Hydration of Carbonyl Groups

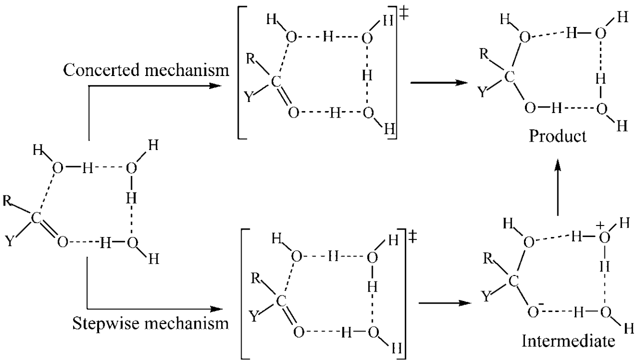
DOI: 10.1002/anie.201008239

Hydration of Carbonyl Groups: The Labile H_3O^+ Ion as an Intermediate Modulated by the Surrounding Water Molecules**

*Binju Wang and Zexing Cao**

Water plays a quite important role in chemical and biological processes, such as acid–base reactions,[1,2] proton transfer in membrane proteins,[3–5] keto–enol tautomerization,[6] and the hydration of carbonyl compounds. The hydration of carbonyl compounds has a long standing interest, both experimentally[7–10] and theoretically.[11–22] In most reactions of carbonyl compounds, such as aldehydes, ketones, esters, amides, the carboxylic acids, and their derivatives, the initial hydration or the nucleophilic addition of water at the carbonyl group, leading to a tetrahedral intermediate, is the rate-determining step. For example, the neutral hydrolyses of carboxylic acid derivatives normally proceed through the addition–elimination mechanism,[9] in which the hydration of the carbonyl group to yield a tetrahedral intermediate is the key step for hydrolysis.

For the hydration of carbonyl compounds, all the previous ab-initio calculations proposed a concerted mechanism for the rate-determining hydration step,[11–20] including the nucleophilic attack of one water molecule onto the carbonyl carbon atom coupled with the concerted proton transfer to the carbonyl oxygen atom assisted by one or more water molecules as shown in Scheme 1. However, most of the calculated Gibbs free energies of activation ($\Delta G^{\neq}$) for the concerted mechanism exceed the experimental value considerably,[23] although calculations with a relatively small basis set happen to predict activation energies comparable to the experimental value. This unexpected agreement between theory and experiment can be ascribed to use of relatively small basis set (see below). In a recent study the initial water autoionization was assumed to be involved in the hydrolysis of esters,[23] and the predicted Gibbs activation energies by molecular dynamics (MD) simulations for the key steps are comparable to $\Delta G^{\neq}$ of 23.8 kcal mol^{-1} for the water autoionization,[24] in agreement with the experimental value of 26.1 kcal mol^{-1}.[25] However, in this mechanism the water autoionization as the rate-determining step is a prerequisite to hydrolysis, implying that the Gibbs free energies of activation ($\Delta G^{\neq}$) are little changed for different esters. Nevertheless, the experimental rate constants for the hydration of esters can vary by 10^7 fold, which approximately corresponds to an activation energy difference of 10 kcal mol^{-1}.



Scheme 1. Concerted and stepwise nucleophilic additions of water to the carbonyl group.

Experimental studies by Bell et al. suggested that the hydration of the carbonyl group may proceed through a stepwise transfer of three protons in a cyclic array of three water molecules,[26] and that an intermediate Eigen ion (H_3O^+)[27] is most likely involved in hydration. However, to date, there is no computational evidence for H_3O^+ as the key intermediate. This situation may arise from the use of inappropriate cluster models for hydrated species in previous computational studies. Theoretical calculations on the Gibbs free energy of hydration for the proton show that the first hydration shell of the proton requires at least four water molecules,[28,29] and the predicted Gibbs free energy of hydration is about 263 kcal mol^{-1}, in good agreement with the experimental results of 262.4[30] and 264.1 kcal mol^{-1}.[31] On the contrary, simple H_3O^+ and $H_5O_2^+$ models in combination with the dielectric continuum solvent underestimate the Gibbs free energy of hydration of the proton by about 16 and 10 kcal mol^{-1},[28] respectively. Such a large deviation can significantly influence the description of thermodynamic and dynamic properties in the proton-transfer process. Accordingly, to locate a H_3O^+ intermediate in the reaction, more water molecules should be included in the cluster continuum model where the first hydration shell of H_3O^+ should be hydrogen-bonded by explicit water molecules.

