Molecular Dynamics Simulation of the Effect of Hydrophobic Cosolutes on the Neutral Hydrolysis of an Activated Ester

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We have studied, by means of molecular dynamics (MD) simulations, the effect of two hydrophobic cosolutes, *tert*-butanol (*t*-BuOH) and ethanol (EtOH), on the neutral hydrolysis of *p*-methoxyphenyl dichloroacetate (MPDA) in water. Shifts were calculated in a pre-equilibrium, defined as a spatial distribution of the reacting molecules satisfying specific geometric constraints. The criteria applied represent the configurations from which the reaction can take place (reactive conformation, RC). The shifts induced by the presence of cosolute, as determined from the simulations, correspond well to the experimentally found rate retardations. In accord with experiments, an almost linear correlation between the concentration of added cosolute and the logarithm of the rate constant was found. This is in agreement with a simple mechanistic model. The percentage of RCs in pure water was calculated to be ~15%, complementing earlier work performed in this group (Lensink, M. F.; Mavri, J.; Berendsen, H. J. C. *J. Comput. Chem.* **1999**, *20*, 886), leading to a calculated rate constant of $k_{calc} = 3.9 \times 10^{-3}$ s^{-1} (exptl: $k_{obs} = 2.78 \times 10^{-3}$ s^{-1}). The molecular structure of the RC was examined more extensively, investigating correlations between the positions of participating molecules.

Introduction

Chemical reactivity in the liquid phase is a subject that continues to offer many challenges to both experimental and theoretical chemists and physicists. Because of its complexity, a general comprehensive theory is lacking. Nevertheless, a variety of theories do exist, the most useful of them still being transition state theory (TST).[1–3] The main advantage of TST is the direct link of kinetics with thermodynamics, making it highly useful for studies of chemical reactivity in diverse media. The differences in reaction rates found for a reaction performed in different solvents can be straightforwardly linked to the differences in chemical potentials of the reactants (initial state, IS) and the activated complex in these solvents.[4–6] This activated complex (transition state, TS) is the structure corresponding to the highest Gibbs energy along the reaction path (excluding the reaction coordinate itself). Within TST, the problem of chemical reactivity therefore reduces to a thermodynamic problem. This is also the weak point of TST: simple mechanistic effects such as the availability of reactive configurations in the initial state disguise as a thermodynamic property.

The solvent is often a major factor of importance in governing the rates of chemical reactions. Besides pure solvents, mixtures of solvents have frequently been studied as reaction media. The most interesting mixtures are those where one of the components is water. Water has many peculiar properties, one of them being its beneficial behavior as a solvent for many organic transformations, despite obvious solubility constraints.[7] Moreover, all life processes are based upon aqueous chemistry. Many studies have been devoted to hydrophobic interactions,[8–12] that may occur between a cosolvent (or cosolute) and a reacting solute, thereby often stabilizing the IS with respect to the TS. For these processes, it is still unclear as to what exactly occurs at the atomic level.

In this paper, we will focus on solvent effects on reaction rates where the solvent consists of water and a low percentage of a simple, inert, monohydric alcohol. The reacting solute is an activated ester molecule, that is easily hydrolyzed in an aqueous environment (solvolysis). In general terms, the rate constants for a reaction at different concentrations of alcohol, compared to the rate at zero concentration, can be expressed as the difference in chemical potentials of the IS and the TS as caused by interactions between the IS and the TS with the alcohol.[13,14] Alternatively, in the molecular or atomic description, one can focus on the local effects that arise upon adding the cosolute, for example, a changed local water density around the reactive center versus a changed macroscopic water activity at a lowered volume fraction of water. For this purpose, one can use molecular dynamics (MD) simulations,[15] where thermodynamic properties follow from computer simulations, based upon a simple atom–atom pair-interaction model. The evolution of atomic coordinates forms trajectories that can give insight into the molecular dynamics of the system at the atomic level. The elegance and ease-of-use makes MD a valuable tool in the study of molecular behavior of organic compounds in aqueous mixtures.

Many simulations of pure water and pure alcohol systems have been performed.[16–18] Despite the inherent simplicity of the pair-interaction potentials that are commonly used, and the fact that these were fitted to the properties of the pure components, the use of traditional combination rules for pair-interaction parameters yields an overall satisfactory agreement with experiment.[19–21] Most simulation studies of water–alcohol mixtures focus on water–methanol,[19–25] but mixtures of water and *t*-BuOH have also received attention.[26,27]

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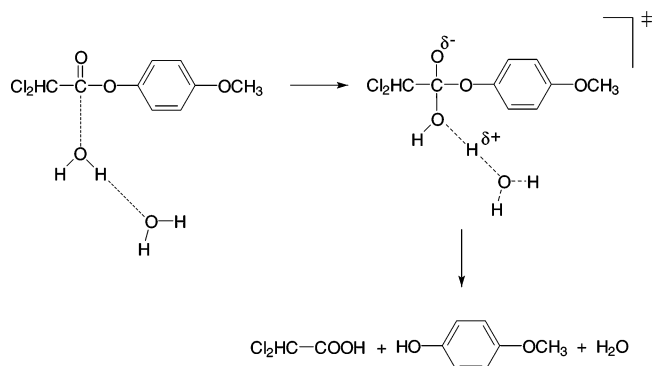
Figure 1. Reaction mechanism for the neutral hydrolysis of *p*-methoxyphenyl dichloroacetate.

