonochemical acceleration or promotion of a reaction occurs in cavitational sites of the medium, the rate of a first-order reaction under sonication can be expressed as follows:

$$v = k_{son,obs}\, c = k_{nonson}\, c + x k^{\circ}_{son} c,$$

where x is the fraction of the reaction medium under perturbation by cavitation at any instant. While the observed sonochemical acceleration is $a_{obs} = k_{son,obs}/k_{nonson}$, the intrinsic sonochemical acceleration is

$$a^{\circ} = \frac{k^{\circ}_{son}}{k_{nonson}} = \frac{1}{x}\left(\frac{k_{son,obs}}{k_{nonson}} - 1\right)$$

Whereas rate constants $k_{son,obs}$ and k_{nonson} can be routinely determined, the values for x are not available in most cases. However, void fractions of 10^{-4} [24] or 2.9×10^{-5} to 4.2×10^{-5} [25] have been calculated for water under sonication. Actually, the active volume including the shell around the bubble may be greater. Hua et al. [26] used a heat-transfer model for the estimation of the lifetime and spatial extent of alleged supercritical water during the cavitational collaps. A value for x, equal to 1.5×10^{-3} in pure water was proposed [26]. Thus, depending on how rigorous conditions the reaction requires, x can take different values; however, it does not much exceed 10^{-3}. In other words, 0.1% of the reaction solution or less is under cavitation simultaneously. This means that quenching of a reaction in the cavitation zone cannot be ascertained experimentally.

Most likely sonochemical effects cannot be caused by direct influence of the sound field on the reacting species on the molecular level, since the energy of ultrasound is too low to alter electronic, vibrational, or rotational states of reacting molecules [19–23].

Following these explanations, it can be concluded that an ionic reaction, which is not switchable to a radical pathway, should not be susceptible to ultrasound effects. However, several examples of homogeneous polar reactions, accelerated by ultrasound, have been found. These are mostly hydrolysis and solvolysis reactions, which have been kinetically investigated for sonication effects.

Acid-catalyzed hydrolysis of methyl or ethyl acetate has been investigated by a number of groups [27–30]. The sonication effects described were from low to moderate, and the rate enhancements less than 60% were found. Under conditions affording more pronounced sonication effects, a many-fold acceleration of the acid-catalyzed hydrolysis of ethyl acetate in water was attained [31]. Still lower acceleration (14–15%) by ultrasound was found for hydrolysis of 4-nitrophenyl esters of a number of aliphatic carboxylic acids in a water-acetonitrile mixture [32]. In contrast, an ultrasonic acceleration by two orders of magnitude was reported by Hua et al. [26] for the hydrolysis of 4-nitrophenyl acetate in water.

Large sonication effects up to 20 times were observed for the solvolysis reaction of 2-chloro-2-methyl-propane in ethanol-water [33–36], iso-propanol-water [34] and *tert*-butanol-water [34] mixtures by Mason's group. Tree different ultrasonic generators operating at 20 kHz [35, 36], 45 kHz [34] and 80 kHz [33] were used. Kinetics of solvolysis of *t*-BuCl was followed conductometrically.

For polar reactions, the solvation of reactants is one of the most important factors governing the rates of the reactions [37]. In binary solvents, the situation is complicated by the selective solvation of species. It means that the composition of the solvation shell around the reacting species should be different from that in the bulk solvent. In solvents capable of hydrogen bonding, the structure of the medium is also of great importance [38]. Explanations of the sonochemical effects based on the idea of perturbation of the molecular organization of the solvation shell of the reaction system have been suggested [16, 36]. Thus, the results of kinetic measurements in binary solvents should be informative in this context.

Further evidence confirming these conclusions emerge from the kinetic study of the KCN-catalysed benzoin condensation of benzaldehyde in water or in ethanol-water binary mixtures carried out under ultrasound and without sonication in the present work.

4. METHODS OF KINETIC MEASUREMENTS

4.1. Acid-catalyzed hydrolysis of aliphatic esters

The kinetics of the acid-catalyzed hydrolysis of esters was followed by GLC determinations of the ester concentration in 1 M HCl solutions. The apparatus for ultrasonic measurements consisted of a stainless steel reaction vessel provided with a cooling jacket and equipped with an electronic thermometer and a titanium sonication horn with 14.5-mm tip diameter, reproducibly immersed into the reaction solution. Ultrasound was generated by an UZDN-2T probe (400 W) disrupter operating at 22 kHz. Its energy output was 55 W in water, estimated calorimetrically in the same reaction vessel (Chapter 5).

For kinetic measurements, 80 mL of the solution was transferred into the reaction vessel, 1 mL of *sec*-butyl alcohol was added as the internal standard for GLC analyses, and the ultrasound was switched on. The reaction temperature was maintained at 18.3±0.3°C by regulating the water circulation in the cooling jacket of the apparatus. After the temperature was equilibrated in the whole system, 0.5 mL of an ester (initial concentration 0.05–0.06 M) was injected into the solution to start the reaction. Aliquots of 0.5 mL were withdrawn at appropriate time intervals and treated three times with 0.2 mL of hexane. The joint hexane extracts were analyzed by GLC. The ratios of peak areas for the ester and the internal standard were plotted against time, and first-order kinetic constants were calculated from the obtained kinetic curves by means of a differential method, the error in the rate constants being ±0.3% or less.

Measurements without sonication were performed similarly in a reaction cell thermostated at 18.3 °C and equipped with a magnetic stirrer.

Esters were reagent grade and used without further purification. Water-ethanol and water-1,4-dioxane binary mixtures were prepared by weighing of necessary amounts of distilled water and carefully purified organic solvents.

4.2. Benzoin condensation of benzaldehyde

Reactions were run on 80 mL batches in a thermostatted glass cell sealed with elastomeric septa under argon atmosphere. In systematic measurements carried out at 65°C in water-ethanol mixtures the initial concentration of benzaldehyde ranged from 0.025 to 0.123 M and that of the catalyst, KCN from 0.023 to 0.069 M.

In order to determine thermodynamic activation parameters, rate constants were measured at 35°C, 50°C and 65°C with initial concentrations of benzaldehyde ranging from 0.0147 to 0.123 M.

Sonication was performed with an immersed titanium horn at 22 kHz (UZDN-2T probe disrupter) whose energy output in water and in aqueous ethanol up to $X_E = 0.37$ was 55 W in all our liquid systems, as determined calorimetrically (Chapter 5). Both under ultrasound and in its absence the reaction mixture was agitated with a magnetic stirring bar.

Aliquots (about 0.05 mL) were periodically removed and injected into the HPLC instrument equipped with a Waters 6000 HPLC pump and a 440 UV detector (254 nm). For HPLC analysis CH_3OH-H_2O (62:38, v/v) was used as the mobile phase, flow rate being 1 mL/min. Benzaldehyde concentration at any given time C_t was calculated from peak areas of benzaldehyde and benzoin by the formula

$$C_t = \frac{S_A}{S_A + aS_B} C_o ,$$

where S_A and S_B are peak areas of the aldehyde and benzoin, respectively, *a* is a calibration coefficient determined experimentally, and C_o the initial benzaldehyde concentration.

Plotting $1/C_t - 1/C_o$ versus time gave excellent straight lines whose slopes were taken as the pseudo-second order rate constants. Dividing the latter by the molar concentration of the catalyst gave third-order rate constants.

For GLC measurements a HP 5880 A instrument with a packed column OV-1 3%, 2.5m×2mm was used.

Benzaldehyde, distilled immediately before use, was free from impurities detectable by HPLC and GLC. Binary aqueous mixtures were prepared by weighing appropriate amounts of ethanol and water.

5. ULTRASONIC POWER MEASUREMENTS

(Carried out in collaboration with Siim Salmar)

Many authors have not reported the acoustic power dissipated in their reaction systems, making it difficult for subsequent researchers to reproduce results or compare reaction conditions. Since numerous physicochemical properties of binary systems depend on the composition non-linearly, it should be clearly determined how much of the ultrasonic energy is absorbed by the system at any component ratio to ensure a confident interpretation of the results.

Several methods are available to estimate the amount of ultrasonic power entered into a sonochemical reaction [20, 39]. Many authors have suggested determining the thermal effect of ultrasound as a mean of obtaining the effective power. It is based on the assumption that almost all the cavitational energy produces heat, and thus the output power can be obtained *via* calorimetry. The other method involves a chemical dosimeter, which monitors the sonochemical generation of a chemical species. The yields of the reaction after an adequate sonication time are regarded as a measure of the power of the ultrasound.

Although chemical dosimetry is generally believed to be the most straightforward method of determining the ultrasonic power in a sonochemical reaction, it cannot be applied to binary solvent systems, because the reaction rate as well as the ultrasonic acceleration probably depends on the solvent composition. However, many authors [40–43] have shown that the results from a chemical dosimeter were directly and linearly related to the calorimetrically determined ultrasonic power. In addition, it is important to notice that a chemical dosimeter may not describe the true acoustic power but describes the sonochemical efficiency for the reaction induced under certain experimental conditions [43].

In this work, the acoustic power entering the systems was determined by calorimetry. Three direct irradiation systems (probe systems) were used. Two different sonicators from Bandelin Electronic (Sonoplus HD 2070, 20 kHz, 70 W and Sonoplus HD 2200, 20 kHz, 200 W) were connected with a standard 500-ml calorimetric system equipped with a mechanical stirrer, a heating system, and a thermocouple. Both sonicators were set to equal output power. The irradiation horns with 12.7-mm tip diameter were immersed reproducibly (1.5 cm below the solution surface) into the sample.

Because of technical reasons, the UZDN-2T probe could not be used in a standard calorimetric system; therefore, for the sake of certainty, calorimetric measurements were also carried out in the stainless steel cell used for the kinetic studies described above, equipped for this work with a magnetic stirrer, a heating system and a thermocouple. For calorimetric measurements, the thermostating jacket was empty to minimize heat losses. Similarly with kinetic measurements, 80 ml samples were used. The temperature was monitored with an EVIKON E6011 temperature registration device.

The water equivalent of the calorimeter and the heat capacities C_p for solutions were determined using all of the equipment in parallel. Before heating or sonication, the solution inside the reactor was thermostated at an appropriate temperature close to ambient temperature (usually about 20°C). Temperature monitoring was started 90 seconds before and stopped 90 s after the heating or sonication period, which lasted 120 s. For the determination of ΔT (1.7–2.4 K) the temperature drifts were extrapolated to the midpoint of the energizing period.

The ultrasonic power that entered into the system was calculated by the following equation:

$$power(W) = \left(\frac{\Delta T}{\Delta t}\right) m \cdot C_p ,$$

where *m* the mass of the sample (g) and C_p is the heat capacity of the solution ($J \cdot g^{-1}$). (ΔT/Δt) is the temperature rise per second.

Ultrasonic power determinations were carried out in the 0–60 wt % region of dioxane-water and ethanol-water binary mixtures. The results of measurements with different equipment agreed within 0.5 to 1.5%. The relative power of ultrasound in the dioxane-water systems is presented in Table 1, with the calorimetric power in pure water taken for a unit. It appears that the calorimetric sonication effect in both dioxane-water and ethanol-water systems depend insignificantly on the solvent composition.

Table 1. Relative power of ultrasound in ethanol-water and 1,4-dioxane-water binary mixtures.

X, wt.%	X = EtOH	Z^a_{rel}	X = dioxane
0[b]	1[c]	1[d]	1[c]
10	1.013	1.038	1.018
20	1.016	1.066	1.021
30	1.014	1.046	1.024
40	1.007	0.989	1.025
50	1.003	0.923	1.012
60	0.990	0.860	1.004

[a] relative acoustic impedance of EtOH-H_2O system at 20°C, from Ref. 44. [b] pure water [c] 39.5 W in the 500 cm^3 calorimeter, and 55 W in the cell for kinetic measurements. [d] 1.48×10^{-6} kg $m^{-2}s^{-1}$

The power output of a sonicating horn will depend on the acoustic load, which can be expressed by the acoustic impedance

$$Z = \rho \cdot C,$$

where ρ is the density of the medium and C is the speed of sound in the fluid. It appears (Table 1) that the delivered power correlates well with the acoustic impedance of the noncavitating system.

If the assumption that almost all the cavitational energy produces heat that is measurable via calorimetry is valid, it follows that at least for the solvent systems under consideration the solvent properties have an insignificant effect on the number of cavitational events as well as the cavitational intensity.

6. ULTRASOUND EFFECT ON HYDROLYSIS OF ESTERS

(Measurements in ethanol-water mixtures carried out
in collaboration with Siim Salmar)

We have investigated the kinetics of the acid-catalyzed hydrolysis of different alkyl acetates in aqueous binary mixtures of ethanol and 1,4-dioxane without sonication and under ultrasound. The used GLC method of analysis allowed direct detection of the reaction products. Therefore it was possible to conclude that no other sonolytic degradation products were formed in this reaction, except those of the ester hydrolysis reaction. Moreover, although the rate constants were calculated from the decrease of the ester concentration in most cases, in several test experiments the formation of alcohol was also monitored and used for calculation of the rate constants. The results of these experiments were in good agreement, supporting the conclusion about the absence of any parallel reaction paths.

Nonsonic and ultrasonic rate constants for ester hydrolyses in water, ethanol-water, and 1,4-dioxane-water binary mixtures are presented in Tables 2 and 3. Although the nonsonic reaction rates decreased gradually with the increase in organic component content, the ultrasonic reactions showed complicated dependences on the solvent composition as is seen in Figures 1 and 2.

Table 2. Results of kinetic measurements in ethanol-water binary mixtures.

Ester	% w/w (X)[a] ethanol in water	Rate constant $k \times 10^5$ s^{-1} Nonsonic	Sonic	Ultrasonic acceleration
EtOAc	0 (0)	9.56	12.40	1.30
	9.1 (0.038)	6.91	8.01	1.16
	18.2 (0.08)	5.62	5.80	1.03
	27.8 (0.131)	5.00	6.78	1.36
	40.0 (0.207)	3.23	7.48	2.32
	50.0 (0.281)	2.37	5.76	2.43
PrOAc	10 (0.042)	1.53	5.36	3.50
	20 (0.089)	1.22	3.19	2.61
	30 (0.144)	1.16	2.24	1.93
	40 (0.207)	0.805	1.44	1.79
	50 (0.281)	0.59	1.05	1.78
BuOAc	10 (0.042)	9.06	24.2	2.67
	20 (0.089)	7.77	17.4	2.24
	30 (0.144)	5.50	9.50	1.73
	40 (0.207)	4.76	7.41	1.56
	50 (0.281)	3.99	5.52	1.38

[a] molar fraction of ethanol

Table 3. Results of kinetic measurements in 1,4-dioxane-water binary mixtures.

Ester	% w/w (X)[a] 1,4-dioxane in water	Rate constant $k \times 10^4$ s^{-1}		Ultrasonic acceleration
		Nonsonic	Sonic	
EtOAc	5 (0.01)	0.82	2.13	2.60
	15 (0.035)	0.68	2.31	3.40
	40 (0.120)	0.54	1.36	2.52
	60 (0.235)	0.46	0.79	1.72
BuOAc	5 (0.01)	0.96	2.27	2.365
	10 (0.022)	0.89	2.07	2.326
	20 (0.049)	0.79	1.52	1.924
	30 (0.081)	0.78	1.41	1.81
	40 (0.120)	0.59	0.84	1.42
	50 (0.170)	0.52	0.66	1.27
	60 (0.235)	0.37	0.36	0.97

[a] molar fraction of 1,4-dioxane

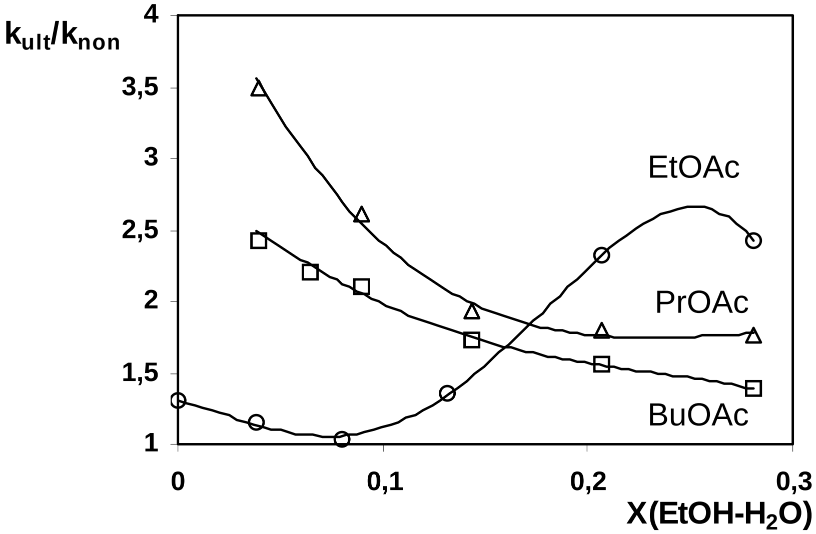


Figure 1. Rate enhancement of ester hydrolysis induced by ultrasonic irradiation in ethanol-water binary mixtures.