Herein we applied a hybrid cluster continuum approach[32] to explore the hydration of carbonyl compounds, and this computational model was shown to be successful for the determination of the Gibbs free energy of solvation[33] and pK_a values for some organic cations,[34] and especially successful for the treatment of protons.[28,29] Such hybrid models

---

[*] B. Wang, Prof. Dr. Z. Cao
Department of Chemistry and State Key Laboratory of Physical Chemistry of Solid Surfaces, College of Chemistry and Chemical Engineering, Xiamen University
Xiamen 360015 (China)
Fax: (+86) 592-218-3047
E-mail: zxcao@xmu.edu.cn

[**] This work was supported by the National Science Foundation of China (20733002 and 20873105) and the Ministry of Science and Technology (2011CB808504).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201008239.

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

allow rigorous location of the transition-state structure. Once a realistic approximation of the reaction coordinate has been obtained, the relative Gibbs free energy profiles can be accurately computed by high-level ab-initio methods.[14] In contrast to the widely suggested concerted mechanism, the stepwise mechanism was verified to be favorable dynamically for all the hydration processes of the carbonyl group in the various compounds considered herein by the extensive and reliable theoretical calculations (see below).

All calculations were performed with the Gaussian 03 package. Geometries of all transition states, reactants, and intermediates involved in reaction were fully optimized by using a hydrated cluster in conjunction with the conductor-like polarizable continuum model (CPCM) at the B3LYP/6-311+G(2df,2p) level of theory. Computational details are described in the Supporting Information. With the above the cluster continuum computational strategy, the Gibbs free energy of hydration of a proton in the form of a $H_9O_4^+$ cluster[35] was predicted to be -262.4 kcal mol^{-1}, in good agreement with the experimental values of -262.4[30] and -264.1 kcal mol^{-1}.[31]

Since the concerted hydration of carbonyl groups was recognized by previous computational studies, various concerted-hydration pathways for the water addition to the carbonyl group of methyl formate as a representative example were investigated, and the predicted Gibbs free energies of activation ($\Delta G^{\neq}$) range from 33.2 to 37.4 kcal mol^{-1} (B3LYP/6-311+G(2df,2p) calculations) as shown in Table S1 of the Supporting Information. Surprisingly, we note that the calculated Gibbs free energies of activation strongly depend on the basis set used, as shown in Table S1 of the Supporting Information. The relatively small 6-31G(d) basis set remarkably underestimates the barrier, yielding values that are on average 8 kcal mol^{-1} lower than those calcluated using the the 6-311+G(2df,2p) basis set. However, these underestimated values (24.9–28.7 kcal mol^{-1}) happen to match the experimental value of 26.1 kcal mol^{-1}.[25]

In the calculations, the cyclic arrays of three and four water molecules were used in the cluster continuum model. Figure 1 presents the optimized structures of species involved in the hydration of methyl formate. The predicted relative Gibbs free energy profiles and thermodynamic values based on the representative cluster continuum models **a** (the four water molecule-mediated hydrated pathway) and **b** (the three water molecule-mediated hydrated pathway) are summarized in Figure 2.

For the cluster model **a**, in which four water molecules are involved in the nucleophilic addition of water to the carbonyl group, the reaction starts from a reactant complex (**R-a**) of the methyl formate with water molecules connected by hydrogen-bond networks. In the hydrated cluster of methyl formate, the lone pairs of the carbonyl oxygen atom are hydrogen bonded to two water molecules as indicated in analysis of X-ray structures.[36] In the first step, the attack of an adjacent water molecule onto the carbonyl carbon atom of the ester group, coupled with the concerted proton abstraction by the second water, yields a tetrahedral anionic intermediate and H_3O^+ intermediate (**Int1-a**). This is the rate-determining step for the overall reaction, and the predicted Gibbs free energy of activation is 25.4 kcal mol^{-1} (**TS1-a**), in good agreement with the experimental value of 26.1 kcal mol^{-1}. Following proton transfer from H_3O^+ to another H_2O through **TS2-a** leads to an intermediate (**Int2-a**). As shown in Figure 2, this step is almost barrier free and isoenergetic. The subsequent proton transfer from H_3O^+ (**Int2-a**) to the carbonyl oxygen atom is assisted by another water molecule and yields a more stable tetrahedral product (**P-a**) with a barrier of 1.2 kcal mol^{-1} (**TS3-a**). The overall hydration of the carbonyl group has Gibbs free energy of reaction $\Delta G = 6.9$ kcal mol^{-1} (298.15 K) as shown in Figure 2, in good agreement with the experimental value of 9.1 kcal mol^{-1}.[25]

