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Origin of Enantioselectivity in CF_3−PIP-Catalyzed Kinetic Resolution of Secondary Benzylic Alcohols

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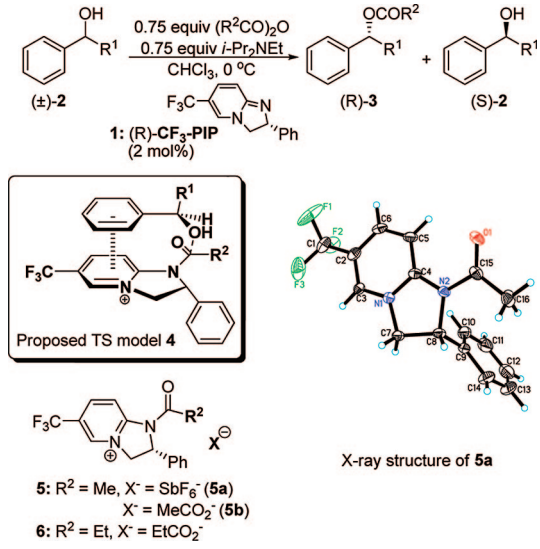
Nonenzymatic enantioselective acyl transfer catalysis has been an active area of research for over a decade.[1] Many of the catalysts developed to date have demonstrated varying degrees of enantioselectivity in kinetic resolution[2] of secondary alcohols. Secondary benzylic alcohols have enjoyed particular popularity as substrates in this reaction.[3,4a−c] However, the origin of enantioselectivity in this process has not been elucidated. In this communication, we present the results of our computational studies, which support the involvement of π-interactions in the chiral recognition of this class of substrates.[5]

In 2004, we introduced a new class of enantioselective acyl transfer catalysts. Among the first-generation catalysts, CF_3−PIP **1** proved to be particularly effective in the kinetic resolution of secondary benzylic alcohols (**2**). Structure−selectivity trends observed in this initial study led us to hypothesize that the chiral recognition depends on $\pi-\pi$ and cation$-\pi$ interactions between the pyridinium ring of the N-acylated catalyst and the benzene ring of the substrate, as shown in the proposed transition state model **4** (Scheme 1).[4a] Later, this hypothesis proved to be valuable as a guide in the development of subsequent generations of related catalysts.[4b,c,f] Their application to benzylic,[4a−c,f] allylic,[4b] and propargylic[4d] alcohols, 4-aryl-oxazolidinones,[4e] and 2-aryl-cycloalkanols[4f] produced results that were also consistent with the π-stacking mechanism.

Scheme 1. CF_3−PIP-Catalyzed Kinetic Resolution



Recently, we were able to obtain an X-ray structure of the N-acetylated CF_3−PIP in the form of hexafluoroantimonate **5a**, which was in accord with the expected conformation. However, the involvement of π-interactions in the transition state is inherently difficult to verify by direct experimental observation. Therefore, we initiated a computational study aimed at elucidating the origin of the enantioselectivity. To the best of our knowledge, the role of *intermolecular* π-interactions in chiral recognition has not been previously investigated by computational methods.[6,7]

The energy-minimized geometry of *N*-acetyl-(*R*)-CF_3−PIP^+ (**5**, X omitted) obtained at the B3LYP/6-31G* level of theory[8,9] was consistent with the X-ray structure of **5a**, the acyl carbonyl being nearly coplanar with the pyridine ring. Transition state geometries for reactions of **5b** and the R- and S-enantiomers of 1-phenylethanol (**2**, R^1 = Me) were investigated next. The acetate anion hydrogen-bound to the hydroxyl group of the substrate was included in the calculations, as suggested by the recent computational studies on achiral acyl transfer catalysis.[10] Each enantiomer of 1-phenylethanol was attached to the unencumbered β-face of **5b**, and all accessible conformations were explored.

