JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Subscriber access provided by ISTANBUL TEKNIK UNIV

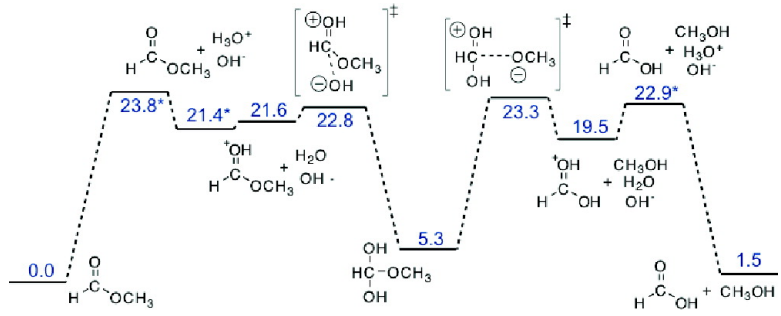
Communication

Molecular Dynamics Prediction of the Mechanism of Ester Hydrolysis in Water

Hakan Gunaydin, and K. N. Houk

J. Am. Chem. Soc., **2008**, 130 (46), 15232-15233 • DOI: 10.1021/ja8050525 • Publication Date (Web): 22 October 2008

Downloaded from http://pubs.acs.org on February 8, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ACS Publications
High quality. High impact.

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Published on Web 10/22/2008

Molecular Dynamics Prediction of the Mechanism of Ester Hydrolysis in Water

Hakan Gunaydin and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095

Received July 1, 2008; E-mail: houk@chem.ucla.edu

Water is an excellent solvent for many reactions; it is essential for life. The roles of solvent water or individual water molecules in catalysis have attracted much current interest. The phenomenon of "on water" catalysis[1] may be related to the surface hydrogen bonding[2] or the unusual acidity of water surfaces.[3] The role of water in altering the rates and selectivities of proline-catalyzed reactions,[4] or altering the regioselectivities of cascade epoxide openings,[5] are among many recent reports of water molecules as catalysts or cocatalysts. Diels−Alder reactions and other pericyclic reactions are accelerated in water.[6] The accelerations of organic reactions such as hydrolysis,[7,8] condensations,[9] Diels−Alder cycloadditions,[8] and the Fisher indole synthesis[8] have been observed in supercritical and near-critical water.

Car−Parrinello molecular dynamics (CPMD) studies of acid- and base-catalyzed hydrolyses reproduce experimental activation free energies ($\Delta G^{\ddagger}$).[10] However, the computed $\Delta G^{\ddagger}$ value for the neutral hydrolysis of N-methyl acetamide by a cyclic mechanism involving two water molecules exceeds the experimental value.[11]

Various calculations of neutral hydrolysis reactions in water postulate the formation of zwitterionic intermediates, networks of water molecules,[12,13] or four-membered cyclic transition states (TS).[14] The computed $\Delta G^{\ddagger}$ values by these mechanisms always exceed the experimentally measured barriers except some of the ones computed with the Marcus theory.[12,14,15] Zwitterionic intermediates are not minima on the gas phase energy surface, and accurate calculations of free energies for the reactions involving putative zwitterionic intermediates have not been achieved.[16]

Autoionization of water is slow but generates both a strong acid (hydronium) and strong base (hydroxide). The dynamical processes by which the fluctuations of water can lead to autoionization have been studied in detail by Chandler and co-workers.[17] We have now explored the hydrolysis mechanism in which the reaction is initiated by water autoionization.[18] We have computed the $\Delta G^{\ddagger}$ for the hydrolysis of methyl formate in pure water with metadynamics (MT)[19] simulations.

The BLYP functional and norm-conserving Troullier−Martins[20] pseudopotentials (PP) were used to describe the electronic structure of the system.[21] The plane wave cutoff for the Kohn−Sham orbitals was set to 85 Ry. The periodic unit cell, with cubic dimensions of 10.1 Å, contained 32 water molecules and 1 methyl formate molecule. The equations of motion were integrated with a time step of 3 au (0.07 fs). The simulations were run at the NVT ensemble at 300 K for 1 M standard state by using a Nose−Hoover thermostat.[22] The MT simulations use the CPMD[23] Lagrangian with a fictitious electron mass of 340 amu. CPMD-MT simulations with similar settings were shown to predict the energetics and dynamics of aqueous phase decomposition of peroxynitrous acid accurately.[24]

The relative free energies of the substrate, products, and the *gem*-diol intermediate in water were computed at the CBS-QB3[25] level of theory; solvation free energy corrections were computed with the CPCM method.[26] The computed energetics are consistent with the previously published data.[27]