We have studied the influence of *tert*-butanol (*t*-BuOH) and ethanol (EtOH) as cosolutes on the neutral hydrolysis of *p*-methoxyphenyl dichloroacetate (MPDA) in aqueous solution.[28-30] In this water-catalyzed reaction, the activated complex (Figure 1) contains two water molecules, with a proton transfer between these two water molecules being the rate limiting step. Concerted with this proton transfer, a covalent bond is formed between the nucleophilic water oxygen and the ester carbonyl carbon. The rate at which this hydrolysis occurs depends not only on the Gibbs energy of the ester but also on the activity of the water molecules involved in the reaction. The molecular picture underlying the thermodynamics was explored by two different approaches: (i) consideration of the fraction of configurations suitable for a reaction to occur and (ii) a simple model in which cosolute molecules can block one or both sides of the reaction center.

For the conversion of any single ester molecule, it is crucial that two water molecules are available, one as the nucleophile and a second one as general base. This notion is taken as the starting point for studying the influence of cosolutes on the reaction using MD simulations. If transition state effects are disregarded, changes in rate (upon adding cosolute) will be the result of changes in the number of configurations that may lead to conversion. The number of these reactive conformations (RCs), denoted by $x_{reactive}$, then directly monitors the influence of cosolute on the rate.

The observed pseudo-first-order rate constant in pure water is $k_{obs} = 2.78 \times 10^{-3}$ s^{-1} at 298 K.[28] The effect of alcohols on the rate of this hydrolysis reaction has been determined (Experimental Section). For low concentrations of solute and cosolute, the assumption can be made that the (co)solute molecules interact with each other independently, resulting in a linear dependence of the logarithm of the observed rate constant on the alcohol concentration.[13,14]

Mechanistic and Thermodynamic Description

Consider the neutral hydrolysis reaction of ester E with water, with the apparent first-order rate $v = k_0[E]$. The reaction can take place by nucleophilic attack by a water molecule on either side of the C$-$(C=O)$-$O plane. In the absence of cosolvent, both sides are available and the overall reaction is composed of two parallel reactions with rate constants $^1/_2k_0$. In the presence of cosolvent C, an EC complex can be formed that will block one side of the plane or a CEC complex is formed with both sides blocked:

$$E + C \rightleftharpoons EC \qquad v = {}^1/_2k_0[EC] \qquad (1)$$

$$EC + C \rightleftharpoons CEC \qquad v = 0 \qquad (2)$$
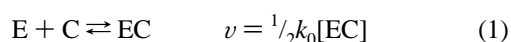
Under the simplest assumption that binding to one side is independent of the occupation of the other side, the first equilibrium has a binding constant of K and the second a binding constant of $^1/_2K$. The factor 2 results from the availability of two binding sites in the first equilibrium versus one binding site in the second. The overall reaction rate is

$$v = k_0[E] + {}^1/_2k_0[EC] \qquad (3)$$

The bruto ester concentration is $[E]_0 = [E] + [EC] + [CEC]$, and the apparent hydrolysis rate is $v = k[E]_0$. From equilibrium considerations, we find that the observed rate constant k relates to the cosolvent concentration, expressed as molality m, as

$$k = \frac{k_0(1 + {}^1/_2Km)}{1 + Km + {}^1/_2K^2m^2} \qquad (4)$$

It appears that this relation is approximately linear in a plot of ln k versus m. This implies that this simple mechanistic model can also be expressed as a linear dependence of the activation Gibbs function in TST on the cosolvent molality.

An alternative way of expressing the influence of C on the reaction rate is to consider the fraction $x_{reactive}$ of water configurations around the ester molecules (on either side of the plane) suitable for the reaction to occur. This fraction is directly accessible from MD simulations. In this work, we assume that the sole action of the cosolvent is its influence on $x_{reactive}$.

