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Theoretical study of the solvent effect on the hydrogen abstraction reaction of the methyl radical with hydrogen peroxide†

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The hydrogen abstraction reaction of the methyl radical with hydrogen peroxide ($CH_3^{\bullet}$ + HOOH $\longrightarrow$ CH_4 + $HOO^{\bullet}$) in both the gas phase and aqueous solution was studied by means of quantum chemical calculations. The gas phase reaction was described at the MP2, QCISD(T) and CCSD(T) levels of theory. To evaluate the effect of the solvent, different continuum solvation models were used. First, as a necessary calibration, the performance of the polarizable continuum model (PCM), the conductor like screening model (CPCM) and the conductor like screening model for real solvents (COSMO-RS) was tested in the calculation of the free energies of hydration for a set of 16 neutral organic molecules. The PCM and CPCM solvation models reproduce the experimental hydration free energies best, with an rms value of about 0.2 kcal mol^{-1}. The solvent effect on both the activation and reaction energies of the reaction of the methyl radical with hydrogen peroxide was subsequently calculated. All solvation models confirm the experimentally observed decrease in reaction rate in going from gas phase to aqueous solution. The PCM and CPCM suggest an increase in activation energy by about 4 kcal mol^{-1}, corresponding thus to a 1000-fold decrease in reaction rate, in good agreement with experiment. The reason for such a strong solvent effect is a larger stabilization of hydrogen peroxide by water.

Introduction

There has been considerable recent interest in the chemistry of hydrogen peroxide (HOOH) and its derivatives, in part due to their involvement in various biological processes. In fact, hydrogen peroxide is often used to inactivate cells, microorganisms, *etc.*[1] Reactions of peroxyl radicals ($ROO^{\bullet}$) with organic substrates are important steps in autoxidation of synthetic polymers, lipid peroxidation and also DNA damage.[2] These compounds also participate in different radical chain reactions, either in the atmosphere or in solution. Nevertheless, the mechanism of the reactions of free radicals with HOOH is not well understood yet.[3]

Let us consider the simplest reaction of hydrogen peroxide with the methyl radical. The latter can abstract a hydrogen atom from hydrogen peroxide (reaction 1) but it is also capable of

$$^{\bullet}CH_3 + H_2O_2 \longrightarrow CH_4 + HO_2^{\bullet} \qquad (1)$$

forming an OH radical according to a radical substitution reaction (2). Recently, it has been observed that the rate

$$^{\bullet}CH_3 + H_2O_2 \longrightarrow CH_3OH + {}^{\bullet}OH \qquad (2)$$

constant of reaction (1) is strongly influenced by the presence of a solvent.[3] While in the gas phase the rate constant is reported to be 3.3×10^7 dm^3 mol^{-1} s^{-1}, the corresponding rate constant in aqueous solution is merely 2.7×10^4 dm^3 $mol^{-1}s^{-1}$, implying a thousandfold rate reduction by the water solvent. This effect has been explained in terms of strong hydrogen bonding between the reactive site (HOOH) and the solvent molecules.[3,4]

There are two distinct actions of a solvent on the course of a chemical reaction: (i) an active participation of solvent molecules as co-reactants in the reacting supermolecule. In this case, the solvent molecules play the role of catalysts and therefore they tend to activate the reaction rather than to deactivate it.[5,6] (ii) A more passive effect of the solvent bulk on the energies of the reactants and, in particular, the transition state. In this case, the reaction could be either accelerated or inhibited. Owing to the fact that there is a decrease of the rate constant of reaction (1) on going from gas phase to solution, it is apparent that case (ii) is actually operative.

In connection with our continuing interest in the solvent effect on organic reactions,[7–10] and in view of the scarcity of quantitative information on the hydrogen abstraction reactions in solution, we have considered the solvent effect on the reaction energy and energy barrier of reaction (1) in calculating the hydration free energies of reactants, products and transition state structure. For this purpose, continuum solvation models, which offer an economic and efficient calculation of solvation free energies, have been used. In these solvation models the solute is placed in a cavity of molecular form inside a dielectric continuum, characterized simply by its relative permittivity (dielectric constant). The polarization of the medium can then be represented by virtual charges on the cavity surface. As a necessary preliminary calibration, different continuum solvation models were first evaluated for the calculation of the free energies of hydration of small neutral organic molecules. Subsequently, the solvent effect on the kinetic parameters of the reaction of the methyl radical with hydrogen peroxide was considered.

