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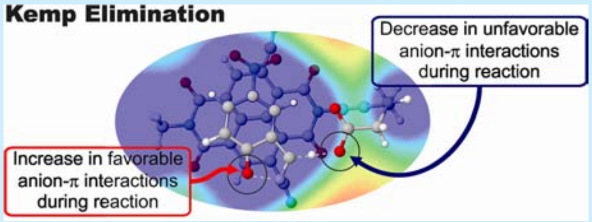
Quantifying the Role of Anion−π Interactions in Anion−π Catalysis

Tongxiang Lu and Steven E. Wheeler*

Department of Chemistry, Texas A&M University, College Station, Texas 77842, United States

Ⓢ *Supporting Information*

ABSTRACT: Matile et al. introduced the concept of anion−π catalysis [*Angew. Chem., Int. Ed.* **2013**, *52*, 9940; *J. Am. Chem. Soc.* **2014**, *136*, 2101], reporting naphthalene diimide (NDI)-based organocatalysts for the Kemp elimination reaction. We report computational analyses of the operative noncovalent interactions, revealing that anion−π interactions actually increase the activation barriers for some of these catalyzed reactions. We propose new catalysts that are predicted to achieve significant lowering of the activation energy through anion−π interactions.

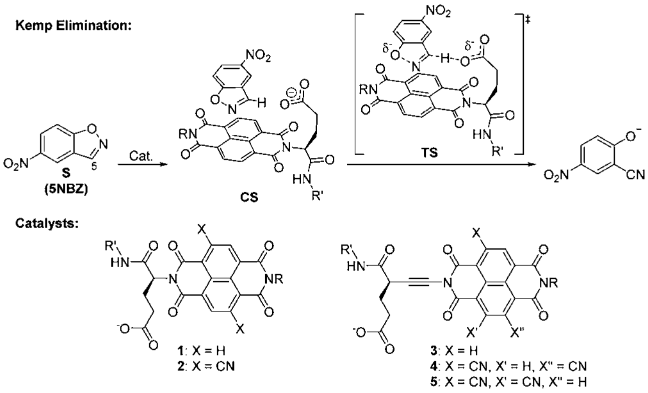


Noncovalent interactions involving aromatic rings provide powerful tools for chemistry and have been exploited in areas ranging from supramolecular chemistry and crystal engineering to organocatalysis.[1] Recent years have witnessed considerable efforts to identify new noncovalent interactions,[2] and anion−π interactions are among a bevy of recent additions to the supramolecular armamentarium.[1i] There has also been significant recent interest in exploiting these noncovalent interactions in the development of more effective organocatalysts,[1e] which can open the door to new catalytic motifs.

Initially proposed in 2002 based on gas-phase computations,[2a−c] anion−π interactions are defined as favorable noncovalent interactions between anions and the faces of π-acidic arenes,[2d,e,3] including substituted benzenes, azabenzenes, and naphthalene diimides (NDIs), among others.[2d,e,4] These noncovalent interactions are primarily electrostatic in nature, although induction and dispersion effects can also contribute.[1c,2e,3,5] In contrast to cation−π interactions,[6] which are ubiquitous in biological systems[7] and have been demonstrated to be pivotal in myriad catalytic processes,[1e,f,8] until recently there were no reports of anion−π catalyzed reactions.

Matile and co-workers[1a,b] recently published the first examples of catalysis based on anion−π interactions. In particular, they demonstrated[1a] that NDIs **1** and **2** (see Scheme 1), with covalently attached carboxylates, catalyze the Kemp elimination of 5-nitrobenzisoxazole (**5NBZ**). Matile's claims of anion−π catalysis were based initially on the observation that transition state stabilization increased with increasing π-acidity of the catalyst.[1a] That is, catalyst **2** was more active than **1**, and both were far more active than the π-basic pyrenebutyrate. In the rate-limiting transition state for the Kemp elimination, the catalytic base removes the proton from carbon 5 of **5NBZ**, resulting in the buildup of negative charge on the substrate. Catalysts **1** and **2** were designed to stabilize this negative charge through anion−π interactions with the π-acidic face of the NDI, and Matile and co-workers[1a] reported Michaelis−Menten kinetics demonstrating transition state stabilization by these catalysts.

