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Hydrogen-Bonding Catalysis of Tetraalkylammonium Salts in an Aza Diels-Alder Reaction

Yusuke Kumatabara,^[a] Shiho Kaneko,^[a] Satoshi Nakata,^[a] Seiji Shirakawa,*^[a] and Keiji Maruoka^[b]

Abstract: Piperidine-derived tetraalkylammonium salt with a noncoordinating counteranion worked as an effective hydrogen-bonding catalyst in an aza Diels-Alder reaction of imines and a Danishefsky diene. The hydrogen-bonding interaction between the ammonium salt and an imine was observed as part of a ¹H NMR titration study.

Tetraalkylammonium salts are important and reliable catalysts in organocatalytic chemistry,^[1] and are mainly employed in phasetransfer catalysis and base catalysis to activate nucleophiles through the formation of ion pairs, such as ammonium enolates.^[2] In the catalysis of tetraalkylammonium salts. Park et al. reported the tetraalkvlammonium salts-catalvzed aza Diels-Alder reaction of imines 1 and a Danishefsky diene 2 (Scheme 1).^[3] Several interesting observations were reported in that study.^[3a] First, the ammonium salt catalysts with an iodide anion promoted the reaction more efficiently than the catalysts with other halide counteranions. The reaction with tetraalkylammonium fluorides gave almost none of the target product 3. These results ruled out the possibility of a base catalysis of the ammonium salts to promote the reaction. Second, cinchona alkaloid-derived ammonium bromides proved to be a more effective catalyst than tetrabutylammonium bromide. The reaction with cinchona alkaloid-derived catalysts produced the products 3 in high yields with almost no the enantioselectivities. Although authors suggested tetraalkylammonium salts worked as Lewis acid catalysts for this reaction,^[4] the theoretical and experimental evidence has never been reported, and the role of the tetraalkylammonium salt has remained unclear. In our recent study on a new dimension of proved tetraalkylammonium salt catalysis, we that tetraalkylammonium salts 4 worked as hydrogen-bonding catalysts^[5] in a Mannich-type reaction through the hydrogenbonding interaction between α-hydrogens of the catalyst and chloride on the substrate (Scheme 2).^[6] The hydrogen-bonding abilities of tetraalkylammonium salts were supported by DFT calculations^[7] and X-ray crystal structure analysis^[8] by other research groups. Based on these reports, we hypothesized that tetraalkylammonium salts could activate imines 1 via a hydrogen-bonding interaction to promote the aza Diels-Alder

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reaction.^[9] Here we clarify the role of tetraalkylammonium salt catalysts in an aza Diels-Alder reaction of imines 1 and Danishefsky diene 2.



 $\mbox{Scheme 1. Effect of tetraalkylammonium salt catalysts in an aza Diels-Alder reaction, as reported by Park.^{[3a]}$



Scheme 2. Tetraalkylammonium salt as a hydrogen-bonding catalyst in Mannich-type reactions, as reported by our group.^[6a]

To prove our hypothesis, we initially investigated the structure-catalytic activity relationships of tetraalkylammonium salts in an aza Diels-Alder reaction of *N*-phenylbenzaldimine **1a** and Danishefsky diene **2** (Table 1). In the absence of a catalyst, the reaction in dichloromethane proceeded very slowly at 0 °C to give product **3a** in a 4% yield after 3 h (entry 1). When tetrabutylammonium iodide was used as a catalyst under these conditions, the reaction was only promoted to a moderate extent (22% yield; entry 2). Next, we examined the ammonium iodides **4a** and **4b**, which possess a piperidine backbone. As expected, the reaction was efficiently accelerated by catalyst **4a** (Y =

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CO₂Me) bearing carboxylate groups, which was an effective hydrogen-bonding catalyst for the Mannich-type reaction in Scheme 2,^[6a] to give product **3a** in a 64% yield (entry 3). The simple piperidine derived-catalyst 4b (Y = H) was also an effective catalyst for the aza Diels-Alder reaction, and the yield of 3a was somewhat improved (67% yield; entry 4). Although catalyst 4a possessed more acidic a-hydrogens that showed superior activity to 4b in our previous work on Mannich-type reactions,^[6a] similar reactivities between 4a and 4b were observed in the present aza Diels-Alder reaction. These different trends might be explained by the differences in the structures of the electrophiles, because steric repulsion was present between the phenyl group of imine 1a and the carboxylate groups of catalyst 4a (Figure 1a). As a result, catalysts 4a and 4b exhibited similar reactivity for the aza Diels-Alder reaction with imines 1. Furthermore, quinuclidine-derived ammonium iodide 5 showed higher reactivity than tetrabutylammonium iodide (57 vs. 22% yields; entries 5 vs. 2). Multiple hydrogen-bonding interactions between a-hydrogens and a counteranion were observed in the X-ray crystal structures of cinchona alkaloidderived quaternary ammonium salts, as shown in Figure 1b.^[10] This multiple binding mode of a-hydrogens on quinuclidine-type ammonium salts was similar to the mode seen in piperidine-type ammonium salts 4 (Figure 1b and Scheme 2).^[6a] Based on these observations, we concluded that an arrangement of α -hydrogens to appropriate positions, which were induced by the cyclic structure, is essential in the design of effective hydrogenbonding catalysts based on tetraalkylammonium salts. In order to further improve the catalytic activity of piperidine-type catalysts 4, tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF⁻) was employed as a non-coordinating counteranion. Finally, we obtained product 3a in high yields using catalysts 4c and 4d, which possessed a BArF⁻ counteranion (85% yield with 4c; 89% yield with 4d, entries 6 and 7).

