Molecular Tweezers for Hydrogen: Synthesis, Characterization, and Reactivity

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · NOVEMBER 2008

Impact Factor: 12.11 · DOI: 10.1021/ja806627s · Source: PubMed

J|A|C|S
COMMUNICATIONS

Published on Web 10/01/2008

Molecular Tweezers for Hydrogen: Synthesis, Characterization, and Reactivity

Victor Sumerin,[†] Felix Schulz,[‡] Michiko Atsumi,[†] Cong Wang,[†] Martin Nieger,[†] Markku Leskelä,[†] Timo Repo,*[,†] Pekka Pyykkö,[†] and Bernhard Rieger*[,‡]

Department of Chemistry, University of Helsinki, P.O. Box 55, FIN-00014 Helsinki, Finland, and WACKER-Lehrstuhl für Makromolekulare Chemie, Technische Universität München, Lichtenbergstrasse 4, D-85747 Garching bei München, Germany

Received August 26, 2008; E-mail: timo.repo@helsinki.fi; rieger@tum.de

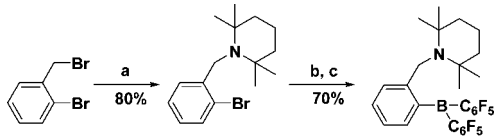
Amine formation is a fundamental reaction in chemical synthesis.[1] The importance of amines and their derivatives such as amides and sulfamides in food, agrochemical, and pharmaceutical industries is well recognized.[2,3] Although countless methods are known for the synthesis of amines, preparations under mild conditions, without generation of waste, and without the use of transition-metals is a challenging goal.[4] Among the various methods, the widely used transition-metal-catalyzed reductions of imines, enamines, and nitriles are probably the most important.[5] Unfortunately, transition-metal catalysts are not only expensive, but their complete removal from the reaction product is generally required in the production of pharmaceutical intermediates due to toxicity concerns.[6] Alternatively, main-group hydride reagents such as $NaBH_4$ and $LiAlH_4$ afford stoichiometric reductions, but involve tedious procedures and produce toxic chemical waste.[7] Metal-free reductions of imines by organocatalysts, in combination with Hantzsch ester as the hydrogen source, are known.[8] Recently, several atom-economical transition-metal-free methods such as Lewis acid-catalyzed amination,[9] hydrosilation,[10] and intermolecular hydroamination[11] were reported. More recently, the first nonmetal system which is able to reversibly activate H_2 was shown in pioneering studies by Stephan and co-workers to be an effective catalyst for the hydrogenation of bulky imines.[12−14] Herein we report the metal-free catalytic hydrogenation of nonsterically demanding imines and enamines.

Understanding the actual mechanism of splitting and liberating H_2 by nonmetals and the nature of dihydrogen bond interaction in these compounds is essential for learning how to design metal-free systems for H_2 storage and new hydrogenation catalysts.[15−17] Although the liberation of H_2 is expected to be thermodynamically uphill, it is envisioned that if the energetic cost is small enough, facile hydrogen liberation can take place.

We recently reported the hydrogen activation by 2,2,6,6-tetramethylpiperidine (TMPNH) in combination with $B(C_6F_5)_3$.[18] Whereas this reaction leads to the stable hydrogenated ionic product $[TMPNH_2]^+[BH(C_6F_5)_3]^-$, an extraordinary intermediate with a strong N−H···H−B dihydrogen bond between the cation and the anion was detected by nuclear magnetic resonance (NMR) spectroscopy. This observation prompted us to investigate a similar intramolecular system for H_2 activation where active B and N centers are located close to each other.[19] In this respect we designed the *ansa*-compound N-TMPN-$CH_2C_6H_4B(C_6F_5)_2$ **1** and developed an effective procedure for the synthesis of a dehydrogenated product **1** starting from 2-bromobenzylbromide, 2,2,6,6-tetramethylpiperidine and $(C_6F_5)_2BCl$.[20]

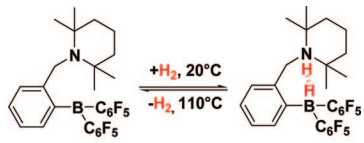
The bright yellow oil **1** was isolated in total yield of 55% and exhibited a single boron resonance in the ^{11}B NMR spectrum at 65.48 ppm indicative of three-coordinate boron (Scheme 1). Moreover, the difference in the chemical shifts $\Delta\delta_{p,m} = 13.61$ ppm of the F atoms in the para and meta positions of the C_6F_5 fragments refers to a neutral boron center.[10]

Scheme 1. Synthesis of Compound **1**[a]



[a] Reagents and conditions: (a) acetone, 95 °C, 48 h, 1.1 equiv K_2CO_3, 0.1 equiv KI, 1 equiv TMPNH; (b) −70 °C, Et_2O, 2 equiv *t*-BuLi; (c) −20 to 20 °C, 12 h, $(C_6F_5)_2BCl$.