Scheme 1



More recently, Matile and co-workers[1b] bolstered their claims through additional experimental data on new anion−π catalysts. In particular, they reported rate data for two catalysts with S-containing substituents that provided further tuning of the π-acidity and catalytic activity. Moreover, they showed that π-stacking interactions are less susceptible to changes in substituents, suggesting that the substituents on the NDI were impacting the activity of these catalysts through their effect on anion−π interactions. Unfortunately, these experimental results did not enable Matile and co-workers to directly quantify the impact of anion−π interactions on the activation energies of these catalyzed reactions.

In this more recent work, Matile and co-workers[1b] also computed solution-phase free energies for **CS** and **TS** for catalysts **1** and **2**, at the PCM-M06-2X/def2-TZVP//PCM-B97D/6-311G(*d*,*p*) level of theory. They then used the model systems depicted in Figure 1a to gain insight into the noncovalent interactions operative in **TS**.[1b] In particular, they evaluated the interaction energy between the substrate and the

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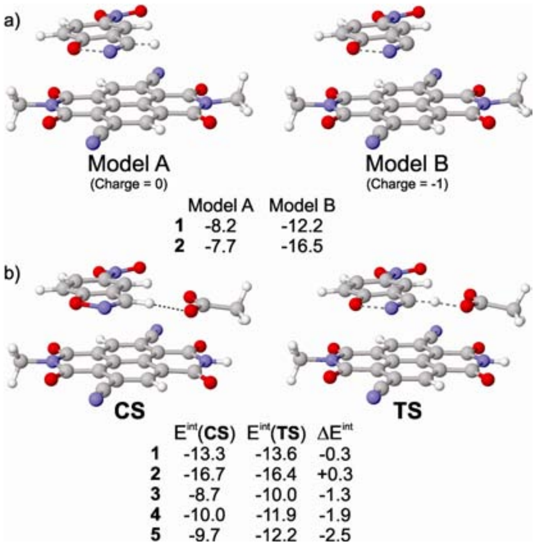

Figure 1. (a) PCM-M062X/def2-TZVP//PCM-B97-D/6-311g(d,p) interaction energies (kcal mol^{-1}, from ref 1b) for model complexes used by Matile and co-workers.[1b] (b) PCM-M062X/def2-TZVP//PCM-B97-D/6-311g(d,p) interaction energies (kcal mol^{-1}) of the substrate−carboxylate complex with the aromatic core of catalysts **1**−**5** based on the **CS** and **TS** geometries, as well as the difference in interaction energies. These interaction energies are not BSSE-corrected.

aromatic core of the catalysts in the geometry of **TS**, with and without the proton on carbon 5. Ultimately, they argued that, because the interaction energies in the deprotonated complex (Model B) were more favorable than the neutral complexes (Model A), anion−π interactions must be stabilizing **TS**.[1b]

Although these models[1b] show that there are favorable noncovalent interactions between the anionic substrate and NDI in the **TS** geometries, they do not address the impact of anion−π interactions on **CS**. For a noncovalent interaction to be responsible for catalysis, it must lower the activation energy by stabilizing **TS** to a greater extent than **CS**. This was not addressed by Matile's models (Figure 1b).[1b] Moreover, the design of these catalysts ignores the role of anion−π interactions between the carboxylate and the catalyst, which will also be affected by the transfer of charge from the carboxylate to the substrate during the reaction.

