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Origin of Enantioselectivity in Benzotetramisole-Catalyzed Dynamic Kinetic Resolution of Azlactones

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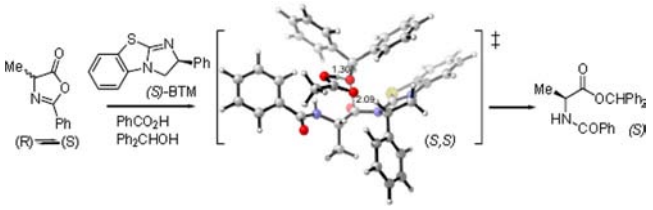
ABSTRACT



Density functional theory (DFT) calculations were performed to investigate the origins of enantioselectivity in benzotetramisole (BTM)-catalyzed dynamic kinetic resolution of azlactones. The transition states of the fast-reacting enantiomer are stabilized by electrostatic interactions between the amide carbonyl group and the acetate anion bound to the nucleophile. The chiral BTM catalyst confines the conformation of the α-carbon and the facial selectivity of the nucleophilic attack to promote such electrostatic attractions.

Among the many interesting facets of the chemistry of azlactones[1] is their reactivity as acyl donors coupled with the extreme ease of racemization. As a consequence, racemic azlactones undergo enantioselective alcoholysis in a dynamic kinetic resolution (DKR)[2] mode, thus enabling an attractive synthetic route to enantioenriched esters of α-amino acids (Figure 1). Besides enzymatic methods,[3] several mechanistically different approaches have been reported to achieve this transformation.[4] In 2010, inspired by the pioneering work of Fu's group[4b] and recent developments in the amidine-catalyzed kinetic resolution of carboxylic acids,[5a,6a] we demonstrated that benzotetramisole (BTM)[7] can catalyze the DKR of azlactones with up to 97% *ee* (Scheme 1).[4f] During that study, we observed a strong dependence of the enantioselectivity on the alcohol nucleophile (di(1-naphthyl)methanol proved to be optimal), which indicated that the alcoholysis step of the catalytic cycle must be both rate- and enantioselectivity-determining. Most intriguingly, we also found that the absolute sense of asymmetric induction was opposite of that observed in our previous study of acyclic chiral acyl donors and explained in terms of stereoelectronic control.[6] In order to explain our experimental observations, we hypothesized that the preferred transition

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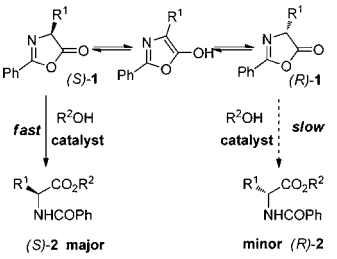
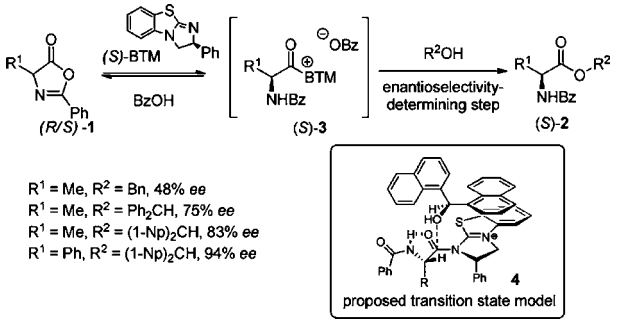


Figure 1. Dynamic kinetic resolution (DKR) of azlactones.

Scheme 1. BTM-Catalyzed DKR of Azlactones



state (TS) is stabilized by cation$-\pi$ interactions between one of the aryl groups on the alcohol and the BTM catalyst as well as an intramolecular hydrogen bonding between the amide N$-$H bond and the acyl oxygen (see model **4**, Scheme 1).

In this communication, we present the first computational study on the catalytic DKR of azlactones to explain the origin of enantioselectivity and explore the effects of substituents on selectivities. The computed TS structures indicate that the stereoselectivity is determined primarily by the electrostatic attractions between the amide group on the α-carbon and the acetate anion bound to the nucleophile. The BTM catalyst confines the conformation around the $C_{acyl}-C_{\alpha}$ bond and directs the π-facial selectivity of the nucleophilic attack.

To minimize calculation times, we constructed simplified diastereomeric transition state structures shown schematically in Figure 2 with acetate used as the counterion in place of benzoate and diphenylcarbinol replacing di(1-naphthyl)methanol. To ensure the adequacy of the computational method employed in the present study, we compared the performance of several levels of theory. Initial geometry optimizations were performed with B3LYP/6-31G(d) and the SMD solvation model in Gaussian 09.[8] However, the free energy difference calculated by this method was very small ($\Delta\Delta G^{\ddagger} = -0.2$ kcal/mol) and, in fact, favored the slow-reacting diastereomer (Table 1, entry 1). On the other hand, the M06-2X functional, which gives better performance in treating cation$-\pi$ and $\pi-\pi$ dispersion interactions and hydrogen bonding interactions,[9] produced a much better agreement with the experimental data when used for single-point calculations on B3LYP-optimized geometries (entry 2 vs 8). B3LYP-D3[10] dispersion corrections and MP2 single-point calculations both provided satisfactory agreement with the experimental results (entries 3 and 4 vs 8). Finally, excellent agreement was obtained by employing M06-2X/6-31G(d) in geometry optimizations (entries 5, 6, and 7).[11] Thus, for the rest of this study, geometries were optimized with M06-2X and the 6-31G(d) basis set and single-point energies were calculated with M06-2X and the 6-311+G(d,p) basis set. The SMD solvation model[12] with chloroform solvent was used in geometry optimizations and single-point energy calculations.