In ethanol-water solutions, small additions of ethanol, remaining in the range of $0 < X_E < 0.08$, exerted strong structure-making effects, accompanied by an increase in the self-association of water molecules. Indeed, the partial molar volume of ethanol is minimal at the alcohol content $X_E = 0.08$ [48], and the solvatochromic parameters distinctly show an enhancement of the structure of water in this region [49]. Further addition of alcohol prevents water from organizing into 3D structures. The structural behavior of these solutions is strongly altered at $X_E > 0.2$. In this region, a large number of ethanol-water bonds are formed, and water-water bonds are broken. All these results have led to a cluster model, including stacked ethanol core and a thin water shell around this core [50, 51]. This model allowed straightforward interpretation of our results: a hydrophobic reagent could be hidden inside the clusters and thus made unavailable for the reaction. If such interaction with the hydrophobic interior of the cluster can be hampered by ultrasound, the reaction should be accelerated accordingly.

On the basis of these findings it can be concluded that ultrasound disrupts the binary solvent structure, permits more favorable solvation and results in enhanced rate of the reaction. The negligible effect of ultrasound at 18 wt% ($X_E = 0.08$) of ethanol can be assigned to the rigidness of the solvent structure.

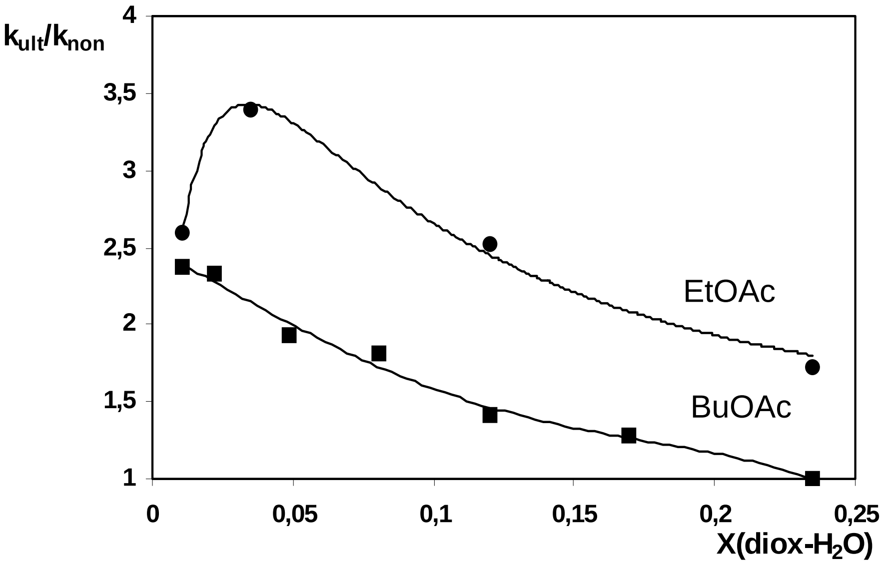


Figure 2. Rate enhancement induced by ultrasonic irradiation, of ester hydrolysis reactions, in 1,4-dioxane-water binary mixtures.

Kinetic data for ester hydrolysis in 1,4-dioxane-water solvent system were usefully complementary to the reasoning above. It has been pointed out that the structure enhancement of long-range order in water-alcohol systems appears to be absent in mixtures of dioxane and water [45, 46]. Moreover, in solutions ranging from pure water up to 0.2 mole fraction of dioxane, this solvent gradually breaks down the structure of water [47].

Consequently, in the region beyond 5 mol % of dioxane (Figure 2) the sonication effect can be attributed to the breakdown of ester-dioxane encounter complexes. Therefore the efficiency of acoustic irradiation was decreasing in parallel with the increase in content of the hydrophobic co-solvent in the mixture. More hydrophobic butyl acetate forms stronger encounter complexes with dioxane, evidently stronger than those with ethanol (cf. Table 2 or Figure 1).

The more complicated features of the sonication effects in the regions up to 15 mol % ethanol or 5 mol % dioxane cannot be interpreted as straightforwardly. Obviously, the perturbing effects of ultrasound on the solvent structure, on solute-solvent interactions and also on possible solute-solute interactions at low co-solvent content may be involved.

The sonication effects in ethanol-water mixtures were studied for three different esters, as shown in Figure 1. Interestingly, the sonication effects (k_{ult}/k_{non}), determined at $X_E > 0.15$ increased in reverse order with hydrophobicity of the esters, and sonication had the smallest effect in the case of butyl acetate, the substrate that should be most powerfully trapped within the clusters.

The plot in Figure 3, representing a linear free-energy relationship [52], demonstrates how the kinetic sonication effects can be quantitatively related to hydrophobicity of the esters, pointing to hydrophobic interaction of these compounds with the solvent. In Figure 3 logarithms of the kinetic sonication effects, observed at $X_E = 0.25$, are plotted *vs* the Hansch-Leo hydrophobicity parameter log P, where P is the partition coefficient of the substrates between 1-octanol and water [53, 54]. We can conclude that the regular decrease in the rate of ester hydrolyses in ethanol-water mixture is mainly due to hydrophobic interactions, i.e. to the ground-state stabilization by this solvent system.

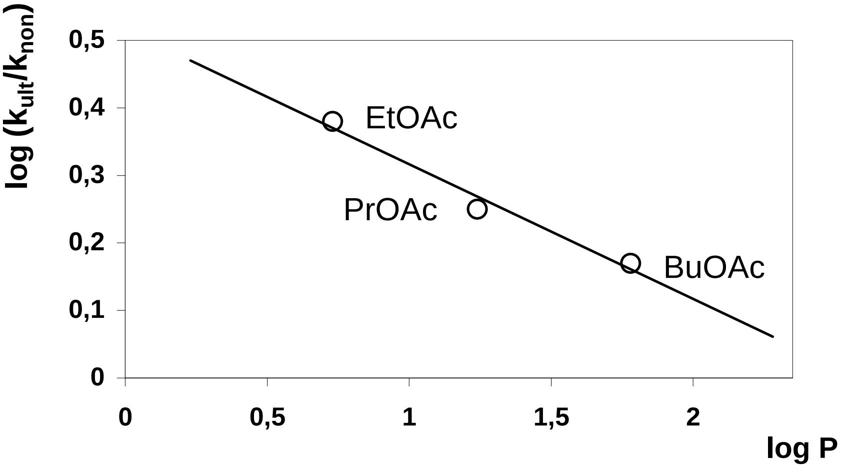


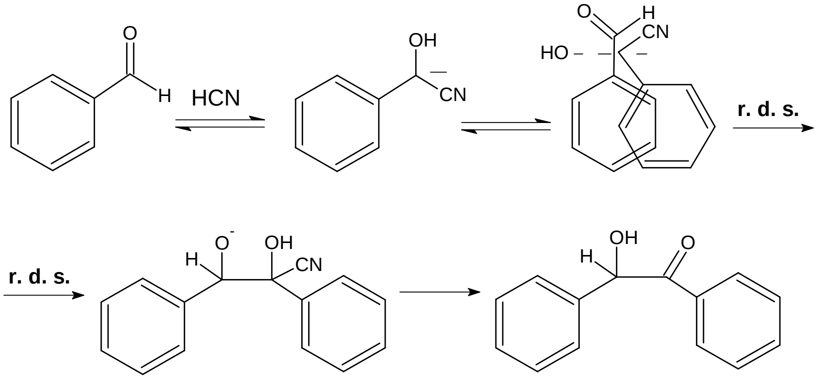
Figure 3. The linear free-energy relationship between kinetic sonication effect for ester hydrolysis and the hydrophobicity parameter log P. X_E was 0.25.

7. ULTRASOUND EFFECT ON BENZOIN CONDENSATION

Kinetics of the benzoin condensation of benzaldehyde in the presence of KCN as catalyst was investigated without sonication and under ultrasound in water and in ethanol-water binary solutions. We have chosen this reaction as a model for the following reasons.

Firstly, the mechanism of this reaction is well established [55] and shown in Scheme 1.

Scheme 1.



Secondly, it has been shown [2, 13] that hydrophobic packing of reactants in the transition state promotes the benzoin condensation reaction. In the rate-determing step of the reaction two benzene rings become stacked, an interaction that in an aqueous solvent is favored by a hydrophobic effect. In ethanolic solutions stacking effects should be greatly reduced; as a matter of fact the reaction is much slower than it is in water [13]. For this reason the reaction was investigated for hydrophobic effects by Breslow *et al* [2, 13].

And finally, a logical conclusion from the results of our sonication experiments with ester hydrolysis was that the rate of a reaction, if promoted by hydrophobic interactions, should decrease in the presence of ultrasound. Although the ultrasonic retardation for chemical reactions was previously predicted in our laboratory [16], this phenomenon has so far not been demonstrated experimentally. This provided a good challenge to investigate into this new aspect of sonochemistry

As expected, we observed that the benzoin condensation reaction was slowed down by ultrasound in pure water and in ethanol-water mixtures up to an ethanol content of 45 wt % (Table 4).

Table 4. Rate constants and sonication effects for the benzoin condensation of benzaldehyde.

EtOH wt%	$k_{nonson} \times 10^3$ [a]	$k_{son} \times 10^3$ [a]	k_{son}/k_{nonson}
0	7.17 ± 0.09	5.76 ± 0.07	0.80
10	4.97 ± 0.08	4.39 ± 0.08	0.88
20	3.47 ± 0.07	3.17 ± 0.06	0.92
30	2.60 ± 0.05	2.21 ± 0.05	0.85
40	1.92 ± 0.02	1.70 ± 0.02	0.89
50	1.38 ± 0.02	1.54 ± 0.02	1.12
60	1.06 ± 0.03	1.27 ± 0.02	1.20

[a] According to Kool and Breslow [13] $k_3 \times 10^3 = 8.9 \pm 2.2$ L^2 $mol^{-2}s^{-1}$ under the same conditions.

Excellent linear fit of kinetic data when treated by the second-order rate law (see Chapter 4), and linear dependence of pseudo-second order rate constants on the catalyst concentration (Figure 4) proved that ultrasound affected exclusively the rate-limiting condensation step of the reaction. Sonochemical degradation of benzaldehyde would have led to an apparent acceleration of the reaction instead of the observed retardation. A loss of benzoin by decomposition could lower the apparent reaction rate; in this case however a curvature of the second-order kinetic plot should be observed. Moreover, GLC analysis of solutions of benzaldehyde and benzoin in the absence of catalyst did not reveal any degradation products; even after the reaction mixture has been sonicated longer than required for the kinetic measurements.

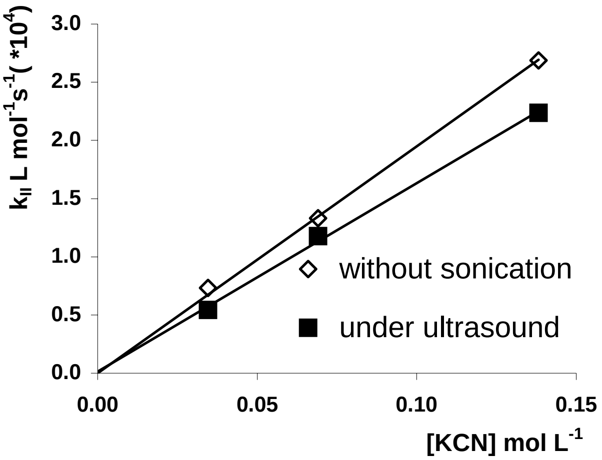


Figure 4. Dependence of the rate of the benzoin condensation of benzaldehyde on the concentration of the catalyst KCN in the 40 wt% ethanol-water solution under ultrasound and without sonication at 65 °C.

The retardation effect of ultrasound was most pronounced in pure water and gradually decreased with increasing ethanol content up to about $X_E = 0.25$ (Table 4), when sonication turned to a promoting factor. The last finding can be interpreted in terms of the structure of aqueous ethanol binary system (Chapter 6). Additions of ethanol up to 25 mol % modified the solution structure but evidently did not entirely prevent the favorable hydrophobic effects which were disturbed by ultrasound.

Ethanol clusters in this region, and more extensively even at higher X_E values, brought about different consequences at different ethanol concentrations. The condensation reaction was favored when clusters host encounter complexes of the reagents. On the other hand, when clusters hosted single reagent molecules, the reaction was slowed down. These effects obviously compete with one another; the small accelerating effect of ultrasound at $X_E > 0.20$ indicated the prevalence of the latter influence.

Hence, when ultrasound destabilized the encounter complexes between the reagents, sonication decreased the reaction rate. On the contrary, when it perturbed the solvent stabilization of the initial state of the reagents, sonication accelerated the reaction.

The observed statistically significant decrease of the rate of benzoin condensation means that the reaction was quenched in 20 % of the total volume, or was hindered in a larger part of the solution. This indicates that a non-radical sonochemical process occurred in the bulk solution, i. e. outside of cavitational bubbles.

Additionally we have determined the rate constants for benzoin condensation of benzaldehyde at 35°C, 50°C and 65°C in water and in aqueous-ethanol mixtures up to 60 wt% ethanol ($0 \leq X_E \leq 0.37$). Calculated activation parameters for this reaction at 25.0 °C are presented in Table 5 and in Figure 5.

Table 5. Isobaric activation parameters for benzoin condensation of benzaldehyde at 25.0 °C.

Content of ethanol wt % (X_E)	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (J/Kmol)	$\Delta G^{\neq}$ (kJ/mol)
0	32.20 ± 0.01	–195.60 ± 0.02	90.52
5 (0.020)	31.94 ± 0.50	–196.83 ± 1.55	90.63
10 (0.042)	41.65 ± 0.87	–167.46 ± 2.70	91.58
15 (0.065)	40.81 ± 1.17	–170.85 ± 3.63	91.75
20 (0.089)	34.90 ± 3.15	–190.42 ± 9.79	91.68
25 (0.115)	32.00 ± 0.94	–201.77 ± 2.92	92.16
30 (0.144)	34.99 ± 1.75	–191.26 ± 5.44	92.01
35 (0.174)	38.74 ± 0.44	–181.15 ± 1.38	92.75
40 (0.207)	39.15 ± 0.05	–181.53 ± 0.17	93.27
45 (0.243)	42.48 ± 1.97	–172.03 ± 6.14	93.77
50 (0.281)	41.89 ± 0.42	–173.61 ± 1.30	93.65
60 (0.370)	41.30 ± 2.74	–178.70 ± 8.53	94.58

The dependence of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ on the solvent composition tends to be complex. However, $\Delta G^{\neq}$ (not shown in Figure 5) increases monotonically as X_E rises from 0 to 0.4 and beyond, due to a strong compensation effect (cf. last column in Table 5).

Following the current notion of ethanol-water binary solvent structure (*vide supra*), Figure 5 can be conveniently divided by a vertical line corresponding to $X_E = 0.15$. In the right-hand region ($X > 0.15$) ethanol clusters prevail, while between pure water and about 30 wt% ethanol ($X \approx 0.15$) considerable changes in the solvent structure, and consequently in solute-solvent interactions, occur. In the latter region the activation parameters, and the sonication effects, show extremes; however, these do not parallel with each other and occur at different solvent ratios. Consequently, activation phenomena are related to the solvent composition in a complicated way. The same seems to apply to sonication effects.