Model systems are depicted in Figure 1b that quantify the *net impact* of noncovalent interactions (both π-stacking and anion−π interactions) on the energy of **TS**, relative to **CS**, for these reactions. These computations are based upon nearly identical optimized geometries[9] and the same levels of theory[10] employed by Matile and co-workers.[1a,b] However, the models in Figure 1b account for the noncovalent interactions of the substrate−carboxylate complex with the aromatic core of the catalysts in **CS** and **TS**. Overall, they show that, for **1**, noncovalent interactions stabilize **TS** only slightly more than they stabilize **CS**. For **2**, the two CN substituents enhance the π-acidity of the NDI and lead to greater noncovalent stabilization of **TS**. However, the data in Figure 1b indicate that the *net* effect of noncovalent interactions is to stabilize **CS** more than **TS**, increasing the activation energy by 0.3 kcal mol^{-1}. This is not consistent with anion−π catalysis.[11]

The problem is, for catalyst **2**, noncovalent interactions preferentially stabilize **CS** over **TS** because the gain in anion−π interactions between the substrate and NDI is overshadowed by the loss of anion−π interactions between the carboxylate and the NDI. The differences in electrostatic interactions operative in **CS** and **TS** are quantified in Figure 2, based on a simple model (see Supporting Information for details). For catalyst **1**, there is a 0.7 kcal mol^{-1} gain in electrostatic interaction between the NDI and the substrate, in accord with the design of this catalyst by Matile et al.[1a,b] However, this is offset by a 1.3 kcal mol^{-1} loss in interactions between the NDI and the carboxylate. This imbalance is even greater for catalyst **2**. In this case, the 1.7 kcal mol^{-1} gain in electrostatic interactions for the substrate is outweighed by a 3.0 kcal mol^{-1} loss for the carboxylate. This difference in electrostatic interactions leads to the net stabilization of **CS**, relative to **TS**, by noncovalent interactions.

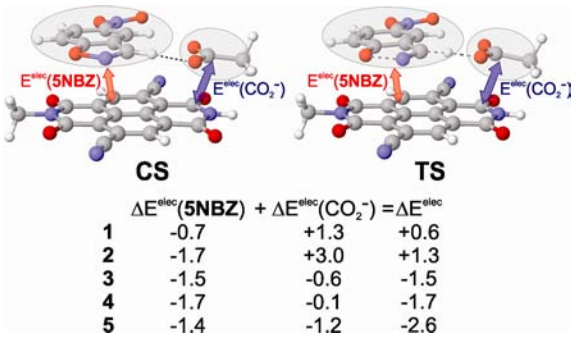

Figure 2. Difference of electrostatic interactions (kcal mol^{-1}) of the substrate and the carboxylate with the aromatic core of the catalyst between **TS** and **CS**, for catalysts **1**−**5**, along with the total difference in electrostatic interactions.

The above analysis reveals that, for **1** and **2**, there is not an electrostatic driving force for the deprotonation of the substrate by the catalytic carboxylate. This can be seen more clearly by examining the electrostatic potential (ESP) due to the aromatic core of the catalyst in the plane of the reaction (see Figure 3a). In particular, there is negligible difference in the ESP at the location of negative charge in **CS** compared to **TS**. Consequently, there is no net electrostatic stabilization during the course of the reaction.

More effective anion−π catalysts can be devised by shifting the substrate and carboxylate to a position above the NDI at which electrostatic forces facilitate the movement of the charge that accompanies this reaction. This is readily accomplished by introducing a rigid ethynyl spacer in the covalent linker to the carboxylate, as in catalyst **3** (see Scheme 1). This rigid linker positions the carboxylate above the electron-rich enthynyl group, where the electrostatic potential is less favorable for anion binding. However, the substrate is still located over the anion-binding face of the NDI (as in catalysts **1** and **2**), allowing anion−π stabilization of the substrate in **TS**. These ESP differences will drive the proton transfer (and accompanying transfer of negative charge from the carboxylate to the substrate) as the reaction proceeds from **CS** to **TS**. These effects can be further enhanced via the modulation of the ESP of the NDI through the introduction of nitrile groups as in catalyst **4**. Additional lowering of the energy of **TS**, relative to **CS**, can be achieved by placing both CN groups adjacent to the covalent linker, as in catalyst **5**. The impact of these changes can be seen in Figure 3b, which shows that, for catalyst **5**, the negative charge moves from an unfavorable position in **CS** to a favorable position in **TS**. This results in a significant