Scheme 2. Reversible H_2 Activation by System **1**,**2**



1 **2**

Compound **1** reacted rapidly with H_2 in toluene solution at 20 °C to give a white suspension of **2** in quantitative yield (Scheme 2). The NMR spectroscopic data exhibited a ^{11}B NMR signal at −20.39 ppm (doublet, $^1J_{BH} = 77$ Hz) and the difference in the chemical shifts of the F atoms ($\Delta\delta_{p,m} = 3.68$ ppm) indicated an anionic four-coordinate borate.[10] The ^1H NMR spectrum showed quartet and a broad singlet resonances at 3.91 ppm (B−H, $^1J_{BH} = 74$ Hz) and 7.55 ppm (N−H), respectively. The observation that the methyl groups in catalyst **2** occur as two singlets (1:1 ratio) accounts for a significant barrier of rotation around the N-benzyl bond. Furthermore, the NMR data revealed that the conversion to **2** was completed in less than 5 min. An X-ray crystallographic study of **2** (Figure 1) showed that the N−H···H−B dihydrogen bond (DHB) is rather short (1.78 Å).[21,22] Thus, the air- and moisture-stable catalyst **2** has been prepared on a gram scale (up to 5 g) by an efficient three-step synthesis from readily available precursors (Schemes 1, 2).

Interestingly, when a toluene solution of **2** (0.1M) was refluxed at 110 °C in a closed system under reduced pressure, or a flow of argon for 3 h, a 50% conversion of **2** to the bright yellow starting compound **1** was observed. Continuing the reaction up to 20 h resulted in the quantitative recovery of product **1**. These findings are in contrast to the nonbridged systems where the bound hydrogen cannot be released thermally after activation.[18]

To gain further insight into the mechanism of these reactions and the nature of the N−H···H−B dihydrogen-bond interaction, we studied theoretically the structure, reaction path, and energetics.

[†] University of Helsinki.
[‡] Technische Universität München.

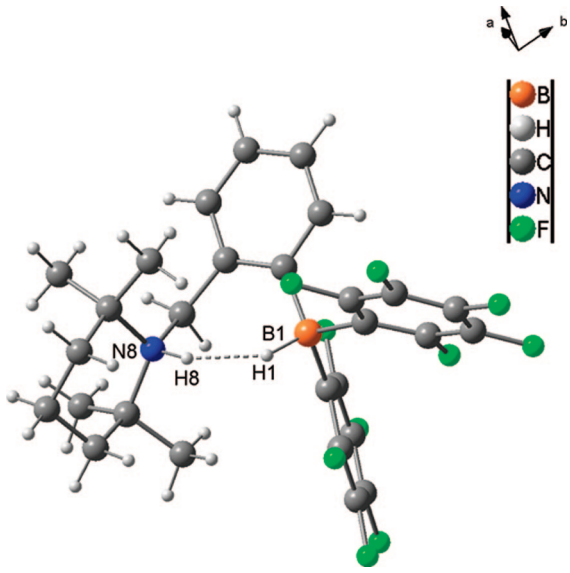


Figure 1. Experimental X-ray structure of **2** (solvent molecules are omitted for clarity).

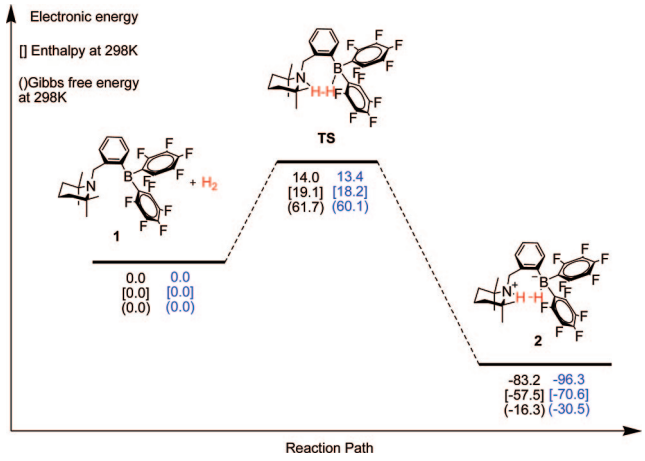


Figure 2. Energies (kJ/mol) of the hydrogen activation reaction by **1** calculated at the PBE/6-31G(d) level of theory: black color, gas phase; blue color, solution in benzene.

