J. Am. Chem. Soc. **1990**, *112*, 7973–7980

Gas-Phase and Solution-Phase Potential Energy Surfaces for $CO_2 + nH_2O$ ($n = 1, 2$)

Kenneth M. Merz, Jr.

Contribution from the Department of Chemistry and the Department of Molecular and Cell Biology, The Pennsylvania State University, University Park, Pennsylvania 16802.

Received April 2, 1990

Abstract: Ab initio and free energy perturbation simulations are used to characterize both the gas-phase and solution-phase potential energy surfaces for the reaction of CO_2 with H_2O. The 3-21G, 6-31G, and 6-31G** basis sets were used to locate and fully optimize all critical points for the reactions of one and two H_2O molecules with CO_2. Where possible, correlation corrections were determined at the MP4/6-31G**//6-31G** level, otherwise, MP2/6-31G**//6-31G** was used. From these calculations our best estimate (MP4/6-31G**//6-31G**) for the activation energy for the reaction of CO_2 with one water molecule is 54.5 kcal/mol and for the dehydration reaction it is 46 kcal/mol. Our best estimate (MP2/6-31G**/6-31G**) for two water molecules reacting with CO_2 is 32.3 kcal/mol and for the reverse reaction it is 25.5 kcal/mol. Zero-point and entropic corrections determined with use of 3-21G vibrational frequencies give free energies of activation (ΔG_{act}) for the one- and two-water reactions of 56.7 ± 1.0 kcal/mol (reverse 41.1 ± 1.0 kcal/mol) and 40.6 ± 1.0 kcal/mol (reverse 25.2 ± 1.0 kcal/mol), respectively. Thus, we predict that the reaction of two water molecules with CO_2 is more facile than with one in the gas phase. This can be rationalized by considering that the reaction of a single water molecule results in a four-electron process (Woodward–Hoffman forbidden), while the reaction of two water molecules involves six electrons (Woodward–Hoffman allowed). The unfavorable entropic contribution for the two-water reaction is not great enough to disfavor this reaction over the one-water case. In order to assess how the gas-phase ab initio results reflect what might be occurring in solution we have developed molecular mechanical parameters that enable us to determine approximate solution-phase ΔG_{act} for these reactions. Using the 6-31G**//3-21G level of theory we have determined interaction energies between the critical points along the reaction profile and used these to determine a set of force field parameters that reproduce these energies. We then used these parameters to evaluate relative free energies of solvation for the critical points using free energy perturbation theory. These combined with the ab initio free energies allowed us to construct an approximate free energy profile for these reactions. We find that the forward ΔG_{act} for the one-water reaction is 49.1 ± 1.4 kcal/mol, while that for two is 21.2 ± 1.3 kcal/mol. The ΔG_{act} for the reverse reactions were found to be 44.1 ± 1.0 and 15.2 ± 1.0 kcal/mol, respectively. The experimental value for the forward and reverse solution-phase ΔG_{act} is 18.4 and 15.3 kcal/mol, respectively. The two-water reaction is in better agreement with experiment and suggests that this reaction is the dominant one in solution.

Introduction

The hydration reaction of CO_2 (**1**) is of significant biological importance because of its role in the pH regulation of blood.[1] However, because the hyration of CO_2 is so slow under physiological conditions an enzyme, carbonic anhydrase (CA), has been designed by nature to carry out this reaction with one of the highest turnover rates known.[2] In the absence of CA, CO_2 reacts with water and hydroxide ion, in aqueous solution, with activation energies (E_a) of 17.7 kcal/mol for the forward and 14.6 kcal/mol for the reverse direction in reaction 1,[3] while for the forward direction of reaction 2 it is 13.1 kcal/mol.[4] CA catalysis, which involves a zinc bound hydroxide ion and not a free one, increases the rate of reaction 2 by about a factor of 10^7. Both reactions 1 and 2 have a role in the elimination of CO_2 from the blood.[1]

$$H_2O + CO_2 \underset{14.6\ \text{kcal/mol}}{\overset{17.7\ \text{kcal/mol}}{\rightleftharpoons}} H_2CO_3 \tag{1}$$

$$OH^- + CO_2 \overset{13.1\ \text{kcal/mol}}{\rightleftharpoons} HCO_3^- \tag{2}$$

The gas-phase reaction of CO_2 with water and hydroxide ion has been studied with use of ab initio calculations. Early ab initio studies employed a Huzinaga basis set[5] and CI calculations to determine a gas-phase E_a of 55.9 kcal/mol for (1)[6] and 0 kcal/mol for (2).[7] The difference in the gas-phase and solution-phase reactivities is thought to be due to solvation effects, and, in the case of (1), other water molecule(s) may be catalyzing the reaction.[6-9] More recent work with the 3-21G basis set[10] explored this latter possibility and found that two water molecules could react with CO_2 via a six-membered cyclic TS reducing the calculated E_a to 15.5 kcal/mol for (1).[10] However, this agreement might be due to basis set limitations,[10] or it may be the result of not taking into consideration enthalpic and entropic effects that will be more unfavorable for the two-water reaction.[10] Reactions 1 and 2 have recently[11] been studied with the 4-31G basis set[12] and the PRDDO method[13] with results analogous to those of the previous efforts.[6-10] The interaction of CO_2 with water has also been extensively studied from both the theoretical[14] and experimental[15] perspectives.

---

(1) Maren, T. H. *Physiological Rev.* **1967**, *47*, 595. Davies, R. E. *Biol. Rev. Cambridge Phil. Soc.* **1951**, *26*, 87. Roughton, F. J. W. *Harvey Lect.* **1943**, *39*, 96.

(2) Merz, K. M.; Hoffmann, R.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1989**, *111*, 5636. For recent reviews see: Silverman, D. N.; Lindskog, S. *Acc. Chem. Res.* **1988**, *21*, 30. Silverman, D. N.; Vincent, S. H. *CRC Crit. Rev. Biochem.* **1983**, *14*, 207. Lipscomb, W. N. *Annu. Rev. Biochem.* **1983**, *52*, 17. Lindskog, S. In *Zinc Enzymes*; Spiro, T. G., Ed.; John Wiley & Sons: New York, 1983. Pocker, Y.; Sarkanen, S. *Adv. Enzymol.* **1978**, *47*, 149. Bertini, I.; Luchinat, C.; Scozzafava, A. *Struct. Bonding (Berlin)* **1981**, *48*, 45.

(3) Magid, E.; Turbeck, B. O. *Biochem. Biophys. Acta* **1968**, *165*, 515.

(4) Pinsent, B. R. W.; Pearson, L.; Roughton, F. J. W. *Trans. Faraday Soc.* **1956**, *52*, 1512.

(5) Huzinaga, S. *J. Chem. Phys.* **1965**, *42*, 1293.

(6) Jönsson, B.; Karlström, G.; Wennerström, H.; Forsen, S.; Roos, B.; Almlöf, J. *J. Am. Chem. Soc.* **1977**, *99*, 4628.

(7) Jönsson, B.; Karlström, G.; Wennerström, H. *J. Am. Chem. Soc.* **1978**, *100*, 1658.

(8) Williams, J. O.; van Alsenoy, C.; Schaefer, L. J. *J. Mol. Struct.* **1981**, *76*, 109.

(9) Jönsson, B.; Karlström, G.; Wennerström, H. *Chem. Phys. Lett.* **1976**, *41*, 317.

(10) Nguyen, M. T.; Ha, T. K. *J. Am. Chem. Soc.* **1984**, *106*, 599.

(11) Liang, J.-Y.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1986**, *108*, 5051.

(12) Hehre, W. J.; Radom, L.; v. R. Schleyer; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley and Sons: New York, 1986; also references cited therein.

(13) Marynick, D. S.; Lipscomb, W. N. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 1341.

(14) Reed, A. E.; Weinhold, F.; Curtiss, L. A.; Pochatko, D. J. *J. Chem. Phys.* **1986**, *84*, 5687 and references cited therein.

(15) Tso, T.-L.; Lee, E. K. C. *J. Phys. Chem.* **1985**, *89*, 1618 and references cited therein (see ref 40).