Computational methods

Gas phase geometry optimizations were performed at the Hartree–Fock (HF) and second order Møller–Plesset perturb-

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† *xyz* coordinates are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b000143k

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ation theory (MP2) levels in conjunction with the d,p-polarized basis sets 6-31G**; all calculations were performed using the GAUSSIAN 98 program.[11] To obtain more accurate energies, single point calculations were made using the coupled-cluster theory CCSD(T) and quadratic configuration interaction QCISD(T), using the 6-31G** and 6-311++G(2df,p) basis sets; CCSD(T) calculations with the larger 6-311++G(3df,3dp) basis set[12] were performed using the program ACESII.[13] For open-shell systems, the unrestricted formalism (UHF, UMP2, UCC) has been employed.

Hydration energies were calculated using the polarizable continuum model (PCM) developed by Tomasi and co-workers.[14] A second solvation model used is CPCM,[15] which is actually an implementation of the COSMO (Conductor-like Screening Model) solvation model[16] in the GAUSSIAN 98 package. The hydration free energies were calculated at the HF/6-31G** level using the GAUSSIAN 98 program. The UAHF (United Atom model for Hartree-Fock) definition[17] was used for the construction of the solute cavity. This cavity was constructed from spheres centered on the atoms of the solute. The radii of these spheres are determined by chemical considerations, such as hybridization, neighbouring atoms and the charge of the molecule. The effect of the solvent bulk on the geometry of the considered species was also tested by performing geometry optimizations with the CPCM solvation model. HF/6-31G** optimizations in aqueous solution yielded structures not significantly different from the gas phase structures, and hence only the parameters of the transition state structure of reaction (1) are reported hereafter. No geometry optimizations in solvent were performed for the calculation of the hydration free energies; actually gas phase structures obtained at the corresponding level of theory (HF/6-31G**) were used. The free energy of hydration contains not only electrostatic and polarization terms, but also cavitation and dispersion-repulsion energy terms, as described in reference 17. To test the effect of the solute cavity and the level of theory, some calculations were also performed with Pauling radii constructing a van der Waals cavity,[18] and using density functional theory (DFT) and the BP86 functional.

In addition, an improved model of COSMO, namely COSMO-RS (Conductor like Screening Model for Real Solvents),[19,20] was considered for hydration free energies using DFT and the DMol^3 package.[21] All parameters were set at the default values for COSMO-RS in Cerius^{2}3.8. The basis sets are double numeric with polarization functions (DNP, version 4.0.0). Calculations based on DFT were perfomed using the VWN-BP functional. For the calibration of the hydration free energies of the test set molecules, the geometries were reoptimized in the presence of the solvent continuum. For the description of the solvent effect on kinetic properties of reaction (1) however, the gas phase (U)MP2 geometries were used, due to the inherent difficulty of DFT for the optimization of transition state structures of abstraction reactions.[22–24] The free energy of hydration calculated with COSMO-RS also contains a non-electrostatic contribution term, evaluated from the area of the solvent accessible surface.

The thermochemical corrections in the reaction enthalpies were evaluated according to standard thermodynamic procedures[25] at a temperature of 298.15 K and a pressure of 1 atm. The (U)MP2 harmonic wavenumbers were scaled by a uniform scaling factor of 0.937.[26] It should be stressed that in this paper we have not considered the competition between reactions (1) and (2) but have rather concentrated on the former.

Results and discussion

Gas phase reaction

The optimized geometries of the species participating in reaction (1) are shown in Fig. 1. The cartesian coordinates of these structures are available as supplementary material. As expected, the reaction path for the hydrogen abstraction in the gas phase is characterized by a sole transition state structure (**TS**). The O–H bond distance in the **TS** (for the O–H bond that is broken) is 0.207 Å longer than that in free hydrogen peroxide ((U)MP2/6-31G** values). The O–O bond length of 1.412 Å in the **TS** has a value between the ones in hydrogen peroxide (1.467 Å) and the hydroperoxyl radical (1.326 Å). The H–O–O–H dihedral angle is much smaller in the **TS** (97.2°) than in free hydrogen peroxide (120.4°). The C–H bond length which is formed in the reaction has a bond distance in the **TS** that is 0.210 Å longer than the C–H distance in free methane. A possible source of error on the energy or geometry of the radical species involved in the reaction may result from spin contamination due to the unrestricted formalism.[27] $\langle S^2\rangle$ values are usually considered as an important indicator of this type of error. Since the $\langle S^2\rangle$ values of the UHF wavefunction for the radical species and TS under consideration were consistently smaller than 0.80, the corresponding unrestricted wavefunctions are expected to behave reasonably.

