HETEROCYCLES, Vol. 101, No. 2, 2020, pp. 580 - 592. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 13th July, 2019, Accepted, 28th August, 2019, Published online, 7th October, 2019
DOI: 10.3987/COM-19-S(F)48

TRIALKYLSULFONIUM AND TETRAALKYLAMMONIUM SALTS AS HYDROGEN-BONDING CATALYSTS IN AN AZA-DIELS-ALDER REACTION: EXPERIMENTAL AND COMPUTATIONAL STUDIES

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Dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday

Abstract – Hydrogen-bonding catalysis by cyclic trialkylsulfonium and tetraalkylammonium salts in an aza-Diels-Alder reaction was investigated. Among the examined onium salt catalysts, cyclic trialkylsulfonium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate possessing a non-coordinating counter anion was the most effective. Details of the activation modes of cyclic trialkylsulfonium and tetraalkylammonium salts were discussed on the basis of DFT calculation.

INTRODUCTION

The synthetic utility of alkyl−onium salts is widely recognized in organic chemistry.[1] Trialkylsulfonium and tetraalkylammonium salts are often utilized as useful reagents in organic synthesis. In addition, tetraalkylammonium salts are employed as reliable catalysts in phase-transfer and ion-pair catalysis via the activation of a nucleophile.[2] In the course of our study on the new possibilities of onium salt catalysis, we have proved that both trialkylsulfonium and tetraalkylammonium salts function as hydrogen-bonding catalysts that activates electrophiles (Figure 1).[3,4] We herein discuss the details of the activation modes

and the catalytic activities of these onium salts as hydrogen-bonding catalysts in an aza-Diels-Alder reaction.[5]

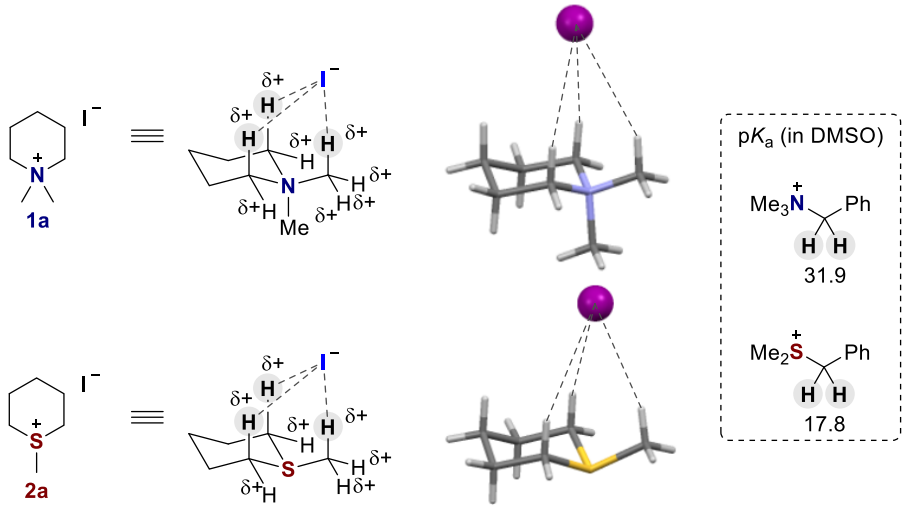


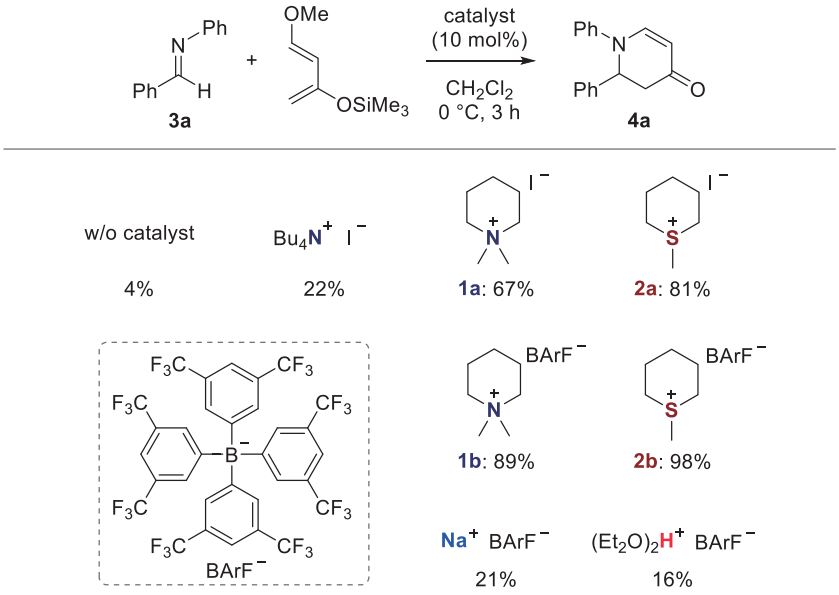
Figure 1. Structures of tetraalkylammonium salt **1a** and trialkylsulfonium salt **2a** as hydrogen-bonding catalysts

