

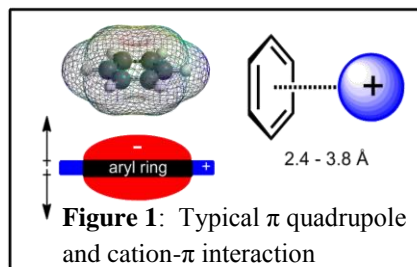
# CATION- $\pi$ INTERACTIONS: APPLICATIONS IN SYNTHESIS

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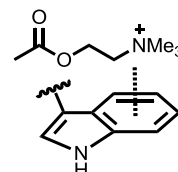
April 1, 2013

## INTRODUCTION:

A cation- $\pi$  interaction is a non-covalent interaction between a cation and the electron dense regions around aromatic  $\pi$  systems (Figure 1). This interaction is primarily electrostatic, but with significant contributions from dispersion and induced dipole forces.<sup>1</sup> The strength of this interaction rivals that of hydrogen bonds and can approach the strength of salt-bridges in proteins. Initial gas phase experiments reported by Kebarle indicated  $K^+$  binding energy with benzene was higher than that of water.<sup>2</sup> These findings were refined in a series of reports from Lisy, followed by two decades of experimental and theoretical studies on the physical properties of the interaction.<sup>3</sup>



The cation- $\pi$  interaction evolved from a physical curiosity to a relevant interaction as a result of several important studies performed by Dougherty and coworkers. The authors reported the favorable binding of aromatic and alkyl quaternary ammonium cations with aromatic organic hosts.<sup>4</sup> This observation led Dougherty to investigate the binding of acetylcholine (ACh) with model  $\pi$ -systems.<sup>5,6</sup> These model studies indicated that aromatic amino acid side chains play a role in the cation binding sites of proteins, such as sites found in ACh esterases through cation- $\pi$  stabilizing interactions (Figure 2). In related studies, Dougherty further characterized the trends in binding affinity between benzene derivatives and cations.<sup>4,5b-d</sup> These reports from Dougherty were the beginning of in depth experimental and computational investigation of the fundamental nature of the cation- $\pi$  interaction.



**Figure 2:** ACh interacts with Trp

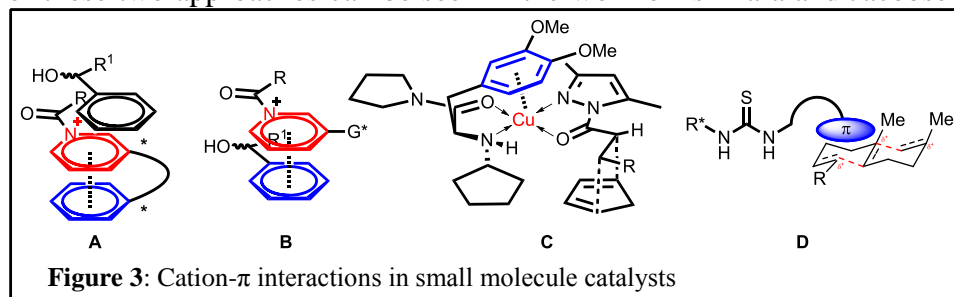
## CATION- $\pi$ IN ASYMMETRIC SYNTHESIS:

Although classical asymmetric synthesis relies on steric or electrostatic destabilization of undesired transition states, recently developed technologies focus on the stabilization of desired transition states. Whereas most synthetic techniques utilize hydrogen bonding in transition state stabilization, cation- $\pi$  interactions provide another type of structural stabilization. In general, synthetic approaches fall into two major categories: increasing the rigidity of the catalyst structure or engineering a cation- $\pi$  interaction between the catalyst and the substrate. The first practical application of small molecule organocatalysts came from Fuji with the development of a catalyst for the kinetic resolution of secondary alcohols.<sup>7</sup> These catalysts contained an aromatic moiety and an acyl pyridinium moiety linked

together by a chiral linker. The chiral linker dictates which face of the pyridinium ring is blocked by the pendant aryl ring and the resultant cation- $\pi$  interaction rigidifies the complex in this preferred conformation (Figure 3, A). In related studies, kinetic resolution technology was furthered by Birman, utilizing cation- $\pi$  interactions as a transition state stabilizing tool, rather than increasing the rigidity of the catalyst (Figure 3, B).<sup>8</sup>

A similar application of these two approaches can be seen in the work of Ishihara and Jacobsen.

Ishihara designed an enantioselective Cu(II) [4+2] and [2+2] catalyst system, utilizing L-alanine derivatives containing an aryl moiety as ligands that



could undergo cation- $\pi$  interactions with the Cu(II) center.<sup>9</sup> This interaction introduces additional steric hindrance, further enhancing the selectivity of the catalyst (Figure 3, C). This technology was extended to [3+2] cycloadditions.<sup>10</sup> Similarly, Jacobsen developed a thiourea catalyzed cationic polyene cyclization. By introducing a large  $\pi$ -surface in the catalyst, Jacobsen was able to utilize a cation- $\pi$  interaction to stabilize the desired transition state with the substrate, increasing the selectivity with  $\pi$ -surface size (Figure 3, D).<sup>11</sup> Jacobsen's strategy relies on an intermolecular cation- $\pi$  interaction to stabilize a desired transition state, whereas Ishihara utilizes a cation- $\pi$  interaction to rigidify the catalyst structure.

## SUMMARY:

Catalysts and reagents that incorporate cation- $\pi$  interactions within the structure of the compound or in the transition state in a reaction have been developed. These developments give chemists more versatility in the rational design of small molecule organocatalysts for asymmetric synthesis.

## REFERENCES

1. Tsuzuki, S.; Mikami, M.; Yamada, S. *J. Am. Chem. Soc.* **2007**, *129*, 8656-8662.
2. Sunner, J.; Nishizawa, K.; Kebarle, P. *J. Phys. Chem.* **1981**, *85*, 1814-1820.
3. Cabarcos, O. M.; Weinheimer, C. J.; Lisy, J. M. *J. Phys. Chem.* **1998**, *108*, 5151-5154.
4. Shepodd, T.J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1983-1985.
5. (a) Dougherty, D.A., *et al. Science.* **1993**, *261*, 1708-1710. (b) Dougherty, D.A., *et al. Proc. Natl. Acad. Sci.* **1998**, *95*, 12088-12093. (c) Dougherty, D.A., *et al. J. Am. Chem. Soc.* **2000**, *122*, 870-874. (d) Dougherty, D.A., *et al. J. Am. Chem. Soc.* **1996**, *118*, 2307-2308.
6. Salonen, L.M.; Ellerman, M.; Deiderich, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4808-4842.
7. Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169-3170.
8. Houk, K.N.; Birman, V.B., *et al. J. Am. Chem. Soc.* **2012**, *134*, 17605-17612.
9. Ishihara, K.; Fushimi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7532-7533.
10. Sakakura, A.; Hori, M. Fushimi, M.; Ishihara, K.; *J. Am. Chem. Soc.* **2010**, *132*, 15550-15552.
11. Knowles, R.R.; Lin, S.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2010**, *132*, 5030-5032.