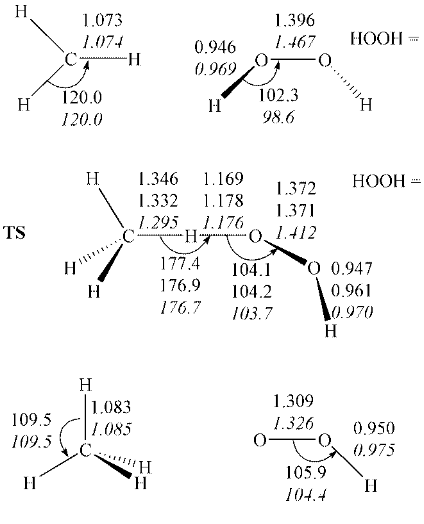

Fig. 1 Optimized geometries of stationary points related to reaction (1). Entries are HF/6-31G** (upper: gas phase), HF/6-31G** (CPCM, in water) and MP2/6-31G** (in italic, gas phase). Bond distances are given in Å, angles in degrees.

Reaction and activation enthalpies are shown in Table 1. Reaction (1) is exothermic by about 16.6 kcal mol^{-1}, as calculated from the bond dissociation enthalpies *D*(HOO–H) and *D*(CH_3–H), which are 88.2 and 104.8 kcal mol^{-1}, respectively.[28] (U)MP2/6-31G** describes the reaction enthalpy well, a value of 16.3 kcal mol^{-1} being obtained. At the CCSD(T) level a larger basis set is needed for an accurate description of the reaction enthalpy. Using the 6-311++G(3df,3dp) basis set a reaction enthalpy of 17.5 kcal mol^{-1} is calculated. QCISD(T) and CCSD(T) with the same basis set give very similar results. If the bond dissociation enthalpies of methane and hydrogen peroxide (O–H bond breaking) are considered separately (see Table 1), the CCSD(T)/6-311++G(3df,3dp) method gives much better results than (U)MP2/6-31G**. An MCSCF study of hydrogen peroxide yielded a bond dissociation energy for the O–H bond of 78.3 kcal mol^{-1}.[29] Generally, the MCSCF method underestimates the experimental energies required for bond cleavage. A significant improvement is thus obtained using the CCSD(T) method in combination with the large basis set and thermochemical corrections.

An experimental estimation of the activation energy of reaction (1) was made from the enthalpy of reaction (1) and the activation energy of the reverse reaction;[30] a value of 7.9 kcal mol^{-1} was obtained. By means of an empirical algorithm that relates the activation energy for the hydrogen atom transfer

Table 1 Bond dissociation enthalpy (D) for HOO–H and CH_3–H, reaction enthalpy (ΔH^r) and activation energy (E_a) of reaction (1) (kcal mol^{-1}), calculated at different levels of theory, using MP2/6-31G** geometries and frequencies

	D(HOO–H)	D(CH_3–H)	ΔH^r	E_a
MP2/6-31G(d,p)	81.4	97.7	−16.3	7.7
CCSD(T)/6-31G(d,p)	79.0	100.0	−22.7	8.2
QCISD(T)/6-311++G(2df,p)	81.8	100.3	−18.5	7.8
CCSD(T)/6-311++G(2df,p)	82.1	100.3	−18.2	8.1
CCSD(T)/6-311++G(3df,3dp)	85.3	102.8	−17.5	
Experiment[a]	88.2	104.8	−16.6	7.9

[a] Ref. 28, 30.