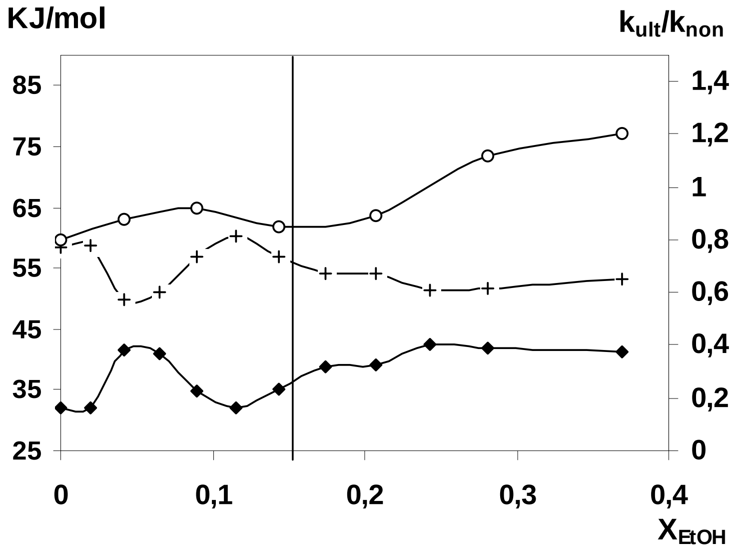


Figure 5. Isobaric activation parameters $\Delta H^{\#}$ (♦) and $-T\Delta S^{\#}$ (+) at 25°C and sonication effects (o) for benzoin condensation of benzaldehyde in water-ethanol binary mixtures (sonication data at 65°C).

The sonication effects for benzoin condensation have a maximum at $X_E \approx 0.07$. However, in this region the benzoin condensation has two extrema for activation parameters, which do not overlap with that of the sonication effect. Obviously, our solvent system affects the reaction by two opposite effects. Hydrophobic stabilization of the ground state retards the reaction, while hydrophobic stabilization of the encounter complex between reagent molecules accelerates it. Sonication suppresses both hydrophobic interactions, thus exerting competing effects on the reaction rate.

We must conclude that the kinetic sonication effects, which can be observed in water-ethanol binary solvents, cannot be directly correlated with trends in activation parameters, although in some cases this relatedness is obvious. The main reason for such disconformity's is that the activation parameters reflect changes in overall solvation energy in the ground state as well in the transition state. At the same time, sonication can merely affect subtle hydrophobic interactions in the solution. However, the advantage of sonication methods is that they are able to reveal particular effects, which remain hidden in conventional kinetics.

8. CONCLUSIONS

Impact of ultrasound on hydrophobic interactions, which govern rate of chemical reactions in water and water-solvent mixtures, has been studied in the present Thesis. For this reason the kinetics of the acid-catalyzed hydrolysis of alkyl acetates in aqueous binary mixtures containing 1,4-dioxane or ethanol, and the kinetics of the KCN-catalyzed benzoin condensation of benzaldehyde in water and in ethanol-water mixtures, was investigated without sonication and under ultrasound at 22 kHz.

The effective power of ultrasound was calorimetrically determined in 1,4-dioxane-water and in ethanol-water binary mixtures. It was found that ultrasonic power depends negligibly on the solvent composition. Therefore the effects of ultrasound observed in experiments were related to the effects of sonication directly on chemical reactions.

Ultrasonic acceleration of ester hydrolysis in ethanol-water and 1,4-dioxane-water binary systems was observed and the results were related to the perturbation of hydrophobic solute-solvent interactions, following the principles of the acoustic-field sonochemistry instead of the generally accepted hot-spot sonochemistry.

The kinetic sonication effects observed for the aliphatic ester hydrolysis were correlated with the Hansch-Leo hydrophobicity parameter (log P) for these substrates, and a linear free-energy relationship was proposed to quantify the hydrophobic interactions between the substrates and the solvent.

Sonochemical effects on benzoin condensation reaction were studied in different ethanol-water binary mixtures, and the thermodynamic activation parameters $\Delta S^{\neq}$ and $\Delta H^{\neq}$ were determined for the same reactions. It was found that ultrasound slowed down the rate of this process and the decrease in reaction rate at increasing content of ethanol in the binary solvent system could mainly reflect stabilization of the reaction ground state, which is largely stabilized by the hydrophobic interaction.

The phenomenon of retardation of chemical reaction by ultrasound was firstly discovered and kinetically described in this study, providing additional evidence for the presence of the acoustic-field sonochemistry effects in bulk solution.

It was concluded that ultrasonication can be used to reveal subtle hydrophobic interactions that may remain hidden in conventional kinetic study. By suppressing hydrophobic stabilization of the encounter complex between the reagents, sonication may hinder the reaction, while perturbing the hydrophobic stabilization of the reaction ground state, it may accelerate the reaction.

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SUMMARY IN ESTONIAN

Ultraheli mõju hüdrofoobsetele interaktsioonidele

Käesolevas töös oli esmalt vaatluse all ultraheli mõju alifaatsete estrite happekatalüütilisele hüdrolüüsile 1,4-dioksaan-vesi ja etanool-vesi binaarsetes segudes. Kineetilisteks ultraheliuuringuteks kasutatud etüül-, propüül- ja butüülatsetaadi happeline hüdrolüüs viidi läbi erinevatel binaarsegu koostistel ultraheliga kiiritades ja ilma ultrahelita.

Jõuti järeldusteni, et homogeensete polaarsete reaktsioonide sonokeemiline kiirenemine leiab aset kogu reaktsioonikeskkonnas. Rõhulained, mis on seotud helilainete levimisega või veelgi tõenäolisemalt lööklained, mis tekivad kavitatsioonimulli kollapsi tagajärjel, mõjutavad reaktsiooni üle kogu süsteemi. Sonikeerimine võib põhjustada muutusi osakeste translatoorses energias, mis viib solventstruktuuri lõhkumiseni või solvatatsioonitasakaalu nihkumiseni. Saadud tulemused võimaldavad järeldada, et ultrahelist tingitud reaktsiooni kiirenemine võib olla seotud lahustatud aine ja lahusti hüdrofoobse interaktsiooni häiritusega.

Lisaks on toodud töös esmakordselt kineetiliste ultraheliefektide ja estrite hüdrofoobsusparameetrite (log P) vaheline sõltuvus. Saadud lineaarne vabaenergia sõltuvus näitab kuidas on mõõdetud ultraheliefektid kvantitatiivselt seotud substraatide ja solventsüsteemi vahel olevate hüdrofoobsete interaktsioonidega.

On teada, et mitmed binaarsete solventsüsteemide füsikokeemilised omadused sõltuvad koostisest mittelineaarselt. Seetõttu määrati ka kuidas ultraheli energia neeldumine sõltub süsteemi koostisest. Kalorimeerilised mõõtmised viidi läbi nii etanool-vesi kui ka 1,4-dioksaan-vesi binaarlahustes. Töö tulemusena selgus, et määratud ultraheli võimsus on väga vähesel määral sõltuv solventsüsteemi koostisest.

Teiseks kineetiliste uuringute alusreaktsiooniks valiti bensoiini kondensatsioonireaktsioon, katalüsaatorina oli kasutusel kaaliumtsüaniid. Reaktsioonid viidi läbi vees ja erinevates vesi-etanool segudes, nii ultraheliga kiiritades kui ka ilma ultrahelita. Samuti arvutati reaktsiooni kiiruskonstantide andmetest bensoiini kondensatsioonireaktsiooni aktivatsiooniparameetrid.

Esmakordselt leitud ultraheli reaktsiooni aeglustav toime on selgeks tõendiks nn heliväija sonokeemia olemasolule lisaks üldiselt aktsepteeritud “hot-spot” sonokeemiale.

ACKNOWLEDGEMENTS

I wish to express my greatest gratitude to my supervisors Prof. Ants Tuulmets and Prof. Jaak Järv for their great guidance and support.

I would like to thank my colleagues and friends in the Department of Chemistry of the University of Tartu for the help during my PhD studies, especially Siim Salmar and Dr. Dmitri Panov for the great atmosphere in our lab.

I am also very thankful to Dr. Olavi Loog for helpful advices about experimental work.

This work has been carried out under the auspices of the European Union COST Action D32 (Working Group D32/006/04). The financial support Estonian Science Foundation (Grant No 4630) is also gratefully acknowledged.

PUBLICATIONS

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Hagu, H., Salmar, S., Tuulmets, A.
Ultrasonic acceleration of ester hydrolysis in ethanol-water and
1,4-dioxane-water binary solvents.
Proc. Estonian Acad. Sci. Chem. **2002**, 51, 235–239.

Proc. Estonian Acad. Sci. Chem., 2002, **51**, 4, 235–239

Ultrasonic acceleration of ester hydrolysis in ethanol–water and 1,4-dioxane–water binary solvents

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Received 9 May 2002

Abstract. Kinetics of the acid-catalysed hydrolysis of butyl acetate in ethanol–water and 1,4-dioxane–water binary solutions was investigated without sonication and under ultrasound at 22 kHz. Rate enhancements by 2.42 times or less were found to decrease with an increase in the content of the hydrophobic co-solvent in the binary solvent. The results suggest that ultrasonic acceleration of the reaction may be interrelated to the perturbation of hydrophobic solute–solvent interactions.

Key words: binary solvent mixtures, ester hydrolysis, ultrasound.

INTRODUCTION

The nature of the sonication effect on heterogeneous processes and free radical reactions is well understood by now [1, 2]. However, the acceleration of homogeneous polar reactions has not been investigated sufficiently, and the background of this phenomenon is not entirely clear.

Known examples of homogeneous polar reactions accelerated by ultrasound are solvolyses of organic halides and hydrolyses of esters. Moderate rate enhancements of 14–60% induced by irradiating the reacting solution with ultrasound have been reported for acid-catalysed or alkaline hydrolyses of esters [3–8]. Under conditions affording more pronounced sonication effects a many-fold acceleration of the acid-catalysed hydrolysis of ethyl acetate was attained in water [7] and ethanol–water mixtures [8]. Larger sonication effects were observed for the solvolysis reaction of *tert*-butyl chloride in ethanol–water and

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tert-butanol–water mixtures [9, 10], and also for the solvolysis of 1-bromo-1-phenylethane in ethanol–water mixtures [11].

It is generally accepted that ultrasonic irradiation affects chemical reactions through acoustic cavitation in the reaction medium [1, 2]. The collapse of cavitation bubbles generates transient hot spots with extremely high local temperature and pressure. It is hardly possible to conceive of a neat heterolytic reaction in a hot-spot region. Also, the effect of a possible temperature gradient after the cavitation collapse proves to be insignificant [12].

For polar reactions the solvation of reactants is one of the most important factors governing the rates of the reactions. In binary solvents the situation is complicated by the selective solvation of species. This means that the composition of the solvation shell around a species is different from the bulk solvent composition. In solvents capable of hydrogen bonding the structuredness of the medium is of great importance [13]. Explanations of the sonochemical effect dealing with the perturbation of the molecular organization of or the solvation in the reaction system have been suggested [10, 12]. In this connection, polar reactions in composite solvents must be the most sensitive to sonication. For this reason we are investigating sonochemistry in binary solvent systems.

Mason et al. [9, 10] studied the effect of ultrasound on the kinetics of *tert*-butyl chloride solvolysis in various alcohol–water mixtures. Acceleration increasing nonlinearly with an increase in the ethanol or *tert*-butanol content was found for the reaction. We are investigating a mechanistically different reaction, viz. the acid-catalysed hydrolysis of esters in organic–water mixtures, to elucidate some more details of the sonication effect on polar reactions. In this report we present the results for the acid-catalysed hydrolysis of butyl acetate in water–ethanol and water–1,4-dioxane binary solvents.

EXPERIMENTAL

The kinetics of the acid-catalysed hydrolysis of butyl acetate was followed by the gas-liquid chromatography (GLC) determination of the ester concentration in 1 M HCl solutions. The binary aqueous mixtures were prepared by weighing the calculated amounts of 1,4-dioxane or ethanol, water, and HCl solution. The experimental apparatus for ultrasonic measurements consisted of a stainless-steel cell reaction vessel provided with a cooling jacket and equipped with an electronic thermometer and a titanium sonication horn immersed reproducibly into the reaction solution. Ultrasound was generated by an UZDN-2T probe disrupter operating at 22 kHz. Its energy output was 34 W in water estimated calorimetrically in the same reaction vessel.

For kinetic measurements 80 mL of the solution was transferred into the reaction vessel, 1.5 mL of *sec*-butyl alcohol was added as the internal standard for GLC analyses, and ultrasound was switched on. The reaction temperature was maintained at $18.3 \pm 0.3\,^{\circ}C$ by regulating water circulation in the cooling jacket of the apparatus. After the temperature was equilibrated in the whole system, 0.5 mL of butyl acetate was injected into the solution to start the reaction. Aliquots of 0.5 mL were taken at appropriate time intervals and treated three times with 0.2 mL of hexane. The joint hexane extracts were analysed by using GLC. The ratios of the peak areas for the ester and the internal standard were plotted against time, and first-order kinetic constants were calculated from the obtained kinetic curves by means of a differential method.

Measurements without sonication were performed similarly in a reaction cell thermostatted at 18.3 °C and equipped with a magnetic stirrer.

RESULTS AND DISCUSSION

Nonsonic and ultrasonic rate constants for the reaction in water–ethanol and water–1,4-dioxane binary mixtures are presented in Table 1. Figure 1 shows the ultrasonic enhancement of the reaction rate as a function of solvent concentration expressed in molar ratios. In Fig. 1 the data from Ref. [8] for the hydrolysis of ethyl acetate at 18.3 °C are also shown.

As Fig. 1 demonstrates the dependence of the ultrasonic effect on solvent composition for ethyl acetate has a complicated shape involving minimum and maximum points. In our previous study [8] it was concluded that these phenomena should be related to the molecular structure of the binary solvent rather than to the reaction mechanism. However, replacement of ethyl acetate by more hydrophobic butyl acetate changed beyond recognition the dependence of the sonication effect on the solvent composition. Moreover, a very similar dependence was obtained in the 1,4-dioxane–water system for the same ester.

Engberts and co-workers (see [14] and references therein) have developed a versatile approach to reactions in binary solvent systems, ester hydrolyses included, basing on an idea about equilibrium formation of encounter complexes between reactants and hydrophobic co-solvents. The more hydrophobic are the reagents and the co-solvents, e.g. alcohols, the more extensively the reagents are included in the encounter complexes, being thus rendered unreactive.

Table 1. Results of kinetic measurements at 18.3 °C

% w/w	Rate constants $k \times 10^4$ s^{-1}				Ultrasonic acceleration	
	1,4-Dioxane–water		EtOH–water			
	Nonsonic	Sonic	Nonsonic	Sonic	1,4-Dioxane	EtOH
10	0.89 ± 0.069	2.07 ± 0.042	0.92 ± 0.0029	2.24 ± 0.0038	2.31	2.42
20	–	–	0.79 ± 0.015	1.66 ± 0.013	–	2.11
30	0.78 ± 0.031	1.41 ± 0.028	0.55 ± 0.0016	0.95 ± 0.0019	1.81	1.73
40	0.59 ± 0.0016	0.84 ± 0.0018	0.48 ± 0.0013	0.74 ± 0.001	1.42	1.56
60	0.37 ± 0.0019	0.34 ± 0.0014	–	–	0.94	–

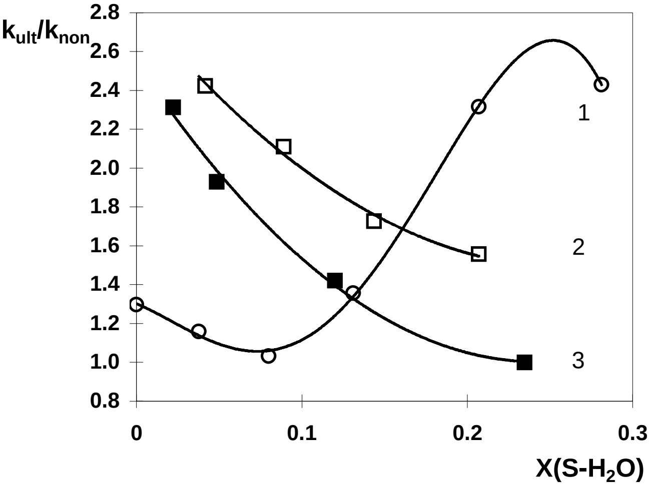

Fig. 1. Rate enhancements induced by ultrasonic irradiation for various solvent compositions (k_{ult} – sonic, k_{non} – nonsonic). 1 – hydrolysis of ethyl acetate (S = EtOH) from Ref. [8]; 2 – hydrolysis of butyl acetate (S = EtOH); and 3 – hydrolysis of butyl acetate (S = dioxane).

