Interplay of Hydrogenation and Dehydrogenation in Isoindoline and Indoline Isomers: A Density Functional Theory Study

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Received: December 28, 2007; Revised Manuscript Received: March 16, 2008

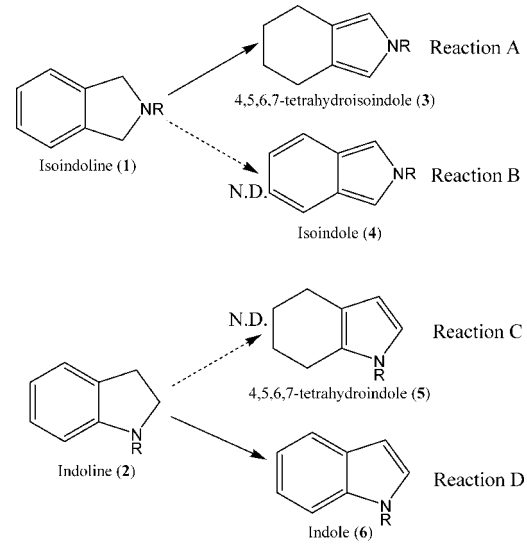
Under the conditions of palladium-catalyzed formate reduction, the isomers isoindoline and indoline undergo distinct hydrogenation and dehydrogenation processes to form 4,5,6,7-tetrahydroisoindole and indole, respectively. In terms of resonance energy, the reduction of isoindoline is accompanied by a loss of aromaticity, whereas the dehydrogenation of indoline occurs with a gain in aromaticity. To rationalize why isoindoline and indoline, under the same conditions of palladium catalysis, form different products, we used density functional theory calculations to investigate the mechanisms of the two reaction pathways. Both processes are initiated through direct oxidative insertion (OxIn) of Pd(0) into the aliphatic C−H bond at the methylene group, followed by β-hydride elimination to form the isoindole and indole. Because isoindole is much less stable relative to indole, it undergoes further hydrogenation on its benzene moiety to form the final product, 4,5,6,7-tetrahydroisoindole. Our theoretical findings rationalize the experimental observations.

Introduction

The study of nitrogen-atom-containing heteroaromatic rings is a significant component of the field of heterocyclic chemistry.[1–5] One such species, indole, is present in the tryptophan side chain, and its derivatives play significant biological roles.[6,7] Although they are less studied, isoindole (an isomer of indole) and its derivatives are popular building blocks for the preparation of phthalocyanines,[8] and they have also been evaluated as inhibitors of the cyclooxygenase COX-2 isoenzyme,[9] human leukocyte elastase,[10] and ribonucleotide reductase.[11] In particular, the degree of aromaticity of indole and isoindole—and that of their corresponding reduced forms, indoline and isoindoline—has been the subject of many studies because of its influence on chemical reactivity.[1,12–14]

Recently, we reported a new synthetic route for the preparation of 4,5,6,7-tetrahydroisoindoles (**3**) from isoindolines (**1**) under the conditions of palladium-catalyzed formate reduction (Reaction A, Scheme 1).[15,16] In this reaction, the site of aromaticity is transferred from the benzene ring to the pyrrole ring, with a net addition of one molecule of H_2. In contrast, under the same reaction conditions, indolines (**2**) undergo dehydrogenation (Reaction D) to form indoles (**6**), that is, the net loss of a molecule of H_2. More interestingly, the corresponding products expected for the dehydrogenation of isoindoline (Reaction B) and the hydrogenation of indoline (Reaction C) are not detected. In reaction A, the product (an *N*-substituted isoindole) possesses pyrrole-like aromaticity, whereas the aromaticity of the reactant (an *N*-substituted isoindoline) is benzene-like, implying that the reaction occurs with a loss of resonance energy. In contrast, when the reactant is changed to an *N*-substituted indoline (reaction D), the aromatic system is extended from 6 π-electrons in the reactant to 10 π-electrons in the product, that is, the degree of aromaticity is enhanced, suggesting a reaction that occurs with a gain in resonance energy. Taken together, under identical conditions of Pd catalysis, a simple shift in the position of the nitrogen atom in isoindoline and indoline isomers leads to opposing modes of reaction, hydrogenation and dehydrogenation, respectively, occurring with a loss and a gain, respectively, in resonance energy.

SCHEME 1: Hydrogenation of Isoindoline (Reaction A) and Dehydrogenation of Indoline (Reaction D) under Conditions of Pd Catalysis[a]



[a] Reactions B (dehydrogenation of isoindoline) and C (hydrogenation of indoline), counterparts to Reactions A and D, respectively, are not detected (N.D.) under these conditions.

We were intrigued to determine the factors that influence the reaction pathways of isoindoline and indoline, and their mechanisms, under the same conditions. Thus, we employed density functional theory calculations to study the mechanistic reaction pathways and their associated energy profiles. Herein, we propose mechanisms to rationalize the experimental observations

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10.1021/jp7121246 CCC: $40.75
Published on Web 05/17/2008

and discuss the factors that lead to isoindoline and indoline forming different products.

Computational Methods

All calculations of the energy profiles of Reactions A−D were performed using gradient-corrected hybrid density functional theory (DFT) within the Gaussian 03 suite of programs[17] on a PC cluster at the National Center for High-Performance Computing, Taiwan. The B3LYP density functional, Becke's three-parameter exchange functional,[18] and Lee−Yang−Parr gradient-corrected correlation functional[19] were employed. On the basis of the extensive benchmarks established by Bickelhaupt and co-workers, the B3LYP level of theory is generally accepted as being suitable for studies of Pd-catalyzed reactions.[20,21] The moderate-sized 6-31G(d,p) basis set[22] for C, N, and H atoms and the LANL2DZ basis set,[23] including the effective core potential for Pd atom (suggested by Langhoff et al.),[24] were used for all calculations in this study. The substituent on the nitrogen atom was modeled as a methyl group; a closed-shell Pd(0) atom was the model catalyst. The calculated stable structures were examined in terms of vibrational frequency calculations with all positive values. Transition states (TSs) were first searched using synchronous transit-guided quasi-Newton (STQN) methods[25] and then examined through vibrational frequency calculations with a single imaginary mode. Furthermore, these TSs were validated using the algorithm of the intrinsic reaction coordinate (IRC),[26,27] in which the reaction coordinates were followed forward and backward starting from the TSs obtained from the STQN calculations to provide their corresponding products and reactants, respectively. Thermal energy at 25 °C and 1 atm was corrected for the energy calculations.