Table 2 Calculated hydration free energies (kcal mol^{-1})

Compound	PCM	CPCM	COSMO-RS	Experiment[a]
CH_4	1.86	1.84	1.71	1.97
CH_3CH_3	1.96	1.96	1.93	1.81
$CH_3CH_2CH_3$	1.95	1.93	2.07	1.97
$CH_3(CH_2)_2CH_3$	2.12	2.11	2.21	2.12
CH_3CHO	−3.72	−3.66	−3.50	−3.50
CH_3COCH_3	−3.77	−3.73	−4.39	−3.85
NH_3	−4.16	−4.17	−5.33	−4.3
CH_3NH_2	−4.48	−4.60	−4.17	−4.6
$(CH_3)_2NH$	−3.99	−4.28	−2.49	−4.3
$(CH_3)_3N$	−2.85	−2.87	−0.58	−3.2
H_2O	−6.18	−6.16	−8.85	−6.29
CH_3OH	−5.27	−5.11	−5.07	−5.09
CH_3CH_2OH	−5.20	−5.35	−4.91	−4.96
$CH_3(CH_2)_2OH$	−4.70	−4.72	−4.80	−4.84
CH_3OCH_3	−2.19	−2.16	−1.38	−1.89
CH_3COOH	−7.16	−7.08	−6.67	−6.70
rms	0.2	0.2	1.1	

[a] Ref. 17, 20.

reaction to properties of the reactants and products involved, an activation energy of 7.3 kcal mol^{-1} is calculated.[30–33] The energy barriers calculated at all considered levels of theory are in very good agreement with the experiment. With the CCSD(T)/6-311++G(2df,p) method, the activation energy is calculated at 8.1 kcal mol^{-1}. An energy barrier at the CCSD(T)/6-311++G(3df,3dp) level was not obtained due to the large computational effort required for the calculation of the **TS**.

Calculation of free energies of hydration using PCM, CPCM and COSMO-RS methods

We now turn to the performance of different continuum solvation models for the calculation of free energies of hydration of neutral molecules. The free energies of hydration were calculated for a test set of 16 neutral organic molecules, consisting of small alkanes, alcohols, aldehydes, ketones, carboxylic acids, amines and water. The results are reported in Table 2, together with the rms (root mean square deviation) values for the set of molecules. Experimental values were obtained from references 17 and 20. It should be noted that the test set contains only closed shell molecules, while in the reaction under consideration also radicals participate. There are however, to our knowledge, no experimental hydration free energies known of radical species.

The results for both PCM and CPCM solvation models are very similar to each other and in excellent agreement with the experimental values. The PCM and CPCM solvation models calculate the hydration free energies with an rms of merely 0.2 kcal mol^{-1} for the test set of molecules. The rms for COSMO-RS hydration free energies is somewhat larger, with a value of 1 kcal mol^{-1}.

For the PCM solvation model, the effect of the cavity form, the non-electrostatic contributions as well as the level of theory is also considered. The UAHF cavities are fitted (for PCM calculations) to reproduce experimental free energies of hydration, and therefore give much better hydration free energies than when van der Waals cavities are used. For the sake of comparison, the hydration free energies of the molecules in the test set were again calculated at the same level of theory (HF/6-31G**) with the PCM solvation model, using Pauling radii in the van der Waals shaped cavity. The rms obtained from the latter calculations was much larger, namely 2.2 kcal mol^{-1}. It is also important that non-electrostatic contributions of the free energies of hydration are included. If only the electrostatic part is considered, the rms amounts to 1.3 kcal mol^{-1}, as compared with 0.2 kcal mol^{-1} for PCM.

The importance of quantum chemical methods for the accuracy of free energies of hydration was also tested at the DFT level, employing the BP86 functional (also with a 6-31G** basis set). If BP86 is used the hydration free energy is systematically underestimated. The reason for this is that the UAHF model uses parameters that are obtained by fitting HF free energies of hydration with experimental values. The Hartree–Fock method usually overestimates the dipole moment of molecules, and the corresponding response of a dielectric in a continuum solvation model will therefore normally be overestimated. In the UAHF model such overestimation is compensated by the fitting with experimental hydration free energies. The cavities, obtained by this fitting, become obviously too large for methods that reproduce better dipole moments of the solutes, for example the DFT/BP86 method, and as a consequence an underestimation of the bulk solvent effect is observed.[15]

In Fig. 2 a correlation between the calculated (PCM, CPCM and COSMO-RS) and experimental free energies of hydration is shown. The best correlation is obtained using the PCM and CPCM solvation model, having correlation coefficients of 0.995 and 0.996 respectively. The correlation coefficient for COSMO-RS is only 0.896. The values of the intercept and slope of the fitted regression lines are equally better for the CPCM solvation model, the slope is nearly 1 and the intercept is only −0.004 kcal mol^{-1}.