As a provisional explanation of our results we suggest an effect of ultrasound on solute–solvent interactions. In the case of ethyl acetate the hydrophobic interaction with ethanol systems seems to be relatively weak and the disturbing effect of ultrasound on the solvent structure is more pronounced. More hydrophobic butyl acetate forms stronger encounter complexes with ethanol and particularly with 1,4-dioxane. In this case the sonication effect consists mainly in the destruction of the encounter complexes. The efficiency of this decreases with increasing content of the hydrophobic co-solvent in the binary solvent mixture.

Further sonochemical investigations of ester reactions in binary solvents are in progress.

ACKNOWLEDGEMENT

This work was supported by the Estonian Science Foundation (ESF grant No. 4630).

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Estri hüdrolüüsi kiirendamine ultraheliga binaarsetes solventides etanool ja vesi ning 1,4-dioksaan ja vesi

Hannes Hagu, Siim Salmar ja Ants Tuulmets

Butüülatsetaadi happekatalüütilise hüdrolüüsi kineetikat uuriti binaarsetes lahustes etanool ja vesi ning 1,4-dioksaan ja vesi ultrahelita ning ultraheliga kiiritades 22 kHz sagedusel. Reaktsiooni kiiruse kasv (kuni 2,42 korda) väheneb hüdrofoobse kaassolvendi sisalduse suurenemisega binaarses solventsüsteemis. Tulemused võimaldavad järeldada, et ultrahelist tingitud reaktsiooni kiirenemine võib olla seotud lahustatud aine ja lahusti hüdrofoobse vastastikmõju häiritusega.

II

Tuulmets, A., Salmar, S., Hagu, H.
Effect of ultrasound on ester hydrolysis in binary solvents.
J. Phys. Chem., *B* **2003**, 107, 12891–12896. doi: 10.1021/jp035714l

J. Phys. Chem. B **2003,** *107,* 12891−12896

Effect of Ultrasound on Ester Hydrolysis in Binary Solvents

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Received: June 17, 2003; In Final Form: September 16, 2003

We have investigated the kinetics of the acid-catalyzed hydrolysis of ethyl, propyl, and butyl acetates in aqueous binary mixtures of ethanol and of 1,4-dioxane without sonication and under ultrasound at 22 kHz. Various rate enhancements were found in the region from pure water up to 50 wt % ethanol and 60 wt % dioxane. The calorimetric measurements performed in the same region indicated an insignificant effect of the solvent composition on the ultrasonic power. It was concluded that the sonochemical acceleration of ester hydrolysis in ethanol−water and 1,4-dioxane−water mixtures may be interrelated with the destruction of the molecular structure of the binary solvent and essentially with the perturbation of hydrophobic solute−solvent interactions. The ultrasonic acceleration of polar homogeneous reactions takes place in the bulk reaction medium. This implies the presence of acoustic-field sonochemistry besides the generally accepted hot-spot sonochemistry.

1. Introduction

A wide range of chemical processes can be promoted or accelerated by ultrasound.[1−3] Sonication affects mostly the rate of reactions, the yields, and in some cases the ratio of the products formed. The nature of the sonication effect on heterogeneous processes seems to be well understood. Cavitation brings about mechanical effects responsible for mass transfer, the activation of the surface of solid reagents or catalysts, the dispergation of particles, and so forth. Many homogeneous and heterogeneous reactions can be initiated or accelerated through the generation of free radicals that give rise to chain reactions in solution. In some cases, ultrasound has been found to change the reaction mechanism from polar to free radical. An ionic reaction that is not switchable to a radical pathway thus should not be susceptible to ultrasound effects. However, few examples of homogeneous polar (heterolytic) reactions accelerated by ultrasound have been found, providing a challenging puzzle for sonochemistry. These are solvolysis and hydrolysis reactions that have been kinetically investigated for sonication effects.

The acid-catalyzed hydrolysis of methyl or ethyl acetate has been investigated by a number of groups[4−7] The sonication effect was low to moderate, and rate enhancements of less than 60% were found. Under conditions affording more pronounced sonication effects, we attained a many-fold acceleration of the acid-catalyzed hydrolysis of ethyl acetate in water.[8]

Still lower acceleration (14−15%) by ultrasound was found for the hydrolysis of 4-nitrophenyl esters of a number of aliphatic carboxylic acids in a water−acetonitrile mixture.[9] In contrast to the aforementioned results, an ultrasonic acceleration by 2 orders of magnitude was reported by Hua et al.[10] for the hydrolysis of 4-nitrophenyl acetate in water.

Large sonication effects with acceleration up to 30 times were observed for the solvolysis reaction of 2-chloro-2-methylpropane in ethanol−water and *tert*-butyl alcohol−water mixtures[11,12] and also for the solvolysis of 1-bromo-1-phenylethane in ethanol−water mixtures.[13]

Reporting the absence of sonochemical effects is usually not considered to be an objective of publications. However, a very small sonication effect was reported for the rates of decarboxylation of 6-nitrobenzisoxasole-3-carboxylate in water.[14]

For polar reactions, the solvation of reactants is one of the most important factors governing the rates of the reactions.[15] In binary solvents, the situation is complicated by the selective solvation of species. This means that the composition of the solvation shell around a species is different from the bulk solvent composition. In solvents capable of hydrogen bonding, the structure of the medium is also of great importance.[16] Explanations of the sonochemical effect dealing with the perturbation of the molecular organization of or the solvation in the reaction system have been suggested.[12,17] Thus, the results of kinetic measurements in binary solvents should be informative in this context.

Mason et al.[11,12] studied the effect of ultrasound on the kinetics of *tert*-butyl chloride solvolysis in alcohol−water mixtures. An acceleration of the reaction increasing nonlinearly with an increase in the ethanol or *tert*-butyl alcohol content was found.

We undertook ultrasonic investigations of a mechanistically different reaction, viz., the acid-catalyzed hydrolysis of esters in aqueous binary mixtures, to elucidate more details of the sonication effect on polar reactions. Whereas in the case of *tert*-butyl chloride the matter of sonication-induced radical processes can still be raised, it is almost excluded when alkyl esters are used. Furthermore, experiments carried out in 1 M HCl solutions prevent possible pH changes due to water sonolysis or nitrogen oxidation products.[18,19]

In our previous paper,[20] we described the ultrasonic hydrolysis of ethyl acetate in ethanol−water solutions. Rate enhancements were found with a minimum at 18 wt % and a maximum at 45 wt % ethanol, reminiscent to some extent of the graph obtained by Mason et al.[12] In the present work, the investigation was extended to other hydrophobic esters. As in solvents capable of hydrogen bonding, the structure of the medium is of great importance. We also studied water−dioxane mixtures as binary solvent systems that supposedly have different structure with

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10.1021/jp035714l CCC: $25.00

respect to those of water−ethanol mixtures. In addition, we present a discussion of the possible ways that ultrasound can affect polar reactions.

2. Experimental Section

2.1. Reagents and Solutions. Water−ethanol and water−1,4-dioxane binary mixtures were prepared by weighing calculated amounts of doubly distilled water and carefully purified organic solvents. For kinetic measurements, appropriate amounts of a titrated HCl solution were also added. Esters were reagent grade and were used without further purification.

2.2. Kinetic Measurements. The kinetics of the acid-catalyzed hydrolysis of esters was followed by gas−liquid chromatography (GLC) determinations of the ester concentration in 1 M HCl solutions. The apparatus for ultrasonic measurements consisted of a stainless steel reaction vessel provided with a cooling jacket and equipped with an electronic thermometer and a titanium sonication horn (with 14.5-mm tip diameter) reproducibly immersed into the reaction solution. Ultrasound was generated by a UZDN-2T probe (400 W, made in the USSR) disrupter operating at 22 kHz. Its energy output was 55 W in water estimated calorimetrically in the same reaction vessel.

For kinetic measurements, 80 mL of the solution was transferred into the reaction vessel, 1 mL of *sec*-butyl alcohol was added as the internal standard for GLC analyses, and the ultrasound was switched on. The reaction temperature was maintained at 18.3 ± 0.3 °C by regulating the water circulation in the cooling jacket of the apparatus. After the temperature was equilibrated in the whole system, 0.5 mL of an ester (initial concentration 0.05−0.06 M) was injected into the solution to start the reaction. Aliquots of 0.5 mL were withdrawn at appropriate time intervals and treated three times with 0.2 mL of hexane. The joint hexane extracts were analyzed by GLC. The ratios of peak areas for the ester and the internal standard were plotted against time, and first-order kinetic constants were calculated from the obtained kinetic curves by means of a differential method, the error in the rate constants being ±0.3% or less.

Measurements without sonication were performed similarly in a reaction cell thermostated at 18.3 °C and equipped with a magnetic stirrer.

2.3. Ultrasonic Power Measurements. The acoustic power entering the systems was determined by calorimetry.

Three direct irradiation systems (probe systems) were used. Two different sonicators from Bandelin Electronic (Sonoplus HD 2070, 20 kHz, 70 W and Sonoplus HD 2200, 20 kHz, 200 W) were connected with a standard 500-mL calorimetric system equipped with a mechanical stirrer, a heating system, and a thermocouple. Both sonicators were set to equal output power. The irradiation horns with a 12.7-mm tip diameter were immersed reproducibly (1.5 cm below the solution surface) into the sample.

Because of technical reasons, the UZDN-2T probe could not be used in a standard calorimetric system; therefore, for the sake of certainty, calorimetric measurements were also carried out in the cell used for the kinetic studies described above, equipped for this work with a magnetic stirrer, a heating system, and a thermocouple. For calorimetric measurements, the thermostating jacket was empty to minimize heat loss. Similarly with kinetic measurements, 80-mL samples were used. The temperature was monitored with an EVIKON E6011 temperature registration device.

The water equivalent of the calorimeter and the heat capacities C_p for solutions were determined using all of the equipment in parallel. Before heating or sonication, the solution inside the reactor was thermostated at an appropriate temperature close to ambient temperature (usually about 20 °C). Temperature monitoring was started 90 s before and stopped 90 s after the heating or sonication period, which lasted 120 s. For the determination of ΔT (1.7−2.4 K), the temperature drifts were extrapolated to the midpoint of the energizing period.

The ultrasonic power that entered the system was calculated by the following equation:

$$\text{power } (W) = \left(\frac{\Delta T}{\Delta t}\right) C_p \cdot M$$

where C_p is the heat capacity of the solution ($\mathrm{J \cdot g^{-1}}$) and M is the mass of the sample (g). ($\Delta T/\Delta t$) is the temperature rise per second.

Ultrasonic power determinations were carried out in the 0−60 wt % region of ethanol−water and dioxane−water binary mixtures. Calorimetrically measured specific heat capacities for ethanol−water mixtures were in agreement with literature data[21] within ±2.2%. The results of measurements with different equipment agreed within 0.5 to 1.5%.

3. Results

The kinetics of the reaction were followed by gas−liquid chromatography. An advantage of the GLC method is the direct analysis of reaction products. No sonolytic degradation products except those from the hydrolysis of esters were detected. Although the rate constants were calculated as a rule from the disappearance of the ester, in some check experiments peaks of the alcohol that was formed were used for calculations. The results agreed within experimental error.

For the effect of ultrasound on the rate of the reaction in ethanol−water and 1,4-dioxane−water mixtures, nonlinear dependences involving extreme points were found. Because many physicochemical properties of binary systems depend on the composition nonlinearly, it should be clearly determined how much of the ultrasonic energy is absorbed by the system at any component ratio to ensure a confident interpretation of the results.

Several methods are available to estimate the amount of ultrasonic power entering a sonochemical reaction.[2,22] Many authors have suggested determining the thermal effect of ultrasound as a means of obtaining the effective power. This is based on the assumption that almost all of the cavitational energy produces heat, and thus the output power can be obtained via calorimetry. The other method involves a chemical dosimeter, which monitors the sonochemical generation of a chemical species. The yields of the reaction after an adequate sonication time are regarded as a measure of the power of the ultrasound.

Although chemical dosimetry is generally believed to be the most straightforward method of determining the ultrasonic power in a sonochemical reaction, it cannot be applied to binary solvent systems because the reaction rate as well as the ultrasonic acceleration probably depends on the solvent composition. However, many authors[23−26] have shown that the results from a chemical dosimeter were directly and linearly related to the calorimetrically determined ultrasonic power. In addition, it is important to notice that a chemical dosimeter may not describe the true acoustic power but describes the sonochemical efficiency for the reaction induced under certain experimental conditions.[26]

TABLE 1: Relative Power of Ultrasound in Ethanol−Water and 1,4-Dioxane−Water Binary Mixtures

X, wt %	X = EtOH	Z_{rel}[a]	X = dioxane
0[b]	1[c]	1[d]	1[c]
10	1.013	1.038	1.018
20	1.016	1.066	1.021
30	1.014	1.046	1.024
40	1.007	0.989	1.025
50	1.003	0.923	1.012
60	0.990	0.860	1.004

[a] Relative acoustic impedance of the EtOH−H_2O system at 20 °C, from ref 27. [b] Pure water. [c] 39.5 W in the 500-cm^3 calorimeter and 55 W in the cell for kinetic measurements. [d] 1.48×10^{-6} kg m^{-2} s^{-1}.

Our ultrasonic power determinations were performed in the 0−60 wt % region of ethanol−water and dioxane−water binary mixtures. The relative power of ultrasound in the systems is presented in Table 1, with the calorimetric power in pure water taken for a unit. It appears that the calorimetric sonication effect depends insignificantly on the solvent composition. The relative data in Table 1 can be considered to be correction coefficients by which the ultrasonic acceleration ratios in this work or published in former papers[11,12,20] should be divided to normalize the data. However, the values in Table 1 are definitely bracketed with the experimental uncertainty limits of these studies and need not be applied.

The power output of a sonicating horn will depend on the acoustic load, which can be expressed by the acoustic impedance

$$Z = \rho \cdot C$$

where ρ is the density of the medium and C is the speed of sound in the fluid. It appears (Table 1) that at least for ethanol−water mixtures the delivered power correlates well with the acoustic impedance of the noncavitating system.

If the assumption that almost all of the cavitational energy produces heat that is measurable via calorimetry is valid, it follows that at least for the solvent systems under consideration the solvent properties have an insignificant effect on the number of cavitational events as well as the cavitational intensity. This result is somewhat unexpected in the context of the complexity and microheterogenity of alcohol−water binary systems (vide infra); however, the total number of bubbles and the energy dissipated per bubble can change as the composition of the solution changes. Hence, the total amount of cavitational energy may remain constant if changes in these two variables counteract each other. However, our results indicate that dependences of the ultrasonic rate enhancement on solvent composition do describe changes in the sonochemical efficiency.

Nonsonic and ultrasonic rate constants for ester hydrolyses in water, ethanol−water, and 1,4-dioxane−water binary mixtures are presented in Tables 2 and 3. For comparison, the data from the previous paper for ethyl acetate hydrolysis in the ethanol−water system are included. Although the nonsonic reaction rates gradually decrease with the increase in organic component content, the ultrasonic reactions show complicated dependences on the solvent composition as is seen in Figures 1 and 2.

