Mechanistic insights on reduction of carboxamides by diisobutylaluminum hydride and sodium hydride—iodide composite

Ong, Derek Yiren; Watanabe, Kohei; Takita, Ryo; Chiba, Shunsuke

2019

Ong, D. Y., Watanabe, K., Takita, R. & Chiba, S. (2019). Mechanistic insights on reduction of carboxamides by diisobutylaluminum hydride and sodium hydride—iodide composite. *Helvetica Chimica Acta*, 102(9), e1900166-. <https://dx.doi.org/10.1002/hlca.201900166>

<https://hdl.handle.net/10356/154840>

<https://doi.org/10.1002/hlca.201900166>

© 2019 2019 Wiley-VHCAAG. All rights reserved. This paper was published in *Helvetica Chimica Acta* and is made available with permission of Wiley-VHCAAG.

Downloaded on 26 Apr 2023 22:34:12 SGT

Mechanistic Insights on Reduction of Carboxamides by Diisobutylaluminum Hydride and Sodium Hydride-Iodide Composite

Derek Yiren Ong,^a Kohei Watanabe,^b Ryo Takita^{*,b}, and Shunsuke Chiba^{*,a}

^a Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371 (Singapore) e-mail: shunsuke@ntu.edu.sg

^b Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan e-mail: takita@mol.f.u-tokyo.ac.jp

Dedicated to Professor Philippe Renaud in celebration of his 60th birthday

The reaction mechanisms on reduction of tertiary carboxamides by diisobutylaluminum hydride (DIBAL) and sodium hydride (NaH)-sodium iodide (NaI) composite were elucidated by the computational and experimental approaches. Reduction of *N,N*-dimethyl carboxamides with DIBAL provides the corresponding amines, whereas that with the NaH-NaI composite exclusively forms aldehyde even at high reaction temperature. DFT calculations revealed that dimeric structural nature of DIBAL and Lewis acidity on its Al center play crucial role to decompose the tetrahedral anionic carbinol amine intermediate through C-O bond cleavage. On the other hand, in the reduction with the NaH-NaI composite, the resulting tetrahedral anionic carbinol amine intermediate could be kept stable, thus providing aldehydes as a sole product by the aqueous workup.

Keywords: Amides • Reduction • Diisobutylaluminum hydride • Sodium hydride • DFT calculation

Introduction

Among a series of metal-based hydride reagents for reduction of π -polar electrophiles,^[1,2] diisobutylaluminum hydride (DIBAL) is one of the most commonly used chemicals in both academics and industries (Scheme 1A).^[3-5] Its reactivity toward various types of electrophiles were explored in details and described in the common textbooks in basic organic chemistry.^[6] For example, reduction of tertiary carboxamides^[7-9] by DIBAL is known to form the corresponding amines (Scheme 1B), despite several exceptions such as reduction of *N*-methoxy-*N*-methylamides (the Weinreb amides).^[10-12] However, the reaction mechanism for the amine formation, especially pertaining to how the process mediates selective cleavage of the C-O bond from the anionic carbinol amine intermediate **I** formed by the 1st hydride transfer, has not clearly been uncovered.

A. Diisobutylaluminum hydride (DIBAL)

B. Reduction of amides by DIBAL

Scheme 1. Diisobutylaluminum hydride (DIBAL).

On the other hand, our group recently disclosed that sodium hydride (NaH) could act as a hydride donor in the presence of NaI or LiI in THF, capable of performing controlled reduction of tertiary carboxamides into aldehydes (Scheme 2).^[13-18] This unique controlled feature could be observed even if the reactions are performed at higher reaction temperature (i.e. reflux in THF), implying that the resulting anionic carbinol amine intermediate **II** is kept extremely stable under the reaction conditions. The protonated hemiaminal **III**, formed by the aqueous work-up, should be immediately decomposed into aldehydes with release of amines. These totally distinct reactivities of DIBAL and NaH toward reduction of carboxamides stimulated us to explore their reaction mechanisms in detail. This article describes their elucidation through the theoretical and experimental approaches.