In this study, the aromaticities of the reactants and products were calculated. The aromatic stability of a given molecule is evaluated by considering the enthalpy required to destroy the aromaticity or the enthalpy gained after the formation of aromaticity.[12,28,29] For example, the addition of one molecule of H_2 to *N*-methyl-4,5,6,7-tetrahydroisoindole converts one C═C double bond and one H−H single bond to two C−H single bonds while destroying the aromaticity of the starting material. Further additions of H_2 occur with similar chemical bond exchange, but no additional aromaticity is lost. Therefore, the aromaticity of *N*-methyl-4,5,6,7-tetrahydroisoindole was evaluated by calculating the enthalpy difference between the first and second hydrogenations; in this case, the value obtained was 15.83 kcal/mol at 25 °C and 1 atm.[30] For some cases, in which there were multiple sites for hydrogenation, the aromaticities were calculated on average. Similar, but modified, calculations were employed to evaluate the aromaticity of *N*-methylisoindole (**4**), that is, in terms of the extra energy gained after the formation of aromaticity for the entire molecule with the loss of one H_2 molecule (Figure S1 in the Supporting Information). In Figure S1(a), one C═C double bond and one H_2 molecule were formed, and two C−H single bonds were broken. The reaction in Figure S1(b) exhibits similar chemical bond "trading" and a gain in aromaticity. The enthalpy difference between the reactions in Figures S1(a) and (b) suggests that the aromatic stabilization of *N*-methylisoindole is 30.75 kcal/mol.

Results

The calculated aromaticities of Reactions A−D have been published previously,[16] and they are outlined in Scheme 2 to assist in our present discussion. For Reaction A, the location of aromaticity is transformed from the benzene moiety in the reactant to the pyrrole moiety in the product, with an aromatic energy loss of 18.92 kcal/mol. On the other hand, Reaction D occurs with the aromatic moiety extended from 6 π-electrons to 10, with a net aromatic energy gain of 10.17 kcal/mol. More interestingly, Reaction B also occurs with its aromatic system extending from 6 to 10 π-electrons, but the aromaticity is slightly lost (3.99 kcal/mol). As expected, Reaction C, with its site of aromaticity transferred from the benzene ring to the pyrrole ring, has an aromatic energy loss of 13.30 kcal/mol.

Schemes 3 and 4 display the proposed reaction mechanisms and energy profiles for Reactions A and D, respectively. In these mechanisms, both reactions are initiated through direct oxidative insertion (OxIn) of Pd(0) into the aliphatic C−H bond at the methylene group. These steps follow the mechanisms proposed by Diefenbach and Bickelhaupt[31−33] from their study of C−H bond activation by Pd(0). The Pd/C−H OxIn mechanistic pathways proceed through several significant states: (1) the isoindoline−Pd (**a2**) and indoline−Pd (**d2**) complexes; (2) the transition states (**a3** and **d3**); and (3) the products of the OxIn reactions, σ-alkyl Pd−isoindoline (**a4**) and σ-alkyl Pd−indoline (**d4**) species. Subsequently, the σ-alkyl Pd−indoline species **d4** undergoes β-hydride elimination[34,35] through transition state **d5** to form the indole **d6** and PdH_2, the final products of Reaction D.

For Reaction A, the σ-alkyl Pd−isoindoline species also undergoes β-hydride elimination[34,35] to provide the isoindole **a8** after the PdH group has migrated to the bridged carbon atom on the opposite side (**a6**). The TS of this 1,3 PdH group migration is structure **a5**. The isoindole is further hydrogenated to form 4,5,6,7-tetrahydroisoindole (**a10**), the final product of Reaction A.

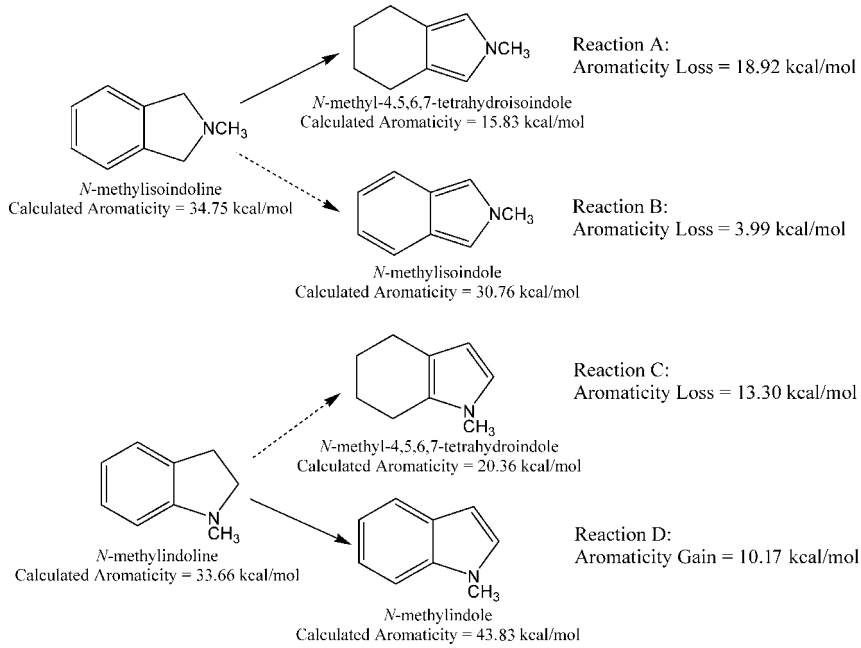
The proposed mechanism for Reaction A includes the TSs **a3**, **a5**, and **a7** for the Pd OxIn insertion, 1,3 PdH migration, and β-hydride elimination steps, respectively. These TSs were further examined using IRC calculations.[26,27] Figures S2−S4 in the Supporting Information display the energy profiles (from IRC calculations) for these TSs in terms of various reaction coordinates. Starting from the TSs, IRC calculations proceeding forward and backward provided corresponding reactant- and product-like structures, the optimization of which resulted in the corresponding reactants and products (or the corresponding local minima of reactants and products), thereby validating the TS calculations. Similar results were obtained (Figures S5 and S6 in the Supporting Information) for the IRC calculations of the TSs **d3** and **d5** for the reaction of indoline (Reaction D).