4. Discussion

TABLE 2: Results of Kinetic Measurements in Ethanol−Water Binary Mixtures

ester	% w/w (X)[a] ethanol in water	rate constant $k \times 10^5$ s^{-1} nonsonic	sonic	ultrasonic acceleration
EtOAc	0 (0)	9.56	12.40	1.30
	9.1 (0.038)	6.91	8.01	1.16
	18.2 (0.08)	5.62	5.80	1.03
	27.8 (0.131)	5.00	6.78	1.36
	40.0 (0.207)	3.23	7.48	2.32
	50.0 (0.281)	2.37	5.76	2.43
PrOAc	10 (0.042)	1.53	5.36	3.50
	20 (0.089)	1.22	3.19	2.61
	30 (0.144)	1.16	2.24	1.93
	40 (0.207)	0.805	1.44	1.79
	50 (0.281)	0.59	1.05	1.78
BuOAc	10 (0.042)	9.06	24.2	2.67
	20 (0.089)	7.77	17.4	2.24
	30 (0.144)	5.50	9.50	1.73
	40 (0.207)	4.76	7.41	1.56
	50 (0.281)	3.99	5.52	1.38

[a] Molar fraction of ethanol.

TABLE 3: Results of Kinetic Measurements in 1,4-Dioxane−Water Binary Mixtures

ester	% w/w (X)[a] 1,4-dioxane in water	rate constant $k \times 10^4$ s^{-1} nonsonic	sonic	ultrasonic acceleration
EtOAc	5 (0.01)	0.82	2.13	2.60
	15 (0.035)	0.68	2.31	3.40
	40 (0.120)	0.54	1.36	2.52
	60 (0.235)	0.46	0.79	1.72
BuOAc	5 (0.01)	0.96	2.27	2.365
	10 (0.022)	0.89	2.07	2.326
	20 (0.049)	0.79	1.52	1.924
	30 (0.081)	0.78	1.41	1.81
	40 (0.120)	0.59	0.84	1.42
	50 (0.170)	0.52	0.66	1.27
	60 (0.235)	0.37	0.36	0.97

[a] Molar fraction of 1,4-dioxane.

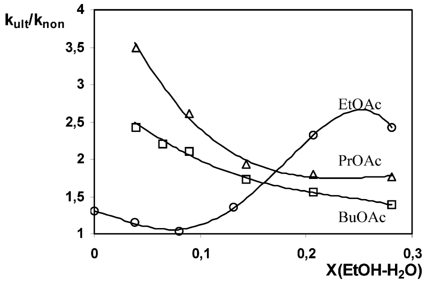

Figure 1. Rate enhancements of ester hydrolysis induced by ultrasonic irradiation in ethanol−water binary mixtures.

4.1. Sonication Effects in Binary Solvent Mixtures. Both our data for the hydrolysis of ethyl acetate (Figure 1) and the data from Mason's group[11,12] for the solvolysis of *tert*-butyl chloride at 20 °C show a distinct maximum in the region of about 50 wt % ethanol. Mason et al.[11,12] have pointed out a coincidence of the maximum in their data with the maxima found in the viscosity, enthalpy of mixing, and sound absorption versus solvent composition curves.[16] These properties of the binary liquid mixture show the existence of a structurally critical region at 0.2−0.3 mol fraction (40−50 wt %) of ethanol. This is also reflected in the volumes of activation $\Delta V^{\#}$. All of the available data for a variety of solvolysis reactions in ethanol−water mixtures show a decrease in $\Delta V^{\#}$ when passing from water to ethanol−water mixtures and a minimum in the region between 0.2 and 0.3 mol fraction of the alcohol.[28]

Recent spectroscopic, X-ray diffraction, and mass spectrometric investigations have shed light on the structure of ethanol−

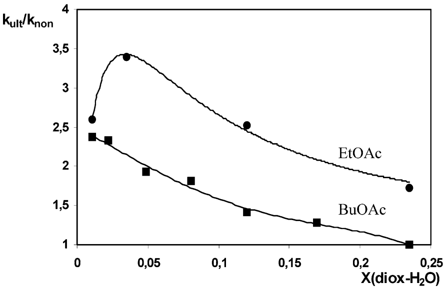

Figure 2. Rate enhancements of ester hydrolysis induced by ultrasonic irradiation in 1,4-dioxane−water binary mixtures.

water solutions.[29−31] It has been concluded that small additions of ethanol in the range of $0 < X_E < 0.08$ (X_E is the ethanol molar ratio) exert a strong structure-making effect accompanied by an increase in the self-association of water molecules. Indeed, the partial molar volume of ethanol is a minimum at $X_E = 0.08$,[32] and the excess solvatochromic parameters distinctly show an enhancement in the structure of water in this region.[33]

Further additions of the alcohol begin to prevent water from organizing into 3D structures. The structural behavior of these solutions is strongly modified at $X_E > 0.2$. In this region, a large number of ethanol−water bonds are formed, and water−water bonds are broken. All of these results have led to a cluster model of a stacked ethanol core and a thin water shell.[29,30] The observations for diluted aqueous solutions of ethanol suggested the evolution of an ethanol polymer structure and a complete breakdown of the bulk water structure at $X_E > 0.1$.

On the basis of of these findings, the application of ultrasound to the reaction would, by disrupting the binary solvent structure, permit more favorable solvation and result in enhanced rates of reaction. The negligible effect of ultrasound at 18 wt % ($X_E = 0.08$) ethanol was assigned to the rigidness of the solvent structure reported in our previous paper.[20]

However, solute−solvent interactions in these complicated systems can be particularly important (e.g., the replacement of ethyl acetate by more hydrophobic esters changed beyond recognition the dependence of the sonication effect on the solvent composition).

Considering the cluster formation in ethanol−water solutions, propyl and butyl esters were used as probes of the possible inclusion of a reagent in the hydrophobic interior of clusters. Indeed, the sonication effect in the region $0.2 < X_E < 0.3$ correlates with the order of hydrophobicity of the esters. Butyl acetate should be the most powerfully held by clusters, and sonication is the least efficient in this case.

Engberts and Blandamer et al.[34−36] have developed a versatile quantitative approach to reactions in binary solvent systems, including ester hydrolyses based on an idea about the equilibrium formation of encounter complexes between reactants and hydrophobic cosolvents. The more hydrophobic the reagents and the cosolvents (e.g. alcohols), the more extensively the reagents are included in the encounter complexes and thus rendered unreactive. From the rate constants for the neutral hydrolysis of *p*-methoxyphenyl-2,2-dichloroalkanoates in dilute aqueous solutions of short-chain alcohols, the molar energies of hydrophobic interactions between the components of the solutions have been estimated to be as small as 1 kJ or less.[36] Nevertheless, 2-fold and greater rate decreases in solutions that are about 2 mol % in alcohol and 10^{-5} M in ester were plausibly assigned to hydrophobic interactions.

Kinetic data for the hydrolysis in the 1,4-dioxane−water solvent system are usefully complementary to the reasonings above. It has been pointed out that the structural enhancement of long-range order in water−alcohol systems appears to be absent in mixtures of dioxane and water.[37,38] Moreover, in solutions ranging from pure water up to 0.2 mol fraction, dioxane gradually breaks down the structure of water.[39]

Consequently, in the region beyond 5 mol % dioxane (Figure 2), the sonication effect can be attributed to the breakdown of ester−dioxane encounter complexes, the efficiency of irradiation decreasing with an increase in the content of the hydrophobic cosolvent in the mixture. More hydrophobic butyl acetate forms stronger encounter complexes with dioxane, evidently stronger than those with ethanol (cf. Table 2 or Figure 1).

The complicated features of the sonication effects in the regions up to 15 mol % ethanol or 5 mol % dioxane cannot be interpreted as straightforwardly. Obviously, the perturbing effects of ultrasound on the solvent structure, on solute−solvent interactions, and also on possible solute−solute interactions at low cosolvent content may be involved.

In contrast to the sonication effects and despite considerable changes in the solvent structure, rate constants for the hydrolyses without ultrasonic irradiation decrease slightly and monotonically with increasing organic cosolvent content (Tables 2 and 3). The same was observed for the solvolysis of *tert*-butyl chloride in ethanol−water mixtures.[11,12,40] Winstein and Fainberg[40] have shown that the activation free energy of *tert*-butyl chloride solvolysis increases smoothly with increasing ethanol content and that the enthalpy and entropy of activation that are manifest clearly express extremes in the region of 15 mol % ethanol. This is also the region of the maximum solvation energy of the initial reagent, *tert*-butyl chloride.[41] A similar compensation effect has been observed for the hydrolysis of ethyl acetate in water−DMSO and water−acetone systems.[42]

Thus, ultrasonication is able to reveal subtle interactions and particular effects of an entropic or enthalpic origin, which remain hidden in conventional kinetics. Ultrasonic studies have been claimed to be an aid in the characterization of the intermolecular forces that are present in solutions and liquid mixtures. In this regard, ultrasound in kinetic investigations may become a useful tool for physicochemical, particularly mechanistic, investigations.

4.2. Mode of Action of Ultrasound. From mean velocities for the first half-lives of reactions without sonication and under ultrasound, the sonochemical efficiency of our experimental equipment was estimated to be 1.3×10^{-9} mol J^{-1} for the hydrolysis of butyl acetate in 40 wt % dioxane and 2×10^{-9} mol J^{-1} for ethyl acetate in 50 wt % ethanol. These numbers are comparable to those reported for OH radical formation in water (3×10^{-10} mol J^{-1}),[43] the sonolysis of 4-nitrophenylacetate (5.7×10^{-9} mol J^{-1}),[44] KI oxidation (6×10^{-9} mol J^{-1}),[26] and Fricke dosimetry (3×10^{-10} mol J^{-1}).[26] If not coincidental, then this comparability is somewhat amazing because all of the data listed above are related to radical formation or degradation reactions (i.e., to high-energy processes), but in our case only weak interactions in the solution are perturbed by the irradiation. This means that similar molar efficiency is associated with an incomparably lower energetic efficiency in the case of these polar reactions. Hence, the question of how ultrasound acts upon homogeneous ionic reactions still needs to be answered.

Cavitation is now generally accepted as the origin of the chemical effects of ultrasound. The sonochemical reaction is thought to occur in the cavitation bubble or in its immediate vicinity.[1−3] Extremely harsh conditions are produced by the collapse of a cavitation bubble. This collapse generates transient hot spots with local temperatures and pressures of several thousand Kelvin and hundreds of atmospheres.[45,46] Under these conditions, standard solvents are in the supercritical state, thus providing a promoting medium for certain reactions.[10,47]

Three regions in which a reaction can take place exist in a cavitating liquid: the gaseous phase inside the bubble, the limit shell around it, and the bulk solution.[47,48] Therefore, a cavitating reaction medium should be considered to be a pseudo-heterogeneous system, and the term “homogeneous sonochemistry” has been claimed to be misleading.[49] This is an expression of the concept that sound energy is focused in small regions and is not able to process into the rest of the material, and thus its effect is felt only at certain points in the medium.

As the sonochemical acceleration or promotion of a reaction presumably occurs in the cavitational microheterogeneties of the reaction medium, the intrinsic rate enhancement of the reaction at this site should be most informative for the investigation and understanding of sonication effects.

The rate of a first-order reaction under sonication can be expressed as follows:

$$v = k_{\text{son,obs}}[c] = k_{\text{silent}}[c] + x k^{\text{o}}_{\text{son}}[c]$$

where *x* is the fraction of the reaction medium under perturbation by cavitation at any instant.

Thus, the intrinsic sonochemical rate constant can be calculated as

$$k^{\text{o}}_{\text{son}} = \frac{k_{\text{son,obs}} - k_{\text{silent}}}{x}$$

Accordingly, whereas the observed sonochemical acceleration is

$$a_{\text{obs}} = \frac{k_{\text{son,obs}}}{k_{\text{silent}}}$$

the intrinsic sonochemical acceleration is

$$a^{\text{o}} = \frac{k^{\text{o}}_{\text{son}}}{k_{\text{silent}}} = \frac{1}{x}\left(\frac{k_{\text{son,obs}}}{k_{\text{silent}}} - 1\right)$$

Whereas rate constants $k_{\text{son,obs}}$ and k_{silent} can be routinely determined, the values for *x* are not available in most cases. Hua et al.[10] have suggested that transient supercritical water (SCW) occurs during ultrasonic irradiation in water, and a heat-transfer model for the estimation of the lifetime and spatial extent of SCW during the cavitational bubble collapse was presented. On the basis of semiquantitative calculations, a value for *x* equalling 0.0015 in pure water was proposed.[10]

Using the value for *x*, intrinsic sonochemical acceleration effects can be estimated from experimental data. However, it should be noted that the value for *x* by Hua et al.[10] concerns the integral volume of the transient SCW. If a reaction cannot be promoted in SCW and requires more rigorous conditions, which are provided in deeper layers of the shell or inside the gaseous phase of the bubble, the value for *x* is considerably smaller. The numbers in Table 4 are presented to depict the range of intrinsic accelerations required to produce the given observed rate enhancements. Obviously, the actual values for *x* fall in the range $0.001 > x > 0.0001$.

TABLE 4: Intrinsic Sonochemical Accelerations, $a°$, for Fractions of the Reaction Medium under Perturbation, X, and for Observed Rate Enhancements by Sonication, a_{obs}

	a^{o}	
X	$a_{\text{obs}} = 2$	$a_{\text{obs}} = 11$
0.01	100	1000
0.001	1000	10 000
0.0001	10 000	100 000

It follows from Table 4 that a reaction moderately accelerated by sonication but located in the cavitational sites has to proceed up to several thousands times faster than in the bulk solution. Such rate enhancements have been reported for only a few reactions and require substantial changes in solvent properties.[15]

Although the intrabubble gas phase is an inconceivable site for ionic reactions to proceed, the liquid shell, particularly in the supercritical state, can provide a favorable medium for reactions. However, the low density, low polarity, and cluster formation indigenous to SCW[50] counteract ester hydrolysis reactions. The bubble−bulk interface can also be a site of accumulation for hydrophobic molecules;[43,44,47] however, estimated concentration limits of species are far too low to provide the required rate enhancements. Moreover, the observed sonication effect increases in the opposite direction to the hydrophobicity of the esters.

Although an extension of the linear Arrhenius equation up to the SCW or hot-spot region temperatures may be acceptable in the case of cleavage or degradation reactions, the same approach is not valid for extremely solvation-dependent solvolysis or hydrolysis reactions. Moreover, the occurrence of high-temperature zones in a cavitating solution provides no adequate explanation of the observed effects in polar reactions because the absence of a sonication effect for a reaction with a positive activation energy has been documented[14] and has also been found in this work (Tables 2 and 3). Besides, no correlation between ultrasound efficiency and activation energy for the solvolysis of *tert*-butyl chloride in ethanol−water mixtures can be observed.[12,40]

From the definition of the activation volume of the reaction,

$$\left(\frac{\mathrm{d}\ln k}{\mathrm{d}P}\right)_T = -\frac{\Delta V^{\#}}{RT}$$

the acceleration caused by pressure can be calculated. Assuming an activation volume equal to -20 cm^{3}mol^{-1}, the rate of the reaction can be doubled by applying a pressure of 800 atm to the reaction solution at the standard temperature. At higher temperatures (e.g., in the cavitation bubbles), considerably greater pressure must be applied. If the reaction is accelerated only at cavitational sites with $x = 0.001$, then the same rate increase can be attained under a pressure greatly exceeding 7500 atm, which is hardly accessible even in the hot spots. Thus, the kinetic pressure effects should also be ruled out.

It follows that the observed acceleration ratios for polar homogeneous reactions, particularly those for ester hydrolysis, cannot be accounted for directly by the phenomena occurring in the cavitation bubbles. It seems to be necessary to take into consideration the bulk solution or at least an essential part of it.

Evidently, ultrasonic waves passing through the medium cause changes in the translational energy of species. The same may occur because of shock waves produced by collapsing cavitational bubbles in the medium. An acoustically induced motion of the water of crystallization in the crystal lattices leading to changes in the melting points of compounds has been pointed out.[51] The perturbation of normal molecular motion in the liquid phase by ultrasound has been detected through its effects on NMR spin−lattice relaxation times.[52,53] From NMR spectra, it has been found that the introduction of 20-kHz ultrasound to a liquid sample induces conformational changes to appropriate constituent molecules of the sample.[53] It has been accepted for a long time that the equilibria involving aggregates present in solution are perturbed by pressure changes produced by sound waves[54] and that extensively exploited relaxation processes in liquids are caused by the re-establishment of the equilibria perturbed by sound waves.[55,56] Our results only corroborate this concept pointing at a highly probable action of ultrasound in the bulk solution.