RESULTS AND DISCUSSION

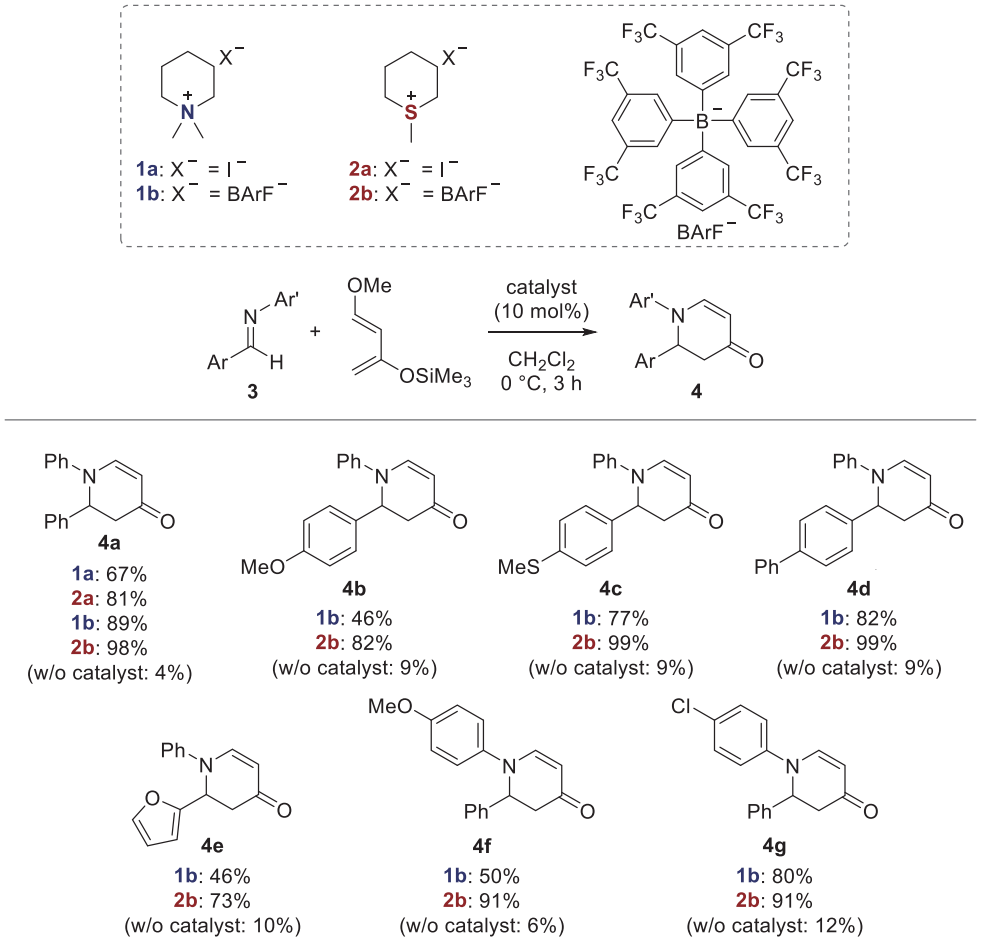
We initially investigated the catalytic activities of tetraalkylammonium and trialkylsulfonium salts in an aza-Diels-Alder reaction of *N*-phenylbenzaldimine **3a** (Scheme 1).[6] In the absence of a catalyst, the reaction with Danishefsky's diene proceeded very slowly at 0 °C to give aza-Diels-Alder product **4a** in 4% yield after 3 h. When tetrabutylammonium iodide was employed as the catalyst under same reaction conditions, the reaction was promoted to a moderate extent (22% yield).[4i] Piperidine-derived cyclic tetraalkylammonium iodide **1a** improved the reactivity to give product **4a** in 67% yield. Related cyclic trialkylsulfonium iodide **2a**, which possesses more acidic α-hydrogens, promoted the reaction efficiently to produce **4a** in good yield (81% yield). Exchanging the iodide counter-anion in onium iodides **1a** and **2a** for tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($BArF^-$; barfate) as the non-coordinating counter-anion (**1b** and **2b**) further improved the yields, and the reaction that used trialkylsulfonium barfate catalyst **2b** gave the highest yield of product **4a** (98% yield). It should be noted that the reactions with sodium barfate (Na^+BArF^-) and tetraarylboric acid (H^+BArF^-) provide product **4a** only in low yields (21 and 16% yields, respectively). These results clearly suggested the importance of cyclic onium salt moieties for efficient promotion of an aza-Diels-Alder reaction.

The substrate generality in the aza-Diels-Alder reaction of imines **3** was examined by using cyclic ammonium and sulfonium salt catalysts **1** and **2** (Scheme 2). In general, both tetraalkylammonium barfate **1b** and trialkylsulfonium barfate **2b** clearly accelerated the aza-Diels-Alder reactions to provide

corresponding products **4** in moderate to good yields. The sulfonium catalyst **2b** was more effective than related ammonium catalyst **1b**.

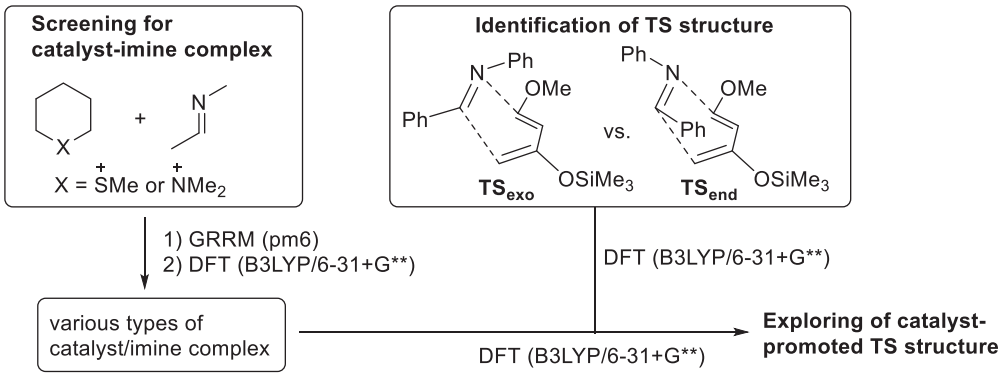


Scheme 1. Effects of catalysts



Scheme 2. Scope of aza-Diels-Alder reaction

To elucidate the origin of the higher catalytic activity of the sulfonium catalyst than the ammonium catalyst, DFT calculations were conducted. Based on the experimental results in which the non-coordinating barfate anion was more effective, the trialkylsulfonium and tetraalkylammonium cation were used as chemical models. The alkyl-onium catalyst/imine complexes were predicted to have a wide variety of interacting modes depending on the number of acidic hydrogen atoms that potentially interact with imine (δ+ in Figure 1). To explore the possible interacting modes of the alkyl-onium catalyst/imine complexes and the corresponding transition state (TS) conformations, the following workflow was adopted (Scheme 3).[7]



