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A New Interpretation of the Reaction Pathway of Deprotonative Metalation with TMP−Zn-ate/TMEDA Complex [TMEDA·Na(μ-^{t}Bu)(μ-TMP)Zn(^{t}Bu)]

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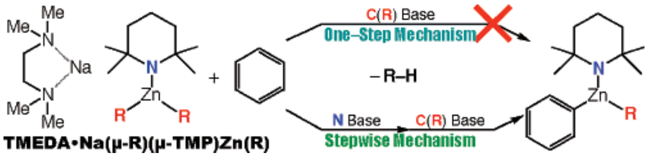
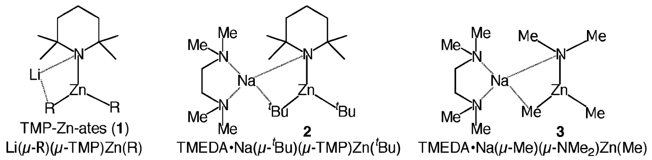
Received August 29, 2007



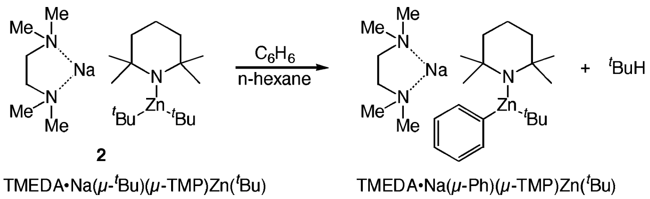
Density functional theory (DFT) calculations of possible reaction pathways and mechanisms for the deprotonation of benzene with Mulvey's reagent, TMEDA·Na(μ-R)(μ-TMP)-Zn(R) (TMEDA=*N*,*N*,*N*′,*N*′-tetramethylethylenediamine, R = alkyl, TMP = 2,2,6,6-tetramethylpiperidide) indicate that the deprotonation of benzene with Mulvey's reagent proceeds through a stepwise mechanism, not a one-step mechanism. In the first step, deprotonation involving the TMP ligand on the reagent is kinetically more favorable than that involving the alkyl ligand.

Multifunctionalized organometallic species are ubiquitous and versatile intermediates in modern synthetic organic chemistry.[1] Deprotonative metalation (also termed "directed *ortho* metalation (DoM)") has been one of the most effective tools for the regioselective construction of functionalized aromatic metal building blocks.[2] Conventional bases for this metalation include simple organometallic compounds of Group 1 metals, such as alkyllithiums and lithium dialkylamide, though recently a new chemistry for unique deprotonative metalation of functionalized aromatics with use of ate complexes has been introduced.[3] In 1999, we reported ate base reagents, TMP−Zn-ates (R_2Zn-(TMP)Li; R = Me or ^{t}Bu (**1**)),[4] that can promote highly chemoselective DoM reactions of functionalized aromatic compounds under mild reaction conditions (Scheme 1). Detailed spectroscopic and density functional theory (DFT) studies on the reaction pathway of TMP−Zn-ates revealed that the TMP ligand on **1** acts as a base.[4d]

SCHEME 1. Various TMP−Zn-ate Reagents



SCHEME 2. Deprotonation of Benzene Mediated by TMEDA·Na(μ-^{t}Bu)(μ-TMP)Zn(^{t}Bu) (2)



More recently, Mulvey and co-workers have reported a series of interesting deprotonative metalation reactions[5] of inert benzene C−H proton using TMEDA-coordinated TMP−Zn-ates exemplified by TMEDA·Na(μ-^{t}Bu)(μ-TMP)Zn(^{t}Bu) (**2**), and they suggested that, in contrast to the original TMP−Zn-ates, the alkyl group on **2** directly abstracts the proton on benzene in *n*-hexane (Scheme 2), based on X-ray crystallographic analysis.[5a] It is well-known that alkylpotassium reagents are powerful enough, but even alkyllithiums are unable to deprotonate benzene.[6] Therefore, their observations and suggestion were rather surprising, yet at the same time, of great

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10.1021/jo701895z CCC: $40.75