However, our results do not permit us to discern the true acoustic field effects from those caused by pressure waves due to the cavitation phenomena. In many cases, the contribution of cavitation is evident because the efficiency of ultrasound increased when hydrolysis was performed under argon[8,10] or decreased with the elevation of the reaction temperature.[11,12]

5. Conclusions

The results of our work, together with literature data, allow us to conclude that the sonochemical acceleration of polar homogeneous reactions takes place mostly in the bulk reaction medium. Pressure waves associated with the propagation of the acoustic waves or essentially the shock waves generated during the cavitation bubble's collapse affect reactions in the medium. Evidently, sonication can cause changes in the translational energy of species, thus leading to a solvent structure break or to a shift of solvation equilibria or likely to both. The ultrasonic acceleration of ester hydrolysis in ethanol−water and 1,4-dioxane−water binary systems can be largely related to the perturbation of hydrophobic solute−solvent interactions. This implies the presence of acoustic field sonochemistry besides the generally accepted hot-spot sonochemistry.

Because ultrasound appeared to be able to control the kinetics of ionic reactions by affecting weak interactions between the species in the bulk solution, the impact of ultrasound on living organisms may be more complex than simple mechanical effects due to cavitation phenomena.

Further work is underway on the aminolysis of esters with the purpose of obtaining better insight into sonication effects in polar homogeneous reactions. Besides, hydrolysis and aminolysis reactions of esters play an important role in the modification of proteins and in other methods of biotechnology. We believe that the application of ultrasound may provide control and refinement of these processes.

Acknowledgment. We are grateful to the Estonian Science Foundation (grant no. 4630) for financial support. We appreciate the helpful discussions provided by Professor Jean-Louis Luche and Professor Jaques Reisse.

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III

Hagu, H., Salmar, S., Tuulmets, A.
Impact of ultrasound on hydrophobic interactions in solutions:
ultrasonic retardation of benzoin condensation.
Ultrason. Sonochem. **2007**, accepted. doi: 10.1016/j.ultsonch.2006.09.012

ARTICLE IN PRESS

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Ultrasonics Sonochemistry xxx (2007) xxx–xxx

Ultrasonics SONOCHEMISTRY

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Impact of ultrasound on hydrophobic interactions in solutions: Ultrasonic retardation of benzoin condensation

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Received 23 July 2006; accepted 1 September 2006

Abstract

Kinetics of the benzoin condensation of benzaldehyde in presence of KCN as the catalyst in water and in ethanol–water binary solutions were investigated without sonication and under ultrasound at 22 kHz. A statistically significant 20% decrease of the rate was observed in water. The retardation effect of ultrasound gradually decreases up to 45 wt% ethanol content. We report an evidence of ultrasonic retardation of reactions and thereby a direct evidence for sonochemical processes in the bulk solution. Ultrasound can disturb solvation of the species in the solution. If breaking down the stabilization of the encounter complexes between the reagents, sonication hinders the reaction while perturbation of the solvent-stabilization of the reagents accelerates the reaction.

Keywords: Benzoin condensation; Hydrophobic interactions; Kinetics; Solvent effects; Ultrasound

1. Introduction

The primary effect of sonication is cavitation, which provides the mechanical energy for all subsequent chemical reactions. Cavitation brings about the erosion of materials, dispergation of particles, etc. Many homogeneous and also heterogeneous reactions can be promoted or accelerated through the generation of free radicals which give rise to chain reactions in solution [1–3].

The relevant mechanisms are not sufficiently understood for homogeneous ionic reactions such as hydrolysis and solvolysis in water and in aqueous binary solutions. According to basic conceptions of sonochemistry, e.g. to the first rule by Luche [2,4], an ionic homogeneous reaction not switchable to a radical pathway should not be susceptible to ultrasound effects. On the contrary, a number of examples of homogeneous polar (heterolytic) reactions accelerated by ultrasound have been found. For reviews of these works see, e.g. our recent papers [5,6].

Sonication studies on solvolysis and hydrolysis reactions in aqueous organic binary solvents have brought to light specific solute–solvent interactions and hydrophobic effects that are not manifested in conventional reaction kinetics [6–11]. It was concluded that the sonochemical acceleration may be interrelated with the destruction of the molecular structure of the binary solvent and essentially with the perturbation of hydrophobic solute–solvent interactions.

Hydrophobic interactions in aqueous solutions have been paid much attention recently [12–14]. The formation of encounter complexes between reactants and hydrophobic cosolvents appears to be particularly important. The more hydrophobic the reagents and the cosolvents, e.g. alcohols, the more extensively the reagents are included in the encounter complexes and thus rendered unreactive.

Recent spectroscopic, X-ray diffraction, and mass spectrometric investigations have shed light on the structure of ethanol–water solutions [15–17]. The structural behavior of these solutions is strongly modified at ethanol content 40–50 wt%. In this region, a large number of ethanol–water bonds are formed, and water–water bonds are broken. These results have led to a cluster model of a stacked ethanol core and a thin water shell [15,16]. Hydrophobic

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1350-4177/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ultsonch.2006.09.012

Please cite this article in press as: H. Hagu et al., Impact of ultrasound on hydrophobic interactions in solutions: ..., Ultrason. Sonochem. (2007), doi:10.1016/j.ultsonch.2006.09.012

reagents can be hidden in the clusters and thus made inaccessible for the reaction. If capable to break the interaction with hydrophobic interior of the cluster, ultrasound accelerates the reaction.

In our recent work [6] ethyl, *n*-propyl, and *n*-butyl acetates were used as probes of the inclusion of a reagent in the clusters. Indeed, the sonication effect ($k_{\text{son}}/k_{\text{nonson}}$) for the acid catalysed hydrolysis in the region correlated with the reverse order of hydrophobicity of the esters. Butyl acetate should be the most powerfully held by clusters, and sonication was the least efficient in this case. Our recent results for the sonication effects on the base-catalysed hydrolysis of 4-nitrophenyl acetate in aqueous ethanol [11] were interpreted well in line with the current understanding of hydrophobic interactions in aqueous solutions. It was found that the accelerating effect of ultrasound could be related to the perturbation of solute–solvent interactions [11].

A logical interference from the findings above was supposedly unfavourable effect of ultrasound upon the reactions promoted by hydrophobic interactions, e.g. Diels–Alder reaction, the benzoin condensation, etc. [12–14].

Ultrasonic retardation of the reactions has never been referred to in the sonochemical literature, therefore it may appear unexpected in general. However, it cannot be excluded, some researchers have encountered the phenomenon taking it for an experimental error or discarding as nonsense. We consider the rationalization of the sonochemical retardation of reactions particularly important.

Our choice for the model reaction was the benzoin condensation of benzaldehyde, a reaction of well established mechanism [18] (Scheme 1) investigated in detail for the hydrophobic effects by Breslow and Kool [12,19].

As expected, we observed slowing down of the reaction by ultrasound in pure water and also in water–ethanol solutions up to 45 wt% ethanol content.

2. Experimental

The binary aqueous mixtures were prepared by weighing calculated amounts of ethanol and water. Reactions were run on 80 mL scale in a thermostated at 65 °C glass cell with septa under argon atmosphere. In the systematic measurements in water–ethanol systems (Table 1) the initial concentration of benzaldehyde was 0.025–0.123 M and that of the catalyst, KCN was 0.023–0.069 M. Sonication was performed with an immersed titanium horn at 22 kHz (UZDN-2T probe disrupter). Its energy output in water was 55 W estimated calorimetrically. Under ultrasound and in absence of sonication the reaction mixture was agitated with a magnetic stirring bar.

Table 1
Rate constants and sonication effects for the benzoin condensation of benzaldehyde

EtOH wt%	$k_{\text{nonson}} \times 10^{3}$[a]	$k_{\text{son}} \times 10^{3}$[a]	$k_{\text{son}}/k_{\text{nonson}}$
0	7.17 ± 0.09	5.76 ± 0.07	0.80
10	4.97 ± 0.08	4.39 ± 0.08	0.88
20	3.47 ± 0.07	3.17 ± 0.06	0.92
30	2.60 ± 0.05	2.21 ± 0.05	0.85
40	1.92 ± 0.02	1.70 ± 0.02	0.89
50	1.38 ± 0.02	1.54 ± 0.02	1.12
60	1.06 ± 0.03	1.27 ± 0.02	1.20

[a] (L^2 mol^{-2} s^{-1}) Mean values of the three measurements at 65 °C.

Aliquots (about 0.05 mL) were periodically removed and injected into an HPLC chromatograph equipped with a Waters 6000 HPLC pump and a 440 UV detector (254 nm). For HPLC analysis $CH_3OH–H_2O$ (62:38, v/v) was used as the mobile phase, flow rate was 1 mL/min. Benzaldehyde concentration at a given time C_t was calculated from peak areas of benzaldehyde and benzoin,

$$C_t = \frac{S_A}{S_A + aS_B} C_0,$$

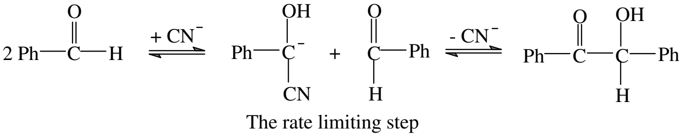
where S_A and S_B are peak areas of the aldehyde and benzoin, respectively, a is a calibration coefficient, and C_0 denotes the initial concentration of benzaldehyde.

Plotting $1/C_t - 1/C_0$ versus time gave excellent straight lines whose slopes were taken as the pseudo-second order rate constants (for an example see Fig. 1). Each condensation was followed to at least 20% conversion. Third-order rate constants were obtained by dividing the pseudo-second-order constants by molar concentration of the catalyst.

For GLC measurements a HP 5880 A instrument with a packed column OV-1 3%, 2.5 m × 2 mm was used.

3. Results and discussion

Excellent linear fit of kinetic measurements when treated by second-order methods, and linear dependence of pseudo-second order rate constants on the catalyst concentration (Fig. 2) evidence for the impact of sonication exclusively on the rate limiting condensation step of the reaction without any noticeable degradation of the reagents or occurrence of other side reactions. Sonochemical degrada-



Scheme 1.

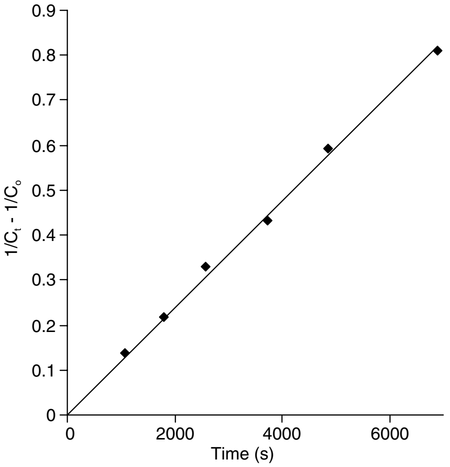


Fig. 1. A typical second-order kinetic plot under ultrasound in 40 wt% ethanol.

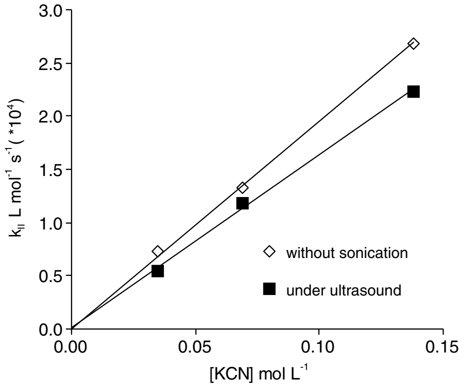


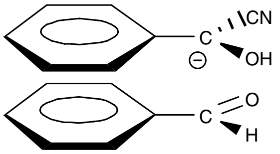
Fig. 2. Dependence of the rate of the benzoin condensation of benzaldehyde on the concentration of the catalyst KCN in the 40 wt% ethanol–water solution under ultrasound and without sonication at 65 °C.

tion of benzaldehyde would have led to apparent acceleration of the reaction instead of the observed retardation. A loss of benzoin by decomposition can result in lowering of the apparent reaction rate, however, would have been reflected by a curviture of the second-order kinetic plot. Moreover, GLC analyses did not reveal any by-products in solutions of benzaldehyde and of benzoin in absence of the catalyst after sonication during a period at least two times longer than in kinetic experiments.

It has been shown [12,19] that hydrophobic packing of the benzaldehyde reactants in the transition state promotes the benzoin condensation. Geometry of the rate determining step of the reaction is shown in Scheme 2, in which the two benzene rings stack next to each other favoured by a hydrophobic effect in an aqueous solvent. In ethanol solution, where stacking effects should be greatly reduced, the reaction is much slower than in water [19].

Accordingly to this, in Fig. 3 a gradual decrease of reaction rate with an increase in the ethanol content can be observed.

The retardation effect of ultrasound is most pronounced in pure water and gradually decreases up to about 45 wt% of ethanol content (Table 1 and Fig. 3). Then, since about 50 wt% of ethanol, sonication turns into a promoting factor. This apparently confusing behavior of the reaction can be attributed to the structure of aqueous ethanol binary system. Additions of ethanol up to 40 wt% modify the structure but evidently do not prevent the hydrophobic effects which are disturbed by ultrasound.



Scheme 2.

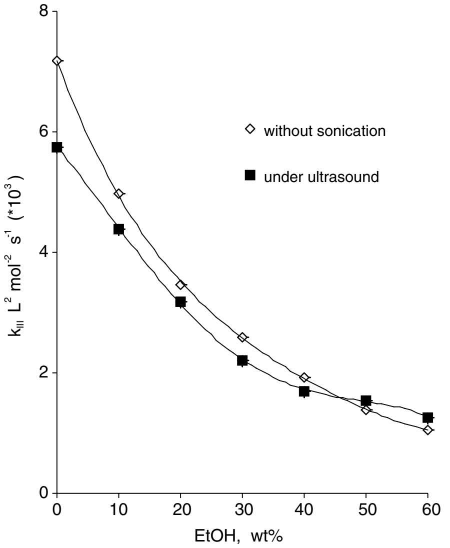


Fig. 3. Plot of third-order rate constants for the benzoin condensation of benzaldehyde versus ethanol content in the aqueous solution under ultrasound and without sonication at 65 °C catalysed with KCN.

Please cite this article in press as: H. Hagu et al., Impact of ultrasound on hydrophobic interactions in solutions: ..., Ultrason. Sonochem. (2007), doi:10.1016/j.ultsonch.2006.09.012

Formation of clusters in the region of further additions of the alcohol can involve different consequences. The clusters able to hold the encounter complexes of the reagents favour the condensation reaction. Otherwise, if the clusters hide single reagent molecules, the reaction gets slowed down. A competition between the effects cannot be excluded. However, a slight accelerating effect of ultrasound in this region points at the prevalence of the latter effect.

Hence, if breaking down the stabilization of the encounter complex between the reagents, sonication decreases the reaction rate while perturbation of the solvent-stabilization of the reagents accelerates the reaction.

Explanations of the sonochemical effect dealing with the perturbation of the molecular organization of or the solvation in the solution have been suggested long ago, however, without quotation definite ways of action [8,9]. Although sonochemical effects, not directly related to cavitation phenomena seem to be beyond of the paradigm of present sonochemistry [20], the possible role of acoustic waves on stereochemical course of reactions has been raised [21]. In one of our recent papers [6] we suggested that shock waves produced by collapsing cavitation bubbles may have a certain effect.

If the sonochemical acceleration or promotion of a non-radical reaction occurs exclusively in cavitational sites of the medium as generally expected, the rate of a first-order reaction under sonication can be expressed as follows:

$$v = k_{\mathrm{son,obs}}c = k_{\mathrm{nonson}}c + xk^{\mathrm{o}}_{\mathrm{son}}c,$$

where x is the fraction of the reaction medium under perturbation by cavitation at any instant, and $k^{\mathrm{o}}_{\mathrm{son}}$ is the rate constant of the reaction inside the cavitation site.