Discussion

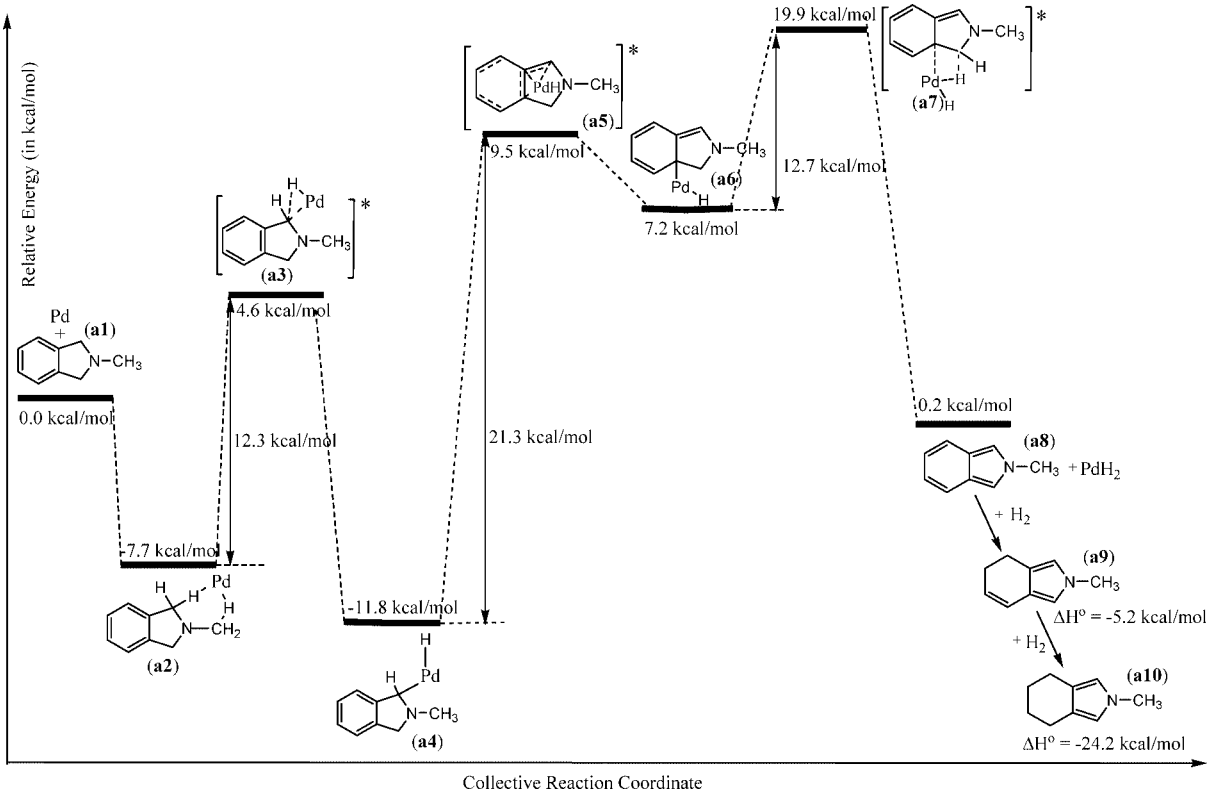
Isoindoline Reaction Profiles and Geometries. The species **a1**−**a10**in Scheme 3 represent the mechanistic pathway for the reaction of isoindoline (Reaction A). The mechanism includes four sequential processes: (a) Pd/C−H OxIn (**a1**−**a4**), (b) 1,3 PdH group migration (**a4**−**a6**), (c) β-hydride elimination (**a6**−**a8**), and (d) hydrogenation (**a8**−**a10**). Figure 1 displays the geometries of species **a1**−**a8**.

Oxidative insertion of transition metals into substrates is a key step in many catalysis reactions; it has been studied widely.[31,36−45] In the InOx reaction, the Pd atom is inserted into the benzylic C−H bond; this process is initiated by the formation of the isoindoline−Pd complex **a2**, which is −7.7 kcal/mol lower in energy than the reactants. In this complex, the Pd atom binds to two H atoms at the methylene and methyl groups; these C−H bond distances are stretched by 0.047 and 0.036 Å, respectively (Figure 1**a2**). The calculated activation energy for

SCHEME 2: Calculated Aromaticities of Reactants and Products in Reactions A−D[16]



SCHEME 3: Proposed Mechanism for Reaction A



the Pd/C−H OxIn reaction is 12.3 kcal/mol; the C−H bond distance of the transition state (Figure 1**a3**) is elongated from 1.157 Å in the complex to 1.649 Å. Along the reaction coordinate in Scheme 3, the C−H bond is broken, and new Pd−H and Pd−C bonds are formed (Figure 1**a4**). The entire Pd/C−H OxIn reaction is exothermic (−11.8 kcal/mol), similar to the calculated C−H activation by Pd in C_2H_6 (−11.6 kcal/mol).[31] We note that the **a2** species is not the only possible isoindoline−Pd complex; that is, the Pd atom might bind to the H atom of the methylene group and to other neighboring atoms. Those complexes are all possible precursors to the event of Pd insertion into the methylene C−H bond.

