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Tetraalkylammonium Salts as Hydrogen-Bonding Catalysts

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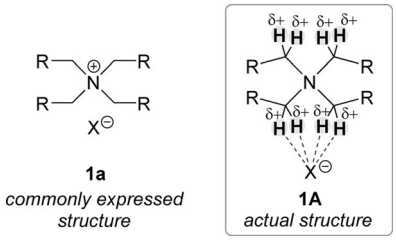
Abstract: *Although the hydrogen-bonding ability of the α hydrogen atoms on tetraalkylammonium salts is often discussed with respect to phase-transfer catalysts, catalysis that utilizes the hydrogen-bond-donor properties of tetraalkylammonium salts remains unknown. Herein, we demonstrate hydrogen-bonding catalysis with newly designed tetraalkylammonium salt catalysts in Mannich-type reactions. The structure and the hydrogen-bonding ability of the new ammonium salts were investigated by X-ray diffraction analysis and NMR titration studies.*

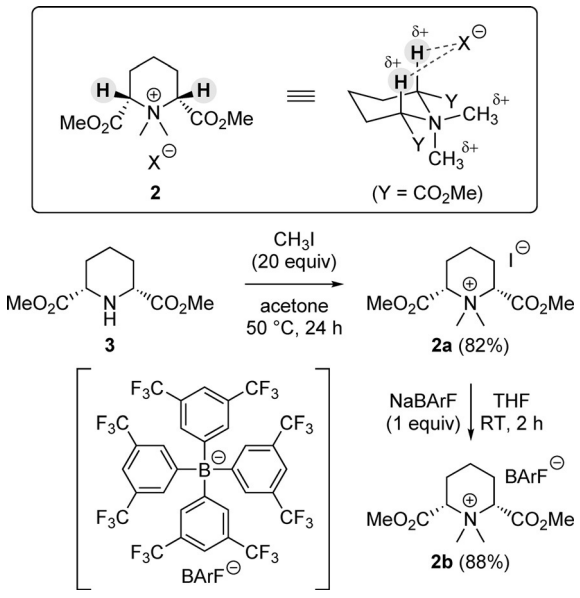
Tetraalkylammonium salts are recognized as representative organocatalysts[1] and are often used as phase-transfer catalysts for the activation of anionic nucleophiles through the formation of an ion pair with an ammonium cation.[2] Although the structures of tetraalkylammonium salts are commonly expressed as **1a**, their actual ionic structure is



discussed differently.[3–5] The positive charge of ammonium salts is delocalized on the α hydrogen atoms, which are known to interact with an anionic counterion through hydrogen bonding, as shown in **1A**. Reetz and co-workers proved the delocalization of the positive charge in tetraalkylammonium salts by X-ray crystal-structure 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 hydrogen atoms on the chiral tetraalkylammonium salt catalyst and the enolate oxygen atom 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 hydrogen atoms on tetraalkylammonium salts, catalysis that could utilize such properties is, to the best of our knowledge, still unknown. Herein, we report the development of tetraalkylammonium salts as hydrogen-bonding catalysts that function on the basis of the characteristic properties of the α hydrogen atoms on the catalyst.[6]

For efficient hydrogen-bonding catalysis, we designed new tetraalkylammonium salts **2**, which were readily prepared by the methylation of the commercially available 2,6-piperidinecarboxylate **3** (Scheme 1). The carboxylate groups at the α carbon atoms of ammonium salts **2** enhance the hydrogen-bonding ability of the α hydrogen atoms. Furthermore, the six-membered piperidine ring fixes the acidic α hydrogen atoms in an arrangement that is appropriate for bidentate binding to an anionic group.[7]

The X-ray crystal structure of ammonium iodide **2a** provided important structural information about the newly prepared tetraalkylammonium salts **2** (Figure 1).[8] As expected, hydrogen-bonding interactions between the α hydrogen atoms and the counteranion (I^-) were clearly observed, and the iodide anion was bound by three α hydrogen atoms, including one α hydrogen atom of the methyl group. Although a similar binding mode was also observed in



