ORGANIC LETTERS

2012
Vol. 14, No. 1
260–263

Investigation of Solvent Effects on the Rate and Stereoselectivity of the Henry Reaction

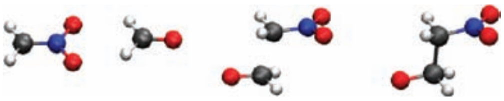
Jakub Kostal, Adelina M. Voutchkova, and William L. Jorgensen*

Department of Chemistry, Yale University, 225 Prospect Street, New Haven, Connecticut 06520-8107, United States

william.jorgensen@yale.edu

Received November 10, 2011

ABSTRACT



A combined computational and experimental kinetic study on the Henry reaction is reported. The effects of solvation on the transition structures and the rates of reaction between nitromethane and formaldehyde, and between nitropropane and benzaldehyde are elucidated with QM/MM calculations.

Since its discovery in 1895,[1] the Henry reaction has become a valuable method for synthesis of C–C bonds. However, the reaction suffers from low selectivity and side products are often encountered. Thus, considerable effort has been invested in developing more selective synthetic methods and in reducing the environmental impact of the reaction by carrying out the reactions either neat[2,3] or in aqueous medium.[4–6] Over the past decade, water has played an increasingly important role as a solvent in many organic reactions, presenting a low-cost and environmentally friendly alternative to the use of organic solvents, while either increasing or not adversely affecting the rate of the reaction.[7] To date, however, only a handful of reports exist of the Henry reaction in water,[4–6] and to the best of our knowledge no experimental kinetic or computational QM/MM studies have been carried out for the uncatalyzed reaction.

To explore the solvent-dependence of the reaction rates and geometries of the transition states (TSs) at the atomic level, the Henry reaction between formaldehyde and nitromethane and the stereosensitive reaction between benzaldehyde and nitropropane (Scheme 1) were investigated using free-energy perturbation (FEP) calculations in conjunction with AM1/MM Monte Carlo (MC) simulations at 25 °C and 1 atm.[8] The MC calculations include 400–700 explicit solvent molecules. Since the pK_a values for nitroalkanes in water are around 9, proton transfer is strongly favored using alkoxide bases. Thus, the present modeling starts from the nitronate ions, though it is noted that with weak bases, such as acetate, proton transfer from nitro compounds is slow.[9]

Computational results were augmented by experimental kinetic studies. The rate constants for the reaction in Scheme 1 with benzaldehyde were determined in H_2O/NaOH and DMSO/KO^{t}Bu by the parallel reaction method.[10] Reactant concentrations, measured as a function of time, were fitted to the integrated second-order rate law, and transition state theory was used to compute the activation barriers from the experimental rate constants.

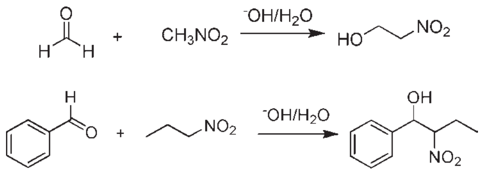
Computed free energies of the fully optimized reactants, TSs, and β-nitroalkoxide products for the reaction between nitromethane anion and formaldehyde in the gas

---

(1) Henry, L.; Seances, C. R. H. *Acad. Sci.* **1895**, *120*, 1265–7.
(2) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 5131–4.
(3) Ballini, R.; Palmieri, A. *Curr. Org. Chem.* **2006**, *10*, 2145–69.
(4) Ballini, R.; Bosica, G. *J. Org. Chem.* **1997**, *62*, 425–7.
(5) Phukan, M.; Borah, K. J.; Borah, R. *Synth. Commun.* **2008**, *38*, 3068–73.
(6) Wang, Z.; Xue, H.; Wang, S.; Wang, Z.; Xue, H.; Wang, S.; Yuan, C. *Chem. Biodiversity* **2005**, *2*, 1195–9.
(7) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095–165.
(8) Acevedo, O.; Jorgensen, W. L. *Acc. Chem. Res.* **2010**, *43*, 142–51.
(9) Major, D. T.; York, D. M.; Gao, J. *J. Am. Chem. Soc.* **2005**, *127*, 16374–5.
(10) Berliner, E.; Gaskin, F. *J. Org. Chem.* **1967**, *32*, 1660–1.

10.1021/ol2030394

Scheme 1. Henry Reactions between Formaldehyde and Nitromethane and between Benzaldehyde and Nitropropane



phase are summarized in Table 1. All energy changes are reported relative to the separated reactants. The semiempirical AM1 method[11] was considered in view of the large number of QM calculations that would be required in the solution-phase MC simulations. In fact, the AM1 results in Table 1 compare well with those from B3LYP[12] and MP2[13] calculations, which are in good agreement with previously reported values from coupled cluster CCSD(T) calculations.[14]

Table 1. Computed Gas Phase Free Energies for the Henry Reaction between Nitromethane Anion and Formaldehyde[a]

	AM1	B3LYP/6-31+G**	MP2/6-31+G**
Separated Reactants	0	0	0
Reactant Complex	4.7	2.3	1.9
TS	8.7	5.3	5.8
Product	6.3	3.9	1.4

[a] Values (in kcal/mol) include the thermal corrections to 25 °C.