Scheme 2. Controlled reduction of amides into aldehydes by NaH-NaI

Results and Discussion

At the outset of the project, we selected *N,N*-dimethyl-2-naphthamide (**1a**) and aliphatic amide **1b** derived from gemfibrozil as the model substrates and examined their reduction by titrated DIBAL^[19] and the NaH-NaI system. Treatment of amide **1a** with 2.2 equiv of DIBAL resulted in smooth double hydride reduction of **1a** at room

temperature to give amine **3a** in 97% yield along with a small amount (<2% yield) of alcohol **4a** (Scheme 3A). In the sharp contrast, the reaction in the presence of 3 equiv of NaH and 1 equiv of NaI afforded 2-naphthaldehyde (**2a**) in 93% yield as a sole product (Scheme 3B).^[15] Exactly the same trend was observed in the reduction of aliphatic amide **1b** (Scheme 4).

A. with DIBAL

B. with NaH-NaI

Scheme 3. Reduction of amide **1a**.

A. with DIBAL

B. with NaH-NaI

Scheme 4. Reduction of amide **1b**.

To gain the insights into the detailed molecular mechanisms, we next performed DFT calculations for the reduction of benzamide as the model substrate at the ω B97X-D/6-311+G**/SMD(THF)// ω B97X-D/6-31+G*/SMD(THF) level of theory. Scheme 5A and B displayed the calculated reaction pathways by a Me_2AlH dimer, which is used as a simplified model of DIBAL herein. The C–O bond scission process starts from the anionic carbinol amine intermediate (**INT1**_{dimer/C–O}) that is generated by the first hydride attack to benzamide (Scheme 5A). The dimeric aluminum complex facilitates the liberation of a dianionic oxygen atom, through the efficient cooperative activation by the two aluminum centers having highly Lewis acidic/oxophilic properties (**TS1**_{dimer/C–O}). Thus, the C–O bond is cleaved with a reasonable activation energy ($\Delta G^\ddagger +13.7$ kcal/mol) to afford an iminium cation together with an oxo-bridged dinuclear aluminum hydride (**INT2**_{dimer/C–O}).

o). We found that the reduction by the resulting hydride species within **INT2**_{dimer/C–O} proceeds smoothly and the amine is obtained with the concomitant formation of an oxo-bridged aluminum dimer (Al–O–Al). In contrast, in the case of the C–N scission process that affords the corresponding alcohol (Scheme 5B), only one of the aluminum centers can be involved in the electrophilic activation of the nitrogen atom. This results in high energy ($\Delta G^\ddagger +37.9$ kcal/mol) for the C–N bond cleavage, which unlikely occurs under the reduction conditions. These theoretical outcomes clearly illustrate the experimentally observed selectivity in amide reduction with DIBAL. It should be noted that the calculations with a monomeric Me_2AlH led to an unreasonable pathway (C–O scission, Scheme 5C) or high activation energy (C–N scission, Scheme 5D). The dimeric structure of DIBAL with Lewis acidic Al centers is indispensable for the controlled selectivity in the amide reduction.

A. With Me_2AlH dimer: C–O bond scission to afford the amine

B. With Me_2AlH dimer: C–N bond scission to afford the alcohol

C. With Me_2AlH monomer: C–O bond scission

D. With Me_2AlH monomer: C–N bond scission

Scheme 5. The calculated reaction pathways for the reduction of benzamide with the dimer (A,B) or monomer (C,D) of Me_2AlH . Energy changes and bond lengths at the ω B97X-D/6-311+G**/SMD(THF)// ω B97X-D/6-31+G*/SMD(THF) level of theory are shown in kcal/mol and Å, respectively.

