

Catalytic Effects of Ammonium and Sulfonium Salts and External Electric Fields on Aza-Diels–Alder Reactions

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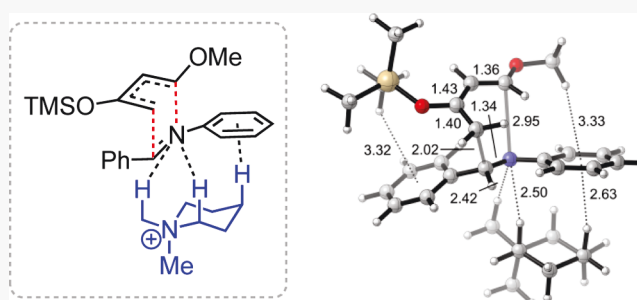
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ABSTRACT: The mechanism of the aza-Diels–Alder reaction catalyzed by tetraalkylammonium or trialkylsulfonium salts is explored with density functional theory. Favorable electrostatic interactions between the dienophile and the charged catalyst stabilize the highly polar transition state, leading to lower free energy barriers and higher dipole moments. Endo selectivity is predicted for both uncatalyzed and catalyzed systems. We also computationally evaluate the effects of oriented external electric fields (EEFs) on the same aza-Diels–Alder reaction, demonstrating that very strong EEFs would be needed to achieve the catalytic strength of these cationic catalysts.



INTRODUCTION

External electric fields (EEFs) are being explored with great interest as a means to lower chemical reaction barriers (Figure 1).¹ To achieve catalysis, the EEF must be oriented to

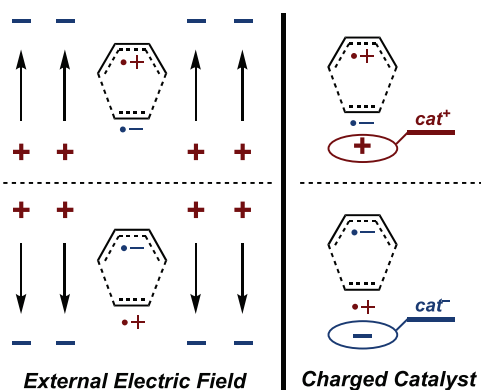


Figure 1. EEFs and charged catalysts most likely to stabilize polar Diels–Alder TSs.

maximize favorable Coulombic interactions with a polar transition state (TS). In the 1990s, Wilcox's studies of ion-pair effects on reaction rates and selectivities demonstrated how electrostatic fields could influence the rates of reactions with polar TSs,² including cycloadditions.^{2c,g} More recently, theoretical studies have demonstrated the potential of electrostatic catalysis to enhance reaction rates and selectivities,³ and a number of experimental examples in addition to Wilcox's have emerged, including the use of ion pairs to alter

gold-catalyzed cyclizations^{3g,h} and the application of oriented electric fields on Diels–Alder and other reactions.⁴ Currently, most methods involve the application of strong EEFs in conjunction with molecular immobilization through surface chemistry techniques.⁴ An alternative approach is to use ionic catalysts to generate intense local oriented fields in the vicinity of the reactants (Figure 1).^{2,5} This approach is akin to enzymatic catalysis, which often relies on the electrostatic effects of strategically located charged or polar functional groups.⁶

In 2015, Maruoka and co-workers demonstrated tetraalkylammonium salt catalysis in Mannich-type reactions (Scheme 1a).⁷ Shortly after, the authors reported the application of tetraalkylammonium and trialkylsulfonium salts as catalysts for the aza-Diels–Alder reactions between imine **1** and Danishefsky's diene **2** (Scheme 1b).⁸ The yield for desilylated aza-Diels–Alder adduct **3** was improved from 4% without the catalyst to 67% with **4a**. Replacing the iodide counterion in **4a** with the noncoordinating BARF anion further improved the yield to 89%. Trialkylsulfonium salts were more effective catalysts for this transformation than tetraalkylammonium salts. NMR titration experiments suggested association of the onium catalysts with the imine (dienophile), but no further evidence was obtained regarding the detailed reaction mechanism or the origins of catalysis. We performed a

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Scheme 1. Mannich and Aza-Diels–Alder Reactions Catalyzed by Ammonium and Sulfonium Salts