0002-7863/90/1512-7973$02.50/0

While it is important to study the gas-phase reactions, it is also important to examine the affect that solvent will have on these reactions in order that we might compare theoretical activation parameters to experimental ones.[3,4] Several theoretical techniques recently have been employed to study solution-phase reactions with free energy perturbation (FEP) techniques in conjunction with both molecular dynamics[16,17] and Monte Carlo[18] simulations.[19] These techniques have been very successful in studying reactions in condensed phases and have allowed for the detailed study of how solvent affects reaction mechanisms.

In the present article we present results on reaction 1 only. Issues that have been addressed include whether this reaction proceeds via a one- or two-water reaction mechanism,[10] what the role of entropy in this reaction is, and, finally, what the role that solvent plays in reaction 1 is. By addressing these issues we expect to bring theory and experiment into agreement, with regard to the activation parameters for reaction 1. Another aspect of this reaction is that it can be considered as a simple model of the hydrolysis of a carbonyl compound at neutral pH. Thus, conclusions reached here will have an impact on our understanding of uncatalyzed water hydrolysis of carbonyl compounds.[20]

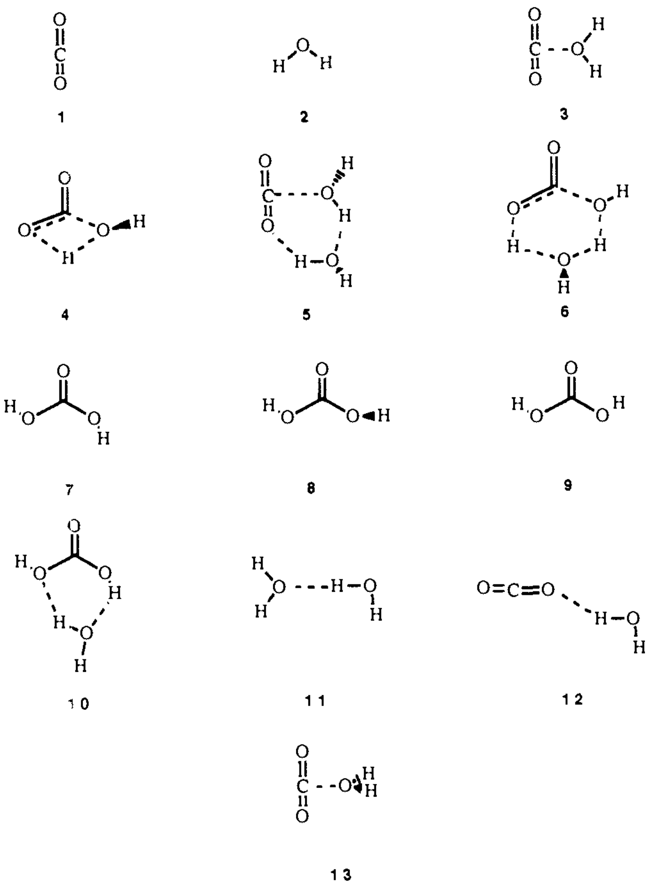
Methodology

Ab Initio Calculations. We first initiated studies using the 3-21G, 6-31G, and 6-31G** basis sets.[12] For each level of theory full geometry optimizations or transition-state locations were done unless otherwise noted. Vibrational frequencies were calculated for each point with the 3-21G level of theory, and the zero-point and entropic corrections were also evaluated at this level of theory.[12] All transition states (TS) were identified as such by the presence of one and only one negative vibrational frequency.[21] Correlation effects were treated with the MP2/6-31G**//6-31G** level of theory for the reaction of CO_2 and two water molecules, while the MP4/6-31G**//6-31G** level was used for the reaction of one water.[12] The reason for this choice was based on the observation that the MP4 and MP2 relative energies were only slightly different for the one-water reaction, which indicated to us that we could get reasonable relative energies and could save substantial CPU time by using the MP2 level of theory to study the two-water reaction. The free energy of activation (ΔG_{act}) was evaluated with use of enthalpies and entropies determined from 3-21G harmonic vibrational frequencies.[12,23] Enthalpies were determined by using the following formula[22]

$$\Delta H^{298}_{calc} = \Delta E^{0}_{e} + \Delta E^{0}_{v} + \Delta(\Delta E_{v})^{298} + \Delta E^{298}_{r} + \Delta E^{298}_{t} + \Delta PV \quad (3)$$

where the first term is the computed relative energy change including correlation, while the second term is the change in zero-point vibrational energy. The third term is the change in vibrational energy on going from 0 to 298 K and was evaluated with use of standard approaches.[23] The fourth, fifth, and sixth terms are the change in rotational, translational, and pressure volume work. The rotational and translational terms are equal to $-RT$ for each degree of freedom lost upon complexation and the pressure volume work is equal to $-RT$ for 1 mol of gas lost (assuming ideal behavior $\Delta PV = -RT$). Entropies were evaluated with standard statistical mechanical approaches.[12,23] Due to an overestimation of the vibrational frequencies at the Hartree–Fock level of theory a scaling factor of 0.89 has been suggested.[12] However, we have not used this here because previous works with ab initio vibrational frequencies to determine enthalpies and entropies have shown little sensitivity to the use of a scaling factor.[22,24] All calculations were done with Gaussian 88[25] on a Multiflow 14/300 computer. Chart 1 gives a pictorial summary of the species for which we carried out ab initio calculations.

Chart 1



Force Field. The AMBER potential function was used throughout and has the following form:[26]

$$\begin{aligned} E_{\text{Total}} = {} & \sum_{\text{bonds}} \frac{K_r}{2}(r - r_{eq})^2 + \sum_{\text{angles}} \frac{k_\theta}{2}(\theta - \theta_{eq})^2 + \\ & \sum_{\text{dihedrals}} \sum_{n} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \\ & \sum_{i<j} \epsilon_{ij}\left[\left(\frac{R_{ij}^*}{R_{ij}}\right)^{12} - \left(\frac{R_{ij}^*}{R_{ij}}\right)^{6}\right] + \\ & \frac{1}{VDW_{\text{scale}}} \sum_{\substack{i<j \\ \text{1-4 terms}}} \epsilon_{ij}\left[\left(\frac{R_{ij}^*}{R_{ij}}\right)^{12} - \left(\frac{R_{ij}^*}{R_{ij}}\right)^{6}\right] + \\ & \sum_{\text{H-bonds}} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}}\right] + \sum_{i<j} \frac{q_i q_j}{\epsilon r_{ij}} + \frac{1}{EE_{\text{scale}}} \sum_{\substack{i<j \\ \text{1,4 terms}}} \frac{q_i q_j}{\epsilon R_{ij}} \quad (4) \end{aligned}$$

The first three terms represent the "bonded" interactions present in a molecule, namely the bond, angle, and torsion interactions. The bond and angle interactions are represented by a quadratic potential, while the torsional interactions are represented by a truncated Fourier series. K_x (where $x = r, \theta$) is the force constant for the bond or angle, while X_{eq} is the experimentally observed equilibrium bond length or angle associated with force constant K_x. X is the calculated value for the bond or angle. V_n, n, ϕ, and γ represent the torsional barrier, the periodicity, the calculated dihedral angle, and, finally, the phase. The next five terms represent the "non-bonded" interactions in a molecule and they are the Lennard-Jones (the $R_{ij}^{-12} - R_{ij}^{-6}$ or 6–12 terms), the hydrogen bond (the

---

(16) Hwang, J.-K.; King, G.; Creighton, S.; Warshel, A. *J. Am. Chem. Soc.* **1988**, *110*, 5297.

(17) Bash, P. A.; Field, M. J.; Karplus, M. *J. Am. Chem. Soc.* **1987**, *109*, 8092. van Duijnen, P. T. *Enzyme* **1986**, *36*, 93.

(18) Chandrasekhar, J.; Smith, S. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 155.

(19) For a recent review on the incorporation of environmental effects see: Drummond, M. L. J. *Prog. Biophys. Mol. Biol.* **1986**, *47*, 1.

(20) Jencks, W. P. *Acc. Chem. Res.* **1980**, *6*, 161 and references cited therein.

(21) McIver, J. W.; Komornicki, A. J. *J. Am. Chem. Soc.* **1972**, *92*, 2625. McIver, J. W.; Kormornicki, A. J. *Chem. Phys. Lett.* **1971**, *10*, 303.