Scheme 3. Workflow for systematic exploration of possible transition state conformations in aza-Diels-Alder reaction

The Global Reaction Route Mapping (GRRM) method[8] was firstly performed at the PM6 level using a simplified model system (exchanging Ar group for Me group) to find various types of alkyl-onium catalyst/imine complexes (**CP**) without prejudice. Whereas the anharmonic downward distortion following (ADDF) approach in the GRRM method can be applied to find all equilibrium structures (EQs) on the potential energy surface, the large-ADDF (*l*-ADDF) search can quickly explore lower energy EQs connected via low isomerization barriers. Therefore, to reduce computational costs, the *l*-ADDF search was performed in two modes: (i) use of a certain optimized structure of alkyl-onium catalyst/imine complex, or (ii) addition of imine with random initial position to alkyl-onium catalyst. All the alkyl-onium catalyst/imine complexes obtained by the GRRM method were further re-optimized at the B3LYP/6-31+G** level.[9] On the other hand, the TS structure in the aza-Diels-Alder reaction without the catalyst was investigated at the B3LYP/6-31+G** level to identify the energetically stable conformation (**TSexo**, **TSend**). Next, the optimal TS structure without the catalyst (DFT) was combined with various types of alkyl-onium catalyst/imine complexes (GRRM/DFT) to systematically explore possible and stable TS conformations. Finally, the most promising TS structures were expanded to the realistic model and optimized at the dispersion-corrected B3LYP-D3/6-31+G** level.

The *l*-ADDF search (LADD = 20, NLowest = 5) in the two modes (i and ii) gave totally 31 EQs (i: 2 EQs, ii: 29 EQs) and 25 EQs (i: 20 EQs, ii: 5 EQs) in sulfonium catalyst/imine and ammonium catalyst/imine complexes, respectively. All the alkyl-onium catalyst/imine complexes obtained by the GRRM method were classified and compensated depending on the structural properties and further re-optimized at the B3LYP/6-31+G** level (Figures 2 and 3). In the sulfonium catalyst/imine complex (**CPs**), two CH moieties form a bridged structure through non-classical CH…N hydrogen bonds, in which imine interacts with both acidic hydrogen atoms simultaneously. Such a bridged structure is the preferential interacting mode in the urea/imine complex.[10] As for the chair-like conformation of the catalyst, four possible bridging modes (**CPs_1** - **CPs_4**) are located within small energy range (< 2 kcal/mol). In contrast, a catalyst structure that has been deformed from the stable chair-like conformation significantly destabilizes the sulfonium catalyst/imine complex (**CPs_5**). In a manner similar to **CPs**, the ammonium catalyst/imine complex (**CPn**) forms a bridged structure through the dual non-classical CH…N hydrogen bond. **CPn** has a wider variety of interacting modes than **CPs** because of the larger number of acidic hydrogen atoms. Whereas the relatively stable **CPn** lower than 1.5 kcal/mol have a chair-like conformation (**CPn_1** – **CPn_4**), a distorted catalyst structure is observed in less stable **CPn_5** – **CPn_8**.

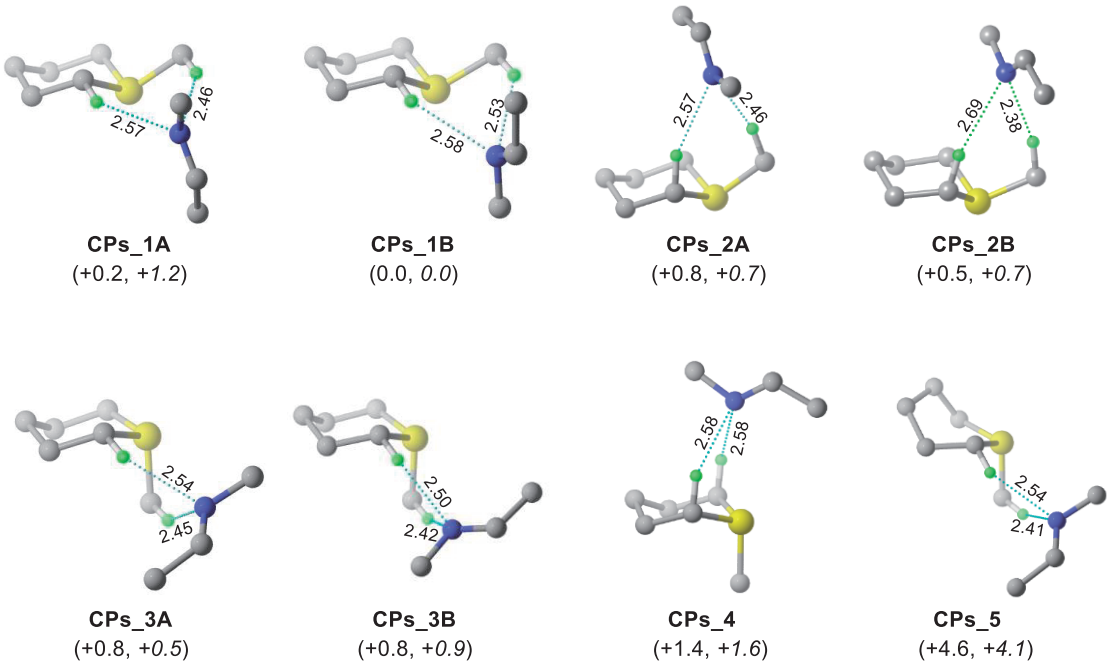


Figure 2. Three-dimensional (3D) structures and relative energies (Gibbs free energies are shown in *italics*) of sulfonium catalyst/imine complexes (**CPs**) at the B3LYP/6-31+G** level. Interacting hydrogen atoms are highlighted in green (other hydrogen atoms are omitted). Hydrogen bond distances are shown in Å.