Table 1. Comparison of Computational Methods for the Reaction of 4-Methylazlactone

entry	method[a]	$\Delta\Delta G^{\ddagger}$ ($\Delta\Delta H^{\ddagger}$) /kcal mol^{-1}
1	B3LYP/6-31G(d)	−0.2 (0.5)
2	M06-2X/6-311+G(d,p)// B3LYP/6-31G(d)	1.9 (2.6)
3	B3LYP-D3/6-31G(d)// B3LYP/6-31G(d)	2.6 (3.3)
4	MP2/6-31G(d)// B3LYP/6-31G(d)	2.1 (2.7)
5	M06-2X/6-31G(d)	1.8 (2.2)
6	M06-2X/6-311+G(d,p)// M06-2X/6-31G(d)	1.2 (1.6)
7	MP2/6-31G(d)// M06-2X/6-31G(d)	1.3 (1.7)
8	experimental data	1.2[b]

[a] The SMD solvation model with chloroform solvent was used in all geometry optimizations and single-point energy calculations. [b] $\Delta\Delta G^{\ddagger}$ calculated from experimental *ee* of 75%.

The transition states **TS-1** and **TS-2** shown in Figure 2 represent the lowest energy conformers identified for the fast- and the slow-reacting enantiomers, respectively (see Supporting Information (SI) for less stable conformers of the transition states). Both structures share several common characteristics. The acyl carbonyl is nearly coplanar with the benzothiazolium moiety and points toward the sulfur atom, due to nonbonded S$-$O interactions.[13] As

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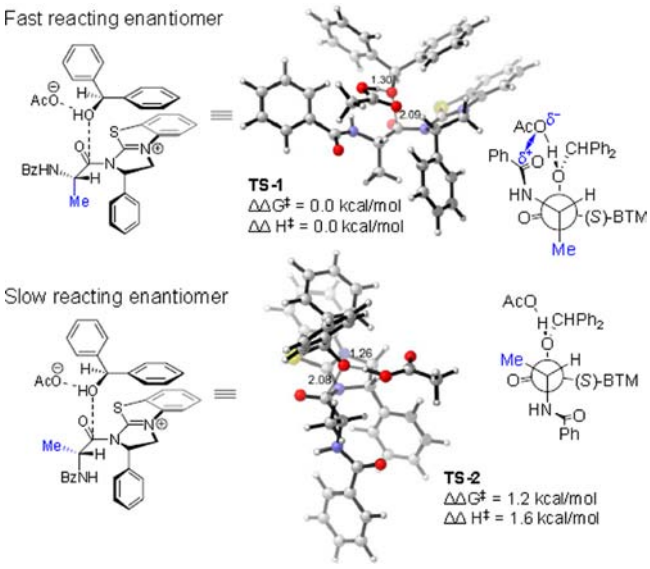

Figure 2. Comparison of the lowest energy TSs for the reaction of 4-methylazlactone and diphenylcarbinol.

expected, the alcohol approaches the carbonyl from the top face, because the bottom face is blocked by the phenyl group at the C2 position of the catalyst. The conformation of the α-carbon is confined so that the hydrogen on C_α points toward the C2-phenyl on the catalyst in both **TS-1** and **TS-2** to minimize steric repulsions. This orientation places the methyl and the benzamide antiperiplanar to the incoming nucleophile in **TS-1** and **TS-2**, respectively. One of the phenyl groups of diphenylcarbinol is almost parallel to the benzothiazolium moiety and positioned over the nitrogen atom at a distance around 3.3 Å, indicating strong cation$-\pi$ interactions. The acetate anion forms hydrogen bonds with the alcohol hydroxyl and the C-2 hydrogen on the dihydroimidazolium ring. Vibrational frequency analysis of the TSs indicates that the nucleophilic attack of the alcohol to the carbonyl and the deprotonation of the hydroxyl group proceed simultaneously via a concerted mechanism. The forming C$-$O bond and the breaking O$-$H bond lengths are similar for both **TS-1** and **TS-2** (2.09 Å vs 2.08 Å for C$-$O and 1.30 Å vs 1.26 Å for O$-$H bonds, respectively). These key features of the TSs are consistent with earlier computational studies on acyl transfer reactions promoted by BTM and related catalysts.[5b,6d,14]

Although at first glance structure **TS-1** resembles the originally proposed model **4** (Scheme 1), a closer look reveals substantial differences between them. Although the intramolecular hydrogen bond between the benzamide hydrogen and the acyl oxygen was originally ascribed primary importance, the optimized geometry of **TS-1** suggests that it is weak at best. Indeed, the H$\cdots$O distance is 2.51 Å, and the N$-$H$\cdots$O angle is 97.9°. Furthermore, the N$-$H bond in the amide is not in the same plane as the acyl carbonyl. Why, then, do the calculations predict the correct general orientation of the acyl moiety and, as a consequence, the correct absolute sense of enantioselectivity?