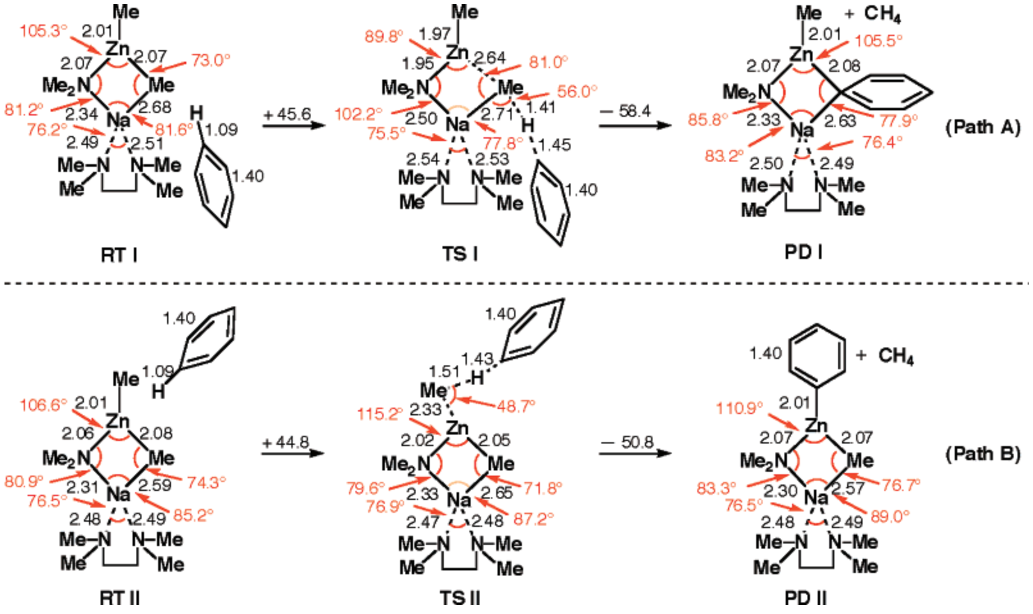
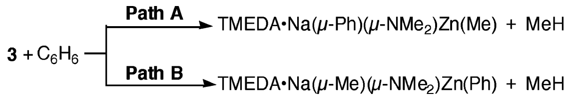


FIGURE 1. Deprotonation for Scheme 3 (one-step mechanism). Bond lengths, angles, and Gibbs free energy changes are shown in Å, deg, and kcal per mol, respectively.

SCHEME 3. Deprotonation of Benzene with the Alkyl Ligand of 3



interest. However, the real reaction pathway, the mechanism, and the role of TMEDA and the spectator TMP ligands in Mulvey's reagent (**2**) remain poorly understood, despite the fact that knowledge of the deprotonation mechanisms would be very helpful in improving the reactivity and selectivity of DoM reactions, as well as in designing more efficient bases. Herein, we report the comprehensive DFT studies on the possible reaction pathways and mechanisms for the deprotonation of benzene with Mulvey's reagent, employing ad rem **2** or TMEDA·Na(μ-Me)(μ-NMe$_2$)Zn(Me) (**3**) as a chemical model for **2**.[7]

The reaction pathways proposed by Mulvey for the deprotonation of benzene with two kinds of alkyl ligands on **3** were first evaluated by means of the B3LYP/631SVPs method[8] (Scheme 3). Figure 1 shows the energy changes for each path, and the geometries of the transition states, intermediates, and products. Although the products were thermodynamically stable, the values of Gibbs energy of activation were found to be very high ($\Delta G^\ddagger = 45.6$ kcal/mol for Path A, $\Delta G^\ddagger = 44.8$ kcal/mol for Path B), which strongly suggests that these pathways are unlikely to operate for kinetic reasons.[9]

Next, we wondered whether **3** might react with benzene in a stepwise manner, as shown in Scheme 4, in which the amido

SCHEME 4. Stepwise Mechanism for Mulvey's Reagent

$$\mathbf{3} + C_6H_6 \xrightarrow{\text{1st step}} \text{TMEDA}\cdot\text{Na}(\mu\text{-Me})(\mu\text{-Ph})\text{Zn(Me)}\ (\mathbf{4}) + \text{Me}_2\text{NH}$$

$$\xrightarrow{\text{2nd step}} \text{TMEDA}\cdot\text{Na}(\mu\text{-NMe}_2)(\mu\text{-Ph})\text{Zn(Me)} + \text{MeH}$$

ligand on **3** first abstracts the proton from benzene, and then the alkyl (Me) ligand of the intermediary phenyldimethylzincate **4** deprotonates the resultant amine (Me$_2$NH) to yield the final product, [TMEDA·Na(μ-Ph)(μ-NMe$_2$)Zn(Me)].