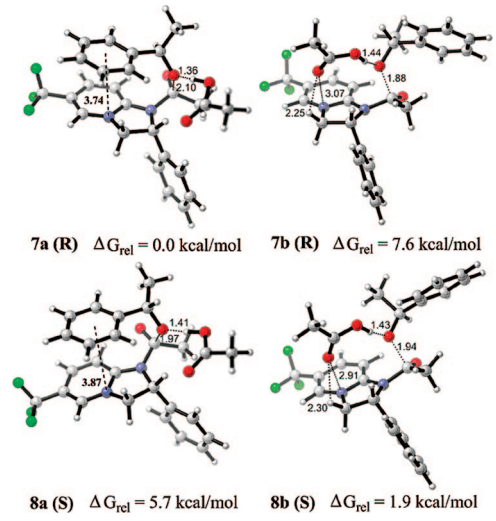


Figure 1. Transition states for reactions of (*R*)- and (*S*)-phenylethanol with **5b**.

(*R*)-1-Phenylethanol, which is the fast-reacting enantiomer in kinetic resolutions with (*R*)-**1**, preferred the slipped-stacked geometry, with the phenyl of the substrate centered approximately over the pyridinium N. In conformer **7a**, representing the global energy minimum, the distance between the center of the phenyl ring and the pyridinium N is 3.74 Å, and the planes of the pyridinium and the benzene rings are at an 8.5° dihedral angle.[11] The lowest-energy splayed conformer **7b** was 7.6 kcal/mol less stable than **7a**. For the diastereomeric transition states with the slow-reacting (*S*)-1-phenylethanol, the situation was reversed. The stacked conformer

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8a was less energetically favorable than the splayed conformer **8b**, presumably due to the A1,3-strain introduced by the methyl group virtually coplanar with the benzene ring in the former.

Finally, we confirmed that the approach of either the R- or the S-enantiomer of the substrate to the α-face of the N-acylated catalyst encumbered by the phenyl substituent at C2 is disfavored relative to the aforementioned β-face conformers **7a** and **8b** (by 6.6 and 10.1 kcal/mol, respectively).

The energy difference between the lowest-energy conformers for the R- and S-enantiomers of the substrate (**7a** and **8b**) is 1.9 kcal/mol. This value was adjusted to 1.6 kcal/mol by introducing solvent correction ($CHCl_3$, CPCM model (UFF radii)), which is in excellent agreement with the experimental data (selectivity factor $s = 12$ obtained in chloroform at room temperature corresponds to $\Delta G_{rel} = 1.5$ kcal/mol) (Table 1, column 1, entries 1 and 5). Encouraged by these findings, we examined the transition states of the R- and S-enantiomers of 1-phenylethanol with *N*-propionyl-(*R*)-CF_3−PIP propionate **6** (R^2 = Et), operating in kinetic resolutions with propionic anhydride (Figure 2). The computed increase in the free energy difference between the energy minimized diastereomeric transition states **9a** and **10b** ($\Delta G_{rel} = 3.5$ kcal/mol in gas phase, or 2.8 kcal/mol in chloroform) is qualitatively consistent with the experimentally observed enhanced enantioselectivity ($s = 26$, $\Delta G_{rel} = 1.9$ kcal/mol)(column 2, entries 1 and 5). Apparently, it reflects the greater steric repulsion between the ethyl group of the acyl substituent and the phenyl of the substrate in the splayed conformer **10b**.

Since B3LYP may underestimate the dispersion interactions that would stabilize **7a**, **8a**, and **9a**,[10] we also calculated these energy differences with methods that are expected to treat such interactions more accurately.[12] Single-point calculations by MP2,[13a] SCS-MP2,[13b] and M05-2X[13c] performed on the real system using B3LYP-optimized geometries overestimated the energy differences by 1−3 kcal/mol compared to the experiment and the B3LYP results (Table 1).