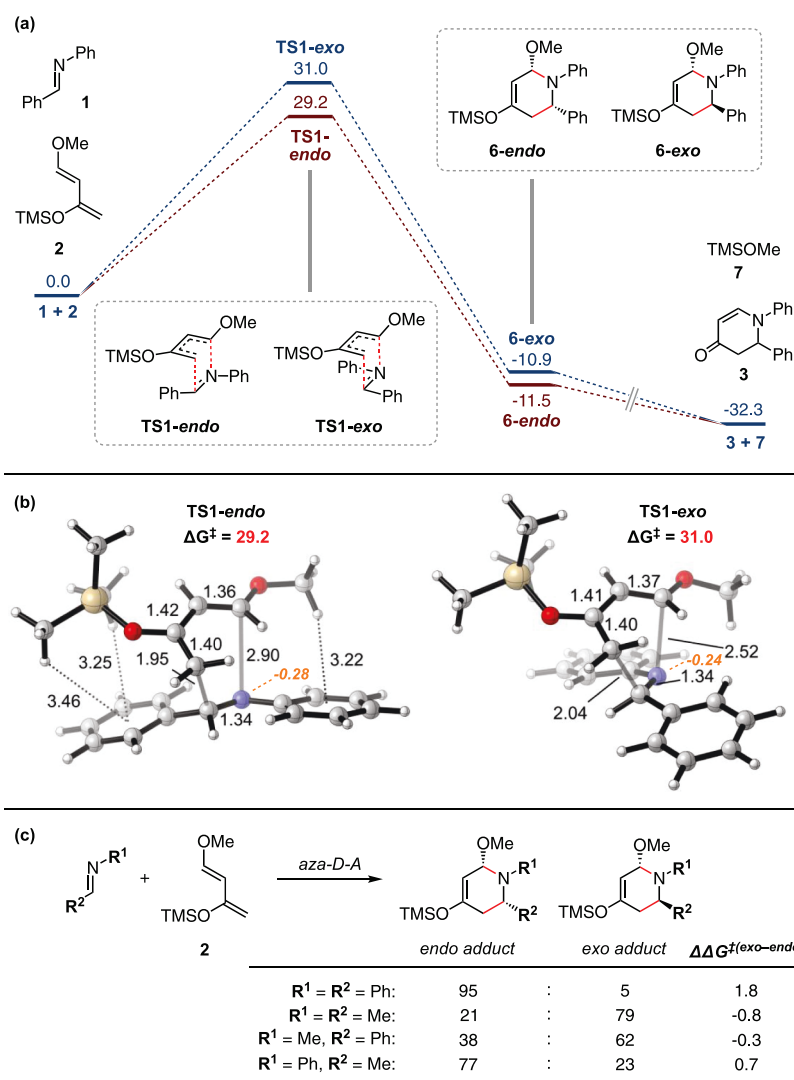
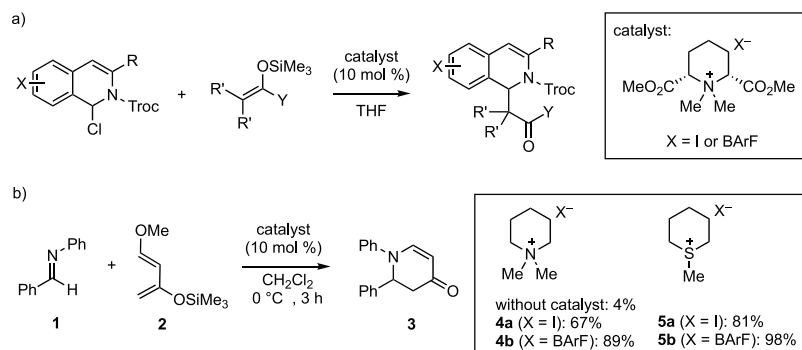


Figure 2. (a) Free energy profile of the aza-Diels–Alder reaction between imine **1** and Danishefsky's diene **2**. Interatomic distances are in Å. Energies are in kcal/mol. (b) Calculated TSs for the aza-Diels–Alder reaction between **1** and **2**. (c) Calculated endo/exo adduct ratios for the aza-Diels–Alder reaction of **2** with differently substituted imines.

computational study with density functional theory (DFT) quantum mechanics to elucidate the mechanism of the aza-Diels–Alder reaction between **1** and **2** and provide insight into how the onium catalysts lower the reaction barriers. The simple structures of the onium catalysts also facilitated a comparison of rate effects to that predicted for EEFs.