Free-energy profiles from the gas and aqueous phase AM1/MM/MC simulations are shown in Figure 1. The computed activation barriers are 6.7 and 14.1 kcal/mol, respectively; the ΔG_{rxn} values are 2.2 kcal/mol in the gas phase and 5.3 kcal/mol in water. The increased barrier in aqueous solution can be attributed primarily to poorer solvation for the more charge-delocalized TS than for the reacting anion. Though the C–C separation is 1.94 Å for the TS in both media, there is a higher occurrence of O–C–C–N *gauche* conformers in water. Near the product the *gauche* and *anti* percentages are 48 and 52 in water but 0 and 100 in the gas phase. The larger *gauche* population in water is due to the greater polarity of this conformer, which leads to a more negative free energy of hydration. In the gas phase, electrostatic repulsion between the oxygens favors the *anti* conformer.

In order to characterize further the differential hydration, solute–water energy pair distribution functions (EPDs) were calculated for four representative FEP windows: near the separated reactants at 5.43 Å, the reactant complex at 3.45 Å, the TS, and the β-nitroalkoxide product (Figure 2). The energy pair distributions record the average number of water molecules that interact with the solute and their corresponding energies. Hydrogen bonding between the solute and water is reflected in the left-most region with the most attractive interaction energies; the large band near 0 kcal/mol results from the weak interactions with the many distant water molecules in the bulk.

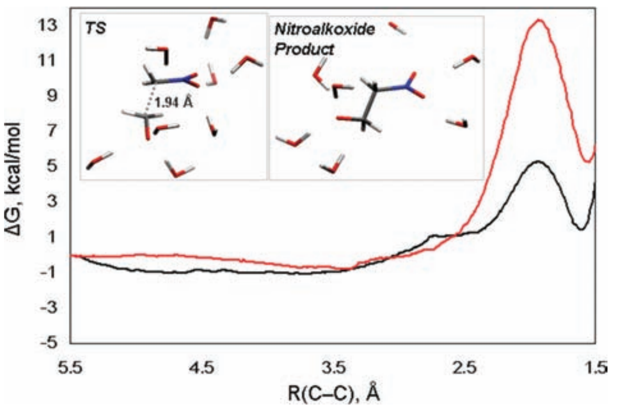


Figure 1. AM1/MC free-energy profiles for the C–C bond formation in the gas phase (black) and in water (red). Snapshots from QM/MM simulations are illustrated above the curves.

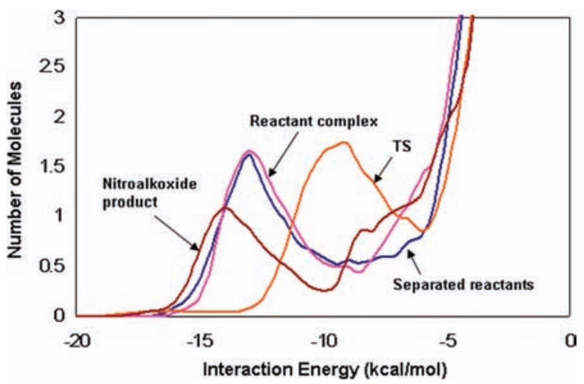


Figure 2. Solute–water energy pair distribution functions for the reaction of formaldehyde and methylnitronate ion.

Proceeding from reactants to the TS, the band centered near −13 kcal/mol, which contains the strong hydrogen bonds with the nitronate oxygen atoms, shifts to the right by ~5 kcal/mol, reflecting the weakening of these interactions. The appearance of the shoulder between ca. −9 to −6 kcal/mol can be assigned to the increase of hydrogen bonding to the incipient alkoxide oxygen. At the TS, the two features overlap, but then they separate in proceeding to the products in which the charge is largely localized on the alkoxy oxygen. The changes in numbers and overall

---

(11) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–9.

(12) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–52. Lee., C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *37*, 785–89.

(13) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618–22. Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503–6.

(14) Zorn, D.; Lin, V. S.; Pruski, M. *J. Phys. Chem. A* **2008**, *112*, 10653–49.

energetics for the hydrogen bonds can be assessed by integrating the energy pair distributions (Table 2). Though the total number of very attractive solute–water interactions remains near 10 in proceeding from reactants to product, the total energetic contributions form these interactions fluctuates in the expected manner, showing diminished stabilization of the transition state.