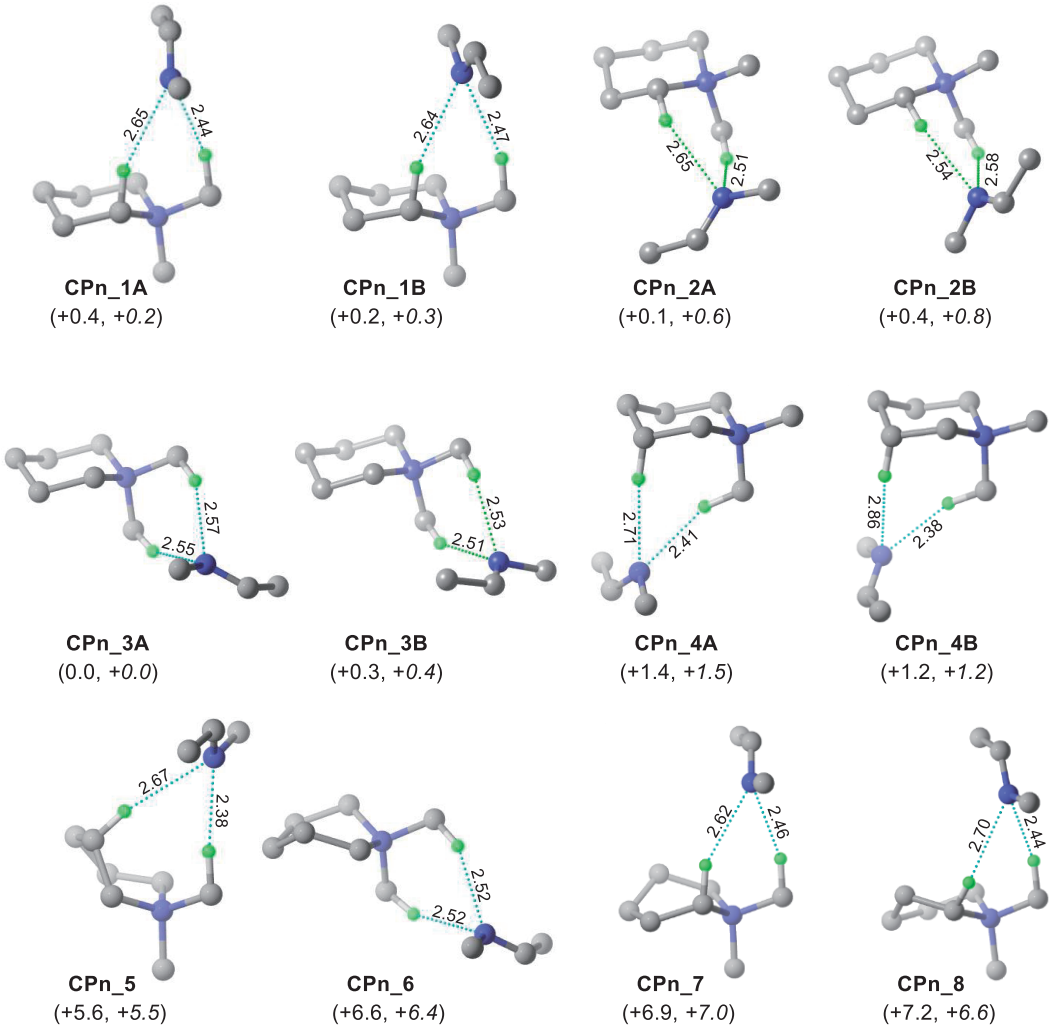


Figure 3. Three-dimensional (3D) structures and relative energies (Gibbs free energies are shown in *italics*) of ammonium catalyst/imine complexes (**CPn**) at the B3LYP/6-31+G** level. Interacting hydrogen atoms are highlighted in green (other hydrogen atoms are omitted). Hydrogen bond distances are shown in Å.

Next, the TS structures in the aza-Diels-Alder reaction without a catalyst were investigated to identify energetically more stable conformations (**TSexo**, **TSend**, Figure 4). Both **TSexo** and **TSend** are located at almost the same energy level. The asynchronicity in bond formation is larger in **TSend** than **TSexo**. With insights into the TS structures in hand, slightly more stable **TSend** was combined with relatively stable **CPs_1** – **CPs_4** and **CPn_1** – **CPn_4** to explore possible TS conformations at the B3LYP/6-31+G** level (using the simplified model system to reduce computational costs).