(22) Del Bene, J. E.; Mettee, H. D.; Frisch, M. J.; Luke, B. T.; Pople, J. A. *J. Chem. Phys.* **1983**, *87*, 3279.

(23) McQuarrie, D. A. *Statistical Thermodynamics*; Harper Row: New York, 1973. Rice, O. K. *Statistical Mechanics, Thermodynamics and Kinetics*; W. H. Freeman and Co.: San Francisco, 1967.

(24) Frisch, M. J.; Del Bene, J. E.; Binkley, J. S.; Schaefer, H. F., III *J. Chem. Phys.* **1986**, *84*, 2279 and references cited therein.

(25) Gaussian 88: Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol. S.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1988.

(26) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S., Jr.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765. Weiner, S. J.; Kollman, Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.

Table I. L-J Parameters

atom type	parameters[a] R^*	ϵ
O-H	1.00	0.0
H-O	1.768	0.152
C=O	1.9	0.13
O=C	1.4	0.18

[a] ϵ_{ij} is given by $(\epsilon_i^* \epsilon_j)^{1/2}$ and R_{ij}^* is given by $R_i^* + R_j^*$ where i and j are atom indices.

10-12 terms), and the electrostatic interactions. R_{ij} is the distance between atoms i and j, R_{ij}^* and ϵ_{ij} are parameters that define the shape of the Lennard-Jones potential for the interaction between atoms i and j, C_{ij}, and D_{ij} define the shape of the hydrogen bond potential, q_i and q_j are the atomic point charges for atoms i and j, and ϵ is the dielectric constant. $1/VDW_{\text{scale}}$ and $1/EE_{\text{scale}}$ are scaling factors for the 1-4 electrostatic and van der Waal terms. In the next section we discuss how the necessary parameters were determined.

Parametrization. In order to carry out free energy perturbation simulations we needed to determine what would be appropriate point charges and Lennard-Jones (L-J) parameters to use in our simulations. We used the AMBER force field given in eq 4, but we did not make use of the 10-12 parameters. We first evaluated point charges using 6-31G** electrostatic potential (ESP) calculations.[27] The L-J parameters were determined first for CO_2 by fitting the force field to reproduce the 6-31G** interaction energy for the formation of **3**. For these calculations on the formation of **3** the water molecule was fixed at the TIP3P water geometry,[28] the CO_2 bond lengths were fixed at the experimental value[29] (1.1437 Å) used in the potential function, and the rest of the geometry was allowed to fully optimize. the TIP3P[28] water geometry was chosen as our model because all of the FEP calculations were going to be done in TIP3P water. Parameter sets were then evaluated for their ability to reproduce CO_2/water (TIP3P L-J parameters and point charges were used) interaction energies, geometries, and the solvation free energy of CO_2 (about 0.0 kcal/mol at 298 K[30]) with use of free energy perturbation simulations.[31] We next evaluated the interaction of water with **3**-**6**. This was accomplished by holding the geometries of **3**-**6** at the calculated 6-31G** geometries and then placing a water molecule with the TIP3P geometry at several preselected sites around the CO_2 water complex. 3-21G geometry optimizations between the complex and the "TIP3P" water molecule were followed by 6-31G** single point energy evaluations. The parameter sets were then tested for their ability to reproduce these interaction energies and geometries. The parameter set that performed the best was then chosen for all subsequent simulations. The final set of L-J parameters is given in Table I. We found that the TIP3P L-J parameters for all hydroxyl "like" hydrogens and oxygens performed the best, while for CO_2 "like" carbons and oxygens we used the parameters given in Table I.

We are next left with the issue of what are the best bond, angle, and dihedral parameters to use. Since we are evaluating the intramolecular contribution to the solution phase-free energy of activation using ab initio calculations, we are only left to evaluate the intermolecular contribution to this quantity. Thus, we assumed that all complexes (e.g. **3**-**6**) were fixed at the 6-31G** geometry and we adjusted the bond, angle, and dihedral parameters to force this geometry. Thus, the reference bond and angle parameters were taken from the ab initio calculations and the bond and angle force constants were chosen to be 500 kcal/Å^2 and 100 kcal/deg^2, respectively. Note that in our models explicit bonds were placed between atoms that might be formally considered to be nonbonded. This was done to ensure that the 6-31G** geometries were maintained. The barrier heights for the torsions were chosen to be 9 kcal/mol for all non-redundant torsions, and the rest of the torsion parameters were chosen so as to best reproduce the calculated value for the torsion angle. This choice of parameters resulted in a very rigid complex, which was our goal.

Simulations. We used free energy perturbation simulations[31] to evaluate (1) the free energy of solvation of water/CO_2 complexes, (2) the relative free energy of solvation between two complexes, and (3) the free energy of association of water with water/CO_2 complexes. The theory behind these techniques has been thoroughly reviewed[31] and will not be given here.

For (1) and (3) we used the slow growth approach[31] in conjunction with electrostatic decoupling.[31,32] In these simulations the electrostatic free energy is first evaluated followed by the van der Waals contribution to the free energy. This approach was used because it was found that when both contributions to the free energy were allowed to simultaneously change anomalously large free energies were obtained. This was traced to the observation that as the L-J interactions were zeroed the hyrogen and oxygen atoms of two water molecules, for example, would come into close contact because of the still substantial electrostatic interactions present. Use of electrostatic decoupling solves this problem because at no time are large point charges present on an atom that does not have a fully represented L-J potential. For (2) since we are determining the relative free energy of solvation between two complexes and because we never explicitly annihilate atoms this allowed us to eliminate the need to use electrostatic decoupling. The slow growth method was still used for the ΔG determination.

In all cases periodic boundary conditions were used along with constant pressure and temperature conditions.[33] The coupling constant used for both temperature and pressure was 0.2.[33] In order to generate the starting simulation box the solute molecule was solvated along all Cartesian axes by 10 Å. Any solvent molecules that came within 2.4 Å of the solute were discarded. This resulted in anywhere between 250 and 350 TIP3P[28] water molecules solvating any given solute. The system was next minimized to a residual gradient of 0.1 kcal/mol and then equilibrated for 18 ps. For all MD simulations a timestep of 1.5 fs, in conjunction with the SHAKE algorithm,[34] was used. In all cases the nonbonded pair list was updated every 50 timesteps and the nonbonded cutoff was 8 Å. Since explicit solvent is present a dielectric constant of 1 was used throughout. The sampling runs covered a total of 45 ps in both the forward ($\lambda = 1 \rightarrow 0$) and backward ($\lambda = 0 \rightarrow 1$) directions for a total of 90 ps of simulation time. For the electrostatic decoupling runs the L-J contribution to the free energy was evaluated in 21 ps, while the electrostatic free energy was determined in 24 ps. For all other runs both the L-J and electrostatic contributions to the free energy were evaluated simultaneously over the 45-ps simulation. For all simulation work the AMBER suite of programs was used.[35]

To evaluate the free energy of solvation of a complex (case 1 above) we slowly "annihilated" (i.e. zeroed intermolecular nonbonded interactions between the solute and solvent molecules) the complex and to evaluate the relative free energy of solvation between two complexes (case 2 above) we simply perturbed between one complex and the other. In order to evaluate the free energy of interaction between two molecules (case 3 above) we used the procedure outlined by Jorgensen,[36] which can be simply summarized as follows: In order to evaluate the free energy

$$\begin{array}{lcll} \text{HO} & \longrightarrow & \text{HG} & \Delta G_{\text{int}} \\ \text{G} & \longrightarrow & \text{O} & \Delta G_{\text{sol}} \\ \hline \text{H} + \text{G} & \longrightarrow & \text{HG} & \Delta G_{\text{bind}} \end{array} \tag{5}$$

of association two simulations have to be done. The second evaluates the free energy of solvation of the "guest" molecule G in water, while the first evaluates the interaction energy between the "host" (H) and the "guest" in water. O implies that the molecule has been "annihilated". By using this approach absolute free energies of binding (ΔG_{bind}) between two molecules can be readily evaluated by simply adding up the two contributions. In order to carry out the HO → HG simulations (for **1** → **3** and **3** → **5**) we treated the complexes as being composed of individual CO_2 and H_2O molecules that did not have explicit bonds between each other. To generate the starting structures for these simulations we first minimized **3** and **5** in the gas phase using 6-31G** ESP derived point charges determined for **3** and **5** and our standard CO_2 and the TIP3P[28] L-J parameters. The resulting minimized structures were then used in subsequent MD simulations. In order to retain the minimized structure during the MD simulations harmonic constraints of 5.0 kcal/Å were used on specific atoms. For **3** the CO_2 carbon and the water oxygen were

---

(27) Williams, D. E.; Yan, J.-M. *Adv. At. Mol. Phys.* **1988**, *23*, 87. Chirlian, L. E.; Francl, M. M. *J. Comput. Chem.* **1987**, *8*, 894. Singh, U. C.; Kollman, P. A. *J. Comput. Chem.* **1984**, *5*, 129.