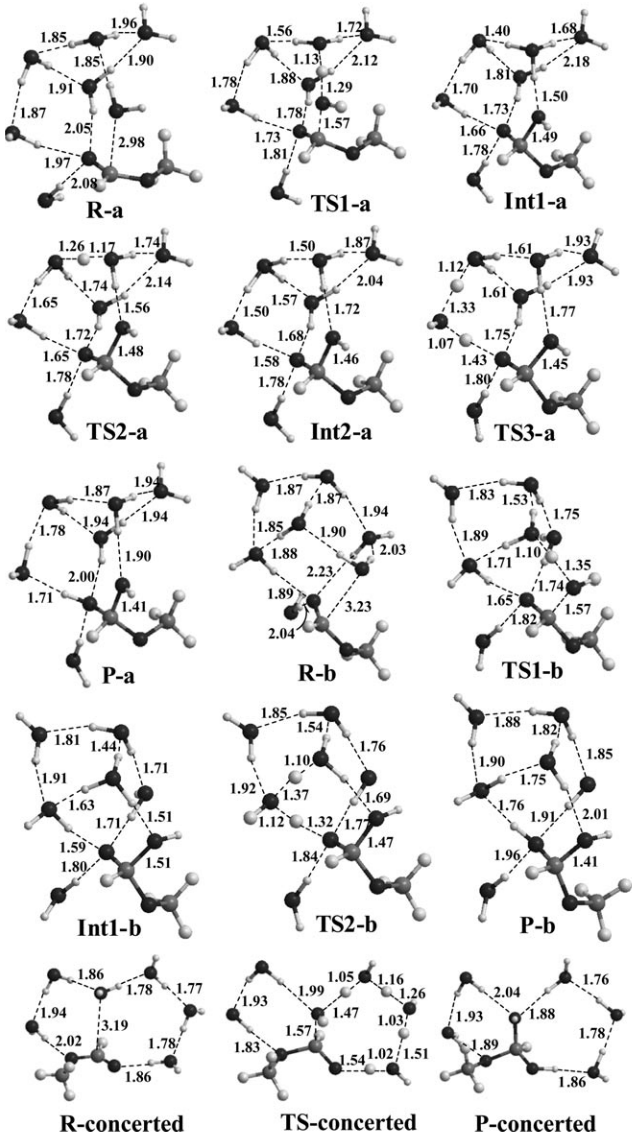


Figure 1. Optimized structures at the B3LYP/6-311+G(2df,2p) level of theory for the hydration of methyl formate. See text for details. O black, C dark gray, H light gray. Interatomic distances in [Å].

In the cluster model **b** for the three water molecule mediated hydrated pathway, the reaction starts from **R-b**, and the initial nucleophilic addition of water at the carbonyl group through **TS1-b** yields a tetrahedral anionic intermediate and

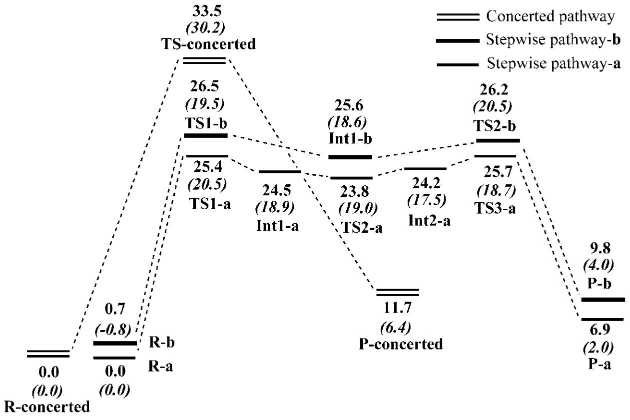


Figure 2. Calculated relative energy profiles ($\Delta G^{\neq}_{calcd}$ and $\Delta E^{\neq}$ in kcal mol^{-1}) for the hydration of methyl formate. $\Delta G^{\neq}_{calcd}$ and $\Delta E^{\neq}$ values are given in normal and italic fonts in parentheses, respectively. The total energies of **R-concerted** and **R-a** are taken as the reference points of relative energies for the concerted and stepwise pathways.