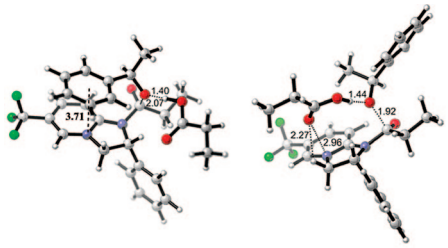

Figure 2. Transition states for reactions of (*R*)- and (*S*)-phenylethanol with **6**.

Table 1. Comparison of Calculation Methods

entry	method	ΔG_{rel} (**8b**−**7a**)[b] kcal/mol	ΔG_{rel} (**10b**−**9a**)[b] kcal/mol
1	B3LYP/6-31G*	1.9 (1.6)	3.5 (2.8)
2	MP2/6-31G*// B3LYP/6-31G*	4.5(5.3)	6.0 (6.3)
3	SCS-MP2/6-31G*// B3LYP/6-31G*	3.7 (4.5)	5.4 (5.7)
4	M05-2X/6-31G*// B3LYP/6-31G*	2.9 (2.7)	4.9 (4.2)
5	experimental data[a]	1.5	1.9

[a] Conditions: 0.25 M 1-phenylethanol, 0.19 M $(MeCO)_2O$ or $(EtCO)_2O$, 0.19 M *i*-Pr_2Net, $CDCl_3$, 23 °C. [b] Data given in paretheses have been computed using CPCM solvent model (UFF radii, $CHCl_3$).

In summary, our computational study lends theoretical support to the π-interaction hypothesis of chiral recognition in the KR of secondary benzylic alcohols catalyzed by CF_3−PIP and provides a more accurate and detailed description of the transition state. The enantioselectivity depends upon two factors: steric repulsion between the methyl and the *ortho*-hydrogen (**7a** ≪ **7b**; **8b** ≪ **8a**)), and the electrostatic attraction between the phenyl and pyridinium in the slipped-parallel geometry (**7a** < **8a**). The results of this investigation are expected to be applicable to our more advanced catalysts and may also shed light on the mechanism of chiral recognition achieved by enantioselective acylation catalysts developed by other groups.

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Supporting Information Available: Kinetic resolution, computational and X-ray data, and complete ref 9. These materials are available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (d) Jarvo, E. R.; Miller, S. J. Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2004; Chapter 43.

(2) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(3) For example, see: (a) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (b) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. (c) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166. (d) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347.

(4) (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (c) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (d) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (e) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859. (f) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115.

(5) For reviews of $\pi-\pi$ and cation$-\pi$ interactions, see: (a) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 651. (b) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.

(6) The importance of intermolecular π-interactions between a N-acylated catalyst and a substrate containing a π-system was apparently first recognized by Fuji et al.: Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169.

(7) For a computational study of *intramolecular* cation$-\pi$ interactions in the structures of enantioselective acylation catalysts, see: Wei, Y.; Held, I.; Zipse, H. *Org. Biomol. Chem.* **2006**, *4*, 4223.

(8) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(9) Calculations were performed in Gaussian 03 (Revision E.01), M. J. Frisch, *et al.* Gaussian, Inc.: Pittsburgh, PA, 2004.

(10) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751.

(11) 3.75 Å was found to be the optimal distance between benzene and the desphenyl analogue of cation **5**. See Supporting Information. It is also close to the optimum previously calculated for pyridinium−benzene π-interactions: Tsuzuki, S.; Mikami, M.; Yamada, S. *J. Am. Chem. Soc.* **2007**, *129*, 8656.

(12) On a simplified model system, calculations of ΔG_{rel} by B3LYP produced good agreement with MP2 and M05-2X (typically within 1 kcal/mol). See Supporting Information for details.

(13) (a) Head-Gordon, M.; Pople, J. A.; Frisch, M. *J. Chem. Phys. Lett.* **1988**, *153*, 503. (b) Grimme, S. *J. Chem. Phys.* **2003**, *118*, 9095. (c) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364.

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