(28) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926.

(29) Herzberg, G. *Molecular Spectra and Molecular Structure III. Electronic Spectra and Electronic Structure of Polyatomic Molecules*; Van Nostrand: New York, NY, 1966.

(30) Wilhelm, E.; Battino, R.; Wilcock, R. J. *Chem. Rev.* **1977**, *77*, 219.

(31) van Gunsteren, W. F. *Protein Engineering* **1988**, *2*, 5. Mezei, M.; Beveridge, D. L. *Ann. N.Y. Acad. Sci.* **1986**, *482*, 1. Jorgensen, W. L. *Acc. Chem. Res.* **1989**, *22*, 184. Kollman, P. A.; Merz, K. M. Jr. *Acc. Chem. Res.* Submitted.

(32) Bash, P. A.; Singh, U. C.; Langridge, R.; Kollman, P. A. *Science* (*Washington, D.C.*) **1987**, *236*, 564.

(33) Berendsen, H. J. C.; Potsma, J. P. M.; van Gunsteren, W. F.; DiNola, A. D.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.

(34) van Gunsteren, W. F.; Berendsen, H. J. C. *Mol. Phys.* **1977**, *34*, 1311.

(35) AMBER 3.0: Singh, U. C.; Weiner, P. K.; Caldwell, J.; Kollman, P. A.

(36) Jorgensen, W. L.; Buckner, J. K.; Boudon, S.; Tirado-Rives, J. *J. Chem. Phys.* **1988**, *89*, 3742.

Table II. Ab Initio Total Energies (hartrees) for **1–13** and Selected ΔE Values

	quantum mechanical model					
	3-21G//3-21G	6-31G//6-31G	6-31G**//6-31G**	MP2/6-31G**//6-31G**	MP3/6-31G**//6-31G**	MP4/6-31G**//6-31G**
1	−186.5612575	−187.514953	−187.6341762	−188.1021892	−188.0896469	−188.1244159
2	−75.5859597	−75.9853592	−76.0236149	−76.2190677	−76.2255811	−76.230519
3	−262.159928	−263.5097793	−263.6629953	−264.3270163	−264.3210767	−264.3606929
(**1** + **2** → **3**) ΔE_{comp}	−8.0 kcal/mol	−5.9 kcal/mol	−3.3 kcal/mol	−3.6 kcal/mol	−3.7 kcal/mol	−3.6 kcal/mol
4	−262.0818205	−263.4127942	−263.5599235	−264.2450515	−264.2362281	−264.2770998
E_a(**3** → **4**)	49.0 kcal/mol	60.9 kcal/mol	64.7 kcal/mol	51.4 kcal/mol	53.2 kcal/mol	52.5 kcal/mol
5	−337.7730957	−339.513593	−339.6990127	−340.5630942		
(**3** + **2** → **5**) ΔE_{comp}	−17.1 kcal/mol	−11.6 kcal/mol	−7.8 kcal/mol	−10.0 kcal/mol		
6	−337.7510796	−339.4694202	−339.6312139	−340.5106347		
E_a(**5** → **6**)	13.8 kcal/mol	27.8 kcal/mol	42.5 kcal/mol	32.3 kcal/mol		
7	−262.1657537	−263.5078303	−263.6570283	−264.3139217	−264.3156899	−264.347122
8	−262.1522357	−263.4942564	−263.6430633	−264.2994214	−264.3015711	−264.3334043
E_a(**7** → **8**)	8.4 kcal/mol	8.5 kcal/mol	8.8 kcal/mol	9.1 kcal/mol	8.9 kcal/mol	8.6 kcal/mol
9	−262.1672814	−263.5095347	−263.6609119	−264.3172879	−264.3190268	−264.3504083
10	−337.783354	−339.5155017	−339.6950669	−340.5513387		
(**7** + **2** → **10**) ΔE_{comp}	−23.6 kcal/mol	−17.2 kcal/mol	−12.3 kcal/mol	−15.1 kcal/mol		
11	−151.1894036	−151.983216	−152.0560602	−152.4490441	−152.4615032	−152.4717063
(**2** + **2** → **11**) ΔE_{comp}	−11.0 kcal/mol	−7.8 kcal/mol	−5.5 kcal/mol	−6.8 kcal/mol	−6.5 kcal/mol	−6.7 kcal/mol
12	−262.1538454					
(**1** + **2** → **12**) ΔE_{comp}	−4.2 kcal/mol					
13	−262.1571932	−263.506771	−263.6613964	−264.3254697	−264.3194459	−264.3591658
(**1** + **2** → **13**) ΔE_{comp}	−6.3 kcal/mol	−4.1 kcal/mol	−2.3 kcal/mol	−2.6 kcal/mol	−2.6 kcal/mol	−2.7 kcal/mol

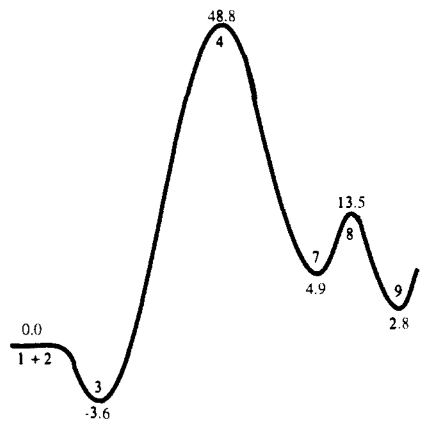


Figure 1. Computed reaction profile (MP4/6-31G**//6-31G**) for $CO_2 + H_2O \rightarrow H_2CO_3$. Bold numbers correspond to complexes and light numbers are relative energies in kcal/mol.

restrained and for **5** all of the atoms involved in the six-membered ring were constrained. In this way we were certain that we were evaluating the free energy associated with the formation of **3** or **5**.

In order to determine the free energy of activation in solution we assumed that this value could be partitioned into an intramolecular free energy that can be determined using ab initio techniques and an intermolecular free energy that can be evaluated using FEP simulations. Thus, the total free energy for a given chemical transformation can be given by

$$\Delta G^{298}_{\text{act.}} = \Delta G^{298}_{\text{intra}} + \Delta G^{298}_{\text{inter}} \qquad (6)$$

where the first term is, for example, the ab initio free energy of activation and the second term is the free energy of solvation difference between the ground state and TS.

Results and Discussion

Ab Initio Calculations. We first looked at the gas-phase reaction of $CO_2 + H_2O$. The reaction profile for $CO_2 + H_2O$ using our best computed energies (MP4/6-31G**//6-31G**) is given in Figure 1. The total energies for the species involved in this reaction are given in Table II. In what follows we will always quote our "best" interaction and activation energies (unless otherwise stated), but in Table II we give the values obtained at lower levels of theory. Pertinent geometrical parameters for **3**, **4**, **7–9** at the 6-31G**/6-31G** level of theory are given in Figure 2. The complexation of one water molecule with CO_2 is computed to be −3.6 kcal/mol. This is to be compared to the 3-21G//3-21G, 6-31G//6-31G, and 6-31G**//6-31G** values of −8,[10] −5.9, and −3.3 kcal/mol, respectively. Thus, the use of basis sets larger than 3-21G reduces the complexation energy by a factor of 2. The inclusion of correlation only has a small affect on the energetics of this process. The structure of **3** is not that unusual in that the isolated geometries of **1** and **2** are not much perturbed upon complexation. The C---OH_2 distance is fairly long being 2.77 Å and the water hydrogens are in the same plane as the oxygen atoms. This orientation allows for the best electrostatic interaction between CO_2 and water and is, therefore, the most stable of all the possible orientations.[37]

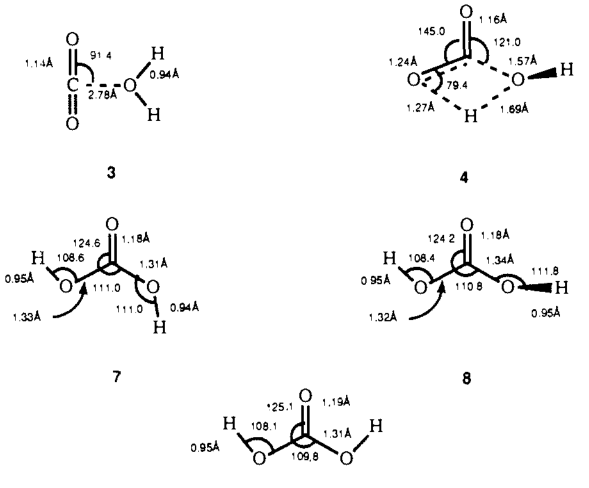


Figure 2. Computed (6-31G**//6-31G**) structures for **3–4** and **7–9**.