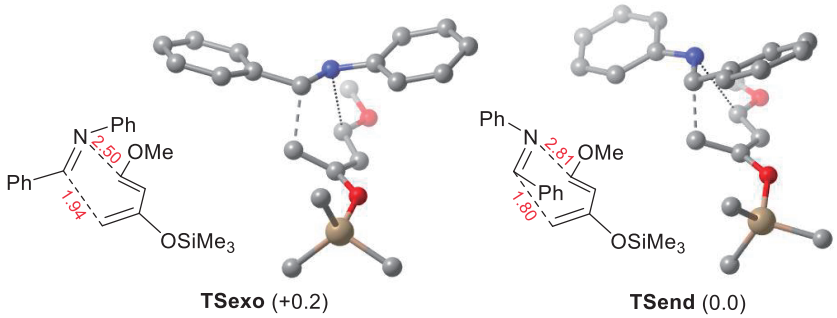


Figure 4. Three-dimensional (3D) structures and relative energies of **TSexo** and **TSend** in aza-Diels-Alder reaction (B3LYP/6-31+G**)

The relative energies of the corresponding TS structures (sulfonium catalyst: **TSs**, ammonium catalyst: **TSn**) show a similar tendency to those of **CP** (Table 1).[11] In **TSs** and **TSn**, the possible TS conformations are located within a small energy range. In the relatively stable TS conformations, the structural properties of the corresponding **CP** and **TSend** are retained, which are the bridged structure through the dual non-classical CH…N hydrogen bond and asynchronous C-C bond formation (Figure 5). One of the two non-classical CH…N hydrogen bonds between catalyst and imine is significantly enhanced because of the developing negative charge on the nitrogen atom in the TS structure. Those computational results indicate that the relative energy difference of **TS** shows good correlation with that of **CP** and the arrangement of substrates on an alkyl-onium catalyst does not affect the stability of **TS**. Therefore, we expanded the energetically most stable **TSs_1A** and **TSn_2B** to a realistic model and investigated them in detail (**TSs_1A_real** and **TSn_2B_real**).

Table 1. Relative energies of various TS structures in the sulfonium catalyst (**TSs**) and the ammonium catalyst (**TSn**) promoted aza-Diels-Alder reaction (B3LYP/6-31+G**)

TSs (sulfonium catalyst)			**TSn** (ammonium catalyst)		
	ΔE	ΔG		ΔE	ΔG
TSs_1A	0.0	0.0	**TSn_1A**	0.0	+2.0
TSs_1B	0.0	+0.8	**TSn_1B**	-0.1	+0.8
TSs_2A	+0.3	+1.4	**TSn_2A**	-0.1	+1.3
TSs_2B	+0.2	+1.3	**TSn_2B**	0.0	0.0
TSs_3A	+0.6	+0.7	**TSn_3A**	-0.3	+1.1
TSs_3B	+0.5	+1.2	**TSn_3B**	-0.2	+1.0
TSs_4	+2.1	+2.4	**TSn_4A,B**	+1.5	+3.1

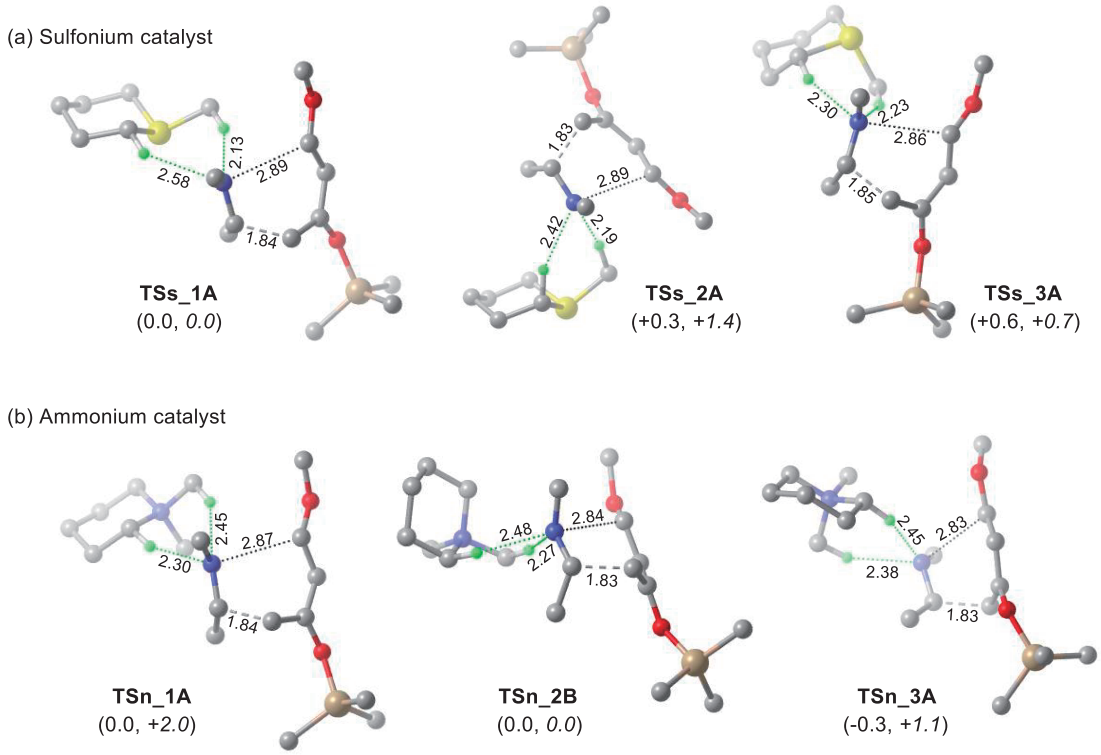


Figure 5. Three-dimensional (3D) structures and relative energies (Gibbs free energies are shown in *italics*) of selected TS conformations (a: **TSs**, b: **TSn**) at the B3LYP/6-31+G** level. Interacting hydrogen atoms are highlighted in green (other hydrogen atoms are omitted). Hydrogen bond distances are shown in Å.