Computational Details

All MD simulations were performed with the GROMACS 1.6 package,[31] using the GROMOS-87 force field[32] and the SPC water model.[33] The systems consisted of a periodic box with, besides the solute and cosolute, approximately 700 water molecules, which were coupled to a temperature bath at 298 K and a pressure bath at 1 bar with coupling constants of 0.1 and 1 ps, respectively.[34] A spherical cutoff of 1 nm was employed. Bond lengths were constrained using the LinCS algorithm.[35] Equations of motion were integrated by the Verlet leapfrog integration scheme with a time step of 2 fs. Partial atomic charges for the solute were determined by fitting them to the electrostatic potential in a solvent reaction field (AM1-SM1[36]) and to the calculated dipole moment.[37] The molecular geometries for EtOH and *t*-BuOH were taken from the optimized potentials for liquid simulations (OPLS) force field.[18] Initial configurations were generated by randomly positioning the solute and cosolute molecules in the box and subsequently adding water molecules. The systems were equilibrated for 300 ps before sampling was started. Simulation lengths were typically between 1.0 and 2.0 ns, which allows time for diffusion over the average distance between solute and cosolvent molecules and therefore suffices to obtain equilibrium distributions for the solute environment.

A reactive conformation (RC) was defined as having the nucleophilic water molecule within a particular distance and angle from the carbonyl functionality (based upon possible orbital overlap during the activation process) and a second water molecule, that is acting as a general base, within a specific distance and angle from the first one (based upon conventional hydrogen bond criteria), as illustrated in Figure 2. The carbonyl planar group is situated in the xy plane. Furthermore, the constraint $r_3 > r_1$ was applied; that is, the carbonyl oxygen$-$water hydrogen distance was greater than the carbonyl carbon$-$water oxygen distance. Similar criteria have been previously used for defining configurations, suitable for a reaction to
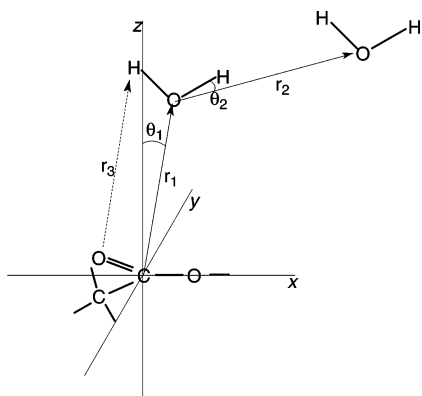
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Figure 2. Frame of axes used for defining the reactive conformations according to the constraint parameters described in the text.

TABLE 1: Computational Results for the Neutral Hydrolysis of MPDA in *t*-BuOH−Water[a]

r_1^{max} (nm)	θ_1^{max} (deg)	r_2^{max} (nm)	θ_2^{max} (deg)	x at 0 mol % *t*-BuOH	x'/x at the following mol % *t*-BuOH			
					0.5	1.0	1.5	2.0
0.36	45	0.31	26	0.146	0.77	0.65	0.49	0.35
0.35	45	0.31	26	0.101	0.78	0.67	0.47	0.37
0.34	45	0.31	26	0.0661	0.78	0.70	0.47	0.39
0.36	35	0.31	26	0.122	0.79	0.65	0.48	0.35
0.36	55	0.31	26	0.156	0.78	0.64	0.49	0.35
0.36	45	0.30	26	0.137	0.78	0.64	0.49	0.35
0.36	45	0.29	26	0.119	0.79	0.66	0.51	0.34
0.36	45	0.31	30	0.149	0.78	0.65	0.49	0.36
0.36	45	0.31	20	0.138	0.77	0.63	0.48	0.34
0.36	45	0.31	26	0.391	0.78	0.70	0.51	0.43

[a] r_1, θ_1, r_2, and θ_2 are as defined in Figure 2. $r_3 > r_1$ except in the last row.

occur.[39] Since the distance and angle criteria are not sharply defined, they were varied to study their effect on the reactive fraction x.

Results

Table 1 shows the dependence of the percentage of RCs on the selection criteria. x stands for the percentage of RCs in the pure aqueous solution ($x_{reactive}$), while x' stands for the same quantity in the *t*-BuOH−water mixture. Table 1 shows that, although the percentage of RCs is rather significantly dependent on the exact values of the selection criteria, the ratio is not. Changes in the maximum angle led to a variation in the ratio typically within 6%, while changes in the maximum distance led to a scattering within 10%.

The last row in Table 1 shows that the criterion $r_3 > r_1$ rules out a large number of RCs, while not changing the ratio x'/x. This is, however, a rather important criterion, since, without it, the nucleophilic water molecule can have a hydrogen pointing toward the carbonyl group and the reaction would not take place. We will therefore apply this criterion unless mentioned otherwise. This criterion was also previously applied[39] for the definition of an RC.