the H_3O^+ intermediate (**Int1-b**). Subsequent proton transfer leads to the product (**P-b**) via the transition state **TS2-b**. The predicted Gibbs free energy of activation for the rate-determining step is 25.7 kcal mol^{-1}, and the overall Gibbs free energy of reaction is 9.1 kcal mol^{-1}, which are in good agreement with the corresponding experimental values of 26.1 kcal mol^{-1} and 9.1 kcal mol^{-1}.[25] As shown in Figure 2, both computational models predict quite similar relative Gibbs free energy profiles. The single-point energy calculations at the MP2/6-311+G(2df, 2p) level based on the B3LYP-optimized structures were performed, and the predicted relative energy profiles are presented in Figure S2 in Supporting Information. Overall, both calculations predict comparable results, and the MP2-predicted Gibbs free energies of activation ($\Delta G^{\neq}$) are systematically underestimated by about 3 kcal mol^{-1} in comparison with B3LYP calculations.

To evaluate the dependence of the methodology and the basis set on the thermodynamic values, different functionals including B3LYP, BMK,[37] and X3LYP,[38] and the HF-based MP2 and CCSD(T) approaches were considered in comparative calculations with the basis sets 6-31G(d), 6-311+G(d,p), and 6-311+G(2df,2p). As Table 1 shows, the calculated activation Gibbs free energies strongly depend on the use of the basis set. The single-point energy calculations with the large basis set still underestimate the activation Gibbs free energies to a certain extent because the small-basis-set-optimized geometries were used. We also tested various cluster models with different configurations of water molecules and hydrogen-bond networks, the optimized transition-state structures are shown in Figure 3. The present calculations show that the mechanistic details and relative reaction energies are less modified, as shown in Table 2.

Table 1: Calculated Gibbs free energies of activation (298.15 K) for the rate-determining step in the hydration of the methyl formate with the cluster model **b**. Zero-point energies (ZPE) are included.

Method	$\Delta G^{\neq}$ [kcal mol^{-1}]			
	6-31G(d)	6-311+G(d,p)	6-311+G(2df,2p)	
B3LYP	13.3	24.9	25.7	22.7[a]
BMK	12.7	23.2	25.7	21.8[b]
X3 LYP	12.2	22.8	25.2	22.2[c]
MP2	16.6	22.3	20.5[d]	20.6[e]
CCSD(T)		25.1[f]		

[a] The optimized geometries and ZPE by B3LYP/6-31G(d). [b] The optimized geometries and ZPE by BMK/6-31G(d). [c] The optimized geometries and ZPE by X3 LYP/6-31G(d). [d] The optimized geometries and ZPE by MP2/6-311+G(d,p). [e] The optimized geometries and ZPE by MP2/6-31G(d). [f] The optimized geometries and ZPE by B3LYP/6-311+G(2df,2p).

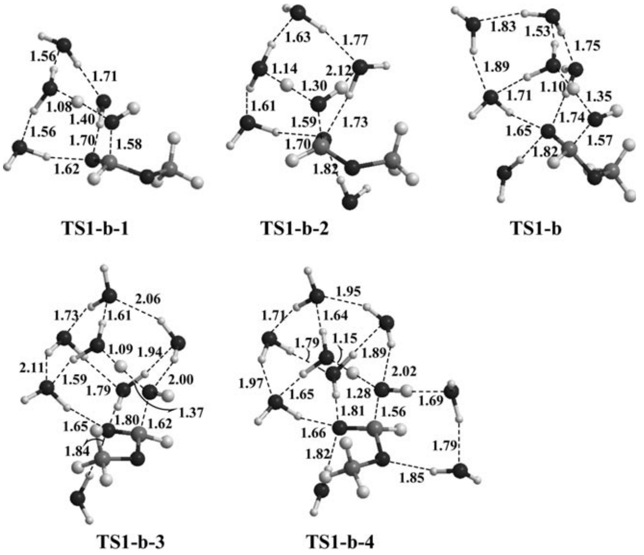


Figure 3. Optimized transition-state structures at the B3LYP/6-311+G-(2df,2p) level of theory for the hydration of methyl formate with different cluster models. O black, C dark gray, H light gray. Interatomic distances in [Å].

Table 2: Calculated Gibbs free energies of activation (298.15 K) for different cluster models (see Figure 3). Zero-point energies (ZPE) are included.