It should be noticed that the observed rate of the reaction consists of the rate in cavitational sites and of the rate in bulk solution presumably not affected by sonication.

The intrinsic sonochemical rate constant, i.e. that for the reaction inside the cavitational sites, can thus be calculated as

$$k^{\mathrm{o}}_{\mathrm{son}} = \frac{k_{\mathrm{son,obs}} - k_{\mathrm{nonson}}}{x}.$$

While the experimentally observed sonochemical acceleration is

$$a_{\mathrm{obs}} = \frac{k_{\mathrm{son,obs}}}{k_{\mathrm{nonson}}}$$

the intrinsic sonochemical acceleration is

$$a^{\mathrm{o}} = \frac{k^{\mathrm{o}}_{\mathrm{son}}}{k_{\mathrm{nonson}}} = \frac{1}{x}\left(\frac{k_{\mathrm{son,obs}}}{k_{\mathrm{nonson}}} - 1\right).$$

Whereas rate constants $k_{\mathrm{son,obs}}$ and k_{nonson} can be routinely determined, the values for x are not available in most cases. However, void fractions of 10^{-4} (Ref. [22]) or 2.9×10^{-5}–4.2×10^{-5} (Ref. [23]) have been calculated for water under sonication. Actually, the active volume including the shell around the bubble may be greater, e.g. Hua et al. [24] used a heat-transfer model for the estimation of the lifetime and spatial extent of alleged supercritical water during the cavitational collapse. A value for x, equal to 1.5×10^{-3} in pure water was proposed [24]. Thus, depending on how rigorous conditions the reaction requires, x can take different values, however, it does not much exceed 10^{-3}. In other words, 0.1% of the reaction solution or less is under cavitation simultaneously. This means that the intrinsic ultrasonic acceleration a^{o} required to produce an observed rate enhancement (a_{obs}) by a factor of two is about 10^3 times or more. On the contrary, quenching of a reaction in the cavitation zone leads to a rate decrease by 0.1% or less and therefore cannot be ascertained experimentally.

Here we report a statistically significant 20% decrease of the rate of benzoin condensation. The observed rate decrease means that the reaction was quenched in 20% of total volume, or the reaction was hindered in a greater part of the solution. This provides a direct evidence for the occurrence of non-radical sonochemical processes in the bulk solution of homogeneous systems, i.e. outside of cavitational sites.

As to the benzoin condensation, if the reaction was switched to a chain mechanism under sonication no rate reduction could be observed and unexpected by-products should have appeared what was not the case (vide supra).

Acknowledgments

The authors thank Dr. O. Loog for his aid in HPLC measurements.

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Please cite this article in press as: H. Hagu et al., Impact of ultrasound on hydrophobic interactions in solutions: ..., Ultrason. Sonochem. (2007), doi:10.1016/j.ultsonch.2006.09.012

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IV

Tuulmets, A., Hagu, H., Salmar, S., Cravotto, G., Järv, J.
Ultrasonic evidence of hydrophobic interactions. Effect of ultrasound on
benzoin condensation and some other reactions in aqueous ethanol.
J. Phys. Chem., *B* **2007**, accepted 02.02.2007. jp0682199

Ultrasonic Evidence of Hydrophobic Interactions. Effect of Ultrasound on Benzoin Condensation and Some Other Reactions in Aqueous Ethanol

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The kinetics of KCN-catalysed benzoin condensation of benzaldehyde in water and ethanol-water binary mixtures was investigated both under ultrasound at 22 kHz and without sonication. Thermodynamic activation parameters were calculated from kinetic data obtained at 35, 50 and 65°C. Evidence that ultrasound can retard reactions is reported and hence a direct proof that sonochemical processes occur in the bulk solution. Former results and literature data for ester hydrolyses and *tert*-butyl chloride solvolysis are involved in the discussion. A quantitative relationship between sonication effects and the hydrophobicity of reagents is presented for the first time. Ultrasound affects hydrophobic interactions with the solvent, which are not manifested in conventional kinetics. When it suppresses the stabilization of the encounter complexes between reagents, sonication hinders the reaction, but accelerates it when it perturbs the hydrophobic stabilization of the ground state of a reagent.

1. Introduction

The hydrophobic effect is the tendency of nonpolar species to aggregate in aqueous solutions so as to reduce their surface of contact with water.[1] These hydrophobic interactions between apolar molecules or apolar parts of molecules in water are important noncovalent driving forces for inter- and intramolecular binding and assembly processes in aqueous chemistry and biochemistry.[2–4] Hydrophobic interactions play a crucial role in protein folding and often in enzyme-substrate interactions.

In solutions, hydrophobic interactions can lead to pairwise associations (1:1 associates or "encounter complexes"), formation of molecular clusters or of large aggregates (micelles, vesicles, etc.). In aqueous systems they can have a strong influence on chemical equilibria and reaction rates.[3–5]

For example, in hydrolysis reactions of esters the formation of hydrophobically stabilized encounter complexes or clusters with cosolutes may make the ester unreactive.[6–8] On the other hand, the Diels-Alder reaction[9] and the benzoin condensation[10] are dramatically accelerated when carried out in water rather than organic solvents. These rate enhancements mostly result from the packing of hydrophobic surfaces of the reagents in the transition state, whose energy it lowers by minimizing hydrocarbon-water contacts.[2–4]

Although hydrophobic interactions can be studied by a large variety of experimental and computational techniques, the determination of chemical reactivities is preferable to other methods.[3,4] For studying hydrophobic interactions, reaction kinetics have the advantage that rate constants can usually be determined easily and with high precision, so that small hydrophobic effects can be detected. However, a quantitative interpretation of the results can often be relatively difficult. In this work we show that ultrasound can also provide a useful approach for these investigations.

We have carried out a kinetic study on the effect of ultrasound on polar homogeneous reactions in solution. The solvent systems involved so far were water and mainly ethanol-water binary mixtures.[11–13]

Nowadays ultrasonic acceleration effects on chemical processes are widely used both in laboratory and industrial practice.[14–16] Sonication mostly affects reaction rates, yields, and in some cases the ratios of reaction products. Besides bringing about mechanical effects, cavitation can promote many homogeneous and heterogeneous reactions by generating free radicals which give rise to chain reactions in solution.

According to current tenets of sonochemistry[15] an ionic homogeneous reaction that cannot switch to a radical pathway should not be susceptible to ultrasound effects. However, a number of examples have been found of homogeneous polar (heterolytic) reactions that are in fact accelerated by ultrasound. Among these, solvolysis and hydrolysis reactions in water and water-organic binary mixtures have been kinetically investigated for sonication effects. Reviews of these studies can be found, e.g., in our recent papers.[12,17]

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 reaction kinetics.[11–13, 18–20] It was concluded that in these cases the sonochemical acceleration may be related to the perturbation of the molecular structure of the binary solvent and, more critically, with the destruction of hydrophobic solute-solvent interactions.

Further evidence confirming those conclusions emerges from the present work, a kinetic study of the KCN-catalysed benzoin condensation of benzaldehyde in water or in ethanol-water binary mixtures carried out under ultrasound and without sonication. For the first time a significant retardation effect of ultrasound was found, providing direct evidence for sonochemical processes occurring in the bulk solution. No less important was our inference that sonication hinders the reaction by breaking down hydrophobic interactions which stabilize the encounter complexes between the reagents. Also the thermodynamic activation parameters for the reaction in aqueous ethanol solutions were determined.

The present discussion, which will involve also our published results together with data from the literature, will examine the prospects for a wider use of ultrasound as a tool for the physico-chemical study of hydrophobic interactions. In view of this goal the section Results and Discussion is divided into four parts: ester hydrolysis, benzoin condensation, solvolysis of *t*-butyl chloride and thermodynamic activation parameters.

2. Experimental Section

2.1. Reagents and Solutions

Benzaldehyde, distilled immediately before use, was free from impurities detectable by HPLC and GLC. Binary aqueous mixtures were prepared by weighing appropriate amounts of ethanol and water.

2.2. Kinetic Measurements

Reactions were run on 80 mL batches in a thermostatted glass cell sealed with elastomeric septa under argon atmosphere. In systematic measurements carried out at 65°C in water-ethanol mixtures the initial concentration of benzaldehyde ranged from 0.025 to 0.123 M and that of the catalyst, KCN from 0.023 to 0.069 M.

In order to determine thermodynamic activation parameters, rate constants were measured at 35°C, 50°C and 65°C with initial concentrations of benzaldehyde ranging from 0.0147 to 0.123 M.

Sonication was performed with an immersed titanium horn at 22 kHz (UZDN-2T probe disrupter) whose energy output in water and in aqueous ethanol up to $X_{EtOH} = 0.37$ was 55 W in all our liquid systems, as determined calorimetrically.[12] Both under ultrasound and in its absence the reaction mixture was agitated with a magnetic stirring bar.

Aliquots (about 0.05 mL) were periodically removed and injected into the HPLC instrument equipped with a Waters 6000 HPLC pump and a 440 UV detector (254 nm). For HPLC analysis CH_3OH-H_2O (62:38, v/v) was used as the mobile phase, flow rate being 1 mL/min. Benzaldehyde concentration at any given time C_t was calculated from peak areas of benzaldehyde and benzoin by eq. 1

$$C_t = \frac{S_A}{S_A + aS_B} C_o \ , \qquad (1)$$

where S_A and S_B are peak areas of the aldehyde and benzoin, respectively, *a* is a calibration coefficient determined experimentally, and C_o the initial benzaldehyde concentration.

Plotting $1/C_t - 1/C_o$ versus time gave excellent straight lines whose slopes were taken as the pseudo-second order rate constants. Dividing the latter by the molar concentration of the catalyst gave third-order rate constants.

For GLC measurements a HP 5880 A instrument with a packed column OV-1 3%, 2.5m×2mm was used.

3. Results and Discussion

3.1. Ester Hydrolysis

Our novel approach to a better understanding of solvent effects on these reactions stemmed from the study of sonication effects on ester hydrolysis in water-ethanol binary solvents. We were able to relate ultrasonic acceleration of ester hydrolysis in ethanol-water mixtures to a perturbation by power ultrasound of hydrophobic solute-solvent interactions.[11–13]

Our previous papers discussed[11–13] those kinetic data in line with the current conception of the structure of ethanol-water solutions. According to it,[21-23] in mixtures with $X_{EtOH} > 0.15$ a large number of ethanol-water hydrogen bonds are formed at the expense of water-water bonds, a result that led to a cluster model envisaging a stacked ethanol core and a thin water shell.[21-23] 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 such interaction with the hydrophobic interior of the cluster can be overcome by ultrasound, the reaction will be accelerated accordingly.

In our recent study[12] ethyl, n-propyl and n-butyl acetates were used as probes of reagent inclusion within the clusters. In fact the sonication effects (k_{son}/k_{nonson}) for hydrolysis, determined in the $X_{EtOH} > 0.15$ range, matched in reverse order the hydrophobicity of the esters. Sonication had the smallest effect in the case of butyl acetate, the substrate that should be most powerfully trapped within the clusters.

Here we present a quantitative proof of the above conclusion. In Fig. 1 logarithms of kinetic sonication effects (at $X_{EtOH} = 0.25$) for acid-catalyzed hydrolysis of aliphatic esters[12] and for base-catalyzed hydrolysis of 4-nitrophenyl acetate[13] are plotted *vs* the Hansch-Leo hydrophobicity parameter, log P, where P is the partition coefficient of the substrate between 1-octanol and water.[24,25]

The plot in Figure 1, representing a linear free-energy relationship,[26] shows how kinetic sonication effects are quantitatively related to the hydrophobic interaction of the esters with the solvent system. The deviation of the point for 4-nitrophenyl acetate should be attributed to the much lower sonication intensity used with this ester[13] (9.1 W/100 ml *vs* 55 W/80 ml for the aliphatic esters).

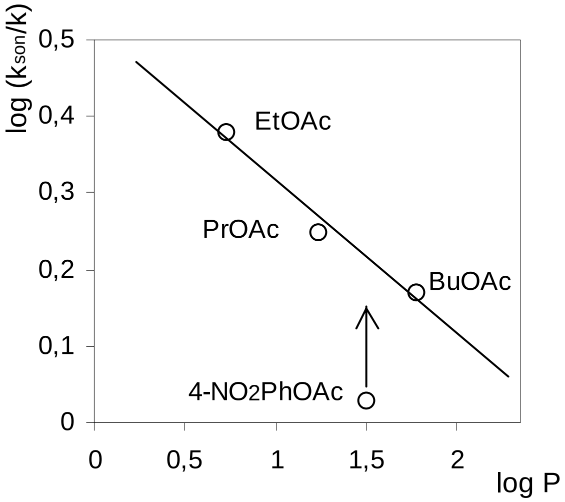


Figure 1. The linear free-energy relationship between kinetic sonication effect for ester hydrolysis and the hydrophobicity parameter log P. X_{EtOH} was 0.25.

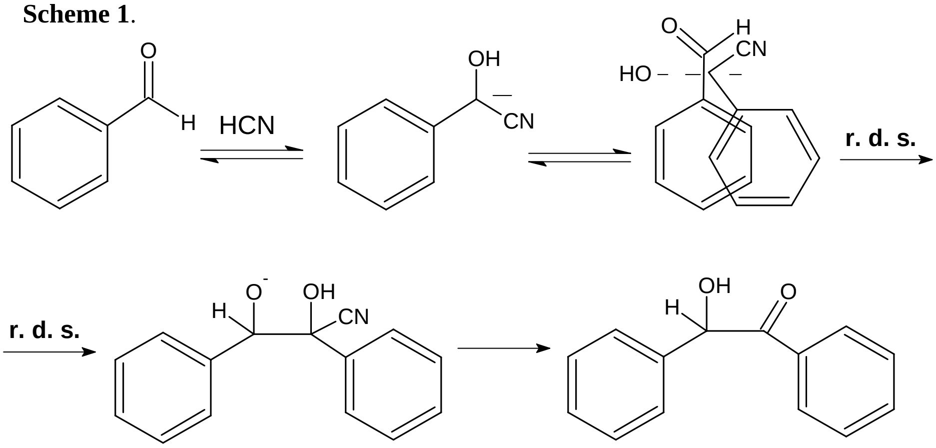
We can conclude that the regular decrease in the rate of ester hydrolyses in ethanol-water is mainly due to hydrophobic interactions, i.e. to ground-state stabilization by this solvent system.

3.2. Benzoin condensation

A logical inference from the results of kinetic sonication experiments with esters was that ultrasound would decrease, rather than increase, the rate of reactions promoted by hydrophobic interactions, like the Diels-Alder reaction, the benzoin condensation, etc.[2–4] We have predicted an ultrasonic retardation for chemical reactions,[20] an effect that has so far been ignored in the sonochemical literature.

We chose the benzoin condensation of benzaldehyde as a model, because its mechanism is well established[27] (scheme 1), and the reaction was investigated in detail for hydrophobic effects by Breslow *et al.*[2,10]

Scheme 1.



It has been shown[2,10] that hydrophobic packing of reactants in the transition state promotes the benzoin condensation. In the rate-determing step of the reaction two benzene rings become stacked, an interaction that in an aqueous solvent is favored by a hydrophobic effect. In ethanolic solutions stacking effects should be greatly reduced; as a matter of fact the reaction is much slower than it is in water.[10]

As was expected, we observed that the reaction was slowed down by ultrasound in pure water and in ethanol-water mixtures up to an ethanol content of 45 wt % (Table 1). In Table 1 the rate constant found in pure water is very close to that determined by Kool and Breslow[10] ($k_3 \times 10^3 = 8.9 \pm 2.2$ L^2 $mol^{-2}s^{-1}$) under the same conditions.

Table 1.

