ORGANIC LETTERS

2009
Vol. 11, No. 15
3242−3245

On the Origins of Kinetic Resolution of Cyclohexane-1,2-diols Through Stereoselective Acylation by Chiral Tetrapeptides

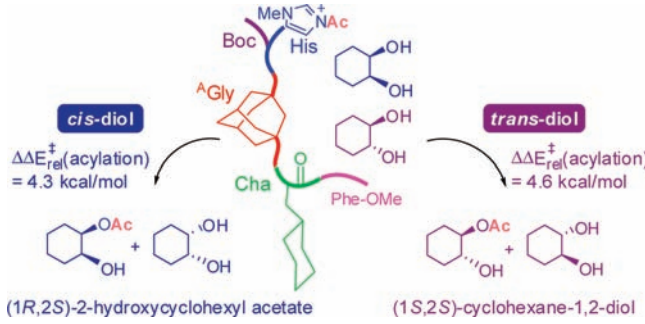
C. B. Shinisha and Raghavan B. Sunoj*

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

sunoj@chem.iitb.ac.in

Received May 27, 2009

ABSTRACT



The relative energies of cyclohexane-1,2-diols and chiral tetrapeptide (2 (Boc) or 3 (Moc)) complexes calculated using DFT indicate a thermodynamic preference for chiral recognition toward (1*R*,2*R*)$_{e,e}$-α isomer. The barrier for stereoselective acyl transfer is identified as lower for *trans*-(1*R*,2*R*)-cyclohexane-1,2-diol, leading to the kinetic resolution (KR) of *trans*-(1*S*,2*S*)-cyclohexane-1,2-diol. The prediction is in concert with the reported experiments for *trans*-diols, while that for hitherto unknown *cis*-diol demands experimental verification. It is proposed that desymmetrization would enable the resolution of *cis*-(1*R*,2*S*)-2-hydroxycyclohexyl acetate.

Kinetic resolutions (KRs) are recognized as an effective protocol toward the generation of enantiopure compounds.[1] Both enzymatic and nonenzymatic KRs have found useful applications with a spectrum of organic compounds.[2] Among the nonenzymatic approaches, KR of alcohols through asymmetric acylation has attracted considerable attention in recent years.[3] An interesting strategy popularized by Miller and co-workers employs small peptides functionalized with nucleophilic *N*-methylimidazole as catalysts for KR of secondary alcohols.[4] Another impressive example on the use of small peptide catalysts due to Schreiner and co-workers demonstrated successful resolution of 1,2-*trans* cycloalkane diols (Scheme 1).[5] These approaches in general rely either on substrate specificity arising due to hydrogen bonding interactions or/and the propensity to exhibit improved order through secondary structures.[6] While the design of newer peptide catalysts for KR continues to grow, efforts toward

(1) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

(2) (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407.

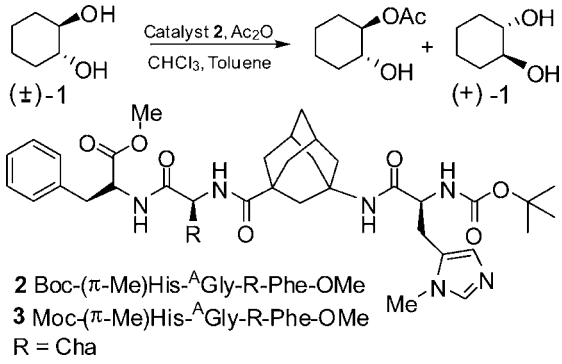
(3) (a) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. (b) Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522. (c) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212.

(4) (a) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (b) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (c) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2824. (d) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (e) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759.

(5) Müller, C. E.; Wanka, L.; Jewell, K.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6180.

10.1021/ol9011822 CCC: $40.75
Published on Web 07/15/2009

Scheme 1. Enantioselective Acylation Reaction Catalyzed by **2**[5]



unravelling the molecular origins of such catalysis are not widely reported.[7] Detailed insights on the mechanism as well as the crucial kinetic factors would indeed help improve the efficiency of such promising methods.

In this letter, we intend to shed light on the origins of KR of 1,2-diols achieved through a chiral tetrapeptide-catalyzed stereoselective acyl transfer reaction. The objectives here are 2-fold: (i) to provide a mechanistic framework toward rationalizing the KR of racemic *trans*-cyclohexane-1,2-diols and (ii) to apply the insights thus obtained toward predicting the likely outcome of, hitherto unknown, meso *cis*-cyclohexane-1,2-diols. Schreiner's tetrapeptide catalysts (**2**), derived from a rigid non-natural γ-aminoadamantanecarboxylic acid, denoted as Boc-(π-Me)His-^{A}Gly-Cha-Phe-OMe and Moc-(π-Me)His-^{A}Gly-Cha-Phe-OMe, are chosen for the present investigation.[8]