Model	$\Delta G^{\neq}$ [kcal mol^{-1}][a]	Model	$\Delta G^{\neq}$ [kcal mol^{-1}][a]
TS1-b-1	25.8(*23.7*)	**TS1-b-3**	26.8(*24.0*)
TS1-b-2	26.7(*23.8*)	**TS1-b-4**	25.7(*20.6*)
TS1-b	25.7(*22.7*)		

[a] The values of $\Delta G^{\neq}$ at the B3LYP/6-311+G(2df,2p) level are given in normal fonts, while those by the MP2 single-point energy calculations based on the B3LYP-optimized geometries and ZPE corrections are given in italics in parentheses.

For comparison, we also explored the concerted-hydration pathways initiated by **R-a** or **R-b**. However, we fail to locate the concerted transition state, and all attempts directly evolve into the stepwise-hydration pathways based on the cluster models **R-a** and **R-b**. Since an Eigen ion (H_3O^+) intermediate has strong tendency to form hydrogen bonds and be stabilized by the surrounding water molecules as observed in **Int1-a** and **Int1-b**, the concerted hydration mechanism is less possible in solution, but it could survive in the cluster continuum model with quite few explicit water molecules.

Except for the methyl formate, we have also studied six esters with both cluster models **a** and **b**, and the experimental and predicted Gibbs energy barriers for the hydration of these esters are compiled into Table 3. Furthermore, selected aldehydes and ketones were investigated by using the cluster model **b**, and corresponding thermodynamic parameters are collected in Table 4. As Table 3 shows, both cluster models **a** and **b** predict quite similar Gibbs free energies of activation, which agree nicely with the experimental values. For the most reactive carbonyl compounds H_2CO and CCl_3CHO, the stepwise-hydration pathway is much favorable dynamically than other ones as shown in Table 4, although both activation energies are relatively underestimated with the cluster model **b**. All these results suggest that the hydration of carbonyl compounds should follow the stepwise mechanism, where the cyclic arrays of three and four water molecules may be involved in the proton transfer process.

Table 3: Experimental and calculated thermodynamic parameters for the hydration of different esters.

Reactant	Experiment[a]			Theory	
	k	$\Delta G^{\neq}$	Ref.	$\Delta G^{\neq}$(**a**)	$\Delta G^{\neq}$(**b**)
HCO_2CH_3	6.3×10^{-7}	26.1	[23]	25.4	25.7
$HCO_2CH_2CH_3$	2.1×10^{-7}	26.8	[39]	26.8	26.5
$CH_3CO_2CH_3$	1.7×10^{-9}	29.6	[40]	31.5	32.2
$CH_3CO_2CH_2CH_3$	2.5×10^{-10}	30.8	[41]	31.9	32.9
$CH_2FCO_2CH_2CH_3$	1.9×10^{-7}	26.9	[42]	27.5	27.8
$CHF_2CO_2CH_2CH_3$	5.7×10^{-5}	23.4	[43]	23.6	23.6
$CF_3CO_2CH_2CH_3$	3.3×10^{-3}	21.0	[42]	21.1	18.3

[a] The activation Gibbs free energies are given in kcal mol^{-1}. The experimental $\Delta G^{\neq}$ are derived from the transition-state theory according to the rate constants (k). $\Delta G^{\neq}$(**a**) and $\Delta G^{\neq}$(**b**) refer to the cluster models **a** and **b**.

Table 4: Experimental and calculated thermodynamic parameters for the hydration of different aldehydes and ketones.

Reactant	Experiment[a]			Theory[b]
	k	$\Delta G^{\neq}$	Ref.	$\Delta G^{\neq}$(**b**)
H_2CO	10	16.2	[44]	11.0
CH_3CHO	6.7×10^{-3}	20.8	[44]	19.9
$(CH_3)_2CO$	8.5×10^{-6}	24.6	[16]	26.3
$CH_2ClCOCH_3$	6.9×10^{-2}	19.2	[45]	23.6
CCl_3CHO	4.5×10^{2}	13.9	[46]	8.8
CH_2FCOCH_3	1.4	17.4	[45]	20.5
CF_3COCH_3	9.5	16.3	[45]	16.0

[a] The activation Gibbs free energies are given in kcal mol^{-1}. The experimental $\Delta G^{\neq}$ are derived from the transition-state theory according to the rate constants (k). [b] $\Delta G^{\neq}$(**b**) refers to the cluster model **b** calculations.