reaction.[a]



1	None ^[c]	4
2	Bu₄N ⁺ I [−]	22
3	4a	64
4	4b	67
5	5	57
6	4c	85
7	4d	89

Reaction conditions: 1a (0.10 mmol), 2 (0.15 mmol). [a] tetraalkylammonium salt (0.010 mmol, 10 mol %), CH₂Cl₂ (2 mL), 0 °C, 3 h. [b] Yield of the isolated product 3a. [c] The reaction was performed without a catalyst.



Figure 1. Hydrogen-bonding interactions on the α-hydrogens of tetraalkylammonium salts.

To further prove the hydrogen-bonding interaction between the α -hydrogens of 4 and imine 1, we performed a ¹H NMR titration study of 4d with imine 1a (Figure 2). As a result of the titration of 1a, clear upfield chemical shifts of the α-hydrogens on 4d were observed in the ¹H NMR measurements of CDCI₃. On the other hand, almost no chemical shift changes were observed for the aromatic protons of the BArF⁻ counteranion moiety. This result strongly supported the proposition that tetraalkylammonium salts could activate imines 1 via hydrogen bonding to promote an aza Diels-Alder reaction.[11]

Table 1. Effect of tetraalkylammonium salts on the aza Diels-Alder



Figure 2. ¹H NMR titration study of tetraalkylammonium salt 4d with imine 1a.

With important information about the hydrogen-bonding catalysis of tetraalkylammonium salts for an aza Diels-Alder reaction in hand, the substrate generality of imines 1 was examined with catalyst 4d. At first, the effect of the substituents on the nitrogen in imines 1 (R') was examined. Imines 1b and 1c were derived from substituted anilines and could be applied to this reaction to give product 3b and 3c in moderate to good yields (80 and 50% yields respectively, entries 1 and 2). Benzylamine derivative 1d could also be applied to this reaction, although the yield of product 3d was only moderate (38% yield, entry 3). Next, we examined the generality of the R group on imines 1. Not only substituted aromatics (1e-1g) but also heteroaromatics (1h and 1i) and alkyl (1j) group-introduced imines could be employed for the reaction to obtain products 3e-3i in moderate to good yields (46-86% yields, entries 4-9). It should be noted that the addition of catalyst 4d produced clear accelerations of each reaction. Although imine 1g possessed a nitro group that could have strongly coordinated with a hydrogen-bonding donor, catalyst acceleration was observed, albeit to only a moderate degree (64% yield with 4d, 23% yield without catalyst, entry 6).



Table 2. Scope of the aza Diels-Alder reaction.^[a]

Entry	1	Yield [%] ^[b]
1	1b : R = Ph, R' = 4-Cl–C ₆ H ₄	80 (12 ^[c]) [3b]
2	1c : R = Ph, R' = 4-MeO $-C_6H_4$	50 (6 ^[c]) [3c]
3	1d : R = Ph, R' = PhCH ₂	38 (trace ^[c]) [3d]
4	1e : R = 3-Br–C ₆ H ₄ , R' = Ph	70 (9 ^[c]) [3e]
5	1f : $R = 4$ -Ph–C ₆ H ₄ , R' = Ph	82 (9 ^[c]) [3f]
6	1g : R = 4-NO ₂ -C ₆ H ₄ , R' = Ph	64 (23 ^[c]) [3g]
7	1h : R = 2-furyl, R' = Ph	46 (10 ^[c]) [3h]
8	1i: R = 2-pyridyl, R' = Ph	86 (17 ^[c]) [3i]
9	1j : R = <i>c</i> -C ₆ H ₁₁ , R' = Ph	58 (20 ^[c]) [3j]

[a] Reaction conditions: 1 (0.10 mmol), 2 (0.15 mmol), catalyst 4d (0.010 mmol, 10 mol %), CH₂Cl₂ (2 mL), 0 °C, 3 h. [b] Yield of the isolated product
 3. [c] The yield in parenthesis refers to the reaction without a catalyst.

In summary, we have demonstrated that tetraalkylammonium salts can function as hydrogen-bonding catalysts to activate imines 1 in an aza Diels-Alder reaction. The structure-catalytic activity relationships of tetraalkylammonium salt catalysts were discussed in this study based on the reported X-ray crystal data of ammonium salts. Furthermore, ¹H NMR titration study was performed to observe the hydrogen-bonding interaction between piperidine-derived tetraalkylammonium salt 4d and phenylbenzaldimine 1a. We are currently investigating a further application of alkylonium salts as hydrogen-bonding catalysts.

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Keywords: aza Diels-Alder reaction • hydrogen bonds • hydrogen-bonding catalysis • organocatalysis • tetraalkylammonium salts

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- [11] The ¹H NMR titration study of tetraalkylammonium salt 4c with imine 1a was also performed. For detail, see the Supporting Information.

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