COMPUTATIONAL METHODS

DFT calculations were performed using Gaussian 09, revision D.01.⁹ Geometry optimizations and frequency calculations were performed at the ω B97X-D/6-31G(d) level of theory¹⁰ with the conductor-like polarizable continuum model (CPCM)¹¹ using dichloromethane ($\epsilon = 8.9$) to incorporate solvation effects. A pruned (99,590) grid (specified by the keyword `int = ultrafine`) was used for optimizations to minimize directional variations in calculated free energy

corrections.¹² Thermal contributions to free energies were calculated from vibrational frequencies using the quasi-rigid rotor harmonic oscillator approach of Grimme¹³ and Head-Gordon's enthalpy corrections.¹⁴ All optimized geometries were verified by frequency computations as minima or first-order saddle-point structures. Single-point energy calculations on the optimized geometries were computed at the ω B97X-D/6-311+G(d,p), CPCM (dichloromethane) level of theory. EEF effects on single-point electronic energies were calculated using the "field = $M \pm N$ " keyword on molecular geometries optimized in the absence of EEFs. Conformational searches were carried out in MacroModel¹⁵ and Spartan '16¹⁶ using the MMFFs force field, and DFT reoptimizations were performed on all conformers within a 10 kcal/mol cutoff. All 3D renderings of stationary points were generated using CYLview.¹⁷

RESULTS AND DISCUSSION

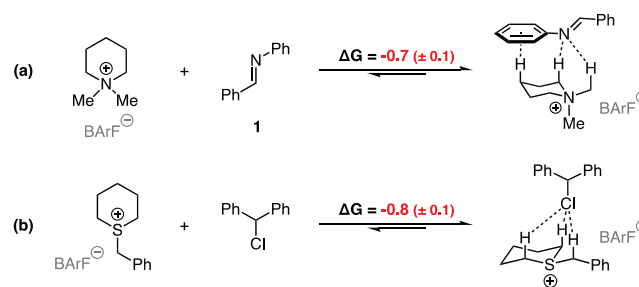
Uncatalyzed Aza-Diels–Alder Reaction. Figure 2a shows the computed free energy profile of the uncatalyzed aza-Diels–Alder reaction between imine **1** and Danishefsky's diene **2**. The free energy barrier is 29.2 kcal/mol for the endo pathway, and the exo pathway is 1.8 kcal/mol higher in energy. These barriers correspond to a very slow process under the reaction conditions, in good agreement with the experimentally observed low yield (4%) of the product. Desilylation of adduct **6** is highly exergonic by 20.8 kcal/mol or more to yield the stable enone product **3**, with the elimination of one stereocenter. Both **TS1-endo** and **TS1-exo** have geometries characteristic of a concerted but asynchronous reaction, with the forming C–C bonds at 2.0 Å and forming C–N bonds at 2.5–2.9 Å (Figure 2b). The favored endo pathway is more asynchronous, with a larger negative Hirshfeld charge (−0.28) on the imine nitrogen at the TS.

Aza-Diels–Alder reactions typically show exo selectivity because of repulsive electrostatic $n-\pi$ interactions between the nitrogen lone pair and the diene π system (the exo-lone-pair effect).¹⁸ To probe the origin of the unusual endo selectivity of this reaction, we calculated the endo/exo ratios for aza-Diels–Alder reactions between **2** and imines with different substituents (Figure 2c). When both of the imine's phenyl rings are substituted by methyl groups, the reaction has a moderate exo preference. With a phenyl substituent in either the R¹ or R² position, the intrinsic exo selectivity is lowered or reversed. These results suggest that the endo selectivity is due to favorable electrostatic $CH\cdots\pi$ interactions between the imine phenyl rings and substituents on the Danishefsky's diene.

Effect of Charged Catalysts and EEFs. Early in our study, we found that commonly used implicit solvent models such as solvent model density (SMD) and CPCM were not adequate for calculating free energies of complexation between imine **1** and charged ammonium or sulfonium catalysts. Though experimental NMR data show exergonic complex formation (Scheme 2), SMD and CPCM solvent models predicted these complexation to be 2–3 kcal/mol uphill at all tested levels of theory (see Supporting Information). As a result, we elected to use experimentally determined ΔG values for the complexation processes¹⁹ while studying the ammonium- and sulfonium-catalyzed aza-Diels–Alder reactions.