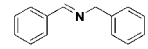
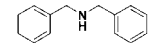
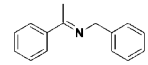
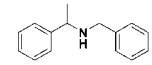
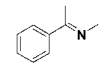
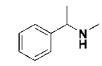
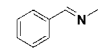
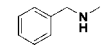
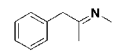
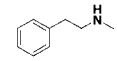
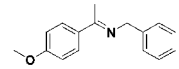
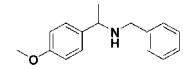
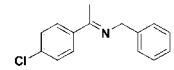
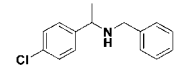
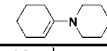
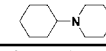
Until now, a broad spectrum of DHB interactions, including medium (1.2−1.7 Å) and short (0.8−1.2 Å) distances, were discussed only from a theoretical point of view.[23] Furthermore, in earlier studies of dihydrogen bonds, the partial charges A-H$^{\delta+}$···B−H$^{\delta-}$ were often emphasized.[24]

Both compound **2** and the simplified system $[NH_4]^+[HB(CH_3)_2(CH_2F)]^-$ (**2a**) were considered.[25,26] The reaction path found (Figure 2) is similar to the reported concerted Lewis acid−Lewis base (LA−LB) mechanisms for the hydrogen splitting by similar phosphine−borane systems.[27,28]

The structure of the starting compound **1** was identified as a minimum on the PBE potential energy surface. This *ansa*-aminoborane makes use of the concept of molecular tweezers for hydrogen. Owing to the constraint geometry and C−H···F−C interactions, which are common for this class of substances,[29] the boron and nitrogen atoms are oriented toward and in close but noncoordinative contact to each other (a B−N distance of 3.43 Å was detected). A hydrogen molecule can easily fit into this void and may interact with both active centers of the amine-borane pair.

An early transition state (**TS**) with a short H−H distance of 0.78 Å has been located and represents the highest stationary point on the reaction pathway and describes an essentially direct route from system **1** and H_2 to catalyst **2**.

Table 1. Catalytic Hydrogenation of Imines and Enamines by the Nonmetal Compound **2**: Catalyst **2** (0.01 mmol, 4%), Substrate (0.25 mmol), and Toluene (0.7 mL) Were Refluxed (110°C) under 2 atm of H_2 Pressure

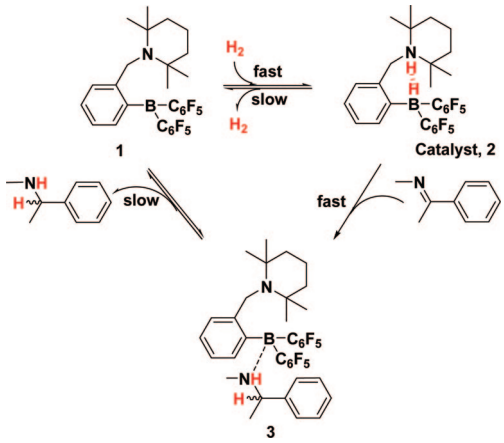
Entry	Substrate	Time (h)	Amine	Yield (%)[a]
1		12		99[b]
2		6		99
3		12		99
4		24		4
5		24		4
6		6		99
7		6		99
8		12		85

[a] Determined by ^{1}H NMR spectroscopy. [b] Catalyst **2** (0.02 mmol, 8%).