Previous work on this reaction has assumed that the TS (**4**) was planar;[6-11] however, we find that there are two negative vibrational frequencies for planar **4**. One corresponds to the hydrogen transfer TS and the second is a motion that carries the non-transferring hydrogen out of plane. Upon relaxation of the planarity constraint this hydrogen twists out of plane by about 60°. This results in a reduction in the E_a of 4.9 kcal/mol at the

---

[37] Damewood, J. R.; Kumpf, R. A.; Mühlbauer, W. C. F. *J. Phys. Chem.* **1989**, *93*, 7640.

[38] Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761. Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 377.

[39] Curtiss, L. A.; Blander, M. *Chem. Rev.* **1988**, *88*, 827 and references cited therein.

[40] Coan, C. R.; King, A. D., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 1857.

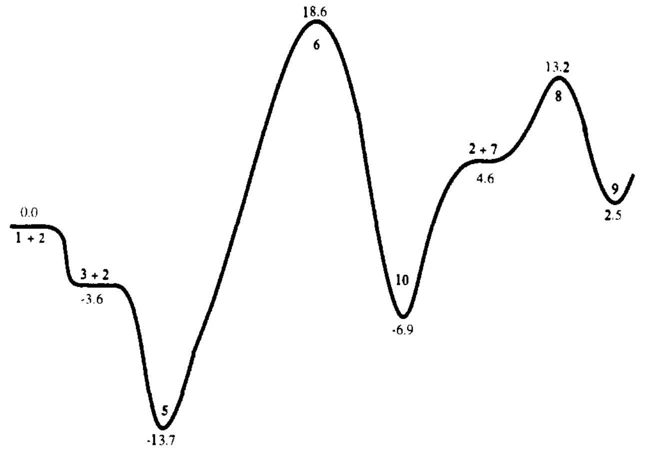


Figure 3. Computed reaction profile (MP2/6-31G**//6-31G**) for $CO_2 + 2H_2O \rightarrow H_2CO_3$. Bold numbers correspond to complexes and light numbers are relative energies in kcal/mol.

MP4/6-31G**//6-31G** level of theory. As a result of this observation we no longer constrained any of the CO_2/water complexes to be planar. As the basis set size increases the computed E_a increases to 64.7 kcal/mol at the 6-31G**//6-31G** level, which decreases to 52.5 kcal/mol upon the inclusion of correlation at the MP4 level. We find that for this reaction going beyond the MP2 single point level has a small influence (about ±1.0 kcal/mol) on the barrier height (Table II). This E_a is consistent with the previous values that fell in the 49–65-kcal/mol range.[6-11]

The geometry of the TS is given in Figure 2 and beyond the nonplanarity of the hydroxyl hydrogen we find that the TS is best characterized as being "late" because the migrating hydrogen is almost fully transferred in the TS. The first product generated from **4** is the cis,trans conformation of carbonic acid **7**, which can undergo an internal rotation, via TS **8**, to give the cis,cis isomer of carbonic acid (**9**). The E_a in the reverse direction (**9** → **4**) is computed to be 46 kcal/mol. The TS between **7** and **9** has the rotating hydroxyl hydrogen at a torsion angle of 90° relative to the plane of the molecule. Thus, the torsion potential has only two minima where the hydrogen is in a cis or trans orientation relative to the C=O bond. The best computed E_a for the conversion of **7** → **9** is 8.6 kcal/mol and this barrier is only slightly affected by a change in basis set size and inclusion of correlation (see Table II). **9** has previously been determined to be the most stable isomer of carbonic acid and our results are consistent with this conclusion.[9,10] We have not investigated the stability of the trans,trans isomer of carbonic acid here, but previously it was found to be significantly less stable than either **7** or **9** and to not be a stationary point on the potential energy surface.[10]

We next investigated the gas-reaction of two water molecules with CO_2. Using simple arguments based on the aromaticity (or antiaromaticity) of TSs we find that the two-water reaction involves a six-electron TS (aromatic) while the one-water reaction involves four (antiaromatic).[10,38] Thus we would expect the two-water reaction to be more facile than the one-water reaction. This conclusion is borne out by our results and previous results.[10] The reaction potential is given in Figure 3 and the 6-31G**//6-31G** geometries for **5**, **6**, and **10** are given in Figure 4. The interaction energy between **1** and **2** at the MP2/6-31G**//6-31G** level of theory is exothermic by 3.6 kcal/mol. The addition of a second water molecule results in **5** which is more stable than **3** + **2** by 10.0 kcal/mol. The net stabilization for **1** + **2** + **2** → **5** is −13.7 kcal/mol, which is to be contrasted to the 3-21G values previously reported of −24.1 kcal/mol.[10] From Table II it is obvious that this stabilization energy is very sensitive to the size of the basis set used as was found for the formation of **3**. The geometry of **5** is nonplanar with the free water hydrogens out of plane and on opposite sides of the plane by about 60°. The C---OH_2 bond is again 2.77 Å, and the hydrogen bond distance between the water molecules is 2.0 Å versus the 2.3 Å hydrogen bond distance between an oxygen from CO_2 and a hydroxyl hydrogen from water. The next step in the reaction scheme is a concerted two-proton shift, which proceeds via the TS **6** to give **10**. The E_a for this reaction is computed to be 32.3 kcal/mol, which is 20.2 kcal/mol lower in energy than the one-water reaction (**3** → **4**). Again we find that this E_a is very sensitive to the basis set size and the inclusion of correlation effects (see Table II). The 3-21G E_a reported previously[10] (with planar **6**) was 15.5 kcal/mol, which when compared to the experimental E_a of 17.7 kcal/mol[3] led the authors to conclude that this reaction goes via a two-water mechanism. Given our results we find that this agreement was the result of basis set limitations[12] and that the disagreement between experiment and theory is still very large (17.7 versus 32.3 kcal/mol). The geometry of **6** is again nonplanar, but instead of having two hydrogens out of plane there is only one. One hydrogen is planar because it becomes a part of carbonic acid, while the nonplanar hydrogen remains a part of a water molecule in the product. The product of the two-water reaction is **10**, which is *cis,trans*-carbonic acid complexed with a water molecule. This complex is 11.5 kcal/mol more stable than isolated **7** and water. The isolated *cis,trans*-carbonic acid then undergoes a rotational transition to finally yield **9**.

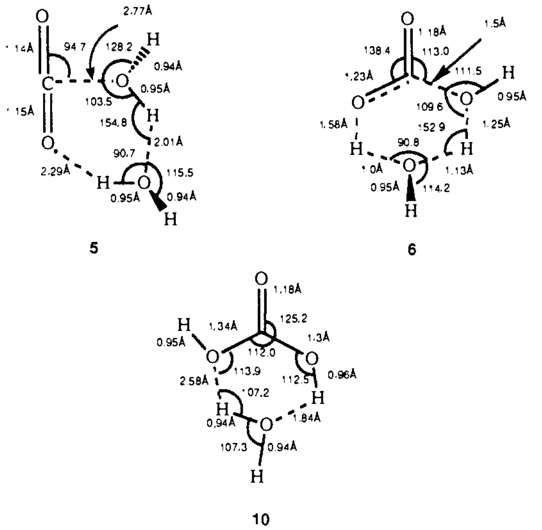


Figure 4. Computed (6-31G**//6-31G**) structures for **5**, **6**, and **10**.