To obtain insight into the steric effect which the phenyl moiety may have on the occurrence of RCs, a correlation was defined between the position of the phenyl ring (indicated by the first arrow between the parentheses) and the position of the RC (defined by the position of the nucleophilic water molecule and indicated by the second arrow), both relative to the MPDA
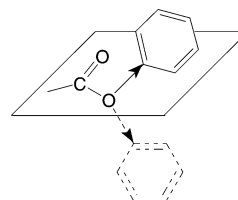

Figure 3. The bond indicated with an arrow is used to determine the position of the phenyl moiety (above or below the plane of the ester group), as described in the text.

TABLE 2: Computational Results for Water−Alcohol Mixtures[a]

mol %	alcohol	x'	x'_{h1}	x'/x'_{h1}	x'/x	$\ln(x'/x)$
0.5	*t*-BuOH	0.112	0.126	0.89	0.767	−0.265
1.0	*t*-BuOH	0.095	0.101	0.88	0.651	−0.430
1.5	*t*-BuOH	0.072	0.079	0.91	0.493	−0.707
2.0	*t*-BuOH	0.051	0.059	0.87	0.349	−1.05
1.0	EtOH	0.123	0.139	0.88	0.842	−0.171
2.0	EtOH	0.097	0.110	0.88	0.664	−0.409
3.0	EtOH	0.074	0.084	0.88	0.507	−0.680
		x	x_{h1}	x/x_{h1}		
	H$_2$O	0.146	0.160	0.91		

[a] Using the criteria $r_1^{max} = 0.36$ nm, $\theta_1^{max} = 45°$, $r_2^{max} = 0.31$ nm, $\theta_2^{max} = 26°$, and $r_3 > r_1$.

carbonyl plane (Figure 3):

$$r_{corr} = -\frac{1}{2}\left(\frac{p(\uparrow|\downarrow) - p(\uparrow|\uparrow)}{p(\downarrow|\uparrow) + p(\uparrow|\uparrow)} + \frac{p(\uparrow|\downarrow) - p(\downarrow|\downarrow)}{p(\uparrow|\downarrow) + p(\downarrow|\downarrow)}\right)$$

For example, $p(\uparrow|\downarrow)$ stands for the probability that the phenyl ring is located above the carbonyl plane ($\uparrow$), given a RC below that plane ($\downarrow$). r_{corr} can range from −1 (phenyl ring and water always on opposite sides of the carbonyl plane) to +1 (always on the same side). A value of 0 indicates no correlation. No dependence of r_{corr} on the presence of cosolute could be detected. Averaged over all the simulations, an anticorrelation of 42% was found ($r_{corr} = -0.42 \pm 0.05$). This means that 29% of the RC is found on the same side as the phenyl ring and 71% on the opposite side. We conclude that the formation of any RCs is negatively affected by the steric hindrance of the phenyl ring on the side of the carbonyl plane where it resides. This effect is independent of the cosolute.

The results for a particular choice of criteria are summarized in Table 2. The values of x' (fraction of RCs in the water−alcohol mixture) show that the presence of cosolute significantly decreases the number of RCs. In Figure 4, the experimental values of $\ln(k/k_0)$ and calculated values of $\ln(k/k_0)$ ($=\ln(x'/x)$) are plotted versus the molality of alcohol. It appears that the experimentally found retardations can conveniently be explained by the decreased number of RCs, although the calculated values are invariably overestimated by a factor of ∼1.5−2. A nearly linear trend is found, as was predicted.[13,14] The solid lines in Figure 4 are fits using the simple mechanistic model (eq 4). The corresponding binding constants are 0.54 and 1.00 for EtOH and *t*-BuOH, respectively, on the basis of the experimental values, and 0.75 and 1.84, respectively, on the basis of the calculations.

An attempt was made to separate effects on nucleophilic water molecules and water molecules acting as general base. x'_{h1} stands for the fraction of RCs in the water−alcohol mixture where the criterion that a second water molecule should be present is left out; that is, it is assumed to be always present. The column x'/x'_{h1} shows that, in close to 90% of the cases
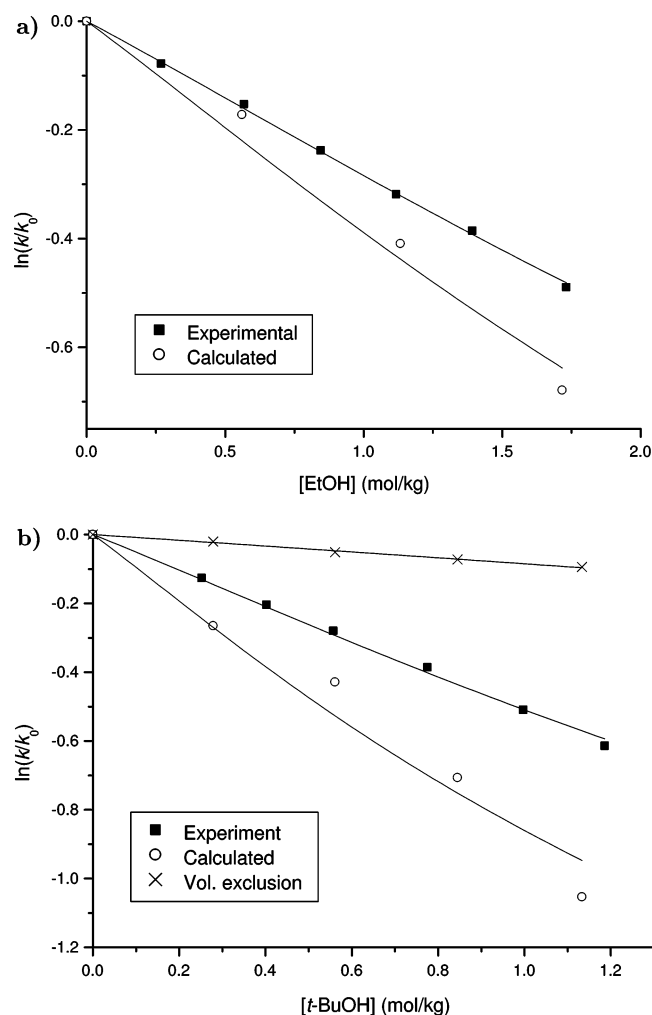
a)