Subsequently, the PdH group migrates to the opposite side of the ring, forming a Pd−C bond at the bridging carbon atom (**a6**). The newly formed Pd−C bond has a bond length of 2.149 Å, relatively longer than the Pd−C bond in **a4** (2.083 Å). The 1,3 PdH group migration is the rate-determining step; its activation energy is 21.3 kcal/mol. This step is highly endothermic mainly because of the partial loss of aromaticity. The transition state structure **a5** of 1,3 PdH group migration is shown

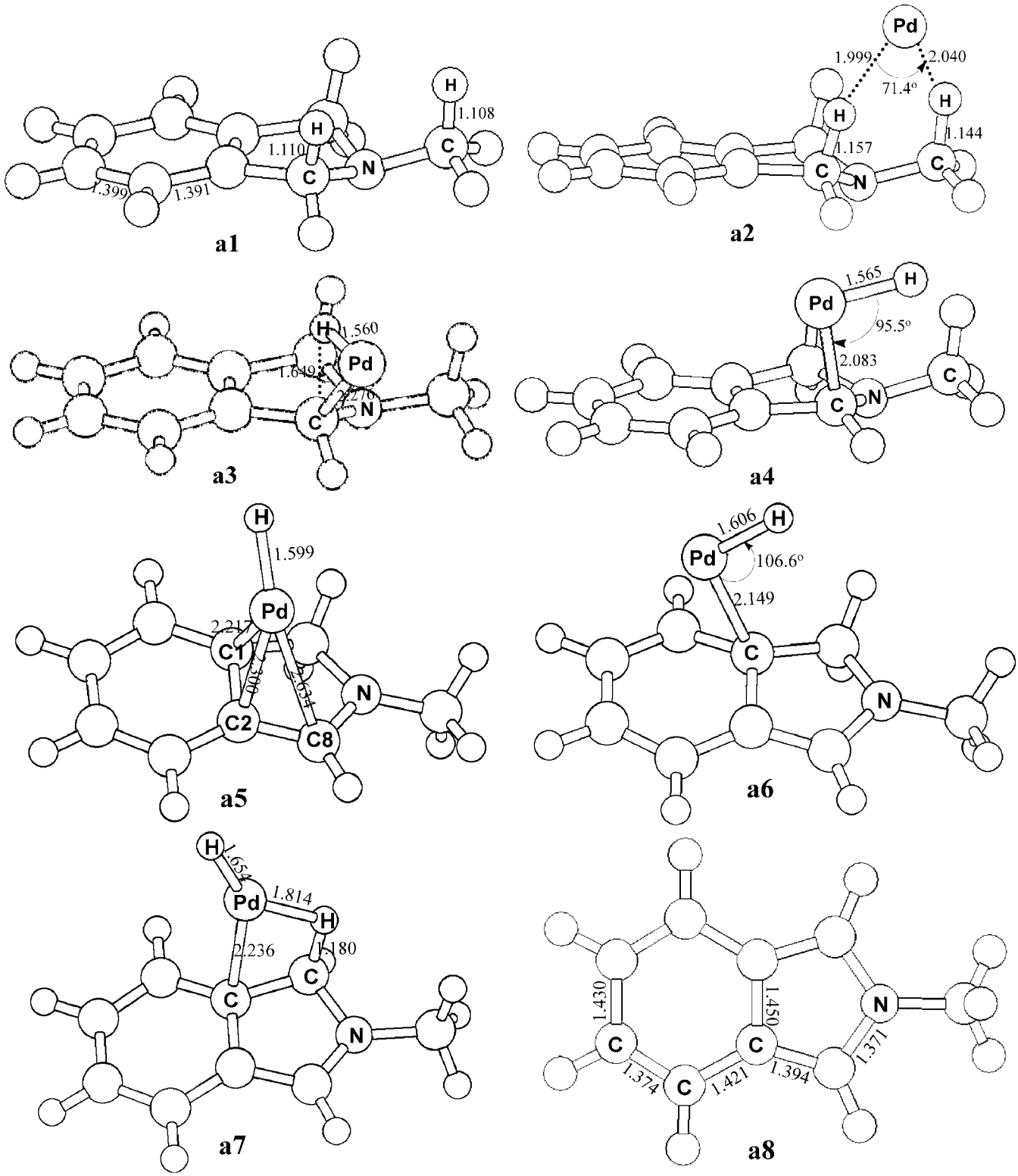
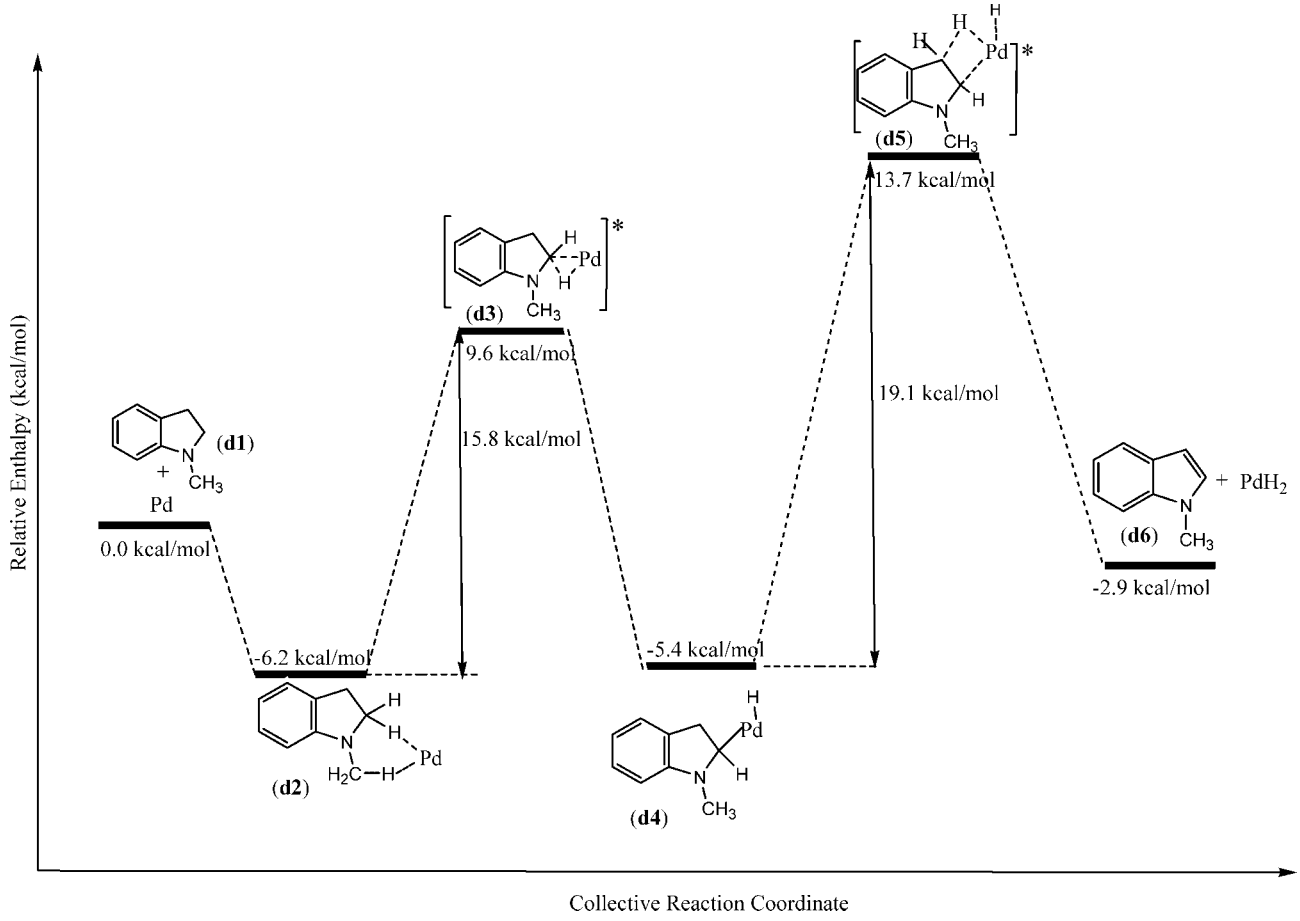