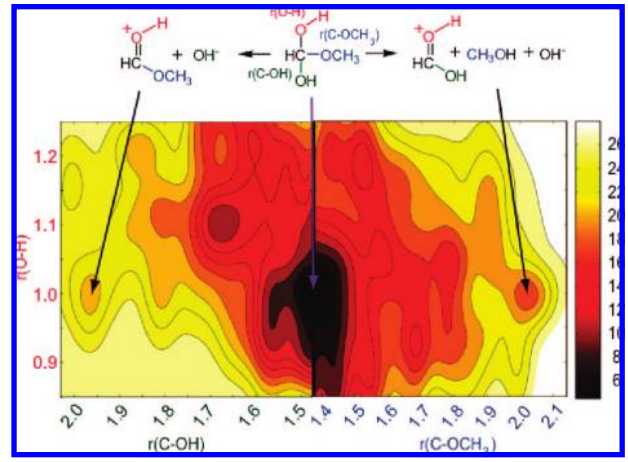


Figure 1. Free energy surface connecting protonated formic acid, methanol, and hydroxide to protonated methyl formate and hydroxide via the *gem*-diol intermediate. The energies are the relative free energies in kcal/mol with respect to methyl formate in water.

Autoionization occurs with a free energy of reaction of 21.4 kcal/mol and a $\Delta G^{\ddagger}$ of 23.8 kcal/mol.[28] From hydroxide and hydronium, separated by many water molecules, the hydrolysis of methyl formate proceeds via the protonation of the carbonyl oxygen of methyl formate by hydronium. A free energy profile reconstructed from MT simulations for the hydrolysis of methyl formate supports this hydrolysis mechanism (Figure 1). Figure 1 shows the formation of protonated methyl formate, the conversion of protonated methyl formate to the *gem*-diol intermediate, and the conversion of the *gem*-diol intermediate to protonated formic acid plus methanol and hydroxide.

The region of the free energy profile for the conversion of the protonated methyl formate plus hydroxide to the *gem*-diol intermediate (Figure 1) was calculated in the reverse direction. The MT simulation was run by using two collective variables: r(C-OH) and r(O−H), as shown in Figure 1. The fictitious masses and force constants for these two collective variables were set to 10 amu and 0.3 au, respectively. The heights of the hills were determined by the shape of the underlying energy surface and set to be at most 10 kcal/mol for the first 200 MT steps and reduced to 5 kcal/mol in the subsequent MT steps.[21] On average, the hill height was 1.3 kcal/mol. The addition of the hills was allowed with a minimum time separation of 75 MD steps and with a minimum displacement of 0.05 Å in the collective variables; if the displacement never exceeds 0.05 Å, the addition of consecutive hills was forced after 150 MD steps. According to MT simulations, the addition of hydroxide to protonated methyl formate requires a $\Delta G^{\ddagger}$ of 1.3 kcal/mol, and the reaction is exergonic by 16.3 kcal/mol. The TS was found to occur at the distances r(C−OH) = 1.96 Å and r(O−H) = 1.07 Å. The overall $\Delta G^{\ddagger}$ for the conversion of methyl formate to the *gem*-diol intermediate via protonated methyl formate, plus the hydroxide intermediate was obtained by summing the free energy

10.1021/ja8050525 CCC: $40.75 © 2008 American Chemical Society

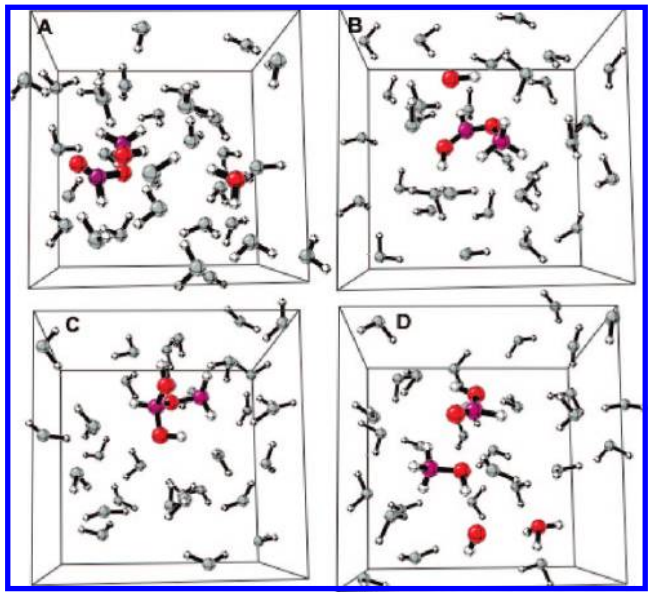


Figure 2. Snapshots from MT simulations of the hydrolysis of methyl formate in water. (A) Methyl formate, hydroxide, and hydronium. (B) Protonated methyl formate and hydroxide. (C) *gem*-Diol. (D) Methanol, formic acid, hydroxide, and hydronium.

