Tetraalkylammonium Salts as Hydrogen-Bonding Catalysts

Seiji Shirakawa,^{*,[a]} Shiyao Liu,^[a] Shiho Kaneko,^[a] Yusuke Kumatabara,^[a] Airi Fukuda,^[a] Yumi Omagari,^[a] and Keiji Maruoka^{*,[b]}

Dedication ((optional))

Abstract: Although the hydrogen-bonding ability of the α -hydrogens on tetraalkylammonium salts is often discussed in the chemistry of phase-transfer catalysts, the catalysis that utilizes the hydrogen-bond donor properties of tetraalkylammonium salts remains unknown. In the present work, we demonstrated hydrogen-bonding catalysis with newly designed tetraalkylammonium salt catalysts in Mannich-type reactions. Both the structure and the hydrogen-bonding ability of the new ammonium salts were investigated via X-ray diffraction analysis and NMR titration studies.

Tetraalkylammonium salts are recognized as representative organocatalysts,^[1] and are often used as phase-transfer catalysts for the activation of anionic nucleophiles through the formation of an ion pair with an ammonium cation.^[2] Although the structures of tetraalkylammonium salts are commonly expressed as **1a** shown in Figure 1, the actual ionic structures are discussed differently.^[3–5] The positive charge of ammonium salts delocalized on the α -hydrogen atoms, which are known to interact with an anionic counterion through hydrogen bonding, as shown in **1A**. Reetz proved the delocalization of the positive charge in tetraalkylammonium salts by X-ray crystal analysis of tetrabutylammonium salts such as tetrabutylammonium enolate and phenoxide.^[3] Furthermore, DFT calculations support the delocalized structures of ammonium salts, which include chiral ammonium salts.^[4,5] The interaction between α -hydrogens on the chiral tetraalkylammonium salt catalyst and the enolate oxygen was thought to be important in the transition-state model of asymmetric phase-transfer reactions.^[5] However, despite the interesting hydrogen-bonding ability of the α -hydrogens on tetraalkylammonium salts, the catalysis that could utilize such properties is, to the best of our knowledge, still unknown. Herein, we report a new dimension of tetraalkylammonium salt as a hydrogen-bonding catalyst that utilizes the characteristic properties of the α -hydrogens on the catalyst.^[6]

Figure 1. Structures of tetraalkylammonium salt.

To realize the efficient hydrogen-bonding catalysis of a tetraalkylammonium salt, we designed a new tetraalkylammonium salt, **2**, which was readily prepared via the methylation of a commercially available 2,6-piperidinecarboxylate, **3** (Scheme 1). The ammonium salt **2** possesses carboxylate groups at the α -carbon, which enhance the hydrogen-bonding ability of the α -hydrogens. Furthermore, the six-membered structure of the piperidine backbone fixes the acidic α -hydrogens to a position that is appropriate for bidentate binding to an anionic group.^[7]

Scheme 1. Design and synthesis of a new tetraalkylammonium salt for use as a hydrogen-bonding catalyst.

- [a] Prof. Dr. S. Shirakawa, S. Liu, S. Kaneko, Y. Kumatabara, A. Fukuda, Y. Omagari
Department of Environmental Science, Graduate School of Fisheries and Environmental Sciences
Nagasaki University
1-14 Bunkyo-machi, Nagasaki 852-8521, Japan
E-mail: seijishirakawa@nagasaki-u.ac.jp
Homepage: <http://seijishirakawa.wix.com/greenchemistry>
- [b] Prof. Dr. K. Maruoka
Department of Chemistry, Graduate School of Science
Kyoto University
Sakyo, Kyoto 606-8502, Japan
E-mail: maruoka@kuchem.kyoto-u.ac.jp

analysis of ammonium iodide **2a** (Figure 2).^[8] The crystal structure of **2a** provided important structural information. As expected, the hydrogen-bonding interactions between the α -hydrogens and the counteranion (I^-) were clearly observed, and the iodide anion was bound by three α -hydrogens including one α -hydrogen of the methyl group. Although a similar binding mode was also observed in the crystal structure of piperidine-derived ammonium iodide **4**,^[9] the distances between the α -hydrogens and the iodide anion were largely different, and the distances were shorter in **2a**. These results indicate that the additional carboxylate moieties of **2a** enhance the hydrogen-bonding ability of the α -hydrogens.