Considering the solvent effect on the nucleophilic attack on the carbonyl carbon, we explored the addition reaction of alcohol to the carbonyl group of aldehydes. Our calculations identify a stepwise mechanism via **TS4** as shown in Figure 4, and the predicted activation Gibbs free energies are 15.5 kcal mol^{-1} for the stepwise mechanism and 26.4 kcal mol^{-1} for the concerted mechanism (via **TS5**). Actually, most additions to the carbonyl group involve nucleophilic attack of a nucleophile onto the carbonyl carbon atom coupled with the proton transfer to the carbonyl oxygen atom, yielding a tetrahedral intermediate.

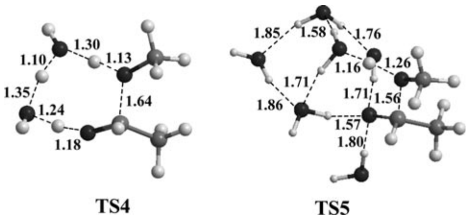


Figure 4. Optimized transition-state structures at the B3LYP/6-311+G(2df,2p) level of theory for the addition of alcohol to aldehydes. **TS4** and **TS5** are responsible for the concerted and stepwise mechanisms, respectively. O black, C dark gray, H light gray. Interatomic distances in [Å].

In summary, extensive cluster continuum model calculations show that the hydration of the carbonyl group proceeds in the stepwise mechanism, and this stepwise-hydration pathway is much more favorable than the widely proposed concerted-hydration pathway. Generally, calculations with the relatively small 6-31G(d) basis set considerably underestimate the barrier by 8 kcal mol^{-1} in average, compared to the 6-311+G(2df,2p) basis set, and the use of a large basis set is required for modeling the hydration of carbonyl group. The barrier for the concerted-hydration pathway is higher than that for the stepwise process by 8 kcal mol^{-1} on average. Although the Eigen ion (H_3O^+) has been identified as an intermediate in various proton transfer processes, such as in acid–base reactions[2] and in membrane proteins,[5] its location strong depends on the use of the cluster continuum model and of the explicit water molecules in the calculation. Interestingly, the reverse process of hydration just corresponds to an acid–base neutralization reaction. Presumably, the mechanism demonstrated herein for the hydration of the carbonyl group is also applicable for the acid–base neutralization. These results also provide a reference for the proton transfer reactions in chemistry and biology.

Received: December 29, 2010
Revised: January 23, 2011
Published online: March 2, 2011

Keywords: carbonyl groups · density functional calculations · hydration · nucleophilic addition · reaction mechanisms

---

[1] M. Rini, B. Z. Magnes, E. Pines, E. T. J. Nibbering, *Science* **2003**, *301*, 349.
[2] O. F. Mohammed, D. Pines, J. Dreyer, E. Pines, E. T. Nibbering, *Science* **2005**, *310*, 83.
[3] H. Luecke, H. T. Richter, J. K. Lanyi, *Science* **1998**, *280*, 1934.
[4] F. Garczarek, K. Gerwert, *Nature* **2006**, *439*, 109.
[5] S. Wolf, E. Freier, M. Potschies, E. Hofmann, K. Gerwert, *Angew. Chem.* **2010**, *122*, 7041; *Angew. Chem. Int. Ed.* **2010**, *49*, 6889.
[6] Y. Matsuda, A. Yamada, K. Hanaue, N. Mikami, A. Fujii, *Angew. Chem.* **2010**, *122*, 5018; *Angew. Chem. Int. Ed.* **2010**, *49*, 4898.