Figure 1. Calculated structures of the species **a1**−**a8** in Scheme 3. Significant bond lengths (in Å) and angles (in degree) are labeled.

in Figure 1**a5**. In this transition state, the Pd atom mainly bonds to the two bridging carbons and weakly bonds to the carbon atom on the pyrrole ring (labeled as C8 in Figure 1**a5**).

Next, the Pd atom of the σ-alkyl Pd−isoindoline species **a6** forms a covalent bond with the H atom at the methylene group, undergoing β-hydride elimination through TS **a7** to form the *N*-methylisoindole **a8** and PdH_2. The activation energy for β-hydride elimination is 12.7 kcal/mol. The TS **a7** comprises a four-membered ring of two C atoms, the Pd, and H atoms. In contrast to species **a6**, whose Pd−H hydrogen atom points toward to the H atom of the methylene group, the transition state **a7** has its Pd−H hydrogen atom pointing away from the H atom of the methylene group. These features indicate that the formation of TS **a7** might either enlarge the C−Pd−H bond angle or occur through rotation of the Pd−C bond. Interestingly, the sum of the energies of the *N*-methylisoindole **a8** and PdH_2 is similar to that of the reactants (*N*-methylisoindoline and Pd).

SCHEME 4: Proposed Mechanism for Reaction D



The mechanism in **a1**−**a8** is a net dehydrogenation, but the *N*-methylisoindole **a8** is subsequently reduced to *N*-methyl-4,5-dihydroisoindole (**a9**), which is further reduced to form the final product of Reaction A, *N*-methyl-4,5,6,7-tetrahydroisoindole (**a10**). More interestingly, both of these hydrogenation reactions are exothermic (−5.2 and −24.2 kcal/mol, respectively), that is, thermally favorable.

Indoline Reaction Profiles and Geometries. Scheme 4 summarizes the mechanistic reaction pathways of indoline. Although indoline and isoindoline form distinct products under otherwise identical conditions of Pd catalysis, they follow similar reaction mechanisms. The major difference is that the hydrogenation step does not occur for indole.

Both transformations are initiated by Pd/C−H OxIn reactions that form substrate−Pd complexes in which the Pd atom binds to two H atoms from the methylene and methyl groups.[46] The energy of the indoline−Pd complex is lower by −6.2 kcal/mol relative to that of the reactants, similar to that of the isoindoline−Pd complex (−7.7 kcal/mol). In the indoline−Pd complex (Figure 2**d2**), the C−H bond distances are elongated by 0.036 Å. The activation energy for the indoline−Pd complex to form the σ-alkyl Pd−indoline species **d3** is 15.8 kcal/mol, which is 3.5 kcal/mol higher than the analogous transition state for isoindoline (**a3**). In this transition state, the C−H bond distance (Figure 2**d3**) is elongated from 1.141 Å in the complex to 1.604 Å. Subsequently, the C−H bond is broken, and the Pd atom inserts into the C−H bond, forming new Pd−H and Pd−C bonds (Figure 2**d4**). Unlike the highly exothermic Pd/C−H OxIn reaction for isoindoline (−11.8 kcal/mol), the entire Pd/C−H OxIn reaction for indoline is only slightly exothermic (−5.4 kcal/mol).

Unlike the situation for the isoindoline reaction, where the PdH group undergoes sequential 1,3 migration and β-hydride elimination, the Pd atom of the σ-alkyl Pd−indoline species **d4** and its neighboring acidic H atom undergo β-hydride elimination to give corresponding products indole and PdH_2. In TS **d5**, where the two C atoms and the Pd and H atoms form a four-membered ring, the acidic H atom at the methylene group is abstracted by the Pd atom, with the C−H bond lengthening to 1.262 from 1.104 Å in **d4**. In addition, the Pd−C bond is also elongated to 2.179 from 2.054 Å in **d4**, implying that the leaving group is PdH_2. The activation energy for the β-hydride elimination is 19.1 kcal/mol higher than that of the OxIn process, which is the rate-determining step for the reaction of indoline. As in the case for the isoindoline reaction, the products (the indole **d5** and PdH_2) and reactants (the indoline **d1** and Pd) are also nearly isoenergetic. Notably, the indole molecule does not undergo further hydrogenation.

Relative Stability of Isoindole and Indole. Although our calculations are consistent with the proposed mechanisms suggesting that, under the conditions of Pd catalysis, isoindoline and indoline are reduced to isoindole and indole, respectively, one question remains unclear: Why is the indole stable after the reaction, whereas the isoindole undergoes further hydrogenations to form 4,5,6,7-tetrahydroisoindole?