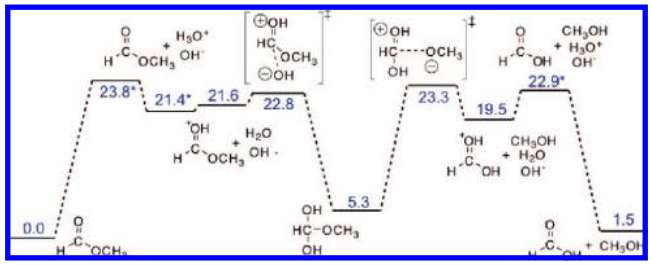


Figure 3. Free energy profile for the hydrolysis of methyl formate. Energies are given in kcal/mol. *Obtained from experimental data.

difference between the *gem*-diol intermediate and methyl formate in water (5.3 kcal/mol) and the $\Delta G^{\ddagger}$ from the MT simulation. This corresponds to an overall $\Delta G^{\ddagger}$ of 22.9 kcal/mol for this step.

A similar simulation was performed for the conversion of the *gem*-diol intermediate to protonated formic acid plus methanol and hydroxide. Two distances, $r(C-OCH_3)$ and $r(O-H)$, were used as two collective variables (Figure 1). The $\Delta G^{\ddagger}$ required for the conversion of the *gem*-diol intermediate to protonated methyl formate plus methanol and hydroxide is 18.0 kcal/mol. This process is endergonic by 14.2 kcal/mol. The TS was found to occur at the distances $r(C-OCH_3) = 1.97$ Å and $r(O-H) = 1.14$ Å. The activation free energy for this TS is 23.3 ± 1.8 kcal/mol with respect to methyl formate in water. This is the same as the water autoionization step, within the error bars of the simulations. MD snapshots from the simulations are shown in Figure 2A−D, respectively.

The overall free energy profile for the hydrolysis of methyl formate is given in Figure 3. The energy profile was constructed from $\Delta G^{\ddagger}$ obtained from MT simulations and the relative free energies among methyl formate, the *gem*-diol intermediate, and products. Experimental data for the autoionization of water were used to construct the free energy profile. Statistical errors in MT simulations are calculated to be ±1.8 kcal/mol.[29] All of the TSs, located along the methyl formate hydrolysis pathway have similar $\Delta G^{\ddagger}$ values, and these agree well with the experimental value of 25.9.[30] Measured $\Delta G^{\ddagger}$ values for hydrolyses of 35 esters in pure water range from 21 to 28 kcal/mol and support the hydrolysis mechanism presented here.

The evolution of enzymes may have proceeded by the gradual perfection of such a dual acid/base catalysis mechanism that occurs spontaneously in water, which may be considered a primordial pre-enzymatic catalyst. The hydrolysis mechanism demonstrated here for esters is also being investigated for the hydrolysis reactions of amides, ketals, ethers, and phosphates in pure water in the absence of added catalysts.

Acknowledgment. We thank the National Science Foundation (Grant CHE-0548209) and DARPA (Grant 130235) for financial support of this research. The computations were performed on the UCLA CNSI and Hoffman ATS clusters.

Supporting Information Available: Full author list for reference 25. This material is free of charge via the internet at http://pubs.acs.org.