Figure 2. X-ray crystal structures of tetraalkylammonium iodides **2a** and **4**.

With important structural information of the tetraalkylammonium salts **2** in hand, the catalyst ability of **2** as a hydrogen-bonding catalyst was investigated in a Mannich-type reaction of *N*-acylisoquinoline **6a**, which was generated *in situ* from 2,2,2-trichloroethyl chloroformate (TrocCl) and isoquinoline, as a benchmark reaction (Table 1).^[10,11] In the absence of a catalyst, the reaction with ketene silyl acetal **7a** proceeded slowly to give product **8aa** in a 7% yield at -78°C for 3 h (entry 1). Then, 10 mol % of ammonium iodide **2a** was employed as a catalyst, and the reaction was moderately promoted (38% yield, entry 2). On the other hand, almost no catalyst-accelerations were observed when the reactions were performed with ammonium iodide **4** (entry 3) or tertiary amine **5** (entry 4). These results clearly indicate that both a quaternary ammonium moiety and carboxylate groups in **2a** were important in promoting the reaction. Further efficient promotion of the reaction was achieved by the use of catalyst **2b** possessing tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF^-) as a non-coordinating counteranion. The reactions with catalyst **2b** gave product **8aa** in a 61% yield within 3 h (entry 5), and in a 90% yield within 6 h

(entry 6). The reaction profiles with ammonium salts **2a**, **2b**, and **4** are shown in Figure 3.

Table 1. Effect of catalysts in the Mannich-type reaction of *N*-acylisoquinoline **6a**.^[a]

Entry	Catalyst	Yield [%] ^[b]
1	None	7
2	2a	38
3	4	9
4	5	6
5	2b	61
6 ^[c]	2b	90
7	2a + $\text{Bu}_4\text{N}^+\text{Cl}^-$ (20 mol %)	10
8	2b + $\text{Bu}_4\text{N}^+\text{Cl}^-$ (20 mol %)	23
9	PhCO_2H	16
10	TsOH	12

[a] Reaction conditions: **6a** (0.20 mmol), **7a** (0.30 mmol) in the presence of catalyst (0.020 mmol, 10 mol %) in THF (4.0 mL) at -78°C for 3 h. [b] Yield of isolated product **8aa**. [c] Reaction was performed for 6 h.

Figure 3. Reaction profiles.

In order to obtain further information about ammonium salts **2** as hydrogen-bonding catalysts, we performed the reactions with catalysts **2a** or **2b** in the presence of tetrabutylammonium chloride (Table 1, entries 7 and 8). In these trials, strong inhibitions of the reactions were observed (entries 2 vs. 7, and 5 vs. 8). Anion exchange was expected to have occurred between **2** and tetrabutylammonium chloride, and the chloride anion (relatively) strongly coordinated to the α -hydrogens of catalyst **2**. Consequently, catalyst **2** could not efficiently activate the substrate **6a** (Scheme 2). The reactions catalyzed by representative Brønsted acids, such as benzoic acid and *p*-toluenesulfonic acid, were also examined, and the reactions would give product **8aa** in only 16 and 12% yields, respectively (entries 9 and 10). Although the acidity of the α -hydrogens of catalyst **2** was not much higher than the representative Brønsted acids, the reaction efficiently promoted by catalysts **2** via multidentate hydrogen bonding.

Scheme 2. Proposed inhibition mode with tetrabutylammonium chloride.

To prove the hydrogen-bonding interaction between the α -hydrogens of **2** and the chloride substrate, we performed NMR titration studies of **2b** with chlorodiphenylmethane **9** as a relatively stable chloride compound (Figure 4). As a result of the titration of **9**, the clear upfield chemical shifts of the tetraalkylammonium core moiety of **2b** were observed in both ^1H and ^{13}C NMR measurements in CDCl_3 . In the titration studies of ^1H NMR, the α -hydrogens of **2b** (H_b , H_c , and H_d in Figure 4a) were shifted more significantly than the hydrogens of methylesters (H_a in Figure 4a). Similar trends were observed in ^{13}C NMR, and the carbons that shifted the most were the α -carbons of **2b** (Figure 4b). It should be noted that almost no chemical shift changes were observed for the carbons of the BArF^- counteranion moiety in the ^{13}C NMR titration studies.