The answer apparently lies in the stabilizing electrostatic interactions between the acetate anion hydrogen-bound to the alcohol and the benzamide carbonyl in **TS-1** ($C_{amide}-O_{acetate}$ distance is 2.91 Å). In fact, similar stabilizing carbonyl$-$carbonyl interactions at such distances are commonly found in crystal structures of small molecules and proteins.[15] Furthermore, electrostatic interactions with the nucleophile have been recognized as an important influence on the π-facial selectivity in nucleophilic additions to cyclic ketones substituted by polar groups.[16] In **TS-2**, on the other hand, the benzamide moiety is antiperiplanar to the incoming nucleophile and thus cannot contribute to the electrostatic stabilization.

Other attractive interactions of the benzamide phenyl group have also been considered: C$-$H$\cdots\pi$ interactions with one of the phenyls on the alcohol in **TS-1** and $\pi-\pi$ interactions with the C2-phenyl group on the catalyst in **TS-2**. Apparently, these two factors cancel each other out and thus do not contribute much to the difference in energy between the two competing transition states. In a test calculation, replacing the benzamide with acetamide leads to essentially the same enantioselectivity (see SI for details).

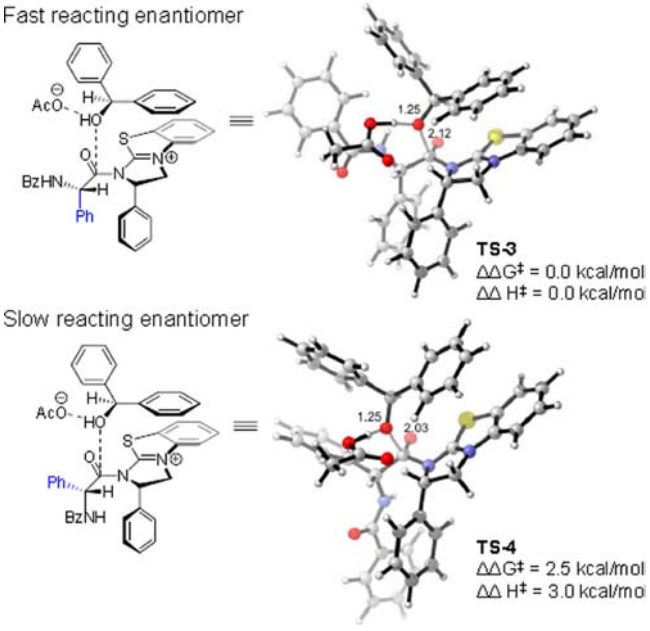

Figure 3. Comparison of the lowest energy TSs for the reaction of 4-phenylazlactone and diphenylcarbinol.

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Finally, it was of interest to analyze the transition states (cf. **TS-3** and **TS-4** in Figure 3) derived from 4-phenylazlactone. The greater energy difference in this case ($\Delta\Delta G^{\ddagger}$ = 2.5 kcal/mol) relative to its 4-methyl analogue ($\Delta\Delta G^{\ddagger}$ = 1.2 kcal/mol) is qualitatively consistent with the higher enantioselectivity displayed by the former substrate in DKR (94% vs 83% ee, respectively, using di(1-naphthyl)methanol; see Scheme 1). This increase may be attributed to the $\pi-\pi$ interactions between the C_{α}-phenyl group and the C2-phenyl on the catalyst (3.84 Å distance between the centers of the benzene rings) as well as the stereoelectronic effect of introducing the polarizable phenyl antiperiplanar to the trajectory of the nucleophilic attack (i.e., Felkin–Anh effect).[6d,17,18]

In conclusion, our computational study has resulted in a refined transition state model explaining the origins of enantioselectivity in the BTM-catalyzed DKR of azlactones. The key stabilizing force favoring the transition state of the fast-reacting enantiomer is not hydrogen bonding, as we surmised originally, but the electrostatic interactions between the benzamide carbonyl and the acetate anion bound to the nucleophile. This surprising conclusion is expected to be applicable to other classes of diastereoselective nucleophilic acyl substitution reactions and related processes.

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Supporting Information Available. Computational details, B3LYP-optimized geometries of **TS-1** and **TS-2**, and optimized Cartesian coordinates. See Supporting Information for full reference to ref 8. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(18) The antiperiplanar $C_{\alpha}-C_{Ph}$ bond in **TS-3** is elongated by 0.013 Å compared to the gauche $C_{\alpha}-C_{Ph}$ bond in **TS-4**, while the antiperiplanar $C_{\alpha}-N$ bond in **TS-4** is only elongated by 0.006 Å. This suggested slightly stronger Felkin–Anh interactions in **TS-3** with phenyl in place of benzamide at the antiperiplanar position.