Table III. Enthalpy, Entropy, and Free Energy of Interaction for the Water Dimer

approach	ΔE, kcal/mol	ΔH, kcal/mol	ΔS, cal/(deg mol)	ΔG, kcal/mol
Frisch et al.[a] (298 K)	−5.34	−3.61	−20.86	2.61
Frisch et al.[a] (373 K)	−5.34	−3.46	−20.34	4.12
present work[b] (298 K)	−6.69	−4.49	−23.03	2.37
experiment[c] (373 K)		−3.59	−18.59	3.34

[a] With MP4/6-311++G(3df,3pd)//MP2/6-311++G(2d,2p) energies and MP2/6-311++G(2d,2p)//MP2/6-311++G(2d,2p) vibrational frequencies. Entropies are taken from ref 39. See ref 24. [b] With MP4/6-31G**//6-31G** energies and 3-21G//3-21G vibrational frequencies. [c] Taken from ref 39.

The conclusion is that the two-water is more favorable than the one-water reaction of CO_2. However, it has been suggested that entropic effects could possibly disfavor the two-water reaction.[10] In order to address this issue we have evaluated the gas-phase free energy profile for these reactions using our "best" interaction energies and 3-21G//3-21G vibrational frequencies. Before evaluating the free energies for the reactions we tested our choice of ab initio model on the well-studied water dimer.[24]

Gas-Phase Free Energies. The water dimer (**11**) has recently been studied with use of Møller–Plesset perturbation techniques[12] and very large basis sets.[24] These calculations have been able to reproduce experimentally evaluated ΔH_{298}, hence, we have used these calculations and experimental information to evaluate the accuracy of our computed free energies. The comparison of our results to those of Frisch et al.[24] and experiment is given in Table

Table IV. Calculated Relative Enthalpies, Entropies, and the Relative Solution and Gas-phase Free Energies

species	H_{298}, kcal/mol	S_{298}, cal/(deg mol)	G_{298},[d] kcal/mol	G_{sol}, kcal/mol	G_{total}, kcal/mol
1[a]	9.7	51.1	-5.5		
2[a]	16.1	45.1	2.6	-5.9 ± 0.9	-3.3 ± 1.3
3[b]	23.3 (23.3)	78.0	0.04 (0.04)	-4.4 ± 0.7	-4.3 (-4.3) ± 1.2
4[a]	73.6	66.5	53.7	-8.4 ± 1.5	43.3 ± 1.8
5[c]	32.0	85.5	6.4	-10.1 ± 1.8	-3.6 ± 2.1
6[c]	61.9	72.7	40.3	-19.3 ± 2.3	21.0 ± 2.5
7[b]	33.4 (33.7)	64.1	14.3 (14.6)	-11.3 ± 1.4	2.9 (3.2) ± 1.7
8[b]	41.7 (42.0)	64.3	22.5 (22.8)		
9[b]	31.4 (31.7)	64.0	12.3 (12.6)	-9.5 ± 0.1	2.8 (3.1) ± 1.0
10[c]	40.1	77.5	17.0	-15.2 ± 1.5	1.8 ± 1.8
11[a]	27.6	67.2	7.6		

[a] Calculated with MP4/6-31G**//6-31G** energies only. [b] Calculated with MP2/6-31G**//6-31G** (MP4/6-31G**//6-31G**) energies. [c] Calculated with MP2/6-31G**//6-31G** energies only. [d] Error limits estimated to be ±1.0.

Table V. Computed Interaction Energies, Enthalpy, Entropy, Free Energies, and Relative Free Energies of Solvation for the Reactions Indicated

reaction	ΔE, kcal/mol	ΔH_{298}, kcal/mol	ΔS_{298}, cal/(deg mol)	ΔG_{298}, kcal/mol	$\Delta\Delta G_{sol}$, kcal/mol
1 + **2** → **3**	-3.6[a]	-2.5 (-4.8)[b]	-18.2 (-25.9)[b]	3.0 ± 1.0 (2.9)[b]	
3 → **4**[c]	52.5	50.3	-11.5	53.7 ± 1.0	-6.0 ± 0.2
7 → **4**[c]	43.9	39.9	2.4	39.2 ± 1.0	4.9 ± 0.1
7 → **8**[d]	9.1, 8.6	8.3, 8.3	0.1	8.3, 8.3 ± 1.0	
9 → **8**[d]	11.2, 10.7	10.3, 10.3	0.3	10.2, 10.2 ± 1.0	
3 + **2** → **5**[e]	-10.12	-7.4	-37.6	3.8 ± 1.0	
5 → **6**[e]	32.3	29.9	-12.8	33.8 ± 1.0	-12.6 ± 0.9
10 → **6**[e]	25.5	21.9	-4.8	23.3 ± 1.0	-8.1 ± 0.3
7 + **2** → **10**[e]	-11.5	-9.4	-31.2	-0.04 ± 1.0	

[a] Both the MP4/6-31G**/6-31G** and MP2/6-31G**/6-31G** energies are identical. [b] See ref 40. [c] Calculated with MP4/6-31G**//6-31G** energies only. [d] The first value given uses MP2/6-31G**/6-31G** energies, while the second uses MP4/6-31G**/6-31G** energies. [e] Calculated with MP2/6-31G**//6-31G** energies only.

III. We first note that out "best" interaction energy is lower than that computed by Frisch et al. presumably because of the smaller basis set we are employing.[12,24] This difference is again reflected in our computed ΔH_{298} and that of Frisch et al. The Frisch et al. ΔH_{373} is in good accord with experiment and their computed ΔH_{298} varies only slightly from ΔH_{373}. Thus, if we assume that their computed ΔH_{298} is close to the experimental value we find that our value is too negative by about 1 kcal/mol. The value computed by Frisch et al. for ΔS_{373} is about 2 cal/(deg mol) too negative relative to the experimental value. This leads to a computed ΔG_{373} that is about 1 kcal/mol too positive. Thus, the calculations of Frisch et al. will likely give ΔG_{298} that are too positive relative to experiment. Due to a fortuitous cancellation of errors our calculated ΔG_{298} is less positive than the value of Frisch et al., which leads us to conclude that our ΔG_{298} for the present case is accurate to about ±1.0 kcal/mol.

The thermodynamics of CO_2 associating with water has been studied experimentally and a comparison of our computed results with the experimental results is given in Table V (reaction **1** + **2** → **3**, see values in parentheses).[40] Our calculated ΔH_{298} is too positive relative to the experimental value, which is consistent with the ab initio results of Damewood et al.,[37] which gave a value of -2.1 kcal/mol with MP2/6-311G**//6-31G** energies and 6-31G** vibrational frequencies. Our calculated entropy is also too positive, which in combination with the calculated enthalpy value gives a ΔG_{298} that is in excellent agreement with experiment. Again this is due to a cancellation of errors. From these results and the water dimer results we conclude that while our computed enthalpies and entropies might have error limits in the range of i.e. ±1-2 kcal/mol and ±4-7 eu, respectively, the resultant free energies should be of reasonable accuracy (i.e. better than ±1.0 kcal/mol). Our test cases were for association processes, but it is expected that the error limits for calculating the activation parameters for reactions should be of a similar magnitude. On the basis of these conclusions we have adopted a value of ±1.0 kcal/mol as the error limits associated with out ΔG values determined with ab initio calculations.

The reaction free energy profile for the one-water reaction is given in Figure 5 and the various contributions to the computed free energies are given in Table IV. Table V presents the thermodynamic quantities for the various reactions discussed below and presented in Figures 5 and 6.

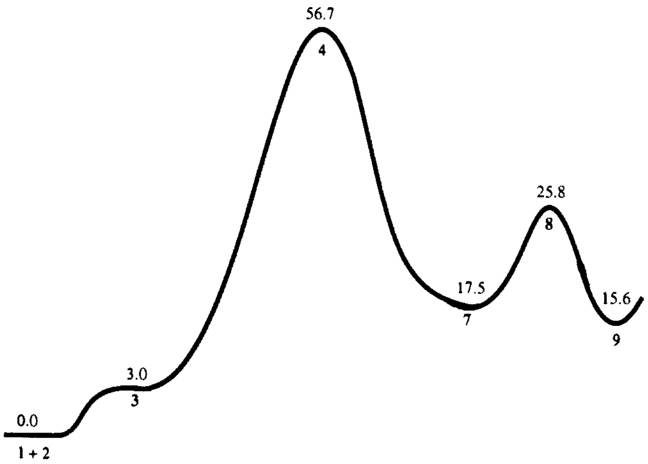


Figure 5.