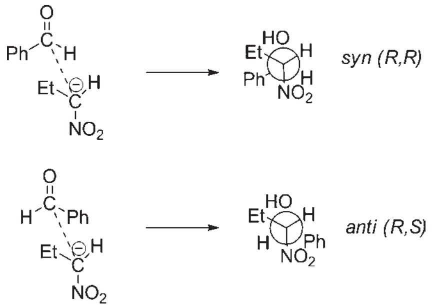
Table 2. Number of Solute–Water Interactions, *N*, and the Sum of Their Interaction Energies, *E*, in kcal/mol[a]

	N	ΔN	$\Sigma_i^N E_i$	$\Delta(\Sigma_i^N E_i)$
Separated Reactants	9.4	0	−95.4	0
Reactant Complex	10.5	1.1	−102.0	−6.6
TS	9.3	−0.1	−80.8	14.6
Product	9.3	−0.1	−88.7	6.7

[a] From integrating EPDs from −20 to −5 kcal/mol.

It should be noted that the β-nitroethoxide product would subsequently isomerize to yield the β-nitroethanol nitronate; i.e., a proton is transferred from the β-carbon to the alkoxide. Computed free energies show that this process is highly exergonic in the gas phase ($\Delta G = -10.6$ kcal/mol with MP2/6-31+G**) as well as in water ($\Delta G = -17.3$ kcal/mol with PCM-MP2/6-31+G**),[15] as expected from the pK_a difference. Thus, the overall reaction to the nitronate is exergonic in water by ca. 10 kcal/mol.

Scheme 2. Stereochemistry of the Henry Reaction between Benzaldehyde and Nitropropane



In the reaction between nitropropane and benzaldehyde (Scheme 1), the resulting β-nitroalkoxide product contains two stereogenic centers. The calculations examined the two diastereomeric reaction pathways leading to the *syn* (*R,R or S,S*) and *anti* (*R,S or S,R*) transition states (Scheme 2). The computed and experimentally determined free energies of activation ($\Delta G^\ddagger$) for this reaction in water and DMSO are listed in Table 3. As expected, the reaction proceeds more slowly in water than in DMSO; the obtained second-order rate constants are 0.91 M^{-1} s^{-1} in water and 52.0 M^{-1} s^{-1} in DMSO. The present experimental investigations also confirmed that the β-nitroalkoxide (**1**) isomerizes to yield the nitronate alcohol product (**2**) (Figure 3). The evidence was obtained by monitoring the reaction by NMR in D_2O, which allowed observation of the product **2** prior to protonation. The benzylic proton (H_α) of **1** is expected to resonate at ~6.7 ppm, while that of **2** at ~5.7 ppm (Modgraph NMR Predict v. 1.1). During the progression of the reaction, only the growth of a peak at 5.85 ppm was observed, indicating **2** as the major product. There is no clear evidence for **1** as the resonance corresponding to H_β could not be followed; it would be indiscernible from the peaks of unreacted nitropropane.

Table 3. Free Energy Changes (kcal/mol) at 25 °C for the Henry Reaction between Nitropropane Anion and Benzaldehyde from MC/FEP Simulations and Experimental Kinetic Studies

	$\Delta G^\ddagger$			ΔG_{rxn}	
	syn	*anti*	exptl	*syn*	*anti*
Gas phase	16.4	15.1	–	14.0	12.4
Water	24.8	22.7	17.5	19.8	16.9
DMSO	22.4	20.5	15.1	19.3	17.3

After acidification, the reaction mixture yielded the β-nitroalcohol as a 3:1 ratio of *syn*/*anti* diastereomers in both water and DMSO. This product ratio is in agreement with previous reports of uncatalyzed nitroaldol reactions.[3,16] It does not arise from the addition step for which the calculations favor the *anti* transition state. Instead, the product distribution is controlled by the reversibility of the reaction and facile epimerization of the nitro-substituted stereocenter. In particular, Seebach et al. showed that, for the reaction of benzaldehyde and nitropropane, the nitronate intermediate undergoes kinetic reprotonation in polar solvents to yield the β-nitroalcohol enriched in the *syn* (*threo*) diastereomer.[16] The relative stabilities of the diastereomeric products were briefly considered here using AM1 calculations with a polarizable continuum model for water (IEF-PCM).[14] The results found the *syn* β-nitroalcohol product to be favored over *anti* in water by ca. 2 kcal/mol (ΔG), which translates to a 97:3 product ratio at 25 °C. In the most stable conformer of the *syn* diastereomer, the ethyl and phenyl substituents are *anti*, while the nitro and alcohol groups are *gauche*, stabilized by a hydrogen bond. Conversely, the *anti* diastereomer has both NO_2/OH and Et/Ph substituent pairs *anti* or *gauche* in its two lowest-energy conformers. These two conformers are only 0.2 kcal/mol apart, and while the first lacks the stabilization of the hydrogen bond between the NO_2 and OH groups, the latter suffers from steric crowding between the ethyl and phenyl substituents.

The results of the QM/MM simulations for the reaction with benzaldehyde in water and DMSO are in reasonable

---

(15) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–94.

(16) Barrett, A. G. M.; Robyr, C.; Spilling, C. D. *J. Org. Chem.* **1989**, *54*, 1233–4. Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101–33. Lehr, F.; Gonnermann, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2258–75.

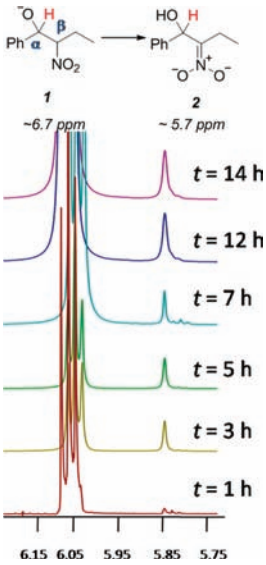


Figure 3. Progression of the reaction between nitropropane and benzaldehyde in water showing growth of the 5.85 ppm peak.

accord with the experimentally determined activation barriers (Table 3). The barrier lowering by 2–3 kcal/mol in DMSO is relatively modest compared to the 6–7 kcal/mol shifts for some S_N2 reactions;[17] however, the methylnitronate is more charge delocalized than prototypical S_N2 nucleophiles such as halide ions. Snapshots corresponding to the TSs and products for the *syn* and *anti* diastereomers in water are shown in Figure 4. The intrinsic preference for having the sterically bulky ethyl and phenyl groups *anti* is consistent with the *anti* TS being favored over the *syn* alternative. The effect of the solvent on this preference is negligible; in both water and DMSO, the difference in the computed barrier heights is ca. 2 kcal/mol. The computed energy pair distributions for this reaction (Figure S2) are qualitatively similar to those for the reaction of formaldehyde plus methylnitronate. In water, the hydrogen bonds to the TS are weaker by ca. 4 kcal/mol than those for the nitronate reactant. In DMSO, the most favorable ion–dipole interactions are ca. 3 kcal/mol weaker for the TS than the reactant. Integration of the energy pair distributions from −16 to −5 kcal/mol shows on average ca. 20 kcal/mol more favorable interactions in water than in DMSO with the gap narrowing by ca. 2 kcal/mol at the TSs.

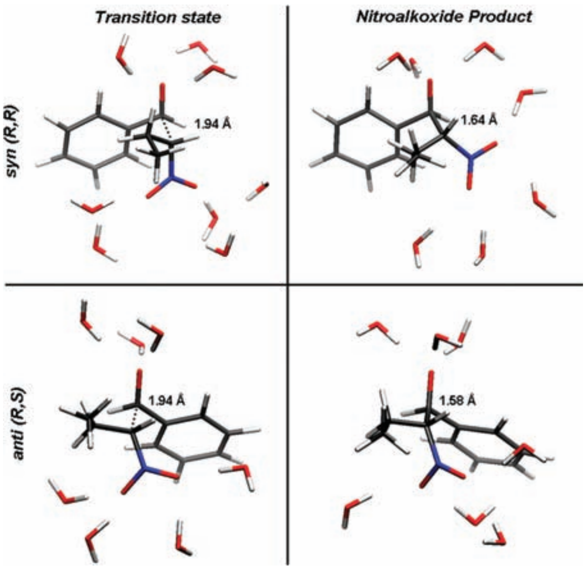


Figure 4. Representative snapshots of TSs and β-nitroalkoxide products corresponding to the *syn* and *anti* diastereomers from QM/MM simulations in water.

In conclusion, QM/MM simulations have been carried out for the Henry reactions of nitromethane and formaldehyde, and of nitropropane and benzaldehyde. In the latter case, the computed free energies of activation agree well with the present experimental results in water and DMSO. The reaction proceeds more slowly in water than in DMSO owing to weakening of the hydrogen bonds between water and the nitronate reactant in proceeding to the charge delocalized transition state. The weakening of the corresponding ion–dipole interactions in DMSO is less pronounced. Though the *anti*-TS for the addition reaction with benzaldehyde is computed to be lower in free energy than the *syn* TS, the preference for *syn* sterechemistry of the β-nitroalcohol product is attributed to the subsequent protonation of β-hydroxynitronate **2**.

Acknowledgment. Gratitude is expressed to the National Institutes of Health (GM32136) and Center for Green Chemistry and Green Engineering at Yale for support and to Drs. Paul T. Anastas and Julian Tirado-Rives for assistance.

Supporting Information Available. Experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

---

[17] Vayner, G.; Houk, K. N.; Jorgensen, W. L.; Brauman, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 9054–58.