Figure 2 shows the energy changes of the whole process, and the geometries of the transition states, intermediates, and products. The activation barrier for the first step was fairly small ($\Delta G^\ddagger = 25.1$ kcal/mol),[10] and much lower than those for Paths A and B. These results clearly indicate that the amido ligand on **3** is the best candidate for direct abstraction of the proton from benzene. Since a similar kinetic preference of the amido ligand was also observed in computational analysis of the reaction between Li(μ-Me)(μ-NMe$_2$)Zn(Me) (**5**) and anisole,[4d] it can be said that the replacement of the lithium cation with the sodium cation and the addition of TMEDA to **5** do not change the relative reactivity (i.e., transference aptitude and selectivity) of the amido ligand to the alkyl ones, but merely increase the basicity of the amido moiety from the kinetic point of view.[11] The sum of the energies of the first-step products (**4** + Me$_2$NH) is −16.0 kcal/mol lower in energy than **TS1**. Thus, the first step in the deprotonation reaction is endothermic (~9.1 kcal/mol), though in fact Me$_2$NH should be further stabilized by aggregation.

Next, DFT studies were continued to evaluate the putative second step. Electrostatic coordination of the lone pair of Me$_2$NH to the sodium cation in **4** results in the formation of a complex (**CP**). To reach the TS of the deprotonation of the N−H

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[7] Although we must keep in mind the possibility that the simplification of the model may lead to underestimation of the steric interactions, the structure provides a valuable starting point for our consideration of the reactivity of **2**: see refs 4c, 4d, and 4e.

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[9] The MP2/631SVPs (single point) energies of activation for Paths A and B are 48.1 (Path A) and 40.4 kcal/mol (Path B).

[10] The MP2/631SVPs (single point) energy of activation for the 1st step deprotonation is 21.7 kcal/mol.

[11] The activation barriers ($\Delta G^\ddagger$) for the deprotonation reaction of benzene with **5** or Na(μ-Me)(μ-NMe$_2$)Zn(Me) (**6**) mediated by the amido or alkyl (μ-Me) ligand were calculated at the same level to be as follows: **5** (amido) 33.7 kcal/mol, **5** (alkyl) 44.2 kcal/mol; **6** (amido) 31.4 kcal/mol, **6** (alkyl) 46.6 kcal/mol.

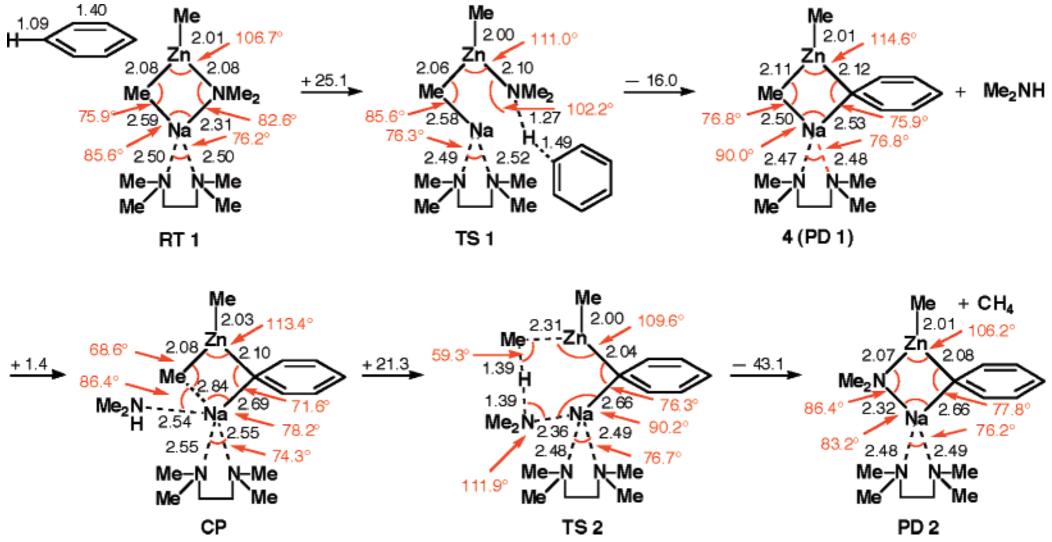

FIGURE 2. Deprotonation for Scheme 4 (stepwise mechanism). Bond lengths, angles, and Gibbs free energy changes are shown in Å, deg, and kcal per mol, respectively.

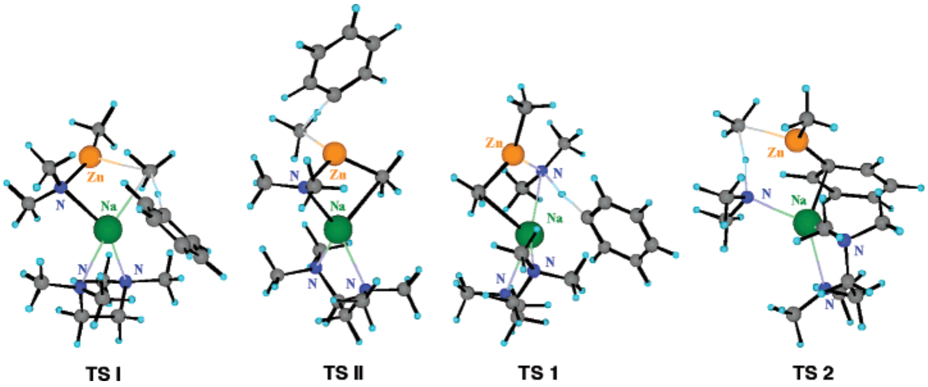

FIGURE 3. 3-D structures of all the calculated transition states in Figures 1 and 2.