The calculated geometries of lowest-energy complexes between **1** and charged -onium catalysts are shown in Figure 3. Short interaction distances are observed between the imine nitrogen and the hydrogens α to the heteroatom on the catalyst, involving favorable electrostatic interactions. These

Scheme 2. Experimental Free Energies of Complexation (in kcal/mol) between Charged Ammonium and Sulfonium Catalysts and Imine Dienophile **1 of Benzhydryl Chloride**



interaction distances are shorter in the sulfonium–imine complex, consistent with the higher acidity of the sulfonium ion. In addition, electrostatic $CH\cdots\pi$ interactions involving the imine phenyl substituents may contribute to the stabilities of these complexes.

Figure 4a shows the free energy profile of the ammonium-catalyzed aza-Diels–Alder reaction between **1** and **2**. We explored the free cation because the most effective salt, with the BARF counterion, is expected to have weak anion association. More strongly coordinating anions (e.g., halides) are found to give less effective catalysis.⁸ The free energy barrier for the catalyzed reaction is 25.2 kcal/mol, which is 4.0 kcal/mol lower than for the uncatalyzed system. The calculated intrinsic reaction coordinate (IRC) of **TS2-endo** confirms that the mechanism remains concerted but asynchronous, with no intervening potential energy surface (PES) minima. Both forming bonds (C–C at 2.02 Å, C–N at 2.95 Å) are longer than in the uncatalyzed **TS1-endo**, indicating an earlier TS (Figure 4b). The magnitude of the endo preference (2.0 kcal/mol) is largely unchanged from the uncatalyzed system (1.8 kcal/mol), consistent with the observation that the same favorable $CH\cdots\pi$ interactions between **1** and **2** still distinguish the endo TS from the exo. In both **TS2-endo** and **TS2-exo**, the CH bonds α to the ammonium N are close to the partially negative imine nitrogen, consistent with the fact that the positive charge on the alkyl ammonium ion is mainly distributed around the α -CHs.²⁰ The distances between the imine nitrogen and the partially charged α hydrogens on the catalyst significantly shorten in the TSs compared to **9**, indicating stronger catalyst–dienophile association due to more favorable Coulombic interactions accompanying charge transfer from the diene to the dienophile.

The sulfonium-catalyzed aza-Diels–Alder reaction between **1** and **2** was calculated to have a barrier of 25.4 kcal/mol (Figure 5a), with the endo TS being preferred over the exo by 1.6 kcal/mol (Figure 5b). The calculated IRC for **TS3-endo** shows that the mechanism moves further in the stepwise direction under sulfonium catalysis, with a very shallow PES minimum detected between the two bond formation events. Attempts to optimize this PES minimum structure as an intermediate failed, with the geometry collapsing to the aza-Diels–Alder product instead. This result indicates that the formation of the second bond is essentially barrierless on the PES, although an entropic intermediate²¹ can be expected to exist on the free energy surface. The sulfonium ion is better at stabilizing the polar TSs, in agreement with the higher product yields obtained with sulfonium catalysts (Scheme 1).

The dipole moment vectors (defined here as negative toward positive) of uncatalyzed TSs **TS1-endo** and **TS1-exo**

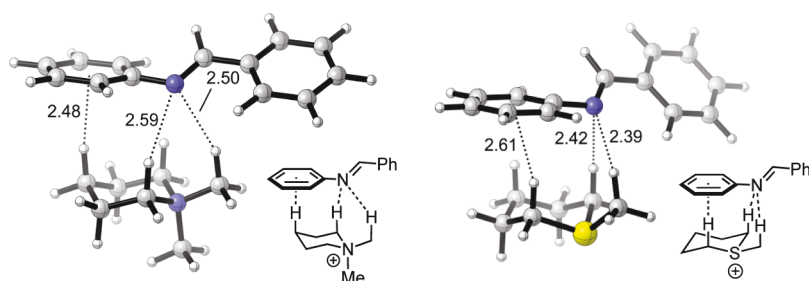


Figure 3. Calculated lowest-energy structures of complexes between imine **1** and charged catalysts. Interatomic distances are in Å.