Solvent effect on the reaction (1) of methyl radical with hydrogen peroxide

Hydration free energies of the participating species, calculated using PCM, CPCM and COSMO-RS, are reported in Table 3. The hydration free energies of methane and methyl radical do not differ much from each other for the solvation models considered. The experimental hydration free energy of methane is 1.97 kcal mol^{-1}, the positive value being due to the apolarity of this molecule. All solvation models give good agreement with this experimental hydration free energy as they reproduce the value with a deviation of, at most, 0.3 kcal mol^{-1}. The hydration free energy of the methyl radical is calculated to be only slightly smaller than in the case of methane. This is in agreement with the findings of Griller and co-workers,[34] that in polar solvents the solvation energies of a hydrocarbon and its corresponding radical are very similar. As a consequence, the contributions of this pair to the overall reaction thermochemistry tend mutually to cancel.

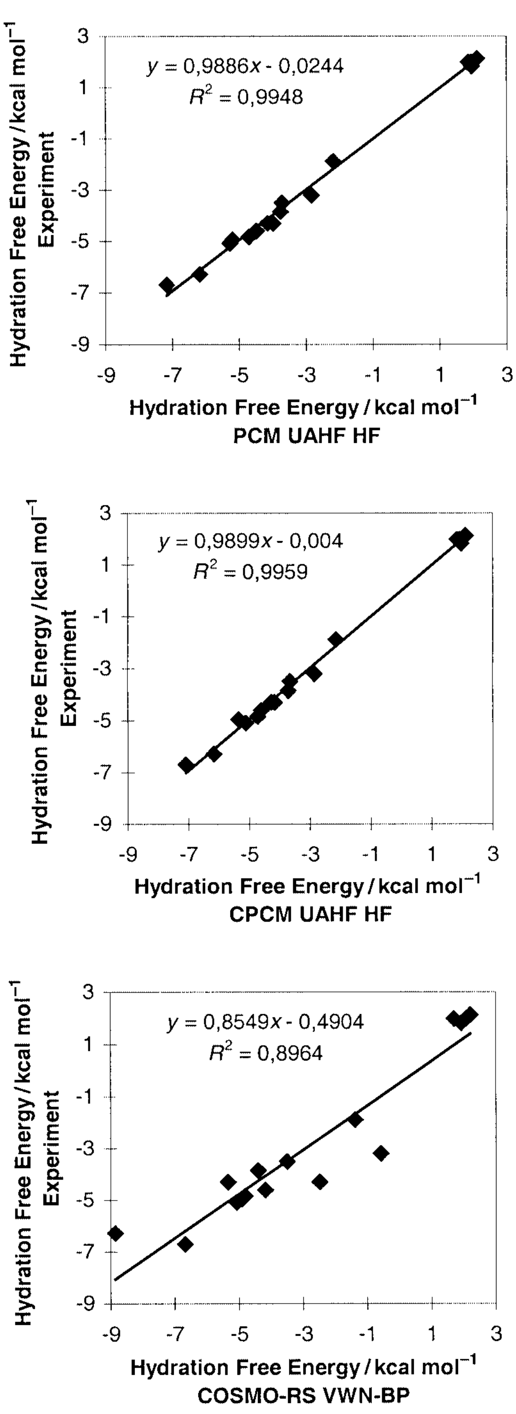

Fig. 2 Calculated *versus* experimental hydration free energies (kcal mol^{-1}) for a test set of neutral solutes, using PCM, CPCM and COSMO-RS solvation models.