The amide reduction by the NaH-NaI composite empirically gave the corresponding aldehydes (Schemes 3B and 4B). We assume that counter ion metathesis between NaH and NaI in THF allows for generation of activated, nanomeric units of NaH, that possesses enhanced nucleophilic hydridic character to promote the present process.^[20] Thus, using a NaH dimer as an appropriate model of the active species, the possibility of the pathways for the C–O and C–N bonds scission from the anionic carbinol amine intermediate **II** was investigated by the same DFT method. In the C–O scission pathway (Scheme 6A), the oxygen atom in the tetrahedral intermediate (**INT1**_{NaH/C–O}) coordinates to the two sodium cations, the structure of which is analogous to that of **INT1**_{dimer/C–O} in the DIBAL reduction (Scheme 5A). However, the Na–O–Na moiety in this complex should have extremely strong basicity, and the calculation implied an unusual deprotonation pathway from the methyl group on the nitrogen atom (**TS1**_{NaH/C–O}). Its activation barrier is too high, and this pathway should not be feasible. On the other hand, as shown in Scheme 6B, the C–N bond scission pathway also requires high activation energy ($\Delta G^\ddagger$ +30.4 kcal/mol), that should prevent the reaction progress. To detect formation of the anionic carbinol amine intermediate, we prepared ¹³C-labeled benzamide **1c** and reduced it under the optimized reaction conditions in THF-*d*₈ (Scheme 6C). The ¹H and ¹³C NMR analyses of the resulting crude mixture showed a doublet peak having a coupling constant of 143 Hz at 5.01 ppm (¹H NMR) and 98.4 ppm (proton-coupled ¹³C NMR), clearly indicating the presence of **5c** having a tetrahedral ¹³C-labeled carbon with one hydrogen atom. These computational and experimental outcomes implied that the anionic carbinol amine intermediate **II** would not be decomposed under the reaction conditions. This is consistent with the previous observation by Olah and co-workers, in which the reactions of tertiary formamide with Grignard reagents afforded the corresponding aldehydes.^[21]

A. C–O bond scission

B. C–N bond scission

C. Observation of the carbinol amine intermediate

Scheme 6. The calculated reaction pathways for the reduction of benzamide with NaH dimer and the experimental observation of the anionic carbinol amine

intermediate. Energy changes and bond lengths at the ω B97X-D/6-311+G**/SMD(THF)// ω B97X-D/6-31+G*/SMD(THF) level of theory are shown in kcal/mol and Å, respectively.

Although the anionic carbinol amine intermediate **II** is found fairly stable under the reaction conditions, we wondered why the aqueous workup can immediately convert it into the corresponding aldehyde. Is it derived from the difference between sodium cation (Na^+) and proton (H^+)? Scheme 7 addressed this question. While the degradation should not proceed with a simply protonated carbinol amine intermediate (Scheme 7A), the presence of a H_2O molecule markedly accelerates the process ($\Delta G^\ddagger$ +10.0 kcal/mol) via the formation of 6-membered ring hydrogen-bonding network (**TS1**_{proton/H₂O}), allowing for the smooth release of aldehyde and amine (Scheme 7B). The proton relay with the aid of H_2O facilitates the expeditious degradation upon an acidic work-up.

A. Proton-promoted degradation of hemiaminal

B. Proton-promoted degradation of hemiaminal in the presence of H₂O

Scheme 7. The calculated reaction pathways for the degradation of the carbinol amine intermediate. Energy changes and bond lengths at the ω B97X-D/6-311+G**/SMD(water)// ω B97X-D/6-31+G* level of theory are shown in kcal/mol and Å, respectively.

The distinct selectivity observed in the reduction with DIBAL or NaH-NaI composite should be reflected mostly by the difference in Lewis acidic properties between Al and Na cations. This could also be ascertained by iterative reduction of amide **1a** with the NaH-NaI system and DIBAL. The anionic carbinol amine intermediate **II**, formed by the reaction of amide **1a** under the NaH-NaI system, was subsequently treated with DIBAL, that could induce the decomposition of **II** and the second hydride transfer to form amine **3a** as the major product (Table 1). It was interestingly found that the lower loadings of DIBAL resulted in incomplete reduction, providing a mixture of aldehyde **2a**, amine **3a**, and alcohol **4a** (entries 1 and 2), whereas the selective formation of amine **3a** was observed in use of 2 equivalents of DIBAL (entries 3 and 4).