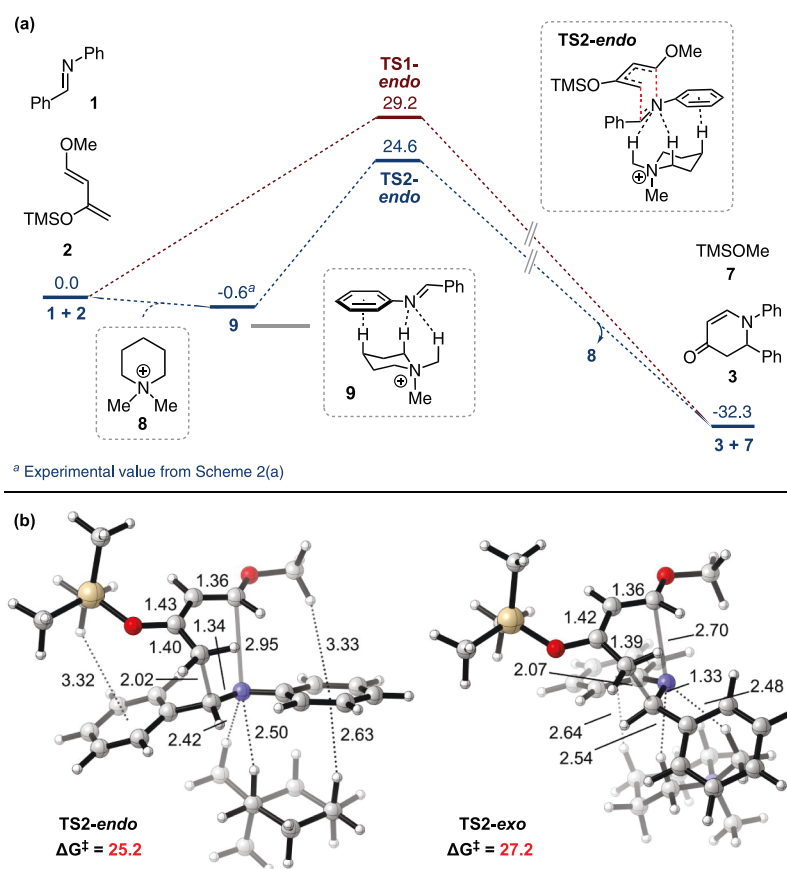


Figure 4. (a) Free energy profile of the aza-Diels–Alder reaction between **1** and **2** catalyzed by ammonium **8**. Interatomic distances are in Å. Energies are in kcal/mol. (b) Calculated TSs for the aza-Diels–Alder reaction catalyzed by ammonium **8**.

are shown in Figure 6a. **TS1-endo** has a larger dipole moment, in line with its more polar and asynchronous nature. We calculated the dipole–cation interaction energy between these TSs and a monovalent cation (Figure 6b),²² assuming an interaction distance r of 5.6 Å from the center of the cationic charge to the center of the TS dipole.^{22–24} For the more asynchronous and polarizable **TS1-endo**, the maximum interaction energies are predicted to be 1.6 kcal/mol, which is qualitatively in agreement with the 10^1 to 10^2 rate acceleration observed experimentally with cationic catalysts. The largest interaction energies are encountered at $\theta = 0^\circ$ (maximum destabilizing effect) and 180° (maximum stabilizing effect). This result is consistent with our observation that in the calculated TSs, the positively charged nitrogen or sulfur centers of the catalysts typically prefer a θ angle very close to the 180° that maximizes the dipole–cation stabilizing effect.

Favorable dipole–cation interactions are expected to polarize the TS and increase the dipole moment. Indeed,

when the charged catalysts are excluded from the TS geometries, we calculated a significant increase in the dipole moments of the diene–dienophile fragments compared to the uncatalyzed TS (Figure 7).