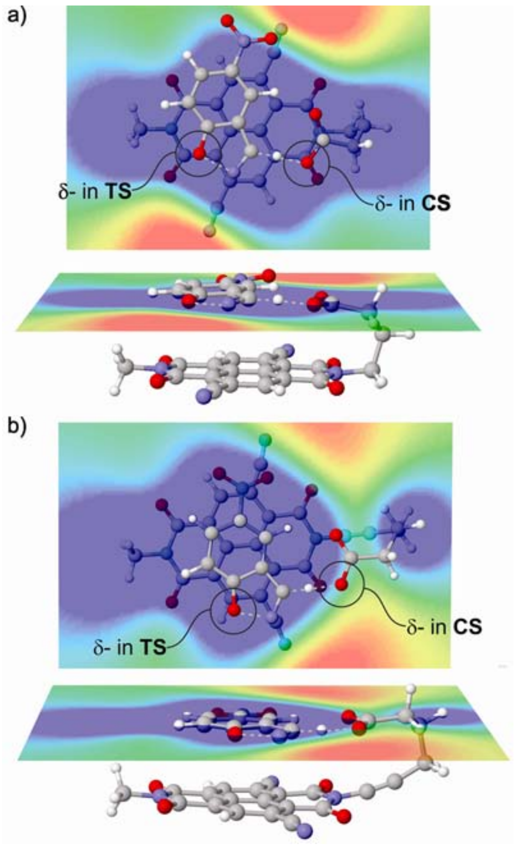

Figure 3. Two views of **TS** for catalysts (a) **2** and (b) **5**, along with the electrostatic potential in the plane of the substrate and carboxylate due to the aromatic core of the catalysts (scale: red = −5 kcal mol^{-1}; blue = +5 kcal mol^{-1}). The primary regions of partial negative charge in **TS** and **CS** are indicated.

stabilization of the transition state through anion−π interactions, without the accompanying stabilization of **CS**.

The same models used to analyze the noncovalent interactions in the reactions catalyzed by **1** and **2** indicate that, for catalysts **3**−**5**, there is a gain in electrostatic stabilization of both the substrate and the carboxylate going from **CS** to **TS** (see Figure 2). Similarly, for **3**−**5**, noncovalent interactions provide substantial stabilization of **TS** relative to **CS** (see Figure 1b), and anion−π interactions undoubtedly lower the activation energy of the Kemp elimination. Indeed, we note that computed activation free energies for the Kemp elimination of **5NBZ** catalyzed by **3**−**5** are about 4 kcal mol^{-1} lower than those for **1** and **2**.[12]

In conclusion, even though catalysts **1** and **2** accelerate the Kemp elimination of **5NBZ** and exhibit anion−π interactions in the transition state, the present computational data indicate that anion−π interactions contribute little, if any, to the lowering of the activation energy for these reactions. This occurs because the gain in anion−π interactions with the substrate going from **CS** to **TS** is overshadowed by a loss of anion−π interactions involving the carboxylate. This is particularly true for catalyst **2**, for which the net impact of noncovalent interactions is to increase the activation energy, and the greater catalytic activity of **2**, compared to **1**, must be due to other effects. On the other hand, for proposed catalysts **3**−**5**, computations show that there is much greater anion−π stabilization in **TS**, compared to **CS**, for both the substrate and the carboxylate. These catalysts are predicted to achieve lower activation barriers than **1** and **2** through the effects of noncovalent anion−π interactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details on theoretical methods, additional data and references, Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wheeler@chem.tamu.edu.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Zhao, Y.; Domoto, Y.; Orentas, E.; Beuchat, C.; Emery, D.; Mareda, J.; Sakai, N.; Matile, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 9940−9943. (b) Zhao, Y.; Beuchat, C.; Domoto, Y.; Gajewy, J.; Wilson, A.; Mareda, J.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2014**, *136*, 2101−2111. (c) Salonen, L. M.; Ellermann, M.; Diederich, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4808−4842. (d) Raju, R. K.; Bloom, J. W. G.; An, Y.; Wheeler, S. E. *ChemPhysChem* **2011**, *12*, 3116−3130. (e) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678−20685. (f) Lin, S.; Jacobsen, E. N. *Nat. Chem.* **2012**, *4*, 817−824. (g) Takenaka, N.; Chen, J. S.; Captain, B. *Org. Lett.* **2011**, *13*, 1654−1657. (h) Lu, T.; Zhu, R.; An, Y.; Wheeler, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 3095−3102. (i) Schneider, H.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3924−3977.