Table 1. Iterative reduction of amide **1a** by NaH-NaI and DIBAL

Entry	DIBAL (equiv)	Temp [°C]	Conv. [%] ^[a]	2a [%] ^[b]	3a [%] ^[b]	4a [%] ^[b]
1	1.0	0	>99	48	39	12
2	1.5	0	>99	18	69	11
3	2.0	0	>99	2	94	4
4	2.0	25	>99	0	98	<1

[a] The reactions were conducted using 0.5 mmol of amide **1a**. [b] ¹H NMR yields based on the internal standard.

Similarly, the iterative reduction of aliphatic amide **1b** needed 2 equivalents of DIBAL to obtain amine **3b** selectively (Scheme 8A). These results suggested that both of the higher Lewis acidity of aluminum and the dimeric structure of DIBAL cooperatively assist the C–O bond scission even from the anionic carbinol amine intermediate **III** (Scheme 8).

A. Iterative reduction of amide **1b**

B. A proposed mechanism

Scheme 8. Iterative reduction of amide **1b** and a proposed mechanism

Conclusions

We have verified the reaction mechanisms on reduction of tertiary carboxamides by DIBAL and the NaH-NaI composite by the computational and experimental approaches. The reduction of amide

with DIBAL is a fundamental reaction in organic chemistry, and the investigations herein identified that the structural requirement of dimeric complex as well as Lewis acidic properties of aluminum centers play a crucial role for the controlled selectivity to afford the amine formation. On the other hand, anionic carbinol amine intermediate **II** formed in the reduction with the NaH-NaI system was found stable under the reaction conditions, leading to the selective aldehyde formation with the aqueous workup. These fundamental mechanistic insights should be beneficial to guide further design and development of new reductive molecular transformation of amides and their derivatives in a highly controlled manner.

Supplementary Material

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/MS-number>.

Acknowledgements

This work was financially supported by Nanyang Technological University (NTU), the Singapore Ministry of Education (Academic Research Fund Tier 1: RG10/17 for S. C.), and JSPS Grant-in-Aid for Scientific Research (C) (19K0662, for R. T.). R.T. thanks the Takeda Science Foundation, The FUGAKU Trust for Medicinal Research, and Uehara Memorial Foundation for financial support. The computations were performed using Research Center for Computational Science at Okazaki, Japan.

Author Contribution Statement

R.T. and S.C. designed the studies. D.Y.O. performed the experiments. K.W. and R.T. conducted DFT calculation. R.T. and S.C. wrote the manuscript.

References

- [1] M. Hudlicky, 'Reductions in Organic Chemistry', Ellis Horwood Ltd., Chichester, U.K., 1984.
- [2] J. Seyden-Penne, 'Reductions by the Alumino- and Borohydrides in Organic Synthesis', Wiley, New York, 1997.
- [3] K. Ziegler, H. Martin, F. Krupp, 'Metallorganische Verbindungen, XXVII Aluminiumtrialkyle und Dialkyl-Aluminiumhydride Aus Aluminiumisobutyl-Verbindungen', *Liebigs Ann.* **1960**, 629, 14–19.
- [4] P. Galatsis, M. Sollogoub, P. Sinaï, 'Diisobutylaluminum Hydride in Encyclopedia of Reagents for Organic Synthesis', John Wiley & Sons, New York, 2008.
- [5] E. Winterfeldt, 'Applications of Diisobutylaluminum Hydride (DIBAH) and Triisobutylaluminum (TIBA) as Reducing Agents in Organic Synthesis', *Synthesis* **1975**, 617–630.
- [6] N. M. Yoon, Y. S. Gyoung, 'Reaction of diisobutylaluminum hydride with selected organic compounds containing representative functional groups', *J. Org. Chem.* **1985**, 50, 2443–2450.
- [7] A. M. Smith, R. Whyman, 'Review of Methods for the Catalytic Hydrogenation of Carboxamides', *Chem. Rev.* **2014**, 114, 5477–5510.
- [8] J. Magano, J. R. Dunetz, 'Large-Scale Carbonyl Reductions in the Pharmaceutical Industry', *Org. Process Res. Dev.* **2012**, 16, 1156–1184.