proton, the methyl group bound to the sodium migrates so that the ill-directed sp^3-like orbital of the carbon atom can interact with the proton, and the Na−Me electrostatic bond cleaves with an overall energy loss of only 21.3 kcal/mol. The final product (**PD2**) is a mixed zincate, possessing methyl, phenyl, and dimethylamido ligands, which is −43.1 kcal/mol lower in energy than **TS2** (Figures 2 and 3). This huge stabilization energy adequately compensates for the energy loss of the first step. The activation barrier for the second-step deprotonation was lower than that for the first step, and the thermodynamically most stable product (**PD2**)[12] was obtained as the final product, in good agreement with the experimental observations that, overall, the alkyl ligand on **2** seems to deprotonate benzene directly to yield a mixed zincate possessing *tert*-butyl, phenyl, and TMP ligands.

In conclusion, we have computationally studied and compared the possible reaction pathways of the deprotonative metalation of benzene with Mulvey's reagent. The computational results for transition states with use of the model complex (**3**) strongly indicate that (1) the deprotonation of benzene with **3** proceeds via a stepwise mechanism and (2) the deprotonation involving the amido ligand on the Zn-ate is generally kinetically more favorable than that involving the alkyl ligand. These are completely different conclusions from those derived from Mulvey's thermodynamic analysis based on an X-ray crystallographic study. Further, (3) the coordination of TMEDA to the sodium cation is crucial for the activation of the deprotonation ability of the amido ligand in a TMP−Zn-ate.[13,14] Our findings strongly suggest that Mulvey's reagent is a well-programmed multifunctional base that deprotonates an inert benzene C−H bond through the cooperation and synergy of the amido (kinetic), methyl (thermodynamic), and TMEDA (mainly kinetic) ligands. The structural and mechanistic knowledge acquired in this research should allow improvement of the reaction system, as well as the logical design of new

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(12) The zinc atom adopts an in-plane disposition with respect to the benzene ring, while the positioning of the sodium atom is more perpendicular in each computational PD structure (**PD I**, **PD 1**, and **PD 2**), which is in good agreement with the real experimental structure in ref 5a. See the Supporting Information for each PD structure.

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(14) It is also important to point out that TMEDA is indispensable to obtain the homogeneous zinc-ate reagent **2**, because the mixture of ^{t}Bu$_2$Zn and NaTMP is insoluble in hydrocarbon media, and does not form a coordination complex in the absence of TMEDA. See ref 13. Although Mulvey and co-workers have reported TMEDA actually has a deactivating effect in the dizincation of benzene in ref 13, it is still possible that TMEDA can enhance the deprotonation ability of the amido ligand at the first monozincation step.

chemoselective base reagents. Further studies are in progress in our laboratory.

Computational Details

All calculations were carried out with the Gaussian 03 program package.[15] Geometries of the reactants, intermediates, transition states (TSs), and products were optimized without any symmetry restriction by using the B3LYP hybrid density functional method.[16] Unless otherwaise stated, Ahlrich's SVP all-electorn basis set[17,18] for Zn and the standard 6-31G* basis set[19,20] for C, N, Na, and H were used in these calculations (denoted as 631SVPs in the text). Normal coordinate analysis has been performed for all stationary points to characterize the TSs (one imaginary frequency) and equilibrium structures, (no imaginary frequency) and to calculate zero point energy correction (ZPC) and Gibbs free energies (at 298.15 K, 1 atm).

Acknowledgment. The reasearch was partly supported by grants from the Astellas Foundation and the Sumitomo Foundation, and a Grant-in-Aid for Young Scientists (A), HOUGA, Priority Area (No. 452 and 459), from the Ministry of Education, Culture, Sports, Science and Technology, Japan (to M.U.). This work was also supported by the Junior Research Associate Program in RIKEN (The Institute of Physical and Chemical Research), Japan (to D.N.). The calculations were performed by using the RIKEN Super Combined Cluster (RSCC) facility. We thank Prof. T. Ohwada (The University of Tokyo) for his assistance.

Supporting Information Available: Cartesian coordinates for all of the optimized structures and their calculated energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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