To estimate the strength of oriented EEFs required to produce catalytic effects comparable to these charged onium catalysts, we calculated the free energy barriers and TS dipole moments under a range of EEF strengths, with the fields oriented either parallel or antiparallel to the TS dipole moment vectors (Figure 8). The results show that the exo TS exhibits higher sensitivity to the applied EEFs, although the endo preference is maintained throughout the EEF range we examined, which covered the range discussed in Coote et al.'s study of the effect of an oriented electric field on a Diels–Alder reaction rate.^{4a} When the EEF applied in the Coote et al. study was increased from -0.05 to -0.75 V/nm, a 4.4-fold increase in measured rate was observed, similar to their calculation of a 0.2 kcal/mol lowering of activation barrier for

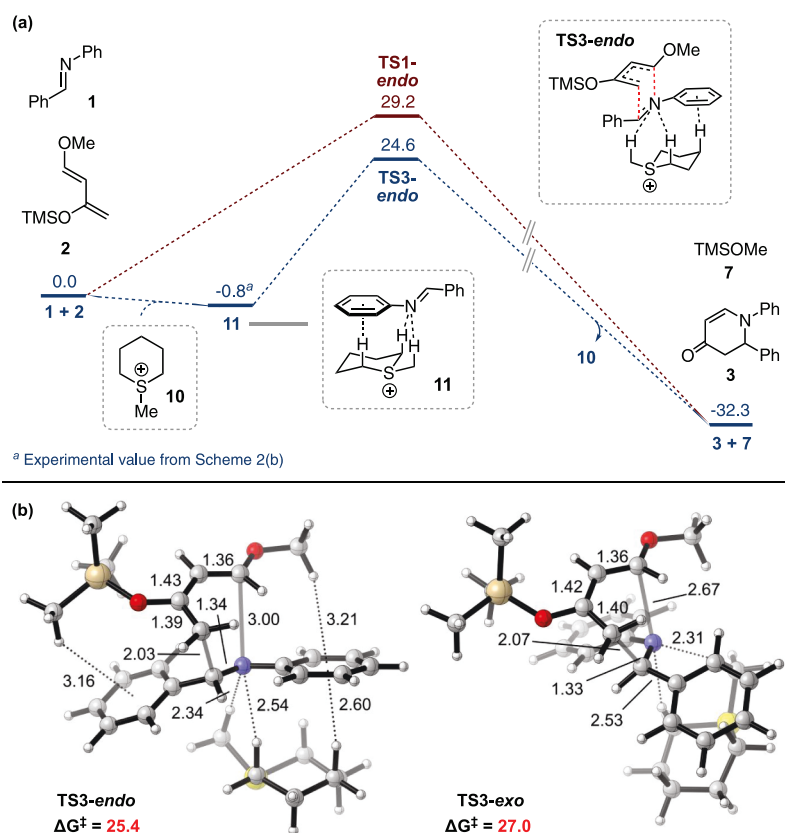


Figure 5. (a) Free energy profile of the aza-Diels–Alder reaction between **1** and **2** catalyzed by sulfonium **10**. Interatomic distances are in Å. Energies are in kcal/mol. (b) Calculated TSs for the aza-Diels–Alder reaction catalyzed by sulfonium **10**.

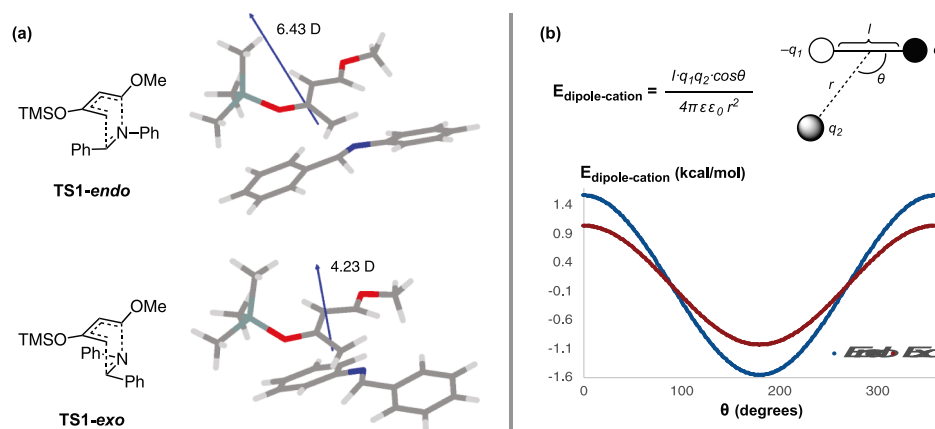


Figure 6. (a) Dipole moment vectors for uncatalyzed aza-Diels–Alder TSs. (b) Plot of dipole–cation interaction energies for uncatalyzed aza-Diels–Alder TSs **TS1-endo** and **TS1-exo**.