Ethanol content wt % (X_{EtOH})	Rate constant (L^2 $mol^{-2}s^{-1}$ ($\times 10^3$))		Sonication effect k_{son}/k_{nonson}
	Without sonication	Under ultrasound	
0	7.17 ± 0.09	5.76 ± 0.07	0.80
10 (0.042)	4.97 ± 0.08	4.39 ± 0.08	0.88
20 (0.089)	3.47 ± 0.07	3.17 ± 0.06	0.92
30 (0.144)	2.60 ± 0.05	2.21 ± 0.05	0.85
40 (0.207)	1.92 ± 0.02	1.70 ± 0.02	0.89
50 (0.281)	1.38 ± 0.01	1.54 ± 0.02	1.12
60 (0.370)	1.06 ± 0.03	1.27 ± 0.02	1.20

The good linear fit of these data to second-order kinetics (see the Experimental Section) proves that ultrasound affects the rate-limiting condensation step of the reaction exclusively. Sonochemical degradation of benzaldehyde would have led to an apparent acceleration of the reaction instead of the observed retardation. A loss of benzoin by decomposition could lower the apparent reaction rate; in this case however a curvature of the second-order kinetic plot should be observed. Moreover, GLC analysis of solutions of benzaldehyde and benzoin in absence of catalyst did not reveal any degradation products after they had been sonicated longer than required by kinetic experiments.

The retardation effect of ultrasound was most pronounced in pure water and gradually decreased with increasing ethanol content up to about $X_{EtOH} = 0.25$ (Table 1), when sonication turned to a promoting factor. The last finding can be interpreted in terms of the structure of aqueous ethanol binary system. Additions of ethanol up to 25 mol% modify the structure but evidently do not entirely prevent the favourable hydrophobic effects which are disturbed by ultrasound.

Ethanol clusters in this region and more extensively in that of higher X_{EtOH} bring about different consequences at different ethanol concentrations. The condensation reaction is favoured when clusters host encounter complexes of the reagents. On the other hand, if clusters host single reagent molecules, the reaction is slowed down. These effects obviously compete with one another, the small accelerating effect of ultrasound for $X_{EtOH} > 0.20$ indicates the prevalence of the latter.

Hence, if it breaks down the stabilization of the encounter complexes between the reagents, sonication decreases the reaction rate; on the contrary, if it perturbs the solvent stabilization of the initial state of the reagents, sonication accelerates the reaction.

The observed statistically significant decrease of the rate of benzoin condensation means that the reaction was quenched in 20% of the total volume, or was hindered in a larger part of the solution. This indicates that a non-radical sonochemical process occurred in the bulk solution, i. e. outside of cavitational bubbles (see the discussion in our previous paper[12]).

Thermodynamic activation parameters of organic reactions in solvent mixtures, particularly in water-organic binary solvents can reveal detailed solvation effects (see the discussion in Section 3.4). To this end we determined rate constants for benzoin condensation of benzaldehyde at 35°C, 50°C and 65°C in water and aqueous mixtures up to 60 wt% ethanol ($0 \leq X_{EtOH} \leq 0.37$). Calculated activation parameters are presented in Table 2 and discussed in Section 3.4, together with related parameters for some other reactions.

Table 2. Isobaric activation parameters for benzoin condensation of benzaldehyde at 25.0 °C.

Content of ethanol wt % (X_{EtOH})	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (J/Kmol)	$\Delta G^{\neq}$ (kJ/mol)
0	32.20 ± 0.01	−195.60 ± 0.02	90.52
5 (0.020)	31.94 ± 0.50	−196.83 ± 1.55	90.63
10 (0.042)	41.65 ± 0.87	−167.46 ± 2.70	91.58
15 (0.065)	40.81 ± 1.17	−170.85 ± 3.63	91.75
20 (0.089)	34.90 ± 3.15	−190.42 ± 9.79	91.68
25 (0.115)	32.00 ± 0.94	−201.77 ± 2.92	92.16
30 (0.144)	34.99 ± 1.75	−191.26 ± 5.44	92.01
35 (0.174)	38.74 ± 0.44	−181.15 ± 1.38	92.75
40 (0.207)	39.15 ± 0.05	−181.53 ± 0.17	93.27
45 (0.243)	42.48 ± 1.97	−172.03 ± 6.14	93.77
50 (0.281)	41.89 ± 0.42	−173.61 ± 1.30	93.65
60 (0.370)	41.30 ± 2.74	−178.70 ± 8.53	94.58

3.3. Solvolysis of *tert*-butyl chloride

The classical work by Mason's group,[18,19] the first comprehensive investigation of sonication effects in polar homogeneous reactions, further inspired us to extend our study to mechanistically different ester hydrolysis reactions in ethanol-water binary mixtures.

The papers by Mason's group have important theoretical implications. From a thorough analysis of experimental data they concluded that the application of ultrasound had led to a perturbation of molecular interactions within the reacting system and that the sonication effects were a direct result of this perturbation.[19]

At present we can develop a more detailed interpretation of the results. The solvolysis of *tert*-butyl chloride is accelerated in polar and protic solvents, as these stabilize the dipolar transition state. However, in water the reaction is much faster than would be expected on the basis of the polarity and hydrogen-bonding ability of water. Abraham *et al*[28] showed that owing to the hydrophobic character of the reagent its ground state is destabilized in water in comparison to other polar protic solvents. Addition of ethanol to the solvent system causes an effective hydrophobic stabilization of the ground state leading to a dramatic decrease of the reaction rate (Figure 2). In Figure 3 we try to schematically picture the cluster-like hydrophobic solvation of a *tert*-butyl chloride molecule.

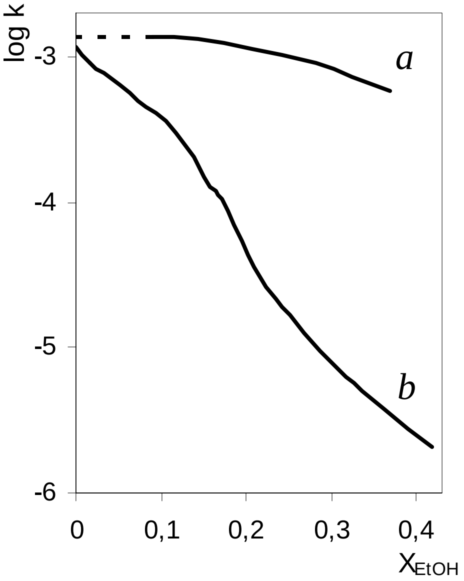


Figure 2. Solvolysis of *tert*-butyl chloride in aqueous ethanol at 0°C. *a* – under ultrasound (see text), *b* – without sonication (Ref 29)

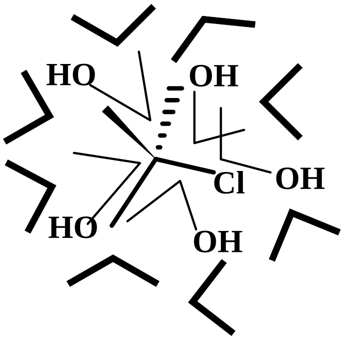


Figure 3. Schematic representation of a *tert*-butyl chloride molecule hydrophobically solvated by ethanol molecules, the cluster being surrounded by water molecules.

The sonication effects for *tert*-butyl chloride solvolysis confirm the above suggestions. In Figure 2 data by Winstein and Fainberg[29] (curve *b*) are compared with reaction rates under sonication (curve *a*). The sonication data were obtained by extrapolation to the zero-degree of Arrhenius plots from the paper by Lorimer *et al*[19]. The sonication effects are large and increase with increasing ethanol content in the binary solvent. However, the reaction rate under US depends only slightly on the solvent composition, which indicates that sonication suppresses hydrophobic ground-state stabilization leaving little play for speculations on medium polarity effects. Extrapolation of curve *a* to pure water results in an almost negligible sonication effect, in accordance with the highly destabilized ground state of *tert*-butyl chloride in water (*vide supra*).

Some explanations of the sonochemical effect based on the shift of the frequency factor in the Arrhenius equation under sonication have been suggested.[19,30–32] However, the reported changes in thermodynamic activation parameters under sonication may largely be artifacts, because in their calculation sums of rate constants ($k_{nonson} + \Delta k_{son}$) appear under logarithm. Indeed, if these are expanded into a logarithmic series we have

$$\ln k_{son} = \ln(k_{nonson} + \Delta k_{son}) = \ln k_{nonson} + \frac{2\Delta k_{son}}{2k_{nonson} + \Delta k_{son}} + ... \quad (2)$$

Limiting the sum to the first two terms we obtain eq. 3

$$\ln k_{son} \approx \ln k_{nonson} + \frac{2(k_{son} - k_{nonson})}{k_{son} + k_{nonson}} \quad (3)$$

and if the sonication effect is small eq. 4 holds

$$\Delta A \approx \frac{2(k_{son} - k_{nonson})}{k_{son} + k_{nonson}} \approx \frac{k_{son}}{k_{nonson}} - 1, \quad (4)$$

with practically no difference of activation energy for the sonicated and nonsonicated reaction, as was actually observed.[30–32]

However, if $\Delta k_{son} >> k_{nonson}$, which is the case for the data from Mason's group[19], the calculated activation parameters, although involving some errors, can reflect the real proportions. For the solvolysis of *tert*-butyl chloride under sonication the values obtained for the activation entropy are largely negative. The most substantial decrease observed was nearly 500 J mol^{-1} K^{-1} in 60 wt% ethanol.[19] Even if some systematic error could be suspected in such large numbers, the established trend in the data indicates a large electrostriction effect in the activation process inherent for polar reactions in low-order media. Because ultrasound cannot affect the transition state, these activation entropy values reflect a great disorder in the solvation of the ground state brought about by ultrasound.

3.4. Thermodynamic activation parameters

In this section we discuss observed sonication effects by comparison with thermodynamic activation parameters for the reactions without sonication in ethanol-water binary solvents.

In Figure 4 the data for the benzoin condensation of benzaldehyde, 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 are plotted together with the activation parameters for the reaction of structurally similar ethyl 4-hydroxybenzoate.

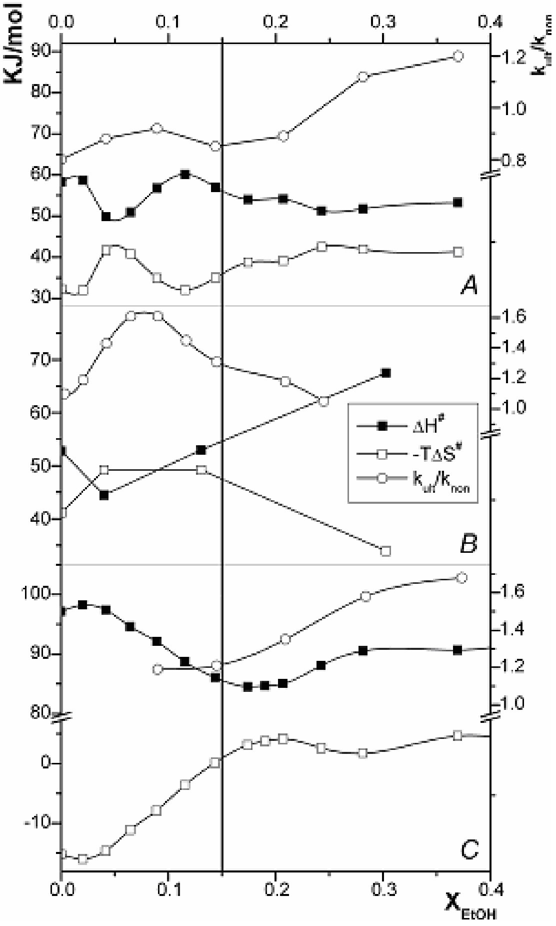


Figure 4. Isobaric activation parameters $\Delta H^{\#}$ and $-T\Delta S^{\#}$, and sonication effects at 25°C in water-ethanol binary mixtures. A – benzoin condensation of benzaldehyde (this work, sonication data at 65°C). B – base-catalyzed hydrolysis of ethyl 4-hydroxybenzoate (data from Ref 33, sonication data for 4-nitrophenyl acetate at 20°C from Ref 13). C – solvolysis of *tert*-butyl chloride (data from Ref 29, sonication data from Ref 18).

For all these reactions the dependences of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ on the solvent composition tend to be complex, i.e. involve minima and maxima. However, $\Delta G^{\neq}$ (not shown in Figure 4) increases monotonically as X_{EtOH} rises from 0 to 0.4 and beyond, due to a strong compensation effect.

Although carried out in the same solvent system, these reactions differ in their mechanisms, therefore we should not expect solvation phenomena as well as sonication effects to be similar. Indeed, the graphs in Figure 4 tend to differ in many details.

Following the current notion of ethanol-water binary solvent structure (cf. section 3.1.), Figure 4 can be conveniently divided by a vertical line corresponding to $X_{EtOH} = 0.15$. In the right-hand region ($X > 0.15$) ethanol clusters prevail, while between pure water and about 30 wt% ethanol ($X \approx 0.15$) considerable changes in the solvent structure, and consequently in solute-solvent interactions, occur. In the latter region all the activation parameters, and some sonication effects too, show extrema; however, these do not parallel with each other and occur at different solvent ratios. Consequently, activation phenomena are related to the solvent composition in a complicated way. The same seems to apply to sonication effects.

The sonication effects for benzoin condensation and for the ester hydrolysis considered here have maxima at $X \approx 0.07$. The entropy loss for the hydrolysis reaction is also maximal at this solvent ratio. However, in this region the benzoin condensation has two extrema for activation parameters which do not overlap with that of the sonication effect.

The most complicated features of the effects are seen with the benzoin condensation. Indeed, our solvent system exerts on the reaction two opposite effects. Hydrophobic stabilization of the ground state retards the reaction, while hydrophobic stabilization of encounter complexes between reagent molecules accelerates it. Sonication suppresses both hydrophobic interactions, thus exerting competing effects on the reaction rate.

In the case of the highly hydrophobic esters considered here, a coincidence of the maxima (*vide supra*) may be not occasional. Evidently, at $X \approx 0.07$ the esters are most weakly held by the solvent framework and the activation is accompanied with the greatest reorganization of the solvation. Further additions of ethanol lead to formation of clusters capable of including ester molecules (cf. section 3.1), which is evidenced by a decreasing sonication effect and an increasing activation enthalpy.

The rate of *tert*-butyl chloride solvolysis is affected not only by hydrophobic stabilization of the ground-state but also by polar solvation of the ground state and of the highly polar transition state. The sonication effect does not seem to be much related to these phenomena, as it increases smoothly with the increase of ethanol content (cf. section 3.3). However, since a reflection point at $X_{EtOH} \approx 0.2$ where the activation parameters show extrema, an increase reverse to that for esters (cf. section 3.1) together with a parallelism with the activation enthalpy can be observed.

We must conclude that sonication effects for reactions in water-ethanol binary solvents cannot be primitively correlated with trends in activation parameters, although in some cases a relatedness is obvious. The main reason for such disconformity is that the activation parameters involve changes in solvation energies when passing from ground states to transition states, all kinds of solvation included. Sonication can merely affect subtle hydrophobic interactions in the solution. However, the advantage of sonication methods is that they are able to reveal particular effects which remain hidden in conventional kinetics.

4. Conclusions

We have found the first evidence for retardation of reactions by ultrasound, besides providing evidence for sonochemical processes in the bulk solution. We also have presented for the first time a quantitative relationship between sonication effects and hydrophobicity of reagents. An analysis of sonication data showed that the decrease in reaction rates with increasing content of ethanol in the binary solvent system was mainly due to ground state stabilization which is largely of hydrophobic origin. Ultrasonication can reveal subtle hydrophobic interactions which remain hidden in conventional kinetics. When it suppresses the stabilization of encounter complexes between the reagents, sonication hinders the reaction; on the contrary, when it perturbs the hydrophobic stabilization of a reagent's ground state, it accelerates the reaction.

Acknowledgment. This work has been carried out under the auspices of the European Union COST Action D32. The authors thank Dr. O. Loog for his aid in HPLC measurements.

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Main scientific publications

1. Tuulmets, A., Salmar, S., Hagu, H. Effect of ultrasound on ester hydrolysis in binary solvents. *J. Phys. Chem., B* **2003**, *107*, 12891–12896
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1. Tuulmetṣ, A., Salmar, S., Hagu, H. Effect of ultrasound on ester hydrolysis in binary solvents. *J. Phys. Chem., B* **2003**, *107*, 12891–12896
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