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[7] M. L. Bender, *Chem. Rev.* **1960**, *60*, 53.
[8] R. P. Bell, *Adv. Phys. Org. Chem.* **1966**, *4*, 1.
[9] J. March, *Adanced Organic Chemistry*, 4th ed. Wiley, New York, **1992**.
[10] K. Adamczyk, M. Premont-Schwarz, D. Pines, E. Pines, E. T. J. Nibbering, *Science* **2009**, *326*, 1690.
[11] B. Kallies, R. Mitzner, *J. Mol. Model.* **1998**, *4*, 183.
[12] G. Schmeer, P. Sturm, *Phys. Chem. Chem. Phys.* **1999**, *1*, 1025.
[13] S. Yamabe, N. Tsuchida, Y. Hayashida, *J. Phys. Chem. A* **2005**, *109*, 7216.
[14] L. Gorb, A. Asensio, I. Tuñón, M. F. Ruiz-López, *Chem. Eur. J.* **2005**, *11*, 6743.
[15] S. Wolfe, C. K. Kim, K. Yang, N. Weinberg, Z. Shi, *J. Am. Chem. Soc.* **1995**, *117*, 4240.
[16] S. Wolfe, Z. Shi, K. Yang, S. Ro, N. Weinberg, C. K. Kim, *Can. J. Chem.* **1998**, *76*, 114.
[17] W. M. F. Fabian, R. Janoschek, *J. Org. Chem.* **1999**, *64*, 3271.
[18] M. T. Nguyen, G. Raspoet, L. G. Vanquickenborne, *J. Phys. Org. Chem.* **2000**, *13*, 46.
[19] Z. Shi, Y. H. Hsieh, N. Weinberg, S. Wolfe, *Can. J. Chem.* **2009**, *87*, 544.
[20] K. Yang, Y. H. Hsieh, C. K. Kim, H. Zhang, S. Wolfe, *Can. J. Chem.* **2010**, *88*, 56.
[21] J. P. Guthrie, *J. Am. Chem. Soc.* **2000**, *122*, 5529.
[22] J. P. Guthrie, V. Pitchko, *J. Am. Chem. Soc.* **2000**, *122*, 5520.
[23] G. Hakan, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 15232.
[24] M. Eigen, L. Z. de Maeyer, *Elektrochem.* **1955**, *59*, 986.
[25] J. P. Guthrie, P. A. Cullimore, *Can. J. Chem.* **1980**, *58*, 1281.
[26] R. P. Bell, J. P. Millington, J. M. Pink, *Proc. R. Soc. London Ser. A* **1968**, *303*, 1.
[27] M. Eigen, *Angew. Chem.* **1963**, *75*, 489; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 1.
[28] G. J. Tawa, I. A. Topol, S. K. Burt, R. A. Caldwell, A. A. Rashin, *J. Chem. Phys.* **1998**, *109*, 4852.
[29] C. G. Zhan, D. A. Dixon, *J. Phys. Chem. A* **2001**, *105*, 11534.
[30] C. E. Klots, *J. Phys. Chem.* **1981**, *85*, 3585.
[31] M. D. Tissandier, K. A. Cowen, W. Y. Feng, E. Gundlach, M. H. Cohen, A. D. Earhart, J. V. Coe, *J. Phys. Chem. A* **1998**, *102*, 7787.
[32] J. R. Pliego, Jr., J. M. Riveros, *Chem. Eur. J.* **2002**, *8*, 1945.
[33] J. R. Pliego, Jr., J. M. Riveros, *J. Phys. Chem. A* **2001**, *105*, 7241.
[34] J. R. Pliego, Jr., J. M. Riveros, *J. Phys. Chem. A* **2002**, *106*, 7434.
[35] B. Wang, Z. Cao, *J. Phys. Chem. A* **2010**, *114*, 12918.
[36] P. Murray-Rust, J. P. Glusker, *J. Am. Chem. Soc.* **1984**, *106*, 1018.
[37] A. D. Boese, J. M. L. Martin, *J. Chem. Phys.* **2004**, *121*, 3405.
[38] X. Xu, W. A. Goddard, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 2673.
[39] D. Stefanidis, W. P. Jencks, *J. Am. Chem. Soc.* **1993**, *115*, 6045.
[40] Y. H. Hsieh, N. Weinberg, S. Wolfe, *Can. J. Chem.* **2009**, *87*, 539.
[41] A. Skrabal, A. Zahorka, *Monatsh. Chem.* **1929**, *54*, 562.
[42] G. Schmeer, J. Barthel, *Z. Phys. Chem.* **1984**, *140*, 17.
[43] W. P. Jencks, J. Carriuolo, *J. Am. Chem. Soc.* **1961**, *83*, 1743.
[44] P. Greenzaid, Z. Luz, D. Samuel, *Trans. Faraday Soc.* **1968**, *64*, 2780.
[45] H. J. Buschmann, E. Dutkiewicz, W. Knoche, *Ber. Bunsen-Ges. Phys. Chem.* **1982**, *86*, 129.
[46] P. E. Sørensen, *Acta Chem. Scand. Ser. A* **1976**, *30*, 673.

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim