Can Hydridic−to−Protonic Hydrogen Bonds Catalyze Hydride Transfers in Biological Systems?

ARTICLE *in* THE JOURNAL OF PHYSICAL CHEMISTRY A · DECEMBER 2010

Impact Factor: 2.69 · DOI: 10.1021/jp1050854 · Source: PubMed

2 AUTHORS:

Simona Marincean
University of Michigan-Dearborn
11 PUBLICATIONS **27** CITATIONS
SEE PROFILE

James E Jackson
Michigan State University
132 PUBLICATIONS **2,479** CITATIONS
SEE PROFILE

Can Hydridic-to-Protonic Hydrogen Bonds Catalyze Hydride Transfers in Biological Systems?

Simona Marincean*,† and James E. Jackson‡

Natural Sciences Department, University of Michigan—Dearborn, Dearborn, Michigan 48128-1491, United States, and Department of Chemistry, Michigan State University, East Lansing, Michigan 48824-1322, United States

Received: June 2, 2010; Revised Manuscript Received: October 26, 2010

Catalysis of hydride transfer by hydridic-to-protonic hydrogen (HHH) bonding in α-hydroxy carbonyl isomerization reactions was examined computationally in the lithium salts of 7-substituted endo-3-hydroxybicyclo[2.2.1]hept-5-en-2-ones. The barrier for intramolecular hydride transfer in the parent system was calculated to be 17.2 kcal/mol. Traditional proton donors, such as OH and NH_3^+, stabilized the metal cation-bridged transition state by 1.4 and 3.3 kcal/mol, respectively. Moreover, among the conformers of the OH systems, the one in which the proton donor is able to interact with the migrating hydride (H_m) has an activation barrier lower by 1.3 and 1.7 kcal/mol than the other possible OH conformers. By contrast, the presence of an electronegative group such as F, which disfavors the migration electronically by opposing development of hydridic charge, destabilizes the hydride migration by 1.5 kcal/mol relative to the epimeric exo system. In both ground and transition states the $H_m\cdots H$ distance decreased with increasing acidity of the proton donor, reaching a minimum of 1.58 Å at the transition state for NH_3^+. Both Mulliken and NPA charges show enhancement of negative character of the migrating hydride in the cases in which HHH bonding is possible.

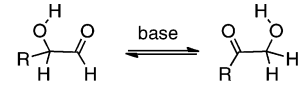
Introduction

Hydridic-to-protonic or dihydrogen bonds are unconventional hydrogen bonds in which a traditional proton donor interacts with a hydridic hydrogen, i.e., one attached to a less electronegative element.[1] There have been numerous reported examples of such hydrogen—hydrogen hydrogen bonds (HHH bonds)[2] and explorations of their effects in crystal engineering, reaction dynamics, and selectivity and activation in catalytic and stoichiometric synthesis processes.[3]

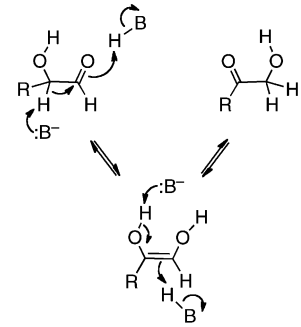
One area notably lacking from the above list is biology. Yet hydridic-to-protonic hydrogen bonding appears to offer a natural opportunity whereby enzymes could accelerate reactions. Specifically, in biological hydride transfers from, e.g., NADH,[4] the transferred hydride typically begins and ends the reaction bonded to sp^3 hybridized carbon sites, thus bearing little charge. But as the proton and its electron pair shift from one partner to another, if they (a) have significant hydridic character in transit and (b) are sterically exposed to nearby residues, then an opportunity exists for the surrounding active site to selectively stabilize the transition state differentially relative to the end points, and hence lower the reaction's activation barrier.

One potential biologically relevant instance in which hydridic-to-protonic hydrogen bonding could be involved is the isomerization of α-hydroxy carbonyl compounds, Scheme 1. This transformation is familiar in the context of aldose-to-ketose sugar isomerizations. It has been reported in biological systems to occur by two distinct mechanisms: (a) via acid- or base-catalyzed proton exchanges to form and reketonize the familiar enediol intermediate or (b) via direct 1,2-hydride shift. Enzymes lacking metal cations catalyze the former, proton-transfer path (the so-called Lobry de Bruyn, Alberda van Ekenstein rearrangement) via a cis enediol,[5] Scheme 1A. On the other hand, metalloenzymes have been reported to favor the hydride shift mechanism,[6] Scheme 1B.

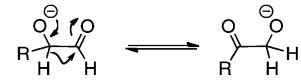
SCHEME 1



A. Proton Transfer Mechanism via Enediol:



B. Hydride Transfer Mechanism

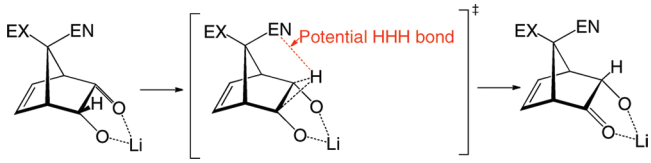


Recently, on the basis of QM/MM studies from the Mo group, it has been suggested that, in the zinc-bearing phosphoglucose isomerase *Pf*PGI, a zwitterionic intermediate is formed that can undergo isomerization via both types of mechanisms. Here, the Zn^{2+} ion is not involved directly in binding the substrate's two

* To whom correspondence should be addressed. Phone: (313) 593-5404. Fax: (313) 593-4937. E-mail: simonam@umd.umich.edu.
† University of Michigan—Dearborn.
‡ Michigan State University.

10.1021/jp1050854
Published on Web 12/08/2010

SCHEME 2



active oxygen sites but rather in proton transfer between solvent and substrate.[7,8]

To elucidate the factors selecting between the two mechanisms, Nagorski and Richard conducted an elegant labeling study on a model system,[9] the isomerization of glyceraldehyde to dihydroxyacetone. Specifically, they showed that, in the presence of Zn^{2+}, unlabeled glyceraldehyde in D_2O buffer solution undergoes isomerization without concomitant deuterium incorporation. They proposed that because the enediol and hydride shift mechanisms have similar uncatalyzed activation barriers in aqueous media, different enzymes have evolved that promote each of them. The role of the Zn^{2+} ion relates to the broader context of Meerwein−Ponndorf−Verley/Oppenauer reactions in alcoholic solvents.[10] Here, when metal-linked cyclic hydride-transfer transition states are structurally possible (inter- or intramolecular), rates increase with increasing Lewis acidity of the metal.[11]

Drawing from mechanistic observations in organic systems, a couple of important hypotheses can be made regarding the envisioned enzyme site: (a) a cyclic transition state that involves a metal cation would favor the hydride-transfer pathway, conserving electrostatic stabilization throughout the reaction; (b) the transition state may be stabilized by HHH bonding if nearby enzyme residues possess proton donors such as NH_3^+ or OH in orientations capable of interacting with the hydride. The above hypotheses can be tested via "gas-phase" computational studies on a model system, Scheme 2, wherein the α-hydroxy carbonyl feature is set in the rigid norbornene framework. The rearrangement is degenerate via a symmetrical transition state, which simplifies analysis of changes along the reaction path. The proton donor moieties can be oriented endo (where HHH bonding is possible) or exo to the migrating hydride, enabling direct energetic comparison between otherwise similarly polarized systems.

Computational Consideration

Using GAUSSIAN 98[12] and GAUSSIAN 03[13] packages, density functional theory (DFT) calculations have been performed using the B3LYP[14] functional theory and 6-311++g**[15] basis set. Although one literature report[2d] has noted a tendency of B3LYP to underestimate the strength of the dispersion interaction in a study of transition metal hydrides, this functional has been successful in reproducing experimental behavior of classical hydrogen bonds,[16] dihydrogen bonds,[3c] and proton/hydride-transfer reactions.[3b,17] As a check on the DFT method's performance, we have examined representative members of our model series at the MP2/6-311++G** level and we have found only minor differences. Stationary points on the potential energy surfaces were characterized by vibrational analysis as minima or transition structures, having zero and one imaginary frequency, respectively. Intrinsic reaction coordinate (IRC) calculations were performed to confirm that reaction paths from transition structures relaxed to the expected ground states. The computed activation barriers were corrected for zero point and thermal vibrational energies. In addition to Mulliken and natural population analysis[18] (NPA) derived charges, atomic electrostatic ones[19] were computed using CHELPG[20] within GAUSSIAN 98. Structures were visualized using MacMolPlt.[21]

Kinetic isotope effects were calculated from the vibrational analysis using Gibbs free energies computed for nondeuterated and deuterated species:[22]

$$k_H/k_D = \exp[-(\Delta G_H - \Delta G_D)/RT]$$

where $\Delta G = G^{‡} - G^{r}$, with ‡ and r referring to transition state and reactant, respectively.

Results and Discussion

The ground state for the reference system, Figure 1, places the migrating hydride (H_m) and the endo hydrogen in close proximity, 2.34 Å apart, which is just slightly below the sum of the van der Waals radii for the two atoms. Thus, any endo-positioned group would be forced to interact with H_m, whether the interaction were stabilizing or destabilizing. In the ground state the Mulliken charge of H_m, the hydride to be transferred, is 0.14, but as the reaction progresses to the transition state, the charge decreases to 0.03, making H_m the least positive hydrogen in the system. The transition state is of C_s symmetry with H_m, the Li atom, and the C7 CH_2 group lying on the mirror plane. The C2 and C3 C−H_m distances are 1.43 Å, compared to 1.12 and 2.14 Å in the ground state. Meanwhile, the H_m to endo-H distance has shrunken to 2.06 Å. The calculated barrier for this reaction is 17.2 kcal/mol.

To probe for the effects of HHH bonding, the protonic H-donor functional groups OH, NH_2, and NH_3^+, as well as electron-withdrawing F, and sterically demanding CH_3 groups were examined. Each was placed on C7 in both endo (EN) and exo (EX) positions with respect to the hydride. With OH and NH_2 groups capable of multiple rotameric orientations, all rotational minima were examined, as illustrated in Scheme 3. Results are summarized in Tables 1 and 2. The structures of the ground and transition states of the endo complexes are shown in Figure 1.

For the substrates with proton donors that are endo to H_m, several trends can be noted: with increasing acidity of EN, the (EN)H···H_m distance decreases in both ground states and transition states, reaching a minimum value of 1.58 Å (transition state for EN = NH_3^+, EX = H). Moreover the hydridic character of H_m as assessed by the Mulliken charges becomes more pronounced in the same direction: for EN = H, the charge is essentially 0, but for EN = NH_3^+, it is negative, −0.12. The barrier for the reaction also decreases by 3.3 kcal/mol from the reference system, EN = EX = H, to the EN = NH_3^+ (EX = H) system, pointing in the direction of a stabilizing interaction that takes place at the transition state, namely, HHH bonding. If that is the case, then when the proton donors are oriented exo to H_m, no effect should be observed. Indeed, for the EX = NH_3^+ case, the activation barrier, H_m charge, and contact distance to C7−H at the transition state are almost identical to those in the parent system. This system's comparisons are amplified by several further observations: (a) the atomic displacements along the reaction coordinate include a rotation of the NH_3^+ group to follow H_m, thereby maintaining the hydrogen bonding interaction; (b) rather than assisting in the reaction, placement of a CH_3 group (nearly isostructural to NH_3^+) in the endo position sterically impedes hydride migration by 0.7 kcal/mol; (c) no H_m-following CH_3 rotation is seen in the reaction coordinate's motions; (d) calculated H_m/D_m kinetic isotope effects are larger for EN = NH_3^+ compared to EX =

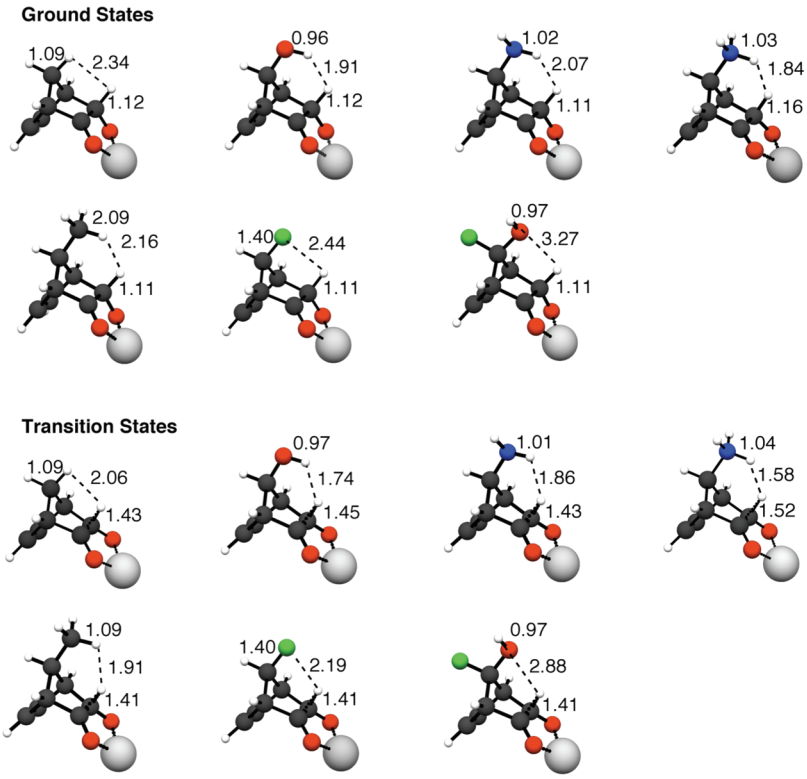
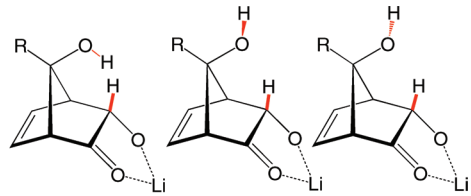


Figure 1. Ground and transition states of selected endo complexes.

SCHEME 3



anti conformer g^+ conformer g^- conformer

NH_3^+, 4.2 and 3.8, respectively, presumably due to a larger degree of dissociation and stabilization of the migrating hydride by HHH bonding; (e) calculated NH_2L^+ (L = H, D) kinetic isotope effects are secondary, as expected, 1.2, 1.0, and 1.0 for endo N−L contacting H_m, endo N−L away from H_m, and exo NH_2L (all conformations), respectively, confirming the involvement of the N−L···H_m contact; (f) the calculated endo-H/-D for EX = NH_3^+ is 1.0; (g) analogous calculated kinetic isotope effects for both EN = CH_3 and EX = CH_3 deviate negligibly from 1.0. The calculated kinetic isotope effects are summarized in Table 3.

The case where the proton donor is OH is slightly more ambiguous. Here, the barrier for hydride transfer is essentially the same regardless of the endo vs exo position of the OH. This result is presumably due to the electronegativity of oxygen, so that, for the exo case, there is positive charge buildup on C7−H (endo), which is in close proximity to H_m. This interpretation is reinforced by observations with the strongly electron withdrawing, but non-H-bonding, F group. Here, the endo complex should gain no stabilization at the transition state, as development of hydridic character in H_m near a partially negative group would be disfavored. As expected, for F the barrier in the endo case is greater by 1.5 kcal/mol, respectively, than for the reference system, EN = EX = H. Meanwhile, as suggested in the OH case above, for EX = F complex, the charge on the C7−H is more positive. However, the charge on H_m at the transition state is essentially similar to the unsubstituted case, suggesting that its interaction with C7−H is weak and purely electrostatic.

TABLE 1: Endo Complexes and Geometry and Energy Characteristics

complex		(EN)H···H_m, Å		charge[a] GS[b] H_m	GS[b] EN(H)	TS[c] H_m	TS[c] EN(H)	barrier,[d,e] kcal/mol
EN	EX	GS[b]	TS[c]					
H	H	2.34	2.06	0.14	0.14	0.03	0.14	17.2
OH, anti	H	1.91	1.74	0.07	0.23	−0.04	0.21	15.8 (0.0)[f]
OH, g^+	H	2.90	2.92	0.16	0.27	0.14	0.27	17.5 (1.7)
OH, g^-	H	3.31	2.92	0.19	0.26	0.14	0.27	17.1(1.4)
NH_2, anti[g]	H	NMF[h]						
NH_2, g^+	H	2.07	1.86	0.11	0.23	0.00	0.20	16.5 (0.0)
NH_2, g^-	H	2.02	1.86	0.08	0.22	0.00	0.20	16.9 (0.5)
NH_3^+	H	1.84	1.58	0.06	0.32	−0.12	0.28	13.9
CH_3	H	2.16	1.91	0.14	0.15	0.04	0.13	17.9
F	H	*2.44*[i]	*2.19*[i]	0.19	N/A	0.12	N/A	17.4
OH, anti	F	NMF[h]						
OH, g^+	F	2.79	2.88	0.16	0.30	0.15	0.13	18.9 (0.5)
OH, g^-	F	3.27	2.88	0.20	0.29	0.15	0.13	18.4 (0.0)

[a] Mulliken charges. [b] Ground state. [c] Transition state. [d] Barriers are corrected with the zero point and thermal vibrational energies. [e] Barriers for EN = H, OH, and NH_3^+ complexes at the MP2/6-311++G** level are 17.7, 16.5, and 15.4 kcal/mol, respectively. [f] Values in parentheses are barrier energies relative to the lowest energy conformer. [g] Anti and g amine complex conformers are defined with respect to the lone pair of nitrogen. [h] No minimum found. [i] F···H_m distance.

The comparison between OH and F complexes deserves special attention. For the endo complexes, OH lowers the activation barrier due to a weak HHH interaction at the transition state, while F raises the activation barrier since it cannot stabilize the hydride. In fact, *at the TS*, in contrast to the GS, the OH rotamer that participates in HHH bonding, Figure 2, is 1.3 kcal/mol more stable than the noninteracting rotamers; this highlights

TABLE 2: Exo Complexes and Geometry and Energy Characteristics

complex		(EN)H···H_m, Å		charge[a] GS[b] H_m	GS[b] EN(H)	TS[c] H_m	TS[c] EN(H)	barrier,[d] kcal/mol
EN	EX	GS[b]	TS[c]					
H	OH, anti	2.28	1.99	0.16	0.22	0.03	0.21	15.9 (0.0)[e]
H	OH, g^+	2.25	1.96	0.13	0.20	0.02	0.27	16.3 (0.4)
H	OH, g^-	2.26	1.96	0.13	0.19	0.02	0.27	16.0 (0.1)
H	NH_2, anti[f]	2.22	1.93	0.13	0.19	0.00	0.20	16.8 (0.4)
H	NH_2, g^+	2.25	1.96	0.13	0.21	0.02	0.22	16.4 (0.0)
H	NH_2, g^-	2.25	1.96	0.13	0.21	0.02	0.22	16.5 (0.1)
H	NH_3^+	2.34	2.02	0.15	0.30	0.02	0.31	16.9
H	CH_3	2.23	1.95	0.13	0.19	0.02	0.19	17.2
H	F	2.30	2.02	0.14	0.20	0.04	0.20	15.9
F	OH, anti	*2.40*[g]	*2.13*[g]	0.19	N/A	0.13	N/A	18.7 (0.0)
F	OH, g^+	*2.34*[g]	*2.12*[g]	0.18	N/A	0.13	N/A	19.1 (0.4)
F	OH, g^-	*2.37*[g]	*2.12*[g]	0.19	N/A	0.13	N/A	18.9 (0.2)

[a] Mulliken charges. [b] Ground state. [c] Transition state. [d] Barriers are corrected with the zero point and thermal vibrational energies. [e] Values in parentheses are barrier energies relative to the lowest energy conformer. [f] Anti and g amine complex conformers are defined with respect to the lone pair of nitrogen. [g] F···H_m distance.

TABLE 3: Calculated Kinetic Isotope Effects (KIE) for the NH_3^+ and CH_3 Complexes

complex		KIE[a]			
EN	EX	$H_m = D$	H = D (H···H_m distance)[b,c]		
NH_3^+	H	4.14	1.19 (1.9)	1.01 (3.0)	1.02 (3.4)
H	NH_3^+	3.79	1.00 (2.3)	1.00 (4.6)	1.01 (4.3)
CH_3	H	3.49	1.01 (2.2)	1.00 (3.0)	1.01 (3.7)
H	CH_3	3.59	0.98 (2.2)	1.00 (4.6)	1.00 (4.2)

[a] KIE were calculated for isolated isotopomeric conformations. [b] Distances in angstroms. [c] Distances shorter than 2.4 Å indicate close H···H_m contacts.

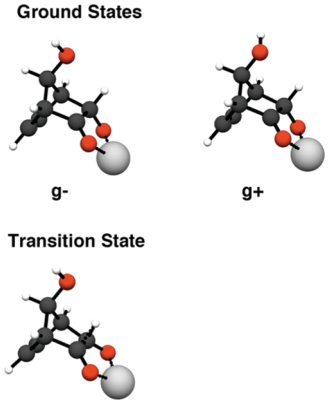


Figure 2. EN = OH, EX = H complexes, gauche conformers.

the relative favorability of the HHH bonding interaction, despite its being in this sterically compressed setting. Thus it appears that the OH group's steric crowding alone actually would impede migration of H_m and that the H-bonding offsets the cost of crowding. The NH_2 case supports this view in that in the endo case there is no minimum for the anti conformer (i.e., with the lone pair anti to C7−H), the NH_2 preferring one of the gauche conformations. By contrast for the EX = NH_2 case the most stable conformer is the anti one, as expected on the basis of gauche interactions.

To summarize, when strongly electronegative substituents are exo, the major role is played by the gas-phase electronegativity of O and F atoms, leading to an increase in the positive charge of the endo H. In other words the hydride interacts with a H that becomes more positive in the direction H < O < F as expected since F is more electronegative than O.

Conclusions

Our computational experiments have asked whether "in-flight" hydridic charge development might open the door to stabilization by HHH bonding in the TSs of hydride transfers. It is perhaps of interest to note that free hydride ion in the gas phase is known to form an 18 kcal/mol hydrogen bond with water.[23] Thus, the modest effects discussed above represent only a small fraction of the limiting potential stabilization associated with full charge development on the hydridic hydrogen. Although the energetic effects uncovered here are small, they represent a novel type of stabilization that biological systems with their many more degrees of freedom might exploit during their reactions.

The α-hydroxy carbonyl isomerization reactions we have examined provide a test bed for the notion of catalysis via HHH bonding. The parent system's intramolecular hydride transfer takes place with a calculated barrier of 17.2 kcal/mol. The cyclic metal cation-bridged transition state is stabilized by HHH bonding with traditional proton donors, such as OH and NH_3^+, by 1.4 and 3.3 kcal/mol, and destabilized by electronegative groups such as F, which do not favor the development of hydridic charge. Further studies will involve experimental investigation of this reaction.

Acknowledgment. Dedicated to Professor G. J. Karabatsos who fostered generations of scholars through his example and actions.

Supporting Information Available: Tables giving coordinates, Mulliken, NPA, and electrostatic (CHELPG) charges, absolute energies, zero point and thermal vibrational corrections of the studied complexes for ground and transition states and figures showing intrinsic reaction coordinate plots. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Custelcean, R.; Jackson, J. E. *Chem. Rev.* **2001**, *101*, 1963–1980.
(2) (a) Epstein, L. M.; Shubina, E. S. *Coord. Chem. Rev.* **2002**, *231*, 165–181. (b) Alkorta, M.; Elguero, J.; Grabowski, S. J. *J. Phys. Chem. A* **2008**, *112*, 2721–2727. (c) Wei, N. N.; Li, P.; Hao, C.; Wang, R.; Xiu, Z. L.; Chen, J. W.; Song, P. *J. Photochem. Photobiol., A* **2010**, *210*, 77–81. (d) Jacobsen, H. *Chem. Phys.* **2008**, *345*, 95–102. (e) Jacobsen, H. *Phys. Chem. Chem. Phys.* **2009**, *11*, 7231–7240.
(3) (a) Marincean, S.; Jackson, J. E. *J. Phys. Chem. A* **2004**, *108*, 5521–5526. (b) Filippov, O. A.; Tsupreva, V. N.; Golubinskaya, L. M.; Krylova, A. I.; Bregadze, V. I.; Lledos, A.; Epstein, L. M.; Shubina, E. S. *Inorg. Chem.* **2009**, *48*, 3667–3678. (c) Filippov, O. A.; Tsupreva, V. N.; Epstein, L. M.; Lledos, A.; Shubina, E. S. *J. Phys. Chem. A* **2008**, *112*, 8198–8204. (d) Lau, C. P.; Ng, S. M.; Jia, G. C.; Lin, Z. Y. *Coord. Chem. Rev.* **2007**, *251*, 2223–2237. (e) Fung, W. K.; Huang, X.; Man, M. L.; Ng, S. M.; Hung, M. Y.; Lin, Z. Y.; Lau, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11539–11544. (f) Gatling, S. C.; Jackson, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 8655–8656.
(4) (a) Zhadin, N.; Gulotta, M.; Callender, R. *Biophys. J.* **2008**, *95*, 1974–1984. (b) Buck, H. *Int. J. Quantum Chem.* **2005**, *101*, 389–395.
(5) Berrisford, J. M.; Hounslow, A. M.; Akerboom, J.; Hagen, W. R.; Brouns, S. J. J.; van der Oost, J.; Murray, I. A.; Blackburn, G. M.; Waltho, J. P.; Rice, D. W.; Baker, P. J. *J. Mol. Biol.* **2006**, *358*, 1353–1366.
(6) Fenn, T. D.; Ringe, D.; Petsko, G. A. *Biochemistry* **2004**, *43*, 6464–6474.
(7) Wu, R.; Xie, H.; Cao, Z.; Mo, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7022–7031.
(8) Wu, R.; Xie, H.; Mo, Y.; Cao, Z. *J. Phys. Chem. A* **2009**, *113*, 11595–11603.
(9) Nagorski, R. W.; Richard, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 794–802.
(10) Watt, T.; Whittleton, S. N.; Whitworth, S. M. *Tetrahedron* **1986**, *42*, 1047–1062.
(11) Evans, D. A.; Mitch, C. H.; Thomas, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 5956–5957.
(12) Frisch, M. J.; Trucks, G. J.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels,

A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.11.1; Gaussian: Pittsburgh, PA, 1998.

(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Rob, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision D.01; Gaussian: Wallingford, CT, 2003.

(14) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654–3665.

(15) (a) McLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980**, *72*, 5639–5648. (b) Raghavachari, K.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654. (c) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265–3269. (d) Clark, T.; Chandrasekhar, G. W.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294–301.

(16) (a) Zhou, Z.; Shi, Y.; Zhou, X. *J. Phys. Chem. A* **2004**, *108*, 813–822. (b) Ireta, J.; Neugebauer, J.; Scheffer, M. *J. Phys. Chem. A* **2004**, *108*, 5692–5698.

(17) Belkova, N. V.; Besora, M.; Baya, M.; Dub, P. A.; Epstein, L. M.; Lledos, A.; Poli, R.; Revin, P. O.; Shubina, E. S. *Chem.—Eur. J.* **2008**, *14*, 9921–9934.

(18) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1988**, *83*, 735–746.

(19) We acknowledge the challenge associated with assigning charges to hydrogen sites in systems such as those considered here, where the exposed surface area of the migrating hydride is minimal and there are multiple contact points between the hydride and other heavy atoms involved. However, relative changes in the migrating hydride's charge for a particular system should provide useful comparative information on charge development during the course of the reaction. We have examined the Mulliken charges because they are used typically when dihydrogen bonded complexes are investigated[6] as evidence for interaction. At a reviewer's suggestion we have included in Supporting Information Mulliken, electrostatic, and NPA charges for the migrating hydride as well as for endo H sites.

(20) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361–373.

(21) Bode, B. M.; Gordon, M. S. *J. Mol. Graphics Modell.* **1998**, *16*, 133–138.

(22) Itou, Y.; Mori, S.; Udagawa, T.; Tachikawa, M.; Ishimoto, T.; Nagashima, U. *J. Phys. Chem. A* **2007**, *111*, 261–267.

(23) De Beer, E.; Kim, E. H.; Neumark, D. M.; Gunion, R. F.; Lineberger, W. C. *J. Phys. Chem.* **1995**, *99*, 13627–13636.

JP1050854