(2) (a) Mascal, M.; Armstrong, A.; Bartberger, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 6274−6276. (b) Alkorta, I.; Rozas, I.; Elguero, J. *J. Am. Chem. Soc.* **2002**, *124*, 8593−8598. (c) Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà, P. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3389−3392. (d) Schottel, B. L.; Chifotides, H. T.; Dunbar, K. R. *Chem. Soc. Rev.* **2008**, *37*, 68−83. (e) Frontera, A.; Quiñonero, D.; Deyà, P. M. *WIREs Comp. Mol. Sci.* **2011**, *1*, 440−459.

(3) Frontera, A.; Gamez, P.; Mascal, M.; Mooibroek, T. J.; Reedijk, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9564−9583.

(4) (a) Wheeler, S. E.; Houk, K. N. *J. Phys. Chem. A* **2010**, *114*, 8658−8664. (b) Dawson, R. E.; Hennig, A.; Weimann, D. P.; Emery, D.; Ravikumar, V.; Montenegro, J.; Takeuchi, T.; Gabutti, S.; Mayor, M.; Mareda, J.; Schalley, C. A.; Matile, S. *Nat. Chem.* **2010**, *2*, 533−538. (c) Mareda, J.; Matile, S. *Chem.—Eur. J.* **2009**, *15*, 28−37. (d) Gorteau, V.; Bollot, G.; Mareda, J.; Matile, S. *Org. Biomol. Chem.* **2007**, *5*, 3000−3012.

(5) (a) Garau, C.; Frontera, A.; Quiñonero, D.; Ballester, P.; Costa, A.; Deyà, P. M. *ChemPhysChem* **2003**, *4*, 1344. (b) Quiñonero, D.; Garau, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà, P. M. *Chem. Phys. Lett.* **2002**, *359*, 486−492. (c) Kim, D.; Tarakeshwar, P.; Kim, K. S. *J. Phys. Chem. A* **2004**, *108*, 1250−1258.

(6) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303−1324.

(7) Gallivan, J. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9459−9464.

(8) (a) Wendt, K. I.; Schultz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812−2833. (b) Gutierrez, O.; Aube, J.; Tantillo, D. J. *J. Org. Chem.* **2012**, *77*, 640−647. (c) Hong, Y. J.; Tantillo, D. J. *Chem. Sci.* **2013**, *4*, 2512−2518.

(9) For both **1** and **2**, we have located alternative conformers of **CS** and **TS** that are 0.5 to 1.0 kcal/mol lower in free energy than those reported by Matile and co-workers and analyzed in Figures 1 and 2. However, the analysis presented here leads to the same conclusions, regardless of which structures are analyzed.

(10) In the model systems in Figure 1b, the covalent linker to the carboxylate has been replaced with a hydrogen, rather than a methyl group as done by Matile et al.

(11) We note that from gas-phase calculations at the same geometries, which should provide a more direct measure of the operative noncovalent interactions, noncovalent interactions stabilize **CS** by 0.8 kcal/mol more than **TS**. For catalyst **2**, gas-phase computations indicate that noncovalent interactions stabilize **CS** by 1.8 kcal/mol more than **TS**.

(12) Computed activation energies (in methanol) are 14.9, 14.3, 10.7, 10.5, and 10.1 kcal/mol for catalysts **1**, **2**, **3**, **4**, and **5**, respectively. See Supporting Information for more details.

(13) All DFT computations were executed using Gaussian09: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision B.01; Gaussian, Inc.: Wallingford, CT, 2009.