Interestingly, the optimized structures of **TSs_1A_real** and **TSn_2B_real** are significantly different from their corresponding simplified models. The introduction of Ph groups on imine has a great impact on the interacting mode between imine and catalyst (Figure 6a). In both TS structures, the dual CH…N hydrogen bond is broken and the alkyl-onium catalyst activates imine through multiple CH/π interaction and a single non-classical CH…N hydrogen bond, as revealed by non-covalent interaction (NCI) analysis (Figure 6b).[12] In **TSs_1A_real**, a significantly strong CH/π interaction (shown in green region) exists between the Ph group derived from benzaldehyde and the S-Me moiety of the sulfonium catalyst. On the other hand, **TSn_2B_real** exhibits relatively weaker (smaller green region) CH/π interaction between the two Ph groups of imine and the ammonium catalyst. The relative stability of TS in the sulfonium and ammonium salt catalyzed aza-Diels-Alder reactions was estimated as the energy differences between TS structures (**TSs_1A_real** and **TSn_2B_real**) and the sum of alkyl-onium catalyst, imine, and diene. **TSs_1A_real** is located at the relatively lower energy level (5.9 kcal/mol) than **TSn_2B_real** (7.7 kcal/mol) in qualitatively consistent with the experimentally observed higher catalytic activity of the sulfonium catalyst. Both **CP** and **TS** in the sulfonium salt catalyzed reaction are more stable than those in the ammonium salt catalyzed reaction (Figure S1 in Supporting Information). Whereas both sulfonium

and ammonium catalysts have rigid structures and would be difficult to deform, the relative energy difference between the substrate parts in **TSs_1A_real** and **TSn_2B_real** is only 0.05 kcal/mol. Therefore, we suppose that the main contributor to the high catalytic activity of the sulfonium catalyst is the interaction energy difference between substrate and catalyst. Indeed, the basis set super position error (BSSE)-corrected interaction energy between substrate and catalyst is 1.1 kcal/mol larger in **TSs_1A_real** than **TSn_2B_real**.

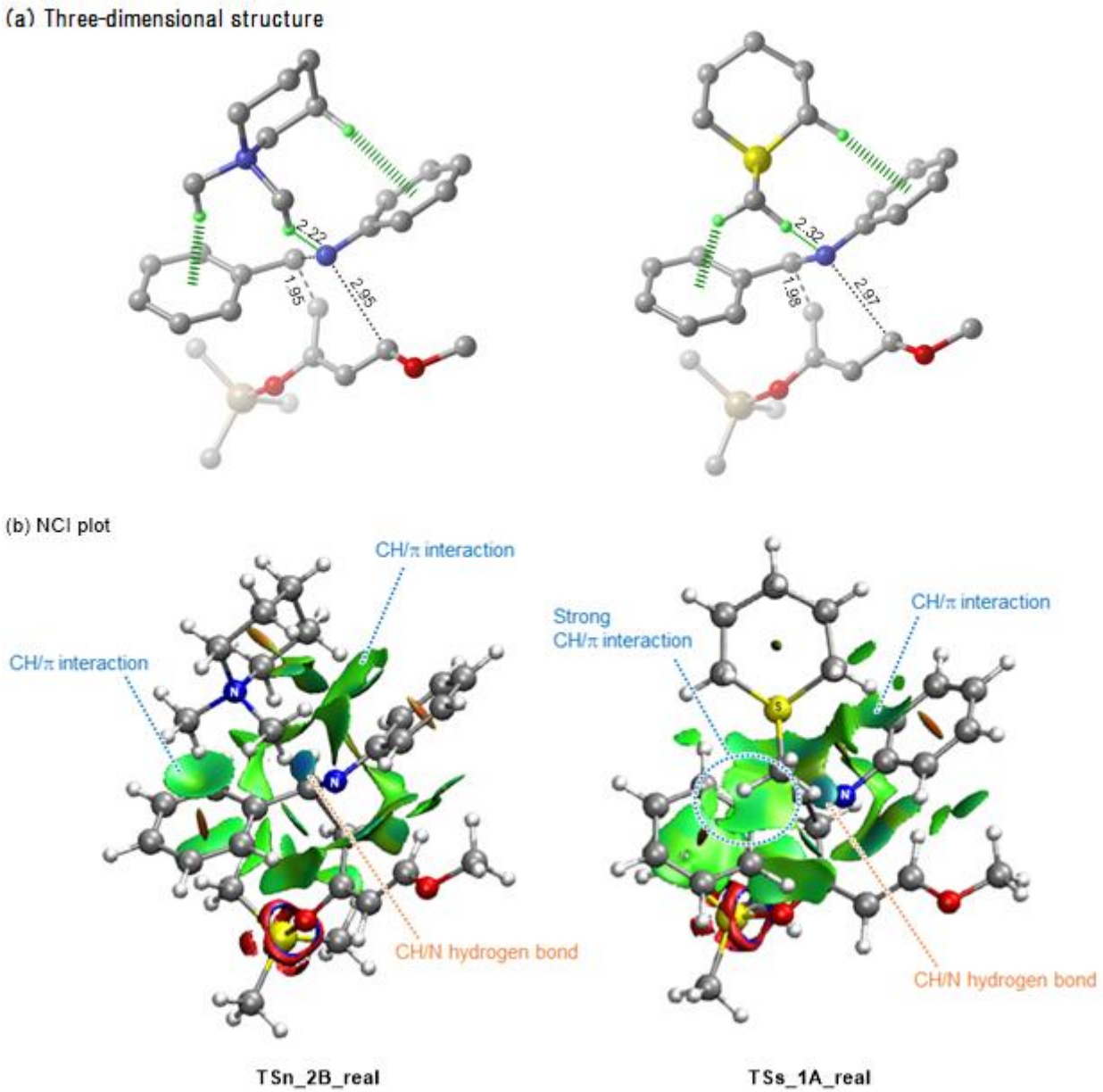


Figure 6. (a) Three-dimensional (3D) structures and (b) NCI plots of **TSs_1A_real** and **TSn_2B_real** at the B3LYP-D3/6-31+G** level. Interacting hydrogen atoms are highlighted in green (other hydrogen atoms are omitted). Hydrogen bond distances are shown in Å. Gradient surfaces correspond to s = 0.25 au and a color scale of $-0.05 < \rho < 0.05$ au (blue, strongly attractive; green, weakly attractive; red, strongly repulsive).