b)

Figure 4. Plots of experimental values of $\ln(k/k_0)$ and calculated values of $\ln(k/k_0)$ ($=\ln(x'/x)$) vs alcohol molality for (a) EtOH and (b) *t*-BuOH. The solid lines represent fits according to eq 4. In the case of *t*-BuOH, also the effect of the reduced concentration of water due to the presence of *t*-BuOH (volume exclusion) is shown.

when the nucleophilic water molecule is present at a reactive position, there is, in fact, also a second water molecule present that can pick up the proton. Since this percentage seems not to depend on the concentration of alcohol, one can conclude that the rate retardation primarily stems from the effect of the cosolute on the *nucleophilic* waters and that there is hardly any effect on the waters acting as general base.

To investigate the effect of the cosolute on the occurrence of any RC or, rather, on the presence of the nucleophilic water molecule, radial distribution functions (RDFs) were calculated for the *t*-BuOH and EtOH carbon atoms around the MPDA carbonyl carbon (Figure 5). The RDFs were calculated over all simulations. The RDFs show a tendency for the cosolute molecules to reside in the vicinity of the carbonyl group, with peaks at 0.5 nm (*t*-BuOH) and 0.45 nm (EtOH). RDFs were also computed for RCs only. Two cases are discerned. In the first case, RDFs were calculated for only the same side of the C—(C=O)—O plane as the nucleophilic water molecule.[38] It is expected that, for a RC to form, no cosolvent molecule can be present near the carbonyl group, and indeed, the peaks in the RDFs became significantly lower, as well as shifted by +0.05 nm. In the second case, RDFs were calculated for only the opposite side of the C—(C=O)—O plane. If the simple blocking model is correct, the presence of a cosolute molecule near one side of the carbonyl group should not hamper the formation of
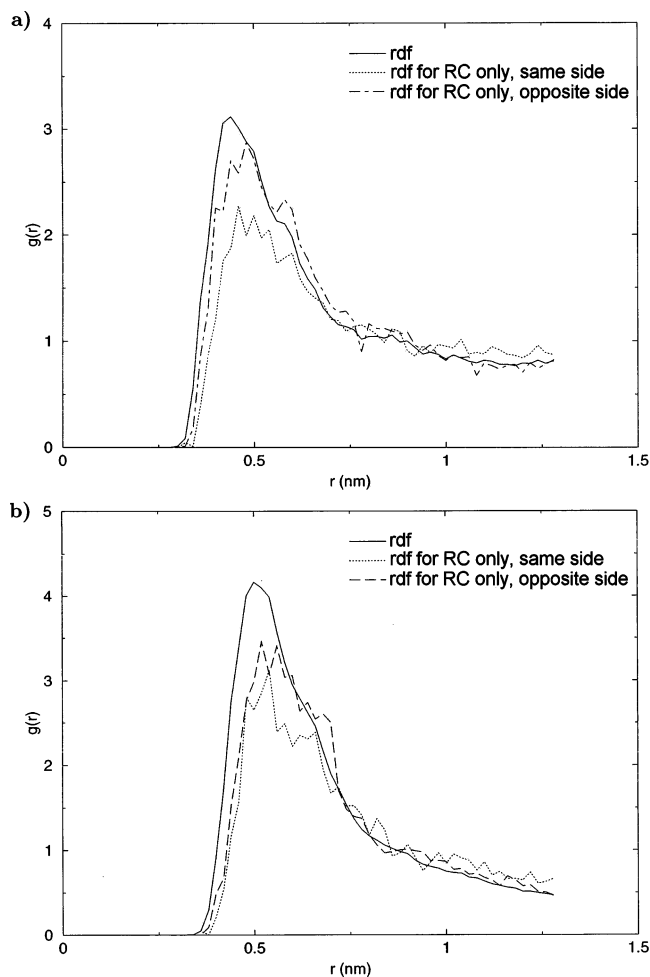
a)

b)