- [9] D. Addis, S. Das, K. Junge, M. Beller, 'Selective Reduction of Carboxylic Acid Derivatives by Catalytic Hydrosilylation', *Angew. Chem. Int. Ed.* **2011**, 50, 6004-6011.
- [10] S. Nahm, S. M. Weinreb, S. M. 'N-methoxy-N-methylamides as effective acylating agents', *Tetrahedron Lett.* **1981**, 22, 3815-3818.
- [11] S. Balasubramaniam, I. S. Aidhen, 'The Growing Synthetic Utility of the Weinreb Amide', *Synthesis* **2008**, 3707-3738.
- [12] M. P. Sibi, 'Chemistry of N-Methoxy-N-methylamides. Applications in Synthesis', *Org. Prep. Proced. Int.* **1993**, 25, 15-40.
- [13] P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, 'Hydride Reduction by a Sodium Hydride-Iodide Composite', *Angew. Chem. Int. Ed.* **2016**, 55, 3783-3787.
- [14] Y. Huang, G. H. Chan, S. Chiba, 'Amide-Directed C-H Sodiation by a Sodium Hydride/Iodide Composite', *Angew. Chem. Int. Ed.* **2017**, 56, 6544-6547.
- [15] G. H. Chan, D. Y. Ong, Z. Yen, S. Chiba, 'Reduction of *N,N*-Dimethylcarboxamides to Aldehydes by Sodium Hydride - Iodide Composite', *Helv. Chim. Acta* **2018**, 101, e1800049.
- [16] D. Y. Ong, C. Tejo, K. Xu, H. Hirao, S. Chiba, 'Hydrodehalogenation of Haloarenes by a Sodium Hydride-Iodide Composite', *Angew. Chem. Int. Ed.* **2017**, 56, 1840-1844.
- [17] C. Tejo, J. H. Pang, D. Y. Ong, M. Oi, M. Uchiyama, R. Takita, S. Chiba, 'Dearylation of arylphosphine oxides using a sodium hydride-iodide composite', *Chem. Commun.* **2018**, 54, 1782-1785.
- [18] D. Y. Ong, Z. Yen, A. Yoshii, J. R. Imbernon, R. Takita, S. Chiba, 'Controlled Reduction of Carboxamides to Alcohols or Amines by Zinc', *Angew. Chem. Int. Ed.* **2019**, 58, 4992-4997.
- [19] T. R. Hoyer, A. W. Aspaas, B. M. Eklov, T. D. Ryba, 'Reaction Titration: A Convenient Method for Titering Reactive Hydride Agents (Red-Al, LiAlH₄, DIBALH, L-Selectride, NaH, and KH) by No-D NMR Spectroscopy', *Org. Lett.* **2005**, 7, 2205-2208.
- [20] Z. Hong, D. Y. Ong, S. K. Muduli, P. C. Too, G. H. Chan, Y. L. Tnay, S. Chiba, Y. Nishiyama, H. Hirao, H. S. Soo, 'Understanding the Origins of Nucleophilic Hydride Reactivity of a Sodium Hydride-Iodide Composite', *Chem. Eur. J.* **2016**, 22, 7108-7114.
- [21] G. A. Olah, G. H. S. Prakash, M. Arvanaghi, 'Synthetic Methods and Reactions; Part 109. Improved Preparation of Aldehydes and Ketones from *N,N*-Dimethylamides and Grignard Reagents', *Synthesis* **1984**, 228-230.

Entry for the Table of Contents

((Insert TOC Graphic here; max. width: 17.5 cm; max. height: 7.0 cm))