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

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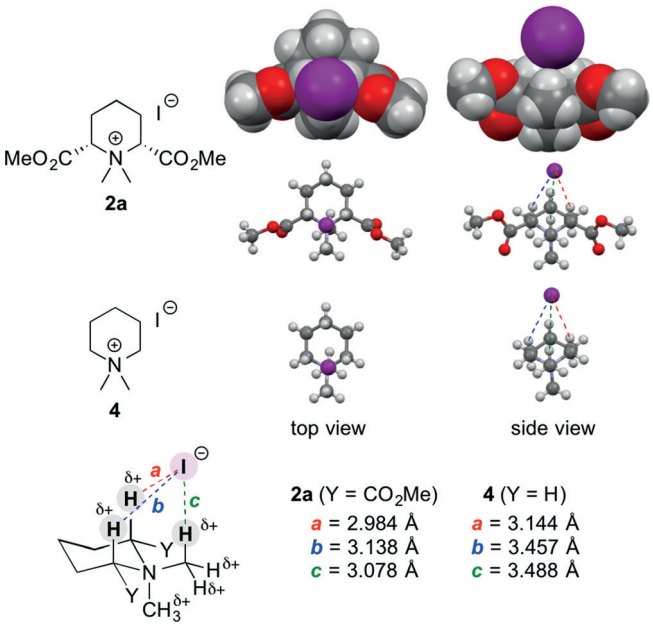


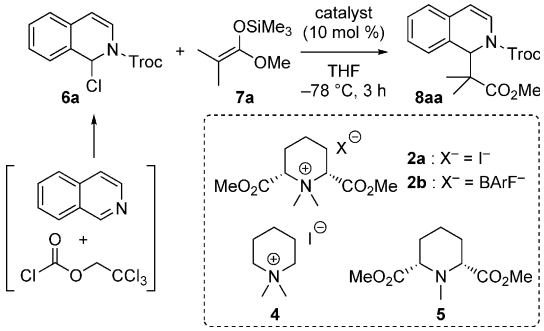
Figure 1. X-ray crystal structures of tetraalkylammonium iodides **2a** and **4**.

the crystal structure of the piperidine-derived ammonium iodide **4**,[9] the distances between the α hydrogen atoms and the iodide anion were very different, and shorter in **2a**. These results indicate that the additional carboxylate moieties of **2a** enhance the hydrogen-bonding ability of the α hydrogen atoms.

The catalytic ability of **2** as a hydrogen-bonding catalyst was investigated in a Mannich-type reaction of *N*-acyl isoquinoline **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 at −78 °C to give product **8aa** in 7% yield after 3 h (Table 1, entry 1). When, ammonium iodide **2a** (10 mol%) was used as a catalyst, the reaction was promoted to a moderate extent (38% yield; Table 1, entry 2). On the other hand, almost no catalyst acceleration was observed when the reaction was performed with ammonium iodide **4** (Table 1, entry 3) or tertiary amine **5** (entry 4). These results clearly indicate that both the quaternary ammonium moiety and the carboxylate groups in **2a** were important in promoting the reaction. Catalyst **2b** with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($BArF^-$) as a noncoordinating counteranion promoted the reaction more efficiently: Product **8aa** was formed in 61% yield within 3 h (Table 1, entry 5), and in 90% yield within 6 h (entry 6). The reaction profiles with ammonium salts **2a**, **2b**, and **4** are shown in Figure 2.

To obtain further information about ammonium salts **2** as hydrogen-bonding catalysts, we performed the reaction with catalyst **2a** or **2b** in the presence of tetrabutylammonium chloride (Table 1, entries 7 and 8). In these experiments, strong inhibition of the reaction was observed. We expect that anion exchange occurred between **2** and tetrabutylammonium chloride, and that the chloride anion coordinated (relatively) strongly to the α hydrogen atoms of catalysts **2**.

Table 1: Effect of different catalysts on the Mannich-type reaction of *N*-acyl isoquinoline **6a** with **7a**.[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** + $Bu_4N^+Cl^-$ (20 mol%)	10
8	**2b** + $Bu_4N^+Cl^-$ (20 mol%)	23
9	$PhCO_2H$	16
10	TsOH	12

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

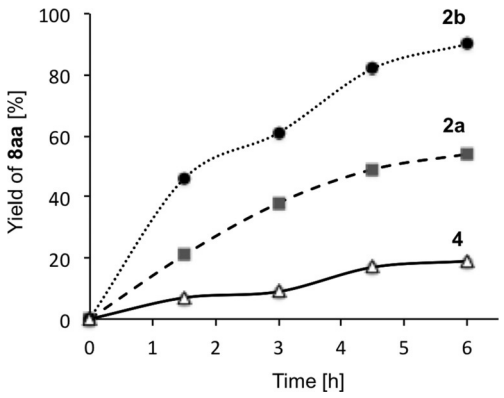
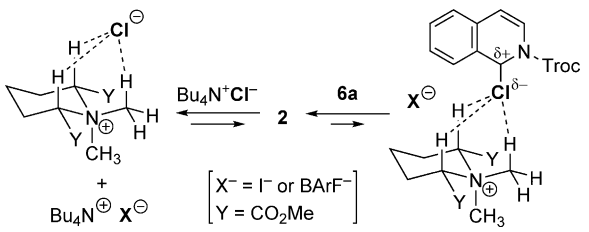


Figure 2. Reaction profiles.