CONCLUSION

In conclusion, we have presented the details of the activation modes of cyclic trialkylsulfonium and tetraalkylammonium salts that are used as catalysts in the aza-Diels-Alder reaction. Various relatively stable interacting modes of each alkyl-onium catalyst/imine complex were identified by the GRRM method followed by DFT calculations. In the corresponding TS structures, multiple CH/π interactions and a single non-classical CH…N hydrogen bond play a crucial role in the activation of imine. The large interaction energy between substrate and catalyst is attributed to the notably high catalytic activity of the sulfonium catalyst in the aza-Diels-Alder reaction.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-AL 400 NMR instrument (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Tetramethylsilane (TMS) was the internal standard (0 ppm) for ^{1}H NMR, and $CDCl_3$ was the internal standard (77.0 ppm) for ^{13}C NMR. The following abbreviations were used to express the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad. High-resolution mass spectra (HRMS) were measured on a JEOL JMS-700N. Infrared spectra (IR) were measured on a JASCO FT/IR-4200 spectrometer. All reactions were monitored by thin-layer chromatography using Merck precoated TLC plates (silica gel 60GF-254, 0.25 mm) and visualization was accomplished by the use of a UV lamp (254 nm) or such dyes as $KMnO_4$. The products were purified by flash column chromatography on silica gel. Dehydrated solvents were purchased from Kanto Chemical.

Synthesis of catalysts 1 and 2.

Catalysts **1** and **2** were prepared according to the literature.[3]

General procedure for aza-Diels-Alder reactions.

To a solution of imine **3** (0.10 mmol) and catalyst (0.010 mmol, 10 mol%) in dehydrated CH_2Cl_2 (2.0 mL) was added Danishefsky's diene (0.15 mmol) at 0 °C under N_2 atmosphere, and the reaction mixture was stirred for 3 h at 0 °C. Then, aqueous 1N HCl (50 μL) was added, and the reaction mixture was further stirred for 5 min at 0 °C. The reaction mixture was quenched by adding H_2O at 0 °C and extracted three times with CH_2Cl_2 at room temperature. The combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 1/0–0/1 as eluent) to give product **4**.

Characterizations of aza-Diels-Alder products 4.

Aza-Diels-Alder products **4**, except **4c**, are known products.[3,6]

2-(4-Methylthiophenyl)-1-phenyl-2,3-dihydropyridin-4(1*H*)-one (4c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.02 (dd, *J* = 0.8, 8.8 Hz, 2H), 5.23–5.29 (m, 2H), 3.29 (dd, *J* = 7.2, 16.8 Hz, 1H), 2.76 (ddd, *J* = 1.2, 3.2, 16.4 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.1, 148.1, 144.6, 138.2, 134.6, 129.5, 126.9, 126.6, 124.4, 118.5, 102.9, 61.3, 43.3, 15.6; IR (neat): 3046, 2920, 1645, 1574, 1493, 1339, 1323, 1302, 1293, 1278, 1205, 757 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{18}NOS$: 296.1109 ($[M+H]^+$), found 296.1109.

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Numbers JP18H04660 (Hybrid Catalysis for M.Y.), JP17KT0011 (for M.Y.) and JP16K05780 (for S.S.).

REFERENCES AND NOTES

1. (a) G. A. Olah, *Aldrichimica Acta*, 1973, **6**, 7; (b) E. Vedejs and F. G. West, *Chem. Rev.*, 1986, **86**, 941; (c) G. K. S. Prakash, *J. Org. Chem.*, 2006, **71**, 3661; (d) *Recent Developments in Carbocation and Onium Ion Chemistry*, ed. by K. K. Laali, American Chemical Society, Washington DC, 2007 (ACS Symposium Series 965); (e) J. B. Sweeney, *Chem. Soc. Rev.*, 2009, **38**, 1027; (f) X. Guo and W. Hu, *Acc. Chem. Res.*, 2013, **46**, 2427; (g) S. Preshlock, M. Tredwell, and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719.
2. (a) E. V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, VCH, Weinheim, 1993; (b) C. M. Starks, C. L. Liotta, and M. Halpern, *Phase-Transfer Catalysis*, Chapman & Hall, New York, 1994; (c) *Handbook of Phase-Transfer Catalysis*, ed. by Y. Sasson and R. Neumann, Blackie Academic & Professional, London, 1997; (d) *Phase-Transfer Catalysis*, ed. by 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 and K. Maruoka, *Acc. Chem. Res.*, 2004, **37**, 526; (g) T. Ooi and K. Maruoka, *Angew. Chem. Int. Ed.*, 2007, **46**, 4222; (h) *Asymmetric Phase-Transfer Catalysis*, ed. by K. Maruoka, Wiley-VCH, Weinheim, 2008; (i) S.-s. Jew and H.-g. Park, *Chem. Commun.*, 2009, 7090; (j) T. Werner, *Adv. Synth. Catal.*, 2009, **351**, 1469; (k) D. Enders and T. V. Nguyen, *Org. Biomol. Chem.*, 2012, **10**, 5327; (l) J. Novacek and M. Waser, *Eur. J. Org. Chem.*, 2013, 637; (m) S. Shirakawa and K. Maruoka, *Angew. Chem. Int. Ed.*, 2013, **52**, 4312; (n) S. Kaneko, Y. Kumatabara, and S. Shirakawa, *Org. Biomol. Chem.*, 2016, **14**, 5367; (o) S. Liu, Y. Kumatabara, and S. Shirakawa, *Green Chem.*, 2016, **18**, 331.
3. (a) S. Shirakawa, S. Liu, S. Kaneko, Y. Kumatabara, A. Fukuda, Y. Omagari, and K. Maruoka, *Angew. Chem. Int. Ed.*, 2015, **54**, 15767; (b) Y. Kumatabara, S. Kaneko, S. Nakata, S. Shirakawa,