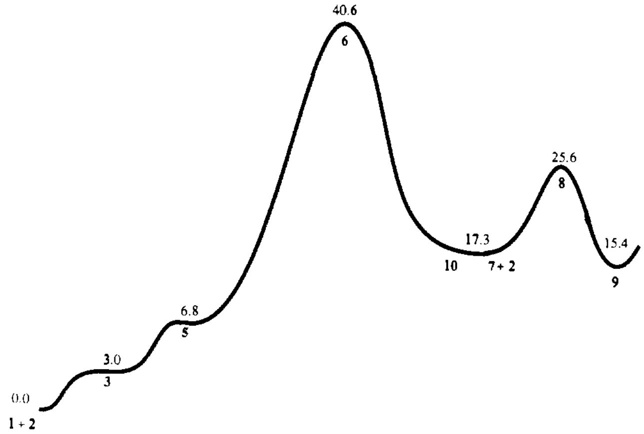


Figure 6.

The formation of the CO_2/water complexes **3** and **5** is found to be uphill in free energy by 2.95 and 3.8 kcal/mol, respectively.

This is due to the severe entropic penalty paid in order to form these complexes (see Table V). Thus, on the free energy surface the formation of these complexes, which are necessary for the reaction to occur, increases the overall barrier height. The activated processes themselves (e.g. **3** → **4**) are affected adversely by entropic effects, but to a lesser extent than the complexation processes. The overall result is that both the one- and two-water reactions have ΔG_{act}'s that are larger (by 2.2 and 8.8 kcal/mol, respectively) than the computed E_a's, but the two-water reaction, not unexpectedly, is affected more strongly. The computed free energy of activation for the one-water reaction in the forward direction is 56.7 ± 1.0 kcal/mol and in the reverse direction it is 41.1 ± 1.0 kcal/mol. The reaction profile for the two-water reaction is given in Figure 6. The computed free energy of activations for the forward and reverse directions are 40.6 ± 1.0 and 25.2 ± 1.0 kcal/mol, respectively. Thus, the conclusion is that entropic effects are **not** large enough in the case of the two-water reaction to make it unfavorable relative to the one-water reaction. The two-water reaction in the gas phase is found to be favored over the one-water reaction by about $\Delta\Delta G_{act} = 16$ kal/mol. We are still left with trying to rationalize our results in light of the solution-phase reaction, which has a free energy of activation of ca. 18.4 kcal/mol in the forward and 15.3 kcal/mol in the reverse direction.[3] For example, it may be that the one-water reaction is favored over the two if explicit consideration of solvent is incorporated into our model. In order to solve this dilemma we have carried out FEP simulations to determine what is the solvation contribution to the free energy of activation. The pertinent results are given in Tables IV and V.

Solvation Free Energies. Before discussing the FEP simulation results we can make a qualitative prediction concerning which reaction might have a larger solvation correction by considering the dipole moments of **3**–**6**. The dipole moments of **3**–**6** are 2.5, 3.8, 1.5, and 6.9 D, respectively. For the one-water reaction the increase in the dipole moment on going from **3** to **4** is only 1.3 D. This is to be contrasted to the 5.4-D change for **5** → **6**. The conclusion, therefore, is that the two-water reaction has a larger amount of charge separation on passing from **5** to **6** than does the one-water reaction. This observation leads to the prediction that the two-water reaction should be more strongly affected by the presence of solvent than would be the one-water reaction. Thus, solvation effects should enhance the already strong preference for the two-water reaction. This qualitative conclusion is borne out by our more quantitative FEP results.

We first need to consider what would be the effect of solvation on the formation of **3** and **5**. Given that the free energy of solvation of CO_2 in water at 298 K is about 0.0 kcal/mol[30] we expect that the formation of **3** or **5** would have a small energetic cost. Thus, we might assume that the free energy to form either **3** or **5** is about 0.0 kcal/mol. To test this assumption we have evaluated the free energy of association for H_2O complexing with **1** and **3** (to form **3** and **5**, respectively) using the approach of Jorgensen et al.[36] In these simulations we evaluated the free energy of solvation of H_2O (our "guest" G here) and the free energy of interaction of H_2O with **1** and **3** (our "host" H here, see eq 5). The free energy of solvation of **2** is given in Table IV, while the ΔG_{int} values for H_2O associating with **1** and **3** are −4.5 ± 0.03 and −9.8 ± 1.2 kcal/mol, respectively. This results in the prediction that the formation of **3** in solution is endothermic by 1.4 ± 0.9 kcal/mol and the formation of **5** is exothermic by −3.9 ± 1.5 kcal/mol. Thus, in order to form **5** a net −2.5 kcal/mol of energy is released. These results suggest that assuming that the free energy of formation of **3** or **5** is ca. 0.0 kcal/mol is approximately correct, but for the one-water reaction the barrier should be increased by ca 1.4 kcal/mol and for the two-water reaction the barrier we need to consider is that between **5** and **6** only. Thus, in order to get an estimate of the free energy of activation for the formation of carbonic acid by the one- or two-water pathway, all we have left to do is to determine the relative free energies of solvation for **3** → **4** and **5** → **6** (Tables IV and V) and correct them accordingly.

For the one-water reaction the forward (**3** → **4**) free energy of activation in the gas phase was estimated to be 53.7 ± 1.0 kcal/mol, which when corrected for solvation effects with the data in Table IV (−4.0 ± 1.7 kcal/mol + 1.4 ± 0.9 kcal/mol) and eq 6 gives a solution-phase free energy of activation of 51.1 ± 2.2 kcal/mol. As a test of the internal consistency of our free energy simulations we have carried out a simulation that perturbs **3** → **4**, which yields a solvation correction of −6.0 ± 0.2 kcal/mol (see Table V). This estimate of the solvation correction is 2 kcal/mol more negative than that calculated by disappearing either **3** or **4** alone and gives a ΔG_{act} of 49.1 ± 1.4 kcal/mol. The difference in the solution correction is probably due to convergence considerations. For example, when we disappeared **3** or **4** we used the electrostatic decoupling approach, which means that for the individual contributions to the free energy (electrostatic and van der Waals) a shorter period of simulation was used to determine their values (21 and 24 ps) than when both contributions were simultaneously determined (45-ps total). We expect that the latter simulations are "converged" relative to the former simulations, and this is borne out by the smaller amount of hysteresis observed for the latter (±1.7 versus ±0.2).[31] This assessment is further supported by the fact that it has been difficult to get converged results for the free energy of solvation of simple solutes like CH_4, while it has been relatively easy to get converged results for *relative* free energies of solvation between CH_4 and CH_3OH, for example.[31] Hence, our best estimate of ΔG_{acl} is 49.1 ± 1.4 kcal/mol.[41]

In what follows we will only discuss ΔG_{act}'s that have been determined with relative free energies of solvation determined by directly perturbing one species into another (see the data in Table V). By using the data in Table IV, solvation corrections can also be evaluated, but as we found for the case described in the paragraph above, these corrections are uniformly smaller (by about 2 kcal/mol) and have a larger uncertainty, which makes them less reliable.

The gas-phase forward ΔG_{act} (**5** → **6**) for the two-water reaction was estimated to be 33.8 ± 1.0 kcal/mol, and the correction for the presence of solvent is estimated to be −12.6 ± 0.9 kcal/mol (Table V), which gives a predicted ΔG_{act} of 21.2 ± 1.3 kcal/mol. Using the available experimental information[3] we have determined that the solution-phase ΔG_{act} is 18.4 kcal/mol, which is in good agreement with our estimate for the two-water reaction. Thus, we predict that the reaction of CO_2 in water is more likely to proceed via a two-water pathway than by a one-water reaction path.