The key to answering this question is to consider the distinct stabilities of isoindole and indole. Because isoindole and indole are isoelectronic molecules, their relative stability can be compared directly from their calculated energies. At the B3LYP/6-31G(d,p) level of theory, *N*-methylisoindole is ∼9.1 kcal/mol higher in enthalpy (25 °C, 1 atm) than *N*-methylindole. In addition, the calculated energies in Scheme 2 indicate that the

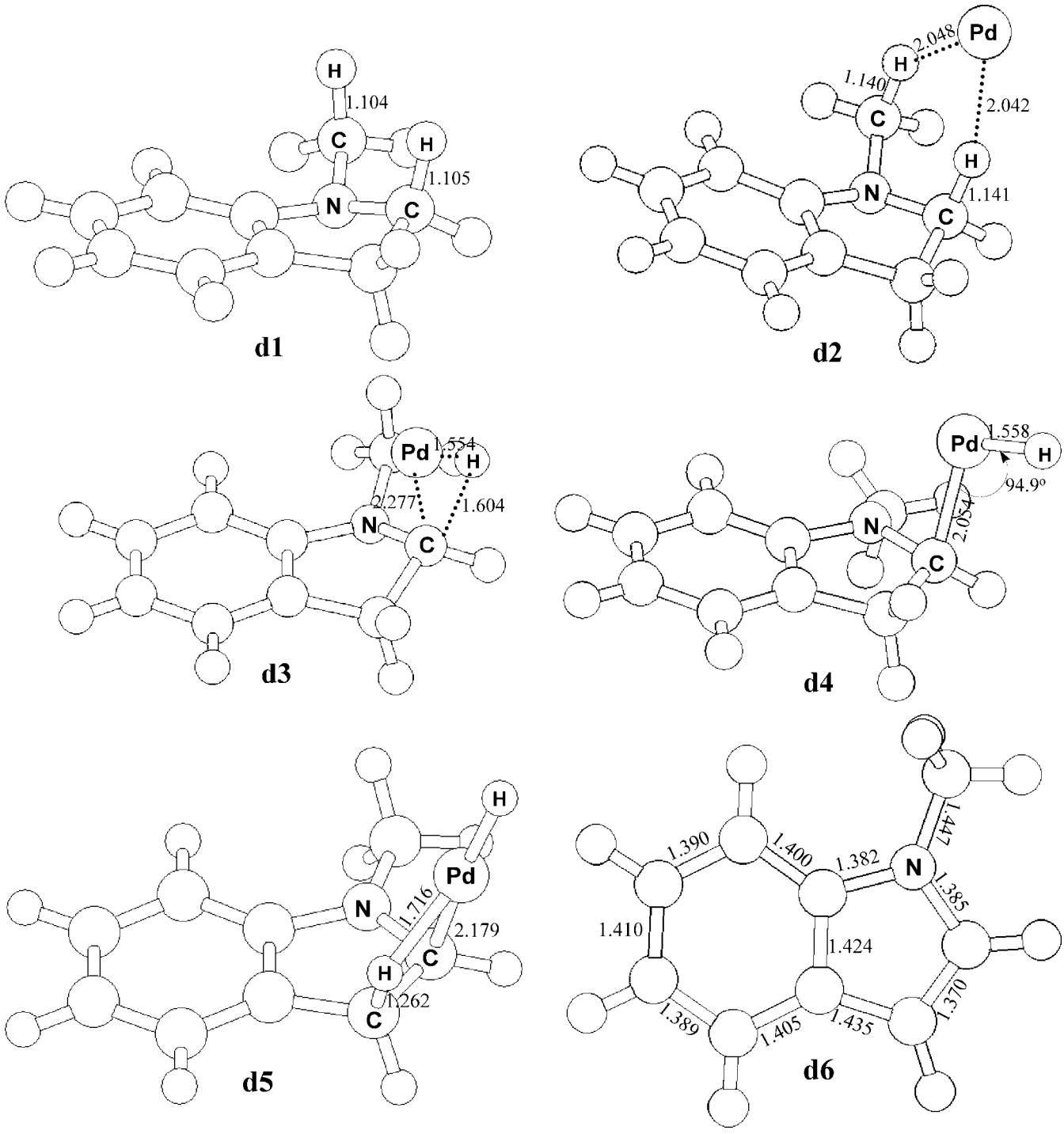


Figure 2. Calculated structures of the species **d1**−**d6** in Scheme 4. Significant bond lengths (in Å) and angles (in degree) are labeled.

aromatic stability of *N*-methylindole is ∼13 kcal/mol higher than that of *N*-methylisoindole, similar to the values reported in previous studies.[13,14,47]

Another criterion generally used to judge the degree of aromaticity of a molecule is bond equalization. The root-mean-square deviations (RMSDs) of the bond lengths on the benzene moiety of *N*-methylisoindole (Figure 1**a8**) and *N*-methylindole (Figure 2**d6**) are 0.031 and 0.014 Å, respectively; that is, the bond length rmsd of *N*-methylisoindole is twice as large as that of *N*-methylindole. The larger bond length rmsd for *N*-methylisoindole suggests that *N*-methylisoindole is less aromatic and has more pronounced diene character on its benzene moiety. X-ray crystal structures of isoindoles[48,49] and their reactivities in Diels−Alder reactions[50–52] support this hypothesis. Our calculations agree with the results of previous graphic theory studies using *n*-center delocalization indices, which suggested that isoindole has a large reduction in the aromaticity of its benzene ring.[13,14] Other investigations using NICS values and HOMO−LUMO gaps have also revealed that isoindole is less stable than indole.[53] Taken together, these studies imply that isoindole is relatively unstable and can, therefore, be further hydrogenated.