For **2**, the calculated B···N distance R(B−N) = 3.32 Å, where R is the distance between two opposite unit charges, is close to the obtained experimental data (3.36 Å). Then the Coulomb attraction becomes $-1/R = -0.16$ atomic units = −413 kJ/mol. This is comparable with the amount of energy required for the heterolytic cleavage of the H−H bond, 432 kJ/mol.[32] According to this calculation the Coulomb attraction between the entire cation and the entire anion can pay for the loss of the strong Heitler−London covalent bond of H_2, or "Coulomb pays for Heitler−London".[33] The two hydrogen atoms in system **2** (NH, BH) can be reunited and thermally released due to the constraint geometry of this *ansa*-ammoniumborate.[20]

To continue our experimental investigation, we examined the reduction of imines with catalyst **2**. Previous nonmetal systems have shown stoichiometric reductions of the imine substrate $PhCH_2N{=}CPh(H)$, because the resulting dibenzylamine inhibits the active boron center because of adduct formation.[13,34,35] At the outset, when a toluene solution of catalyst **2** (4 mol percent) with the imine from benzaldehyde and benzylamine was refluxed under 2 atm of H_2 for 24 h, a 51% conversion of imine to amine was observed. Continuing the reaction for up to 48 h gave 60% conversion. To increase the yield, we heated the starting imine with 8 mol percent of catalyst **2** under the same H_2 pressure (2 atm) in toluene for 12 h. This setup resulted in the formation of dibenzylamine in 99% yield (Table 1, entry 1). Moreover, a stoichiometric

Scheme 3. Proposed Mechanism for the Catalytic Hydrogenation of Imines by **2**



reduction of the substrate $PhCH_2N{=}CPh(H)$ with **2** occurs rapidly upon mixing at 80 °C and no side-products were detected in these reactions.

These data support a proposed mechanism for the catalytic hydrogenation of imines (Scheme 3). An important step is the suppression of the activity of the catalyst by amine−borane adduct formation (**3**), and hence the sensitivity to steric factors at the α positions of the imine is crucial. Repeating the reaction either with *p*-R-$C_6H_4CH_2N{=}CPh(CH_3)$ or $CH_3N{=}CPh(CH_3)$ (where R is H, Cl, or MeO) led to selective hydrogenation, providing *N*-benzyl-α-methylbenzylamines or *N*-methyl-α-methylbenzylamine, respectively, in almost quantitative yields (Table 1, entries 2, 3, 6, 7).[36] However, even small changes in the carbonyl or amine site geometry of the imines can significantly affect the reactivity. Thus, when less steric imines such as $CH_3N{=}CPh(H)$, and $CH_3N{=}CCH_2Ph(CH_3)$ were reduced with catalyst **2**, the corresponding amines were obtained only in 4% yield (Table 1, entries 4, 5). Furthermore, the cyclohexanone piperidine enamine was hydrogenated to *N*-cyclohexylpiperidine in good yield (Table 1, entry 8).

In summary, we have devised the first *ansa*-aminoborane which is able to reversibly activate H_2 under mild conditions through an intramolecular mechanism. The structural and theoretical findings show that the dihydrogen interaction in our molecular tweezers is partially covalent in nature. Moreover, the results reported here highlight the substantial scope for the preparation of amines by nonmetal catalytic reduction of imines and enamines.

Acknowledgment. Supported was provided by the DAAD (D/05/51658), Academy of Finland (123248), the Finnish CoE of Computational Molecular Science, Magnus Ehrnrooth Foundation (C.W.), Academy of Finland, and JSPS (M.A.). CSC, Espoo provided computing resources. The authors are very grateful to Dr. S. Heikkinen for help with NMR.

Supporting Information Available: Experimental procedures, characterization data of all new compounds, copies of NMR spectra, and X-ray crystallography data of **2**. This material is available free of charge via the Internet at http://pubs.acs.org. Structure parameters for compound **2** are also available free of charge from Cambridge Crystallographic Data Centre under reference number CCDC-694515.