For the reverse of the one-water (dehydration) reaction we need to determine our zero in energy. From our ab initio calculations we found that **9** was more stable than **7**. However, one might expect the opposite to be true in solution since **9** has a small dipole moment (0.2 D), while **7** has a more substantial one (3.5 D). The gas-phase ΔG_{rxn} for **7** → **9** is computed to be −2.0 ± 1.0 kcal/mol and the solvation correction is estimated to be 4.6 ± 0.1 kcal/mol (obtained via perturbing **7** → **9** directly), which suggests that **7** is mare stable than **9** in water ($\Delta G_{rxn}(aq) = +2.6 \pm 1.0$ kcal/mol). Hence, in order to estimate the solution-phase ΔG_{act} all we need consider is the conversion of **7** to **4**. The gas-phase ΔG_{act} for **7** → **4** was computed to be 39.2 ± 1.0 kcal/mol, and we estimate (using the data in Table V) that the solvation correction is +4.9 ± 0.1 kcal/mol. This leads to the prediction that the solution-phase ΔG_{act} is 44.1 ± 1.0 kcal/mol. Comparing this value to the experimental ΔG_{act} of 15.3 kcal/mol[3] suggests that the unimolecular decomposition of **7** cannot be responsible for the dehydration of carbonic acid. This result is consistent with our results for the forward reaction that indicate that the one-water reaction cannot be responsible for the hydration and dehydration of CO_2.

In order to determine the free energy of association for **7** + **2** → **10** we again made use of the approach pioneered by Jor-

---

(41) The error limits were estimated by taking the error limits in all of the ab initio data to be on the order of ±1.0 kcal/mol and the free energy data error limits were taken from the degree of hysteresis that was observed in doing the simulations in the forward ($\lambda = 1 \rightarrow 0$) and the reverse directions ($\lambda = 0 \rightarrow 1$). These error limits were then combined with use of standard propagation of errors techniques[42] to give our final estimate of the total error.

(42) Barrante, J. R. *Applied Mathematics for Physical Chemistry*; Prentice-Hall: Englewoods Cliffs, NJ, 1974.

gensen.[36] ΔG_{sol} for water is given in Table IV, and ΔG_{int} was determine to be -11.2 ± 0.5 kcal/mol. This gives an estimate of -5.2 ± 1.0 kcal/mol for the free energy associated with this process. Thus, in order to estimate the ΔG_{act} for the reverse of the two-water reaction all we need consider is the affect solvent has on **10** → **6**. Using the data from Table V we estimate ΔG_{act} for this reaction to be 15.2 ± 1.0 kcal/mol. Our computed value of 15.2 ± 1.0 kcal/mol is in excellent agreement with the experimental ΔG_{act} of 15.3 kcal/mol.[3] From both the forward and reverse directions it is clear that the two-water reaction is in better agreement with experiment than is the one-water reaction.

Conclusions

Using a combination of ab initio and statistical mechanical techniques we have been able to provide insight into how CO_2 reacts at neutral pH in water to form carbonic acid (i.e. uncatalyzed reaction of CO_2 with water). We have found that the reaction of two water molecules with CO_2 is significantly more favorable and is in better agreement with available experimental activation parameters than is the reaction of CO_2 with one water molecule. These results suggest that for hydrolysis reactions the participation of more than one water molecule is likely.[16] The present reaction is an example of what Jencks has called a preassociation mechanism,[16] where the reactants come together in an encounter complex, which subsequently undergoes a reaction step. Thus, two water molecules associate with CO_2 and then undergo a Woodward–Hoffmann allowed six-electron process that generates carbonic acid and water. While the entropic penalty paid in the two-water reaction in the gas phase is high (about 9.0 kcal/mol) it is not enough to disfavor this reaction. Thus for hydration and dehydration processes at neutral pH in water the two-water process has to be considered a viable pathway. Our results also demonstrate that solvent plays a significant role in favoring one reaction type over another even when the reactants and products are neutral. Finally, we find that when determining solvation corrections for reactions it is best to perturb between, for example, the reactant and transition state than it is to evaluate the absolute free energy of the separate molecules and then taking the difference.[31]

Acknowledgment. We would like to thank the Center for Academic Computing at the Pennsylvania State University for generous allocations of IBM 3090-600S computer time. Numerous discussions with Mark Maroncelli were also very helpful in completing this work. A grant from the NSF for the purchase of a Multiflow 14/300 is also acknowledged.

Mechanistic Studies of Olefin Epoxidation by a Manganese Porphyrin and Hypochlorite: An Alternative Explanation of "Saturation Kinetics"

James. P. Collman,[*,†] John. I. Brauman,[†] Philip D. Hampton,[†] Hiroo Tanaka,[‡] D. Scott Bohle,[†] and Robert T. Hembre[†]

Department of Chemistry, Stanford University, Stanford, California 94305-5080, and Mitsubishi Kasei Corporation, Research Center 1000, Kamosnida-cho, Midon-ku, Yokohama 227, Yokohama, Japan.

Received December 18, 1989. Revised Manuscript Received June 26, 1990

Abstract: The catalytic epoxidation of olefins with Mn(TMP)Cl with phase-transfer catalysis and hypochlorite has been reexamined from the point of view of material balance and stability of this system in the presence of three axial ligands. The efficiency (yield of epoxide formation based on OCl^- consumed) is found to fall off with decreasing olefin concentration and to be influenced by the nature of the axial base. With *t*-BuPy as the axial ligand, the stirred system in the absence of olefin is found to be stable over prolonged periods and does not lose OCl^- titer. This leads to the conclusion that, in the presence of low olefin concentration, the missing OCl^- equivalents must be consumed in a side reaction with the olefin. It is proposed that extensive byproduct oxidations account for loss of OCl^-, low efficiency, and apparent "saturation kinetics" we previously reported.

Many studies of catalytic olefin epoxidation have been inspired by interest in the enzyme family cytochrome P-450.[1] The mechanism by which an oxygen atom is transferred from a metalloporphyrin to an olefin has been widely debated.

Several years ago we studied catalytic olefin epoxidation with manganese porphyrins, hypochlorite anion, an axial ligand, and a phase-transfer agent in biphasic media.[2] This system was modelled after the efficient catalyst first developed by Meunier.[3] Under stringently controlled conditions we found evidence for saturation kinetics.[2c] At high olefin concentrations we showed the epoxidation rate to be zero order in olefinic substrate, whereas at low olefin concentrations the rate becomes first order in olefin. Furthermore, different olefins react at different rates. These observations led us to make a controversial proposal: that a metallaoxetane intermediate is in rapid equilibrium with a $M{=}O$ species and olefin substrate and that this intermediate irreversibly breaks down to the epoxide product.

Since that time, the kinetic behavior of this reaction has been examined by several research groups.[4-6] Diverse, conflicting interpretations have been advanced to explain this complicated system. Nolte and co-workers have proposed that Mn(V)–oxo formation is the rate-determining step in this system and suggest dimerization of the unhindered Mn(TPP)$^+$ catalyst may be responsible for the difference in rates for this catalyst.[4] They also

---

[†] Stanford University.

[‡] Mitsubishi Kasei Corporation.

(1) (a) *Cytochrome* P-450. *Structure, Mechanism, and Biochemistry*; Oritz de Montellano, P. R., Ed.; Plenum Press: New York, 1986; Chapter 7 and 8. (b) For a review of the controversy in metalloporphyrin-catalyzed epoxidations, see: Hampton, P. D. Ph.D. Dissertation, Stanford University, 1989; Chapters 2, 3, 5, and 6.

(2) (a) Collman, J. P.; Kodadek, T.; Raybuck, S. A.; Meunier, B. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 7039. (b) Collman, J. P.; Brauman, J. I.; Meunier, B.; Raybuck, S. A.; Kodadek, T. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3245. (c) Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T.; Raybuck, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 2000.

(3) (a) Guilmet, E.; Meunier, B. *Tetrahedron Lett.* **1980**, 4449. (b) Guilmet, E.; Meunier, B. *Nouv. J. Chim.* **1982**, *6*, 511. (c) Bortolini, O.; Ricci, M.; Meunier, B.; Friant, P.; Ascone, I.; Goulon, J. *Nouv. J. Chim.* **1986**, *10*, 39. (d) Robert, A.; Meunier, B. *Nouv. J. Chim.* **1988**, *12*, 885.

0002-7863/90/1512-7980$02.50/0 © 1990 American Chemical Society