Figure 4. NMR titration studies of **2b**.

The substrate scope of the Mannich-type reaction of *N*-acylisoquinolines **6** catalyzed by ammonium salts **2** was investigated (Scheme 3). The catalysts **2** accelerated the reactions with ketone-derived silyl enol ethers **7b** and **7c** to give corresponding products **8ab** and **8ac**. The reactions with 3-methylisoquinoline derivative **6b** and 8-bromoisoquinoline derivative **6c** were also efficiently accelerated by catalyst **2b** to obtain products **8ba** and **8ca** in good yields. On the other hand, poor accelerations by catalysts **2** were observed in the reactions with 5-nitroisoquinoline derivative **6d** to produce product **8da**, which probably was caused by hydrogen-bonding interactions between catalysts **2** and the nitro group of **6**, which suppressed the coordination to chloride in **6** (Scheme 3).

Scheme 3. Scope and limitation in the Mannich-type reaction of *N*-acylisoquinolines **6**.

To expand the utility of hydrogen-bonding catalyst **2b**, we also examined the regioselective reaction with 2-methylpyridine **10** (Scheme 4).^[12] The reaction was efficiently promoted by catalyst **2b** to give product **11** in high yields with high regioselectivity. This is a valuable example of the highly regioselective dearomatization of a pyridine derivative.^[13]

Scheme 4. Regioselective reaction of 2-methylpyridine **10**.

In summary, a new dimension of tetraalkylammonium salts as hydrogen-bonding catalysts was opened in the present work. The structure and binding abilities of newly designed tetraalkylammonium salts **2** were investigated via X-ray diffraction analysis and NMR titration studies. The hydrogen-bond donor ability of ammonium salt catalysts **2** was evaluated in the Mannich-type reactions of *N*-acylisoquinolines **6**. Furthermore, the catalyst **2** could be applied to highly regioselective reaction with 2-methylpyridine **10**. Further applications of the hydrogen-bonding catalysts **2** as well as the development of new (chiral) catalysts based on this chemistry are underway by our group.

Acknowledgements

This work was partially supported by Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT (Japan), Grant-in-Aid for Specially promoted Research from JSPS, and Nagase Science and Technology Foundation.

Keywords: acidity • catalysts • hydrogen bonds • organocatalysis • tetraalkylammonium salts

- [1] For reviews on organocatalysis, see: a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, 40, 3726; *Angew. Chem.* **2001**, 113, 3840; b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, 43, 5138; *Angew. Chem.* **2004**, 116, 5248; c) D. W. C. MacMillan, *Nature* **2008**, 455, 304; d) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**.
- [2] For reviews on phase-transfer catalysis, see: a) E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed., VCH, Weinheim, **1993**; b) C. M. Starks, C. L. Liotta, M. Halpern, *Phase-Transfer Catalysis*, Chapman & Hall, New York, **1994**; c) *Handbook of Phase-Transfer Catalysis* (Eds.: Y. Sasson, R. Neumann), Blackie Academic & Professional, London, **1997**; d) *Phase-Transfer Catalysis* (Ed.: M. E. Halpern), American Chemical Society: Washington DC, **1997** (ACS Symposium Series 659); e) M. J. O'Donnell, *Aldrichimica Acta* **2001**, 34, 3; f) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, 46, 4222; *Angew. Chem.* **2007**, 119, 4300; g) *Asymmetric Phase-Transfer Catalysis* (Ed.: K. Maruoka), Wiley-VCH, Weinheim, **2008**; h) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, 52, 4312; *Angew. Chem.* **2013**, 125, 4408.
- [3] a) M. T. Reetz, S. Hütte, R. Goddard, *J. Am. Chem. Soc.* **1993**, 115, 9339; b) M. T. Reetz, S. Hütte, R. Goddard, *J. Phys. Org. Chem.* **1995**, 8, 231; c) M. T. Reetz, S. Hütte, R. Goddard, C. Robyr, *Chem. Eur. J.*