References

(1) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.
(2) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502.
(3) Petersen, M. K.; Iyengar, S. S.; Day, T. J. F.; Voth, G. A. *J. Phys. Chem. B* **2004**, *108*, 14804–14806. Petersen, P. B.; Saykally, R. J. *J. Phys. Chem. B* **2005**, *109*, 7976–7980. Mucha, M.; Frigato, T.; Levering, L. M.; Allen, H. C.; Tobias, D. J.; Dang, L. X.; Jungwirth, P. *J. Phys. Chem. B* **2005**, *109*, 7617–7623. Buch, V.; Milet, A.; Vacha, R.; Jungwirth, P.; Devlin, P. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 7342–7347.
(4) Klussmann, M.; Iwamura, H.; Mathew, S. P., Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621–623.
(5) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189–1192.
(6) Blake, J. F.; Lim, D.; Jorgensen, W. L. *J. Org. Chem.* **1994**, *59*, 803–905. Breslow, R.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923–9924.
(7) Lesutis, H. P.; Glaser, R.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **1999**, *1999*, 2063–2064. Duan, P.-G.; Wang, X.; Dai, L.-Y. *Chem. Eng. Technol.* **2007**, *30*, 265–269.
(8) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, *2005*, 3672–3679.
(9) Nolen, A. N.; Liotta, C. L.; Eckert, C. A.; Glaser, R. *Green Chem.* **2003**, *5*, 663–669.
(10) Zahn, D. *Chem. Phys. Lett.* **2004**, *383*, 134–137. Blumberger, J.; Ensing, B.; Klein, M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 2893–2897. Blumberger, J.; Klein, M. L. *Chem. Phys. Lett.* **2006**, *422*, 210–217.
(11) Callahan, B. P.; Yuan, Y.; Wolfenden, R. *J. Am. Chem. Soc.* **2005**, *127*, 10828–10829.
(12) Guthrie, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 5529–5538. Guthrie, J. P.; Pitchko, V. *J. Am. Chem. Soc.* **2000**, *122*, 5520–5528.
(13) Zhan, D. *Eur. J. Org. Chem.* **2004**, *2004*, 4020–4023.
(14) Kallies, B.; Mitzner, R. *J. Mol. Model.* **1998**, *4*, 183–196. Krug, J. P.; Popelier, L. A.; Bader, R. F. W. *J. Phys. Chem.* **1992**, *96*, 7604–7616.
(15) Schmeer, G.; Sturm, P. *Phys. Chem. Chem. Phys.* **1999**, *1*, 1025–1030. Yamabe, S.; Tsuchida, N.; Hayashida, Y. *J. Phys. Chem. A* **2005**, *109*, 7216–7224. Antonczak, S.; Ruiz-Lopez, M. F.; Rivail, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 3912–3921. Antonczak, S.; Ruiz-Lopez, M. F.; Rivail, J. L. *J. Mol. Model.* **1997**, *3*, 434–442. Gorb, L.; Asensio, A.; Tunon, I.; Ruiz-Lopez, M. F. *Chem. Eur. J.* **2005**, *11*, 6743–6753.
(16) Balta, B.; Aviyente, V. *J. Comput. Chem.* **2004**, *25*, 690–703.
(17) Geissler, P. L.; Dellago, C.; Chandler, D.; Hutter, J.; Parrinello, M. *Science* **2001**, *291*, 2121–2124.
(18) Zhang, X.; Houk, K. N. *J. Org. Chem.* **2005**, *70*, 9712–9716.
(19) Laio, A.; Parrinello, M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99* (20), 12562–12566.
(20) Troullier, N.; Martins, J. L. *Phys. Rev. B* **1991**, *43*, 1993–2006.
(21) Lensink, M. F.; Mavri, J.; Berendsen, H. J. *J. Comput. Chem.* **1999**, *20*, 886–895.
(22) Nose, S. *J. Chem. Phys.* **1984**, *81*, 511–519. Hoover, W. G *Phys. Rev. A* **1985**, *31*, 1695–1697.
(23) Car, R.; Parrinello, M. *Phys. Rev. Lett.* **1985**, *55*, 2471. CPMD, http://www.cpmd.org/, Copyright IBM Corp 1990-2008, Copyright MPI für Festkörperforschung Stuttgart 1997-2001.
(24) Gunaydin, H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10036–10037.
(25) Gaussian 03, Revision C.02, Frisch, M. J. et al. Gaussian, Inc., Wallingford, CT, 2004.
(26) Takano, Y.; Houk, K. N. *Chem. Theory Comp.* **2005**, *1*, 70–77.
(27) Guthrie, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 6999–7003.
(28) Eigen, M.; de Maeyer, L. *Z. Elektrochem.* **1955**, *59*, 986. Luz, Z.; Meiboom, S. *J. Am. Chem. Soc.* **1964**, *86*, 4768–4769.
(29) Laio, A.; Rodriguez-Fortea, A.; Gervasio, F. L.; Ceccarelli, M.; Parrinello, M. *J. Phys. Chem. B* **2005**, *109*, 6714–6721. Ensing, B.; DeVivo, M.; Liu, Z.; Moore, P.; Klein, M. L. *Acc. Chem. Res.* **2006**, *39*, 73–81. Raiteri, P.; Laio, A.; Gervasio, F. L.; Micheletti, C.; Parrinello, M. *J. Phys. Chem. B* **2006**, *110*, 3533–3539.
(30) Guthrie, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5892–5904.

JA8050525