Figure 5. Plots of the radial distribution functions of the carbon atom next to the hydroxy group for (a) EtOH and (b) *t*-BuOH around the carbon atom of the carbonyl group of the ester. Further explanation is given in the text.

a RC with the nucleophilic water molecule on the other side. However, we find that, also in this case, the peaks have lower intensity, albeit not as low as in the first case. The effect is more prominent for *t*-BuOH than for EtOH. The phenyl ring, that was found to be anticorrelated with the occurrence of a RC, most likely is responsible for this effect: it will transfer the occupancy by the cosolute molecule to the other side of the C—(C=O)—O plane, because it necessarily cannot occupy the same space as the cosolute molecule.

Figure 6 shows the positions of the nucleophilic water molecules, projected in the *xy* plane, for the pure aqueous solution and for two concentrations of *t*-BuOH. No correlation is found between the position of a reactive water molecule relative to the ester molecule: within the cone of the applied selection criteria, the RCs are distributed evenly. This is the case for the pure water simulation as well as in the presence of cosolute, indicating that the cosolute has no preference to bind to a specific region of the ester molecule. This is confirmed also by RDFs around different positions in the MPDA molecule.

Discussion

In a previous study, we simulated the pH-independent hydrolysis reaction in pure water.[39] A configuration involving two water molecules bound at an ionic distance, as depicted in Figure 1, was used as the starting point, from which the reaction rate was calculated by combining a Gibbs energy calculation
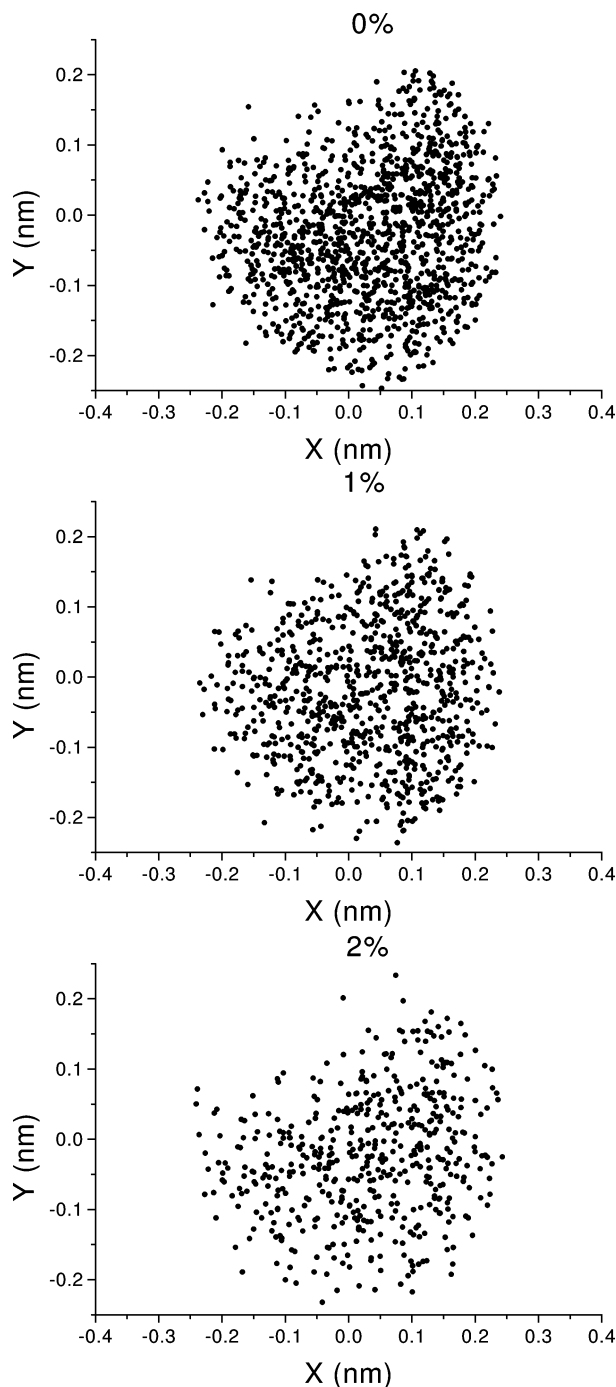
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Figure 6. Scatter plot showing the RC nucleophilic water oxygens projected onto the *xy* plane over a 1.6 ns MD simulation of a MPDA−*t*-BuOH−water system. The slightly empty region in the northwest corner corresponds to the carbonyl oxygen. For the coordinate axes, see Figure 2.