and K. Maruoka, *Chem. Asian J.*, 2016, **11**, 2126; (c) S. Kaneko, Y. Kumatabara, S. Shimizu, K. Maruoka, and S. Shirakawa, *Chem. Commun.*, 2017, **53**, 119.

4. For related studies, see: (a) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 994; (b) M. T. Reetz, S. Hütte, and R. Goddard, *J. Am. Chem. Soc.*, 1993, **115**, 9339; (c) M. T. Reetz, S. Hütte, and R. Goddard, *J. Phys. Org. Chem.*, 1995, **8**, 231; (d) M. T. Reetz, S. Hütte, R. Goddard, and C. Robyr, *Chem. Eur. J.*, 1996, **2**, 382; (e) M. T. Reetz, S. Hütte, and R. Goddard, *J. Prakt. Chem.*, 1999, **341**, 297; (f) R. Goddard, H. M. Herzog, and M. T. Reetz, *Tetrahedron*, 2002, **58**, 7847; (g) C. E. Cannizzaro and K. N. Houk, *J. Am. Chem. Soc.*, 2002, **124**, 7163; (h) T. Ohshima, T. Shibuguchi, Y. Fukuta, and M. Shibasaki, *Tetrahedron*, 2004, **60**, 7743; (i) Y. Park, E. Park, H. Jung, Y.-J. Lee, S.-s. Jew, and H.-g. Park, *Tetrahedron*, 2011, **67**, 1166; (j) T. C. Cook, M. B. Andrus, and D. H. Ess, *Org. Lett.*, 2012, **14**, 5836; (k) C. Thomas, A. Milet, F. Peruch, and B. Bibal, *Polym. Chem.*, 2013, **4**, 3491; (l) C. Thomas, S. Brut, and B. Bibal, *Tetrahedron*, 2014, **70**, 1646; (m) T. Kamachi and K. Yoshizawa, *Org. Lett.*, 2014, **16**, 472; (n) C. P. Johnston, A. Kothari, T. Sergeieva, S. I. Okovytyy, K. E. Jackson, R. S. Paton, and M. D. Smith, *Nat. Chem.*, 2015, **7**, 171; (o) Q. Peng and R. S. Paton, *Acc. Chem. Res.*, 2016, **49**, 1042; (p) J. Novacek, J. A. Izzo, M. J. Vetticatt, and M. Waser, *Chem. Eur. J.*, 2016, **22**, 17339; (q) P. Nagorny and Z. Sun, *Beilstein J. Org. Chem.*, 2016, **12**, 2834.
5. For preliminary communications, see references 3b and 3c.
6. (a) Y. Yuan, X. Li, and K. Ding, *Org. Lett.*, 2002, **4**, 3309; (b) C. Loncaric, K. Manabe, and S. Kobayashi, *Chem. Commun.*, 2003, 574; (c) Y. Takeda, D. Hisakuni, C.-H. Lin, and S. Minakata, *Org. Lett.*, 2015, **17**, 318; (d) M. Kaasik, A. Metsala, S. Kaabel, K. Kriis, I. Järving, and T. Kanger, *J. Org. Chem.*, 2019, **84**, 4294; (e) J. Kollmann, Y. Zhang, W. Schilling, T. Zhang, D. Riemer, and S. Das, *Green Chem.*, 2019, **21**, 1916.
7. For selected examples of the similar workflow that explored possible TS conformations, see: (a) G. P. Petrova, H.–B. Li, K. Maruoka, and K. Morokuma, *J. Phys. Chem. B*, 2014, **118**, 5154; (b) M. Hatanaka and K. Morokuma, *ACS Catal.*, 2015, **5**, 3731; (c) F. Duarte and R. S. Paton, *J. Am. Chem. Soc.*, 2017, **139**, 8886; (d) M. Odagi, H. Araki, C. Min, E. Yamamoto, T. J. Emge, M. Yamanaka, and D. Seidel, *Eur. J. Org. Chem.*, 2019, 486.
8. (a) K. Ohno and S. Maeda, *Chem. Phys. Lett.*, 2004, **384**, 277; (b) K. Ohno and S. Maeda, *J. Phys. Chem. A*, 2006, **110**, 8933; (c) S. Maeda, K. Ohno, and K. Morokuma, *Phys. Chem. Chem. Phys.*, 2013, **15**, 3683.
9. Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven,

J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

10. P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 10012.
11. Facial selectivity of imine should be considered. In several TS structures, the diastereomeric TS structures corresponding to the facial selectivity were compared and found to have almost the same energy level.
12. (a) E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen, and W. Yang, *J. Am. Chem. Soc.*, 2010, **132**, 6498; (b) J. Contreras-García, E. R. Johnson, S. Keinan, R. Chaudret, J.-P. Piquemal, D. N. Beratan, and W. Yang, *J. Chem. Theory Comput.*, 2011, **7**, 625.