A hybrid DFT (B3LYP/6-31G*) and semiempirical MO (PM3) treatment using the ONIOM2 methodology is employed for geometry optimization. All the intermediates and transition states are, respectively, characterized as minima and first-order saddle points using frequency analysis. Additionally we have carried out 10% displacement of the transition geometry along the direction of the imaginary frequency and reoptimized the perturbed structure using the "calcfc" option available in the program. This was to ensure whether the transition state is genuine and connects the reactant and the product. Energies of such stationary points are subsequently refined using single-point energy calculations at the B3LYP/6-31G* level of theory.[9] Such approaches have been successfully used in explaining the mechanism and stereoselectivity of organic reactions.[10] The most crucial part of the reacting system including the diol and (π-Me)His-acylium fragments is described using density functional theory (higher layer), while the peptide backbone is treated as a lower layer using the semiempirical PM3 method.

The KR is envisaged to proceed first through the formation of inclusion complexes facilitated by chiral recognition between the host peptide and diols, and then a stereoselective acyl transfer reaction takes place under the chiral environment. While the latter reaction holds the key to KR, the initial inclusion complexes can be equally critical. The problem is therefore approached in two important steps. The identification of important lower energy inclusion complexes between different stereoisomers of the diol and the host peptide is undertaken first. The stereoselective acyl transfer reactions are then studied by precisely identifying the corresponding transition states. The chiral recognition of diols offered by two tetrapeptides Moc-(π-Me)His-^{A}Gly-Cha-Phe-OMe (**3**) and Boc-(π-Me)His-^{A}Gly-Cha-Phe-OMe (**2**)[11] is examined by considering a series of likely inclusion complexes as shown in Figure 1. The stabilization of these complexes appears to depend on the relative stereochemical disposition between the diol hydroxyl groups and the extent of intermolecular interactions with the peptide residues. In the lowest-energy inclusion complex for the *trans*-diol, the configuration is identified as $(1R,2R)_{e,e}$-α. It is identified that these complexes are primarily stabilized by an anchoring hydrogen bonding interaction between the C═O group of the amino acid backbone of the catalyst and the diol hydroxyl group. Interestingly, such an interaction is noticed in all of the lower-energy complexes. A representative geometry of an inclusion complex depicting this is provided in Figure 2a.

A comparison of the computed relative energies of *trans*- and *cis*-1,2-cyclohexanediol complexes is given in Figure 1. It is noticed that the *trans*-(1*R*,2*R*)-diol···acylium complex is more stable by 4.3 kcal/mol than the energetically nearest diastereomeric *trans*-(1*S*,2*S*)-diol···acylium complex. In the case of *cis*-diols, the *cis*-(1*R*,2*S*)-diol···acylium complex is found to be the most preferred complex. The relative energies of these complexes suggest a likely thermodynamic propensity toward selective chiral recognition by the host peptide. The differential binding of diastereomeric diols can be

(6) (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (b) Formaggio, F.; Barazza, A.; Bertocco, A.; Toniolo, C.; Broxterman, Q. B.; Kaptein, B.; Brasola, E.; Pengo, P.; Pasquato, L.; Scrimin, P. *J. Org. Chem.* **2004**, *69*, 3849. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

(7) Although KRs of diols with the help of peptides are largely unexplored, DFT studies on stereoselective acyl transfer in secondary alcohol as well as certain desymmetrization reactions are recently reported. See: (a) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751. (b) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836. (c) Oh, S. H.; Rho, H, S,; Lee, J. W.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7872.

(8) (a) ^{A}Gly = γ-aminoadamantanecarboxylic acid. (b) In the real system on which experiments were performed, only Boc protection is employed. See ref 5.

(9) (a) From a computational standpoint, the present catalyst−substrate complexes are relatively large, in particular for transition state searches, for full DFT calculations. We have therefore resorted to hybrid ONIOM2 calculations where the higher and lower layers are, respectively, treated at the B3LYP/6-31G* and PM3 methods. The approach is denoted as ONIOM2(B3LYP/6-31G*:PM3). (b) All calculations have been performed using Gaussian03 suite: Frisch, M. J. *Gaussian 03*, Rev C.02; Gaussian Inc. (full citation is provided in Supporting Information). (c) Dapprich, S.; Komáromi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. J. *J. Mol. Struct. (THEOCHEM)* **1999**, 461. (d) Vreven, T.; Morokuma, K. *J. Comput. Chem.* **2000**, *21*, 1419. (e) Morokuma, K. *Bull. Korean Chem. Soc.* **2003**, *24*, 797.

(10) (a) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770. (b) Zhang, X.; Du, H.; Wang, Z.; Wu, Y.-D.; Ding, K. *J. Org. Chem.* **2006**, *71*, 2862. (c) Shinisha, C. B.; Sunoj, R. B. *Org. Biomol. Chem.* **2008**, *6*, 3921.

(11) Wanka, L.; Cabrele, C.; Vanejews, M,; Schreiner, P. R. *Eur. J. Org. Chem.* **2007**, 1474.

