Tetraalkylammonium Salts as Hydrogen-Bonding Catalysts


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 bonding to an anionic group.[7]

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

To obtain structural information of newly prepared tetraalkylammonium salts 2, we performed an X-ray diffraction

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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.

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-acylisouquinoline 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-acceleration was 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-acylisouquinoline 6a.\(^{12}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield [%]</th>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>6[^c]</td>
<td>2b</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2a + Bu(_4)N(^+)Cl(^-) (20 mol %)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2b + Bu(_4)N(^+)Cl(^-) (20 mol %)</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PhCO(_2)H</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>TsOH</td>
<td>12</td>
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[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 2. X-ray crystal structures of tetraalkylammonium iodides 2a and 4.

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 multideterminate hydrogen bonding.

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 13C NMR measurements in CDCl₃. In the titration studies of 1H NMR, the α-hydrogens of 2b (Hb, Hc, and Hd in Figure 4a) were shifted more significantly than the hydrogens of methylesters (Ha in Figure 4a). Similar trends were observed in 13C 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 13C NMR titration studies.

The substrate scope of the Mannich-type reaction of N-acylisouquinolines 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-methylisouquinoline 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-nitroisouquinoline 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).
Regioselectivity. This is a valuable example of 10.

Scheme 3. Scope and limitation in the Mannich-type reaction of N-acetylquinolines 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-acetylquinolines 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.

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[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.


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.