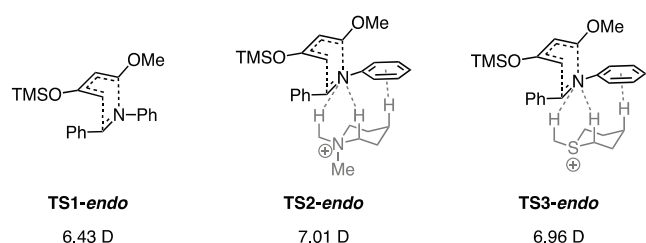


Figure 7. Calculated dipole moments of diene–dienophile fragments in aza-Diels–Alder TSs.

this type of voltage change.^{4a} As the free energy barriers are reduced, we find that the TSs become more polarized with

larger dipole moments (Figure 8). This polarization effect is also stronger for the more sensitive exo TS. At an EEF strength of 1.3 V/nm, the endo TS is stabilized by ~1.7 kcal/mol, similar in magnitude to the maximum dipole–cation interaction energy achieved at a distance of 5.6 Å (Figure 6b).

CONCLUSIONS

We have explored computationally the effect of ammonium and sulfonium catalysts on aza-Diels–Alder reactions with highly polar TSs. The catalysts are predicted to significantly lower the reaction free energy barriers by as much as 4 kcal/mol that would provide a several hundredfold increase in rate, while the impact on endo/exo selectivity was small. The origin

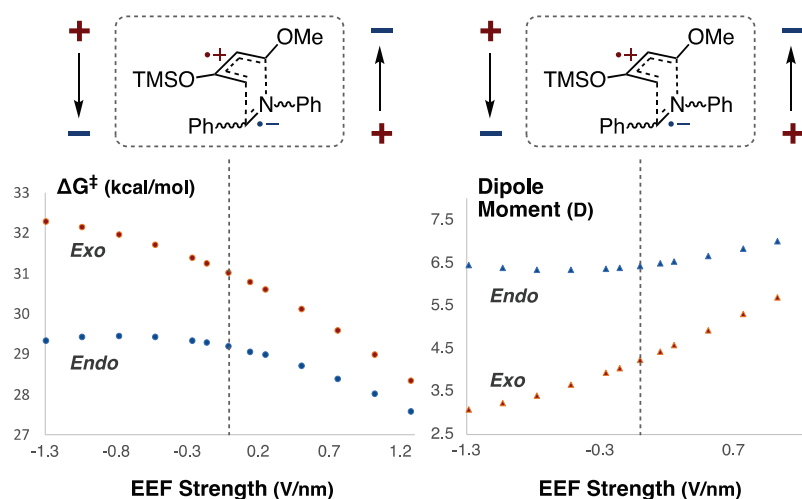


Figure 8. Calculated free energy barriers and TS dipole moments for the aza-Diels–Alder reaction between **1** and **2**, with EEFs applied parallel (or antiparallel) to the dipole moment vectors shown in Figure 6a.

of catalysis is attributed to favorable electrostatic interactions between the cationic catalysts and the developing negative charges on the dienophile in the TSs. As the free energy barriers are lowered, the TSs also became more polarized with larger dipole moments. Unfortunately, only yields of reaction, not reaction rates, have been measured for these reactions to date, so that a quantitative comparison of calculations and experiment is not possible. We show that intense local fields generated by the ammonium and sulfonium ions are comparable in catalytic strength to the strongest EEFs currently being applied in electrostatic catalysis. This chemical approach, demonstrated in the work of Wilcox² and Kanan,^{3g,h} is easily implemented in the synthetic laboratory. Our work highlights the great potential of charged catalysts and ion pairs as a scalable and practical approach to the electrostatic catalysis of reactions with polar TSs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.9b03446>.

Computational details, energies, and cartesian coordinates of computed structures (PDF)

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Notes

The authors declare no competing financial interest.

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(24) The equation shown in Figure 6b holds for r significantly larger than l . In the ammonium- and sulfonium-catalyzed systems, r and l are of approximately the same magnitude. We propose a more sophisticated treatment in the Supporting Information, which yields the same qualitative results and does not impact any of our conclusions.