References

(1) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999.
(2) Kleemann, A.; Engel, J. *Pharmaceutical Substances*, 4th ed.; Thieme: Stuttgart, Germany, 2001.
(3) Albert, A. *Selective Toxicity*, 7th ed.; Chapman & Hall: London, 1985.
(4) Smith, M. B. *Compendium of Organic Synthetic Methods*; Wiley-VCH: New York, 2001; Vol. 9, pp 117−140.
(5) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1998; Vol. 2, pp 1−96.
(6) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889–900.
(7) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-VCH: New York, 2001; pp 1203−1204; 1544−1564.
(8) Huang, Y. *Synlett* **2007**, 2304–2305.
(9) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617–4620.
(10) Blackwell, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. E. *Org. Lett.* **2000**, *2*, 3921–3923.
(11) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795–813.
(12) Welch, G. C.; Juan, R. R. S.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124–1126.
(13) Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 8050–8053.
(14) Spies, P.; Schwendemann, S.; Lange, S.; Kehr, G.; Fröhlich, R.; Erker, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7543–7546.
(15) Kenward, A. L.; Piers, W. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 38–41.
(16) Kubas, G. J. *Science* **2006**, *314*, 1096–1097.
(17) Crabtree, R. H. *Science* **1998**, *282*, 2000–2001.
(18) Sumerin, V.; Schulz, F.; Nieger, M.; Leskelä, M.; Repo, T.; Rieger, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 6001–6003.
(19) Roesler, R.; Piers, W. E.; Parvez, M. *J. Organomet. Chem.* **2003**, *680*, 218–222.
(20) The terms *ansa*-aminoborane and *ansa*-ammoniumborate [ansa (la.) = "handle"] refer to the use of the successful concept of *ansa*-metallocenes where a bridge between two Cp-ligands forces them into a distinct geometry and hence influences the specific reactivity of these compounds.
(21) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Chichester, U.K., 1999; pp 283−287.
(22) Crabtree, R. H.; Siegbahn, P. E. M.; Eisenstein, O.; Rheingold, A. L.; Koetzle, T. F. *Acc. Chem. Res.* **1996**, *29*, 348–354.
(23) Grabowski, S. J.; Sokalski, W. A.; Leszczynski, J. *Chem. Phys.* **2007**, *337*, 68–76.
(24) Bakhmutov, V. I. *Dihydrogen Bonds*; Wiley-VCH: New York, 2008.
(25) Concerning the dynamics, CH_5^+ and the isoelectronic BH_5 have complicated proton motions on a very complicated potential energy surface. Although the simplest model reaction $NH_3 + BH_3 + H_2 = [NH_4]^+[BH_4]^-$, would be quantum chemically appealing, a potential minimum can only be found for the right-hand-side at Hartree-Fock level. If we simplify the BH_3 hydrogen atoms by methyl- and fluoromethyl-groups, we get **2a** that can be studied.
(26) Theoretical calculations were carried out using Gaussian 03 at PBE/6-31G(d) level. Solvation effects were evaluated with the PCM method. The ADF code was used for the Morokuma analysis.
(27) Rokob, T. A.; Hamza, A.; Stirling, A.; Soos, T.; Papai, I. *Angew. Chem., Int. Ed.* **2008**, *47*, 2435–2438.
(28) Guo, Y.; Li, S. *Inorg. Chem.* **2008**, *47*, 6212–6219.
(29) (a) Mountford, A. J.; Hughes, D. L.; Lancaster, S. J. *Chem. Commun.* **2003**, 2148–2149. (b) Further NMR studies to investigate the nature of the C−H···F−C interaction are underway, cf. Plenio, H.; Diodine, R. *Chem. Ber.* **1997**, *130*, 633–640.
(30) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48–76.
(31) Neutron diffraction experiments are underway.
(32) Tolman, W. B. In *Activation of Small Molecules*; Tye, J. W., Darensbourg, Y., Hall, M. B., Eds.; Wiley-VCH: Weinheim, Germany, 2006; pp 121−158.
(33) More quantitative estimates for the simplified system **2a** showed that the cation and anion charge centers are located very close to the N and B atoms, respectively. In a Morokuma energy decomposition for **2a**, the ionic (electrostatic), Pauli repulsion, and orbital interaction energies were−474, +167, and−176 kJ/mol, respectively. An issue is the possibility of curve crossing between ionic and covalent states of the loaded complexes at large *R*. However for **2a**, the vertical ionization potential (borate) is bigger than the electron affinity (ammonium) and hence there is no such crossing. The ionic ground-state of the type $[NH_4]^+[HB(CH_3)_2(CH_2F)]^-$ prevails when *R* approaches infinity.
(34) Chase, P. A.; Jurca, T.; Stephan, D. W. *Chem. Commun.* **2008**, 1701–1703.
(35) Chen, D.; Klankermayer, J. *Chem. Commun.* **2008**, 2130–2131.
(36) Previous nonmetal systems have shown stoichiometric reductions of the imine substrates *p*-R-$C_6H_4CH_2N{=}CPh(CH_3)$ and $CH_3N{=}CPh(CH_3)$ (Table 1, entries 2, 3, 6, 7).

JA806627S