of an activated state prior to the proton transfer with a quantum dynamical simulation of the proton transfer rate. A rate constant of $k_{AS} = 2.7 \times 10^{-2}$ s^{-1} was found. The criteria that define the starting configuration equal those applied to the RC in the current work and represent an additional entropic term in the Gibbs function, since the RC is present in the system only a fraction of the time ($x_{reactive}$). If we include this additional term in the calculation of the rate constant, using the selection parameter values from the first row in Table 1 ($x_{reactive} = 0.146$), we get an overall rate constant of $k_{calc} = x_{reactive}k_{AS} = 3.9 \times 10^{-3}$ s^{-1}, which is in excellent agreement with the experimentally observed value of $k_{obs} = 2.78 \times 10^{-3}$ s^{-1}.

In the presence of cosolvent, the occurrence of the RC decreases because cosolvent molecules bind to the ester in a way that prevents formation of the RC. Both experimental and theoretical results are in agreement with a simple model that assumes a binding constant of K (expressed in reciprocal molal). However, the measured binding constants (0.54 and 1.00 for C = EtOH and *t*-BuOH, respectively) are smaller than the binding constants predicted from simulation (0.75 and 1.84, respectively). This is most likely due to inaccuracies in the force field used, which has not been optimized for the interactions occurring in this specific application. A difference of a factor of 2 in binding constants represents <2 kJ/mol in the free energy of binding, which is an inaccuracy to be expected from unoptimized force fields. We shall briefly discuss other possible causes.

Since water is a (much) smaller molecule than ethanol or *tert*-butanol, simple volume exclusion would already cause an apparent binding constant when the latter is expressed as a concentration ratio (molarity, mole fraction, or molality). However, volume exclusion of water accounts for only 15% of the experimentally found rate retardation (Figure 4).[40] Therefore, the rate retardation is not solely due to random encounters between solute and cosolute molecules but involves an element of true binding. Volume exclusion is automatically included in MD simulations.

We have assumed that there is no effect of the cosolute on the reaction rate of the RC, once formed. This is certainly an oversimplification, and there are three possible effects. First, the activated complex from which the proton transfer to the second water molecule takes place may have a different Gibbs energy of activation, for example, by a difference in stabilization of the more polar activated state because of the reduced dielectric permittivity of the water−cosolute mixture. This would raise the activation barrier and lower the reaction rate. Another cosolute effect could be on the potential curve seen by the transferring proton: after the proton transfer, the complex is more polar and could therefore be less stabilized by the solvent in the presence of cosolute. This would also decrease the reaction rate. Finally, the potential fluctuations that drive the proton transfer could be influenced (most likely reduced) by the presence of the cosolute and also reduce the reaction rate. While all these effects need further investigation, they would lower the reaction rate and could explain a lower experimental rate compared to the rates predicted by MD. We do find the opposite, however, and conclude that these effects are small compared to the inaccuracies of the force field.

Conclusions

To our knowledge, this is the first MD study of chemical reactivity in mixed aqueous solutions. While we were able to reproduce the nearly linear relation between the logarithm of the rate constant and cosolute concentration, the absolute slope is still off by a factor of 2. However, the results prove the possibility of calculating the trends in rate retardation effects versus cosolute concentration. The results show that the prevention of nucleophilic water molecules from approaching the carbonyl functionality is the main cause of the retardations and that this is caused by alcohol molecules preferentially solvating the ester molecule. In previous work, we examined the step RC → TS in pure water in detail, separating the final reaction rate constant calculation into various classical and quantum-mechanical and dynamical contributions.[39] In the present study, we have considered an extension to that calculation, correcting

for the probability of the RC, leading to satisfactory agreement with experiment.

Experimental Section

p-Methoxyphenyl dichloroacetate (MPDA) was prepared according to literature.[41] Ethanol and *tert*-butanol were analytical grade. Demineralized water was distilled twice in an all-quartz unit. Solutions were made up by weight and contained HCl to suppress catalysis by hydroxide ions. The pHs of the solutions were in the range 3.5−4.5.

Pseudo-first-order rate constants were determined by following the change in absorption at 288 nm for about six half-lives using a Perkin-Elmer λ5 spectrophotometer. Approximately 9 μL of a concentrated stock solution of MPDA in acetonitrile (2 × 10^{-2} mol dm^{-3}) was added to the reaction medium (2.5 mL) in quartz cells, thermostated to 25.0 °C. Rate constants were determined using a fitting program and were reproducible to within 1%.

References and Notes

(1) Glassstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes: The Kinetics of Chemical Reactions, Viscosity, Diffusion and Electrochemical Phenomena*; McGraw-Hill: New York, 1941.