Table 3 Hydration energies (ΔG_{hydr}) and effect of the solvent water on the activation energy (ΔE_a) and reaction energy ($\Delta\Delta E^r$), calculated using PCM, CPCM, and COSMO-RS (kcal mol^{-1})

	PCM	CPCM	COSMO-RS
ΔG_{hydr} ($^{\bullet}CH_3$)	1.70	1.69	1.29
ΔG_{hydr} (H_2O_2)	−11.14	−11.20	−8.47
ΔG_{hydr} (CH_4)	1.84	1.84	1.71
ΔG_{hydr} ($HO_2^{\bullet}$)	−6.94	−6.84	−6.66
ΔG_{hydr} (TS)	−5.38	−5.34	−4.73
ΔE_a	4.06	4.17	2.45
$\Delta\Delta E^r$	4.34	4.51	2.23

In contrast, the hydration energy of hydrogen peroxide, the hydroperoxyl radical and transition structure **TS** do differ significantly from each other. All solvation models show the largest free energy of hydration in the case of hydrogen peroxide. With the PCM and CPCM models, a difference of more than 4 kcal mol^{-1} is observed between the hydration free energy of hydrogen peroxide and that of its radical. COSMO-RS predicts smaller differences (1.8 kcal mol^{-1}). The hydration free energy of the **TS** is between 1 and 2 kcal mol^{-1} smaller than that of the hydroperoxyl radical, dependent on the solvation model considered.

The geometry of the **TS** was also reoptimized using the CPCM solvation model at the HF/6-31G** level. The resulting geometries are shown in Fig. 1. The geometry changes induced by the solvent continuum are small. The largest difference in bond distances is observed for the terminal O–H bond, being 0.015 Å. The C–H bond that is formed in the reaction becomes 0.014 Å shorter, while the O-H bond which is broken becomes only 0.009 Å longer. According to the Hammond postulate, one would expect that the geometry of the TS becomes more reactant-like in solution, since the reaction becomes less exothermic (see below) in solution. However the calculations show a geometry change in the opposite direction. Although such an anti-Hammond behaviour is not unusual, we note that the changes are quite small and the parameters obtained by the distinct methods might not be directly compared to each other. We should say that there are very small changes in geometry following solvation.

Table 3 also summarizes the effect of the aqueous medium on the activation and reaction energies, calculated using different continuum solvation models. The predicted solvent effect on the activation energy is largest for the PCM and CPCM calculations, they both predict that, when going from the gas phase to aqueous solution, the activation energy is increased by about 4 kcal mol^{-1}. COSMO-RS predicts a similar decrease in reaction rate, but at a much smaller extent.

The observed rate constant k of a one-step reaction can be calculated from the activation energy E_a *via* the Arrhenius equation $k = A\exp(-E_a/RT)$. Since the geometries of the reactants and transition state structure are not much modified due to the presence of the solvent, it is reasonable to assume that the frequency factor A has the same order of magnitude in both gaseous and aqueous phases. An increase in activation energy of 4 kcal mol^{-1} then roughly corresponds to a decrease in the reaction rate by a factor of 1000, following the change of medium, in agreement with experimental observations.[3]

It is thus apparent that the larger stabilization of hydrogen peroxide in water constitutes the main reason for a negative solvent effect on the activation energy as was previously suggested.[4] The fact that the PCM and CPCM continuum models reproduce this trend so well could lead us to conclude that the stabilization of hydrogen peroxide in water is primarily determined by electrostatic interactions. However, the effect of hydrogen bonding may be implicitly incorporated in both PCM and CPCM models, as they both use the UAHF definition for the construction of the solute cavities. The parameters, used for the determination of the atomic radii, are fitted to reproduce experimental hydration free energies. Owing to this fitting, the effect of hydrogen bonding can be (partly) parametrized in the atomic radii.

The results in Table 3 show that not only the reaction rate is influenced by the solvent, but also the chemical equilibrium is shifted. Since the hydration energy of the products is around −5 kcal mol^{-1}, whereas the hydration free energy of the reactants is −9.5 kcal mol^{-1}, the reaction energy is about 4.5 kcal mol^{-1} smaller in aqueous solution than in the gas phase.

Concluding remarks

The hydrogen abstraction of hydrogen peroxide by the methyl radical was studied in the gas phase and in aqueous medium, using different continuum solvation models. The calculations confirm the large solvent effect on the reaction rate: in water the reaction proceeds much more slowly than in the gas phase. The reason is a larger hydration free energy of hydrogen peroxide. Although all solvation models considered (PCM, CPCM and COSMO-RS) predict the smaller activation barrier in aqueous solution, PCM and CPCM describe the solvent effect most accurately.

Acknowledgements

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