Consequently, catalysts **2** could not efficiently activate substrate **6a** (Scheme 2). Catalysis of the reaction by representative Brønsted acids, such as benzoic acid and *p*-toluenesulfonic acid, was also examined. Under these conditions, product **8aa** was formed in only 16 and 12% yield, respectively (Table 1, entries 9 and 10). Although the acidity of the α hydrogen atoms of catalysts **2** was not much higher than that of the representative Brønsted acids, the reaction was efficiently promoted by catalysts **2** through multidentate hydrogen bonding.

To gain evidence for the hydrogen-bonding interaction between the α hydrogen atoms of **2** and the chloride substrate, we performed NMR titration studies of **2b** with chlorodiphenylmethane (**9**) as a relatively stable chloride compound (Figure 3). As a result of the titration with **9**, clear upfield



Scheme 2. Proposed inhibition mode with tetrabutylammonium chloride.

shifts of the NMR signals for the tetraalkylammonium core of **2b** were observed in both the ^{1}H and ^{13}C NMR spectrum in $CDCl_3$. In the ^{1}H NMR titration studies, the signals for the α hydrogen atoms of **2b** (H_b, H_c, and H_d in Figure 3a) were shifted more significantly than those for the hydrogen atoms of the methyl esters (H_a in Figure 3a). Similar trends were observed in ^{13}C NMR spectra, and the carbon-atom signals that shifted the most were those of the α carbon atoms of **2b** (Figure 3b). Almost no chemical-shift changes were observed for the carbon atoms of the $BArF^-$ counteranion in the ^{13}C NMR titration studies.

The scope of the Mannich-type reaction of *N*-acyl isoquinolines **6** under the catalysis of ammonium salts **2** was investigated (Scheme 3). The catalysts **2** accelerated the reactions of **6a** with ketone-derived silyl enol ethers **7b** and **7c** to give the corresponding products **8ab** and **8ac**. Reactions of 3-methylisoquinoline derivative **6b** and 8-bromoisoquinoline derivative **6c** were also efficiently accelerated by catalyst **2b** to afford products **8ba** and **8ca** in good yield. On the other hand, poor acceleration by catalysts **2** was observed in reactions of 5-nitroisoquinoline derivative **6d** to produce product **8da**, probably owing to the suppression of coordina-