(2) Laidler, K. J.; King, M. C. *J. Phys. Chem.* **1983**, *87*, 2657.

(3) Truhlar, D. G.; Hase, W. L.; Hynes, J. T. *J. Phys. Chem.* **1983**, *87*, 2664.

(4) Blandamer, M. J.; Burgess, J.; Engberts, J. B. F. N. *Chem. Soc. Rev.* **1985**, *14*, 237.

(5) Buncel, E.; Wilson, H. *J. Chem. Educ.* **1980**, *57*, 629.

(6) Reichart, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, Germany, 1988.

(7) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic: New York, 1998.

(8) Pratt, L. R.; Chandler, D. *J. Chem. Phys.* **1977**, *67*, 3683.

(9) Pratt, L. R.; Chandler, D. *J. Chem. Phys.* **1980**, *73*, 3434.

(10) Ben-Naim, A. *Hydrophobic Interactions*; Plenum: New York, 1980.

(11) Franks, F. *Faraday Symp. Chem. Soc.* **1982**, *17*, 7.

(12) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545.

(13) Blokzijl, W.; Engberts, J. B. F. N.; Jager, J.; Blandamer, M. J. *J. Phys. Chem.* **1987**, *91*, 6022.

(14) Blandamer, M. J.; Burgess, J.; Engberts, J. B. F. N.; Blokzijl, W. *Annu. Rep. Prog. Chem., Sect. C* **1990**, *87*, 45.

(15) Van Gunsteren, W. F.; Berendsen, H. J. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 992.

(16) Jorgensen, W. L. *J. Am. Chem. Soc.* **1980**, *102*, 543.

(17) Postma, J. P. M. Ph.D. Thesis, University of Groningen, The Netherlands, 1985.

(18) Jorgensen, W. L. *J. Phys. Chem.* **1986**, *90*, 1276.

(19) Stouten, P. F. W.; Kroon, J. *Mol. Simul.* **1990**, *5*, 175.

(20) Ferrario, M.; Haughney, M.; McDonald, I. R.; Klein, M. L. *J. Chem. Phys.* **1990**, *93*, 5156.

(21) Pálinkás, G.; Bakó, I.; Heinzinger, K.; Bopp, P. *Mol. Phys.* **1991**, *73*, 897.

(22) Jorgensen, W. L.; Madura, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 1407.

(23) Okazaki, S.; Touhara, H.; Nakanishi, K. *J. Chem. Phys.* **1984**, *81*, 890.

(24) Tanaka, H.; Walsh, J.; Gubbins, K. E. *Mol. Phys.* **1992**, *76*, 1221.

(25) Skaf, M. S.; Ladanyi, B. M. *J. Phys. Chem.* **1996**, *100*, 18258.

(26) Tanaka, H.; Nakanishi, K.; Touhara, H. *J. Chem. Phys.* **1984**, *81*, 4065.

(27) Kusalik, P. G.; Lyubartsev, A. P.; Bergman, D. L.; Laaksonen, A. *J. Phys. Chem. B* **2000**, *104*, 9533.

(28) Engbersen, J. F. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1975**, *97*, 1563.

(29) Holterman, H. A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1980**, *102*, 4256.

(30) Holterman, H. A. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1983**, *48*, 4025.

(31) Berendsen, H. J. C.; van der Spoel, D.; van Drunen, R. *Comput. Phys. Commun.* **1995**, *95*, 43; http://www.gromacs.org/.

(32) van Gunsteren, W. F.; Berendsen, H. J. C. *GROMOS, Groningen Molecular Simulation Package*; Biomos B.V.: Nijenborgh 16, 9747 AG Groningen, The Netherlands, 1987.

(33) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Hermans, J. In *Intermolecular Forces*; Pullman, B., Ed.; Reidel: Dordrecht, The Netherlands, 1981; p 331.

(34) Berendsen, H. J. C.; Postma, J. P. M.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.

(35) Hess, B.; Bekker, H.; Berendsen, H. J. C.; Fraaije, J. G. E. M. *J. Comput. Chem.* **1997**, *18*, 1463.

(36) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1994**, *116*, 3892.

(37) Besler, B. H.; Merz, K. M., Jr.; Kollman, P. A. *J. Comput. Chem.* **1990**, *11*, 431.

(38) It is thus not fully radial, as only configurations with $\theta_1 > 0$ are considered.

(39) Lensink, M. F.; Mavri, J.; Berendsen, H. J. C. *J. Comput. Chem.* **1999**, *20*, 886.

(40) This is estimated by taking the logarithm of the volume fraction of water in the mixtures. Volume data taken from: de Visser, C.; Perron, G.; Desnoyers, J. E. *Can. J. Chem.* **1977**, *55*, 856.

(41) Buyle, R. *Helv. Chim. Acta* **1964**, *47*, 2449.