- 1996, 2, 382; d) M. T. Reetz, S. Hütte, R. Goddard, *J. Prakt. Chem.* **1999**, 341, 297; e) R. Goddard, H. M. Herzog, M. T. Reetz, *Tetrahedron* **2002**, 58, 7847.
- [4] a) M. T. Reetz, *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 994; *Angew. Chem.* **1988**, 100, 1026; b) C. E. Cannizzaro, K. N. Houk, *J. Am. Chem. Soc.* **2002**, 124, 7163.
- [5] a) T. Ohshima, T. Shibusuchi, Y. Fukuta, M. Shibasaki, *Tetrahedron* **2004**, 60, 7743; b) T. C. Cook, M. B. Andrus, D. H. Ess, *Org. Lett.* **2012**, 14, 5836; c) T. Kamachi, K. Yoshizawa, *Org. Lett.* **2014**, 16, 472.
- [6] For reviews on hydrogen-bonding catalysis, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, 32, 289; b) P. M. Pihko, *Angew. Chem. Int. Ed.* **2004**, 43, 2062; *Angew. Chem.* **2004**, 116, 2110; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, 107, 5713; d) T. J. Auvil, A. G. Schafer, A. E. Mattson, *Eur. J. Org. Chem.* **2014**, 2633.
- [7] It was difficult to prepare and isolate *trans*-isomer of ammonium salt **2**.
- [8] The crystal structure of **2a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1423221). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.
- [9] W. A. Henderson, V. G. Young, Jr., P. Fylstra, H. C. De Long, P. C. Trulove, *Cryst. Growth Des.* **2006**, 6, 1645.
- [10] a) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, 44, 6700; *Angew. Chem.* **2005**, 117, 6858; b) A. G. Schafer, J. M. Wieting, T. J. Fisher, A. E. Mattson, *Angew. Chem. Int. Ed.* **2013**, 52, 11321; *Angew. Chem.* **2013**, 125, 11531; c) J. M. Wieting, T. J. Fisher, A. G. Schafer, M. D. Visco, J. C. Gallucci, A. E. Mattson, *Eur. J. Org. Chem.* **2015**, 525.
- [11] a) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, 122, 6327; b) Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, 129, 6686; c) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, 130, 7198; d) F. Kniep, S. H. Jungbauer, Q. Zhang, S. M. Walter, S. Schindler, I. Schnapperelle, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2013**, 52, 7028; *Angew. Chem.* **2013**, 125, 7166; e) A. Berkessel, S. Das, D. Pekel, J. M. Neudörfl, *Angew. Chem. Int. Ed.* **2014**, 53, 11660; *Angew. Chem.* **2014**, 126, 11846; f) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, O. García Mancheño, *J. Am. Chem. Soc.* **2014**, 136, 13999.
- [12] a) K. Akiba, A. Ohtani, Y. Yamamoto, *J. Org. Chem.* **1986**, 51, 5328; b) T. Itoh, M. Miyazaki, K. Nagata, A. Ohsawa, *Heterocycles* **1997**, 46, 83; c) S. Yamada, T. Misono, M. Ichikawa, C. Morita, *Tetrahedron* **2001**, 57, 8939; d) O. García Mancheño, S. Asmus, M. Zurro, T. Fischer, *Angew. Chem. Int. Ed.* **2015**, 54, 8823; *Angew. Chem.* **2015**, 127, 8947.
- [13] J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, 112, 2642.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

A new dimension of tetraalkylammonium salts as hydrogen-bonding catalysts was opened. The hydrogen-bond donor ability of newly designed ammonium salt catalysts was evaluated in the Mannich-type reactions. The hydrogen-bonding ability of the catalyst was also investigated via NMR titration studies.

S. Shirakawa,* S. Liu, S. Kaneko, Y. Kumatabara, A. Fukuda, Y. Omagari, and K. Maruoka*

Page No. – Page No.

A New Dimension of Tetraalkylammonium Salt Catalyst: Hydrogen-Bonding Catalysis