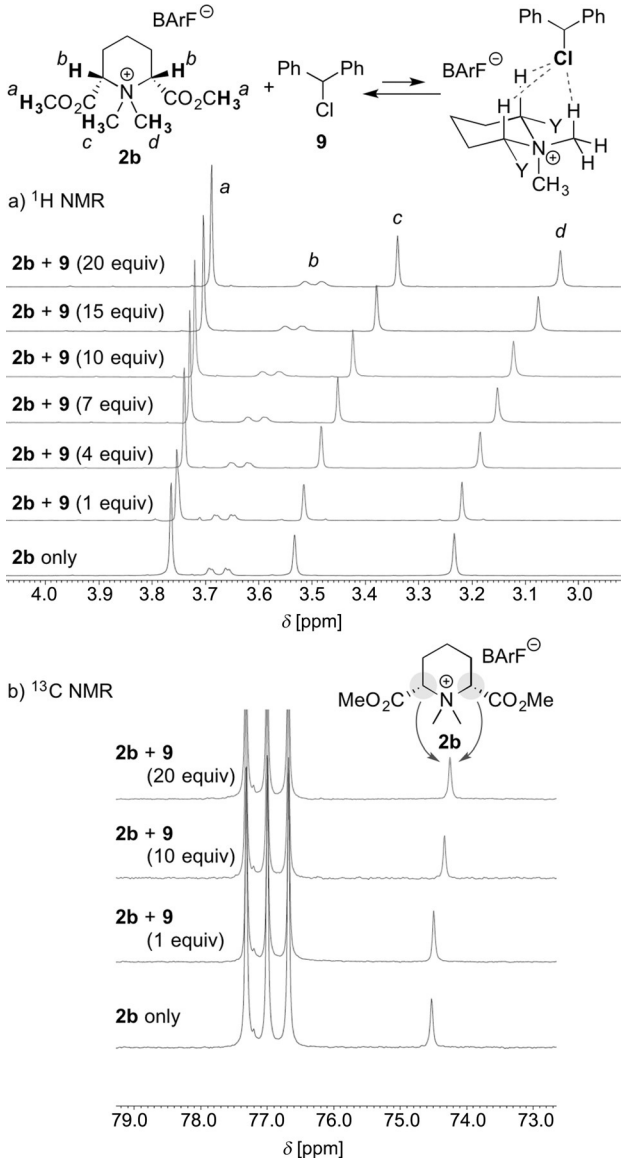
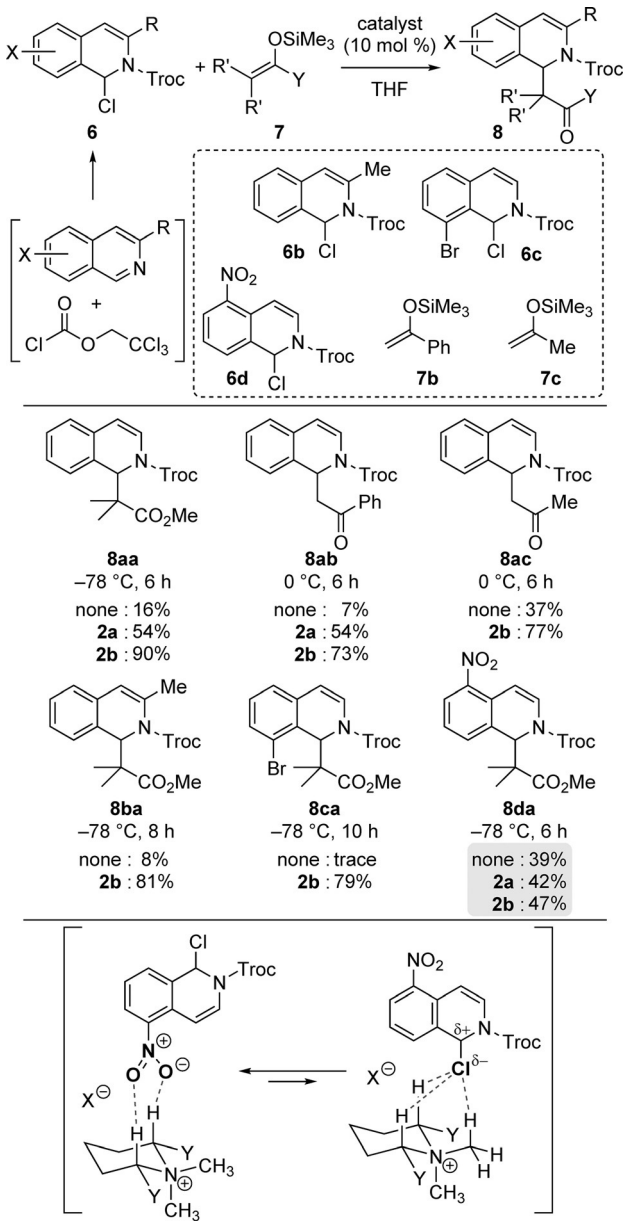


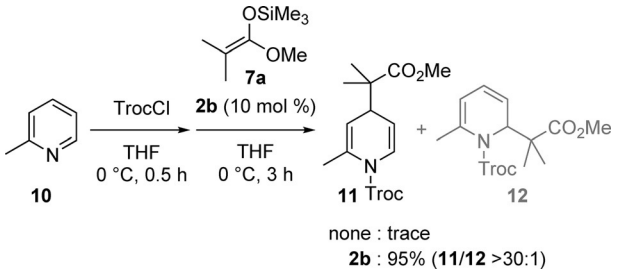
Figure 3. NMR titration studies of **2b**.



Scheme 3. Scope and limitation of the Mannich-type reaction of *N*-acyl isoquinolines **6**.

tion to the chloride atom in **6** as a result of hydrogen-bonding interactions between catalysts **2** and the nitro group of **6** (Scheme 3).

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



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

In summary, we have introduced the concept of tetraalkylammonium salts as hydrogen-bonding catalysts. The structure and binding ability of newly designed tetraalkylammonium salts **2** were investigated by X-ray diffraction analysis and NMR titration studies. The hydrogen-bond-donor ability of catalysts **2** was evaluated in Mannich-type reactions of *N*-acyl isoquinolines **6**. Furthermore, catalyst **2b** promoted a highly regioselective reaction of 2-methylpyridine (**10**). We are currently investigating further applications of catalysts **2** as well as the development of new (chiral) hydrogen-bonding catalysts of this type.

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Keywords: acidity · hydrogen bonds · hydrogen-bonding catalysts · organocatalysis · tetraalkylammonium salts

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