Another question remained unanswered: Why is the isoindole hydrogenated on the benzene ring and not on the pyrrole moiety? As indicated in Scheme 3 and Figure 3, the hydrogenation on the benzene moiety of isoindole is a thermally favorable

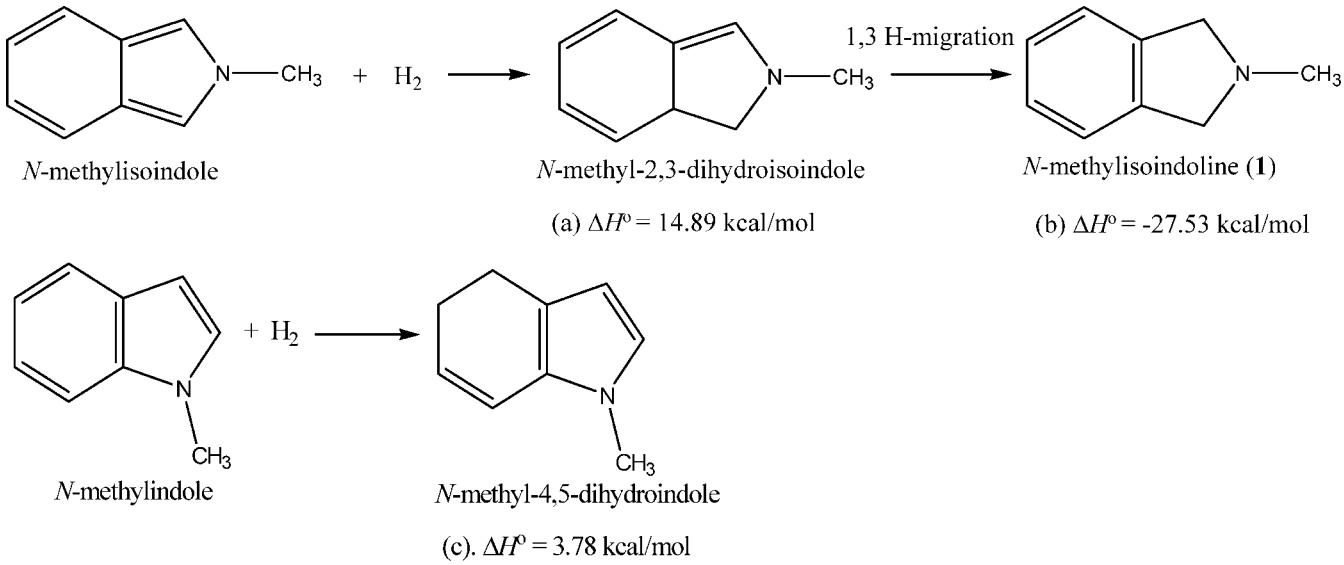


Figure 3. Enthalpy changes for (a) hydrogenation of the pyrrole moiety of isoindole to form *N*-methyl-2,3-dihydroisoindole, (b) 1,3 H atom migration of *N*-methyl-2,3-dihydroisoindole to form the reactant isoindoline, and (c) hydrogenation of the benzene moiety of indole to form *N*-methyl-4,5-dihydroindole.

exothermic reaction, whereas hydrogenation on its pyrrole moiety is a thermally unfavorable endothermic reaction. More importantly, the isoindole is hydrogenated to form *N*-methyl-2,3-dihydroisoindole, which can undergo an exothermic 1,3 H atom migration to form the original reactant, isoindoline ($\Delta H^\circ = -27.53$ kcal/mol, i.e., thermally favorable). In other words, even if hydrogenation occurs on the pyrrole moiety of isoindole, it will not alter the reaction pathway. Similar arguments are also applicable for indole; if hydrogenation occurs on the pyrrole moiety, the product is the original reactant, indoline; in contrast, hydrogenation on the benzene moiety of indole will destroy the aromaticity, which is thermally unfavorable (endothermic reaction, Figure 3c).

Summary

In the main, the Pd-catalyzed reactions of indoline and isoindoline share the same mechanism. Initially, the substrates undergo Pd/C−H InOx reactions, followed by dehydrogenation (β-hydride elimination) to form their corresponding reduced species (isoindole and indole, respectively). The indole molecule is stable and is the final product of the Pd-catalyzed reaction of indoline; in contrast, the isoindole is merely an intermediate in the reaction of the isoindoline and is further hydrogenated on its benzene moiety to form the 4,5,6,7-tetrahydroisoindole, which is the final product. This dichotomy arises primarily from the fact that isoindole is relatively unstable in comparison with indole. Our calculated reaction mechanisms rationalize the distinct reactions of isoindoline and indoline under otherwise identical conditions of Pd catalysis.

Acknowledgment. We thank the National Science Council of Taiwan (Grant No. 96-2113-M-008-006-MY2) for financial support and the National Center for High-Performance Computing of Taiwan for providing computer time and facilities.

Supporting Information Available: Energy profiles from the intrinsic reaction coordinate calculations; the calculated aromaticity of *N*-methylisoindole. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777.

(2) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; Wiley: New York, 1997.

(3) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

(4) Joule, J. A.; Nills, K. *Heterocyclic Chemistry*; Blackwell Publishing: Oxford, U. K., 2000.

(5) *Comprehensive Heterocyclic Chemistry*; Sundberg, R. J., Ed.; Pergamon: Oxford, U.K., 1984; Vol. 4.

(6) Mahindroo, N.; Huang, C. F.; Peng, Y. H.; Wang, C. C.; Liao, C. C.; Lien, T. W.; Chittimalla, S. K.; Huang, W. J.; Chai, C. H.; Prakash, E.; Chen, C. P.; Hsu, T. A.; Peng, C. H.; Lu, I. L.; Lee, L. H.; Chang, Y. W.; Chen, W. C.; Chou, Y. C.; Chen, C. T.; Goparaju, C. M. V.; Chen, Y. S.; Lan, S. J.; Yu, M. C.; Chen, X.; Chao, Y. S.; Wu, S. Y.; Hsieh, H. P. *J. Med. Chem.* **2005**, *48*, 8194.

(7) Venable, J. D.; Cai, H.; Chai, W.; Dvorak, C. A.; Grice, C. A.; Jablonowski, J. A.; Shah, C. R.; Kwok, A. K.; Ly, K. S.; Pio, B.; Wei, J.; Desai, P. J.; Jiang, W.; Nguyen, S.; Ling, P.; Wilson, S. J.; Dunford, P. J.; Thurmond, R. L.; Lovenberg, T. W.; Karlsson, L.; Carruthers, N. I.; Edwards, J. P. *J. Med. Chem.* **2005**, *48*, 8289.

(8) Gilchrist, T. L. *Heterocyclic Chemistry*; Addison Wesley: Essex, England, 1997; Vol. 3.

(9) Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; De Nanteuil, G. *J. Med. Chem.* **2000**, *43*, 4582.

(10) Kerrigan, J. E.; Walters, M. C.; Forrester, K. J.; Crowder, J. B.; Christopher, L. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 27.

(11) Nandy, P.; Lien, E. J.; Avramis, V. I. *Anticancer Res.* **1999**, *19*, 1625.

(12) Katritzky, A. R.; Jug, K.; Oniciu, D. C. *Chem. Rev.* **2001**, *101*, 1421.

(13) Mandado, M.; Otero, N.; Mosquera, R. A. *Tetrahedron* **2006**, *62*, 12204.

(14) Mandado, M.; Gonzalez-Moa, M. J.; Mosquera, R. A. *J. Comput. Chem.* **2007**, *28*, 127.

(15) Hou, D. R.; Hsieh, Y. D.; Hsieh, Y. W. *Tetrahedron Lett.* **2005**, *46*, 5927.

(16) Hou, D. R.; Wang, M. S.; Chung, M. W.; Hsieh, Y. D.; Tsai, H.-H. G. *J. Org. Chem.* **2007**, *72*, 9231.

(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; 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.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; 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.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(18) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(19) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(20) de Jong, G. T.; Sola, M.; Visscher, L.; Bickelhaupt, F. M. *J. Chem. Phys.* **2004**, *121*, 9982.

(21) de Jong, G. T.; Geerke, D. P.; Diefenbach, A.; Bickelhaupt, F. M. *Chem. Phys.* **2005**, *313*, 261.
(22) Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081.
(23) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270.
(24) Langhoff, S. R.; Pettersson, L. G. M.; Bauschlicher, C. W.; Partrodge, H. J. *J. Chem. Phys.* **1987**, *86*, 268.
(25) Peng, C.; Schlegel, H. B. *Isr. J. Chem.* **1993**, *33*, 449.
(26) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.
(27) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.
(28) Lewis, D.; Peters, D. *Facts and Theories of Aromaticity*; Macmillan Press: London, U.K., 1975.
(29) Hehre, W. J.; Burke, L. D.; Shusterman, A. J.; Pietro, W. J. *Experiments in Computational Organic Chemistry*; Wavefunction, Inc.: Irvine, CA, 1993.
(30) We confirmed the accuracy of using the B3LYP/6-31G(d,p) theoretical level by also calculating the aromaticities of benzene and pyrrole; the values we obtained, 35.9 and 21.7 kcal/mol, respectively, agree well with those obtained experimentally (36 and 21 kcal/mol, respectively). For the experimental aromaticities of benzene and pyrrole, see: March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992.
(31) For a thorough collection of literature citations relevant to these catalytic reactions, see: Diefenbach, A.; Bickelhaupt, F. M. *J. Phys. Chem. A* **2004**, *108*, 8460.
(32) Diefenbach, A.; Bickelhaupt, F. M. *J. Organomet. Chem.* **2005**, *690*, 2191.
(33) de Jong, G. T.; Bickelhaupt, F. M. *ChemPhysChem* **2007**, *8*, 1170.
(34) Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 9205.
(35) Murahashi, S.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.
(36) Cheong, M.; Ziegler, T. *Organometallics* **2005**, *24*, 3053.
(37) Privalov, T.; Linde, C.; Zetterberg, K.; Moberg, C. *Organometallics* **2005**, *24*, 885.
(38) de Almeida, K. J.; Cesar, A. *Organometallics* **2006**, *25*, 3407.
(39) Zenkina, O.; Altman, M.; Leitus, G.; Shimon, L. J. W.; Cohen, R.; van der Boom, M. E. *Organometallics* **2007**, *26*, 4528.
(40) Baker, R. J.; Jones, C.; Murphy, D. M. *Chem. Commun.* **2005**, 1339.
(41) Kremzow, D.; Seidel, G.; Lehmann, C. W.; Furstner, A. *Chem.—Eur. J.* **2005**, *11*, 1833.
(42) McGrath, T. D.; Franken, A.; Kautz, J. A.; Stone, F. G. A. *Inorg. Chem.* **2005**, *44*, 8135.
(43) Ziegler, T.; Li, J. *Organometallics* **1995**, *14*, 214.
(44) Deng, L.; Ziegler, T. *Organometallics* **1996**, *15*, 3011.
(45) Ziegler, T.; Folga, E.; Berces, A. *J. Am. Chem. Soc.* **1993**, *115*, 636.
(46) Similar to the isoindoline−Pd complex, the **d2** species is one of several possible indoline−Pd complexes, for example, the Pd atom might also bind to its neighboring carbon or nitrogen atom. Those complexes are all possible precursors to the event of Pd inserting into the methylene C−H bond.
(47) Jursic, B. S. *J. Mol. Struct.: THEOCHEM* **1999**, *468*, 171.
(48) Bonnett, R.; Hursthouse, M. B.; North, S. A.; Throtter, J. *J. Chem. Soc., Perkin Trans.* **1985**, *2*, 293.
(49) Simons, S. S.; Ammon, H. L.; Doherty, R.; Johnson, D. F. *J. Org. Chem.* **1981**, *46*, 4739.
(50) Malpass, J. R.; Sun, G. X.; Fawcett, J.; Warrener, R. N. *Tetrahedron Lett.* **1998**, *39*, 3083.
(51) Kreher, R. P.; Sewarteross, G.; Vogt, G. *Chem. Ber. Recl.* **1992**, *125*, 183.
(52) Kreher, R. P.; Seubert, J.; Schmitt, D.; Use, G.; Kohl, N.; Muleta, T. *Chem. Ber.* **1990**, *123*, 381.
(53) Martinez, A.; Vazquez, M. V.; Carreon-Macedo, J. L.; Sansores, L. E.; Salcedo, R. *Tetrahedron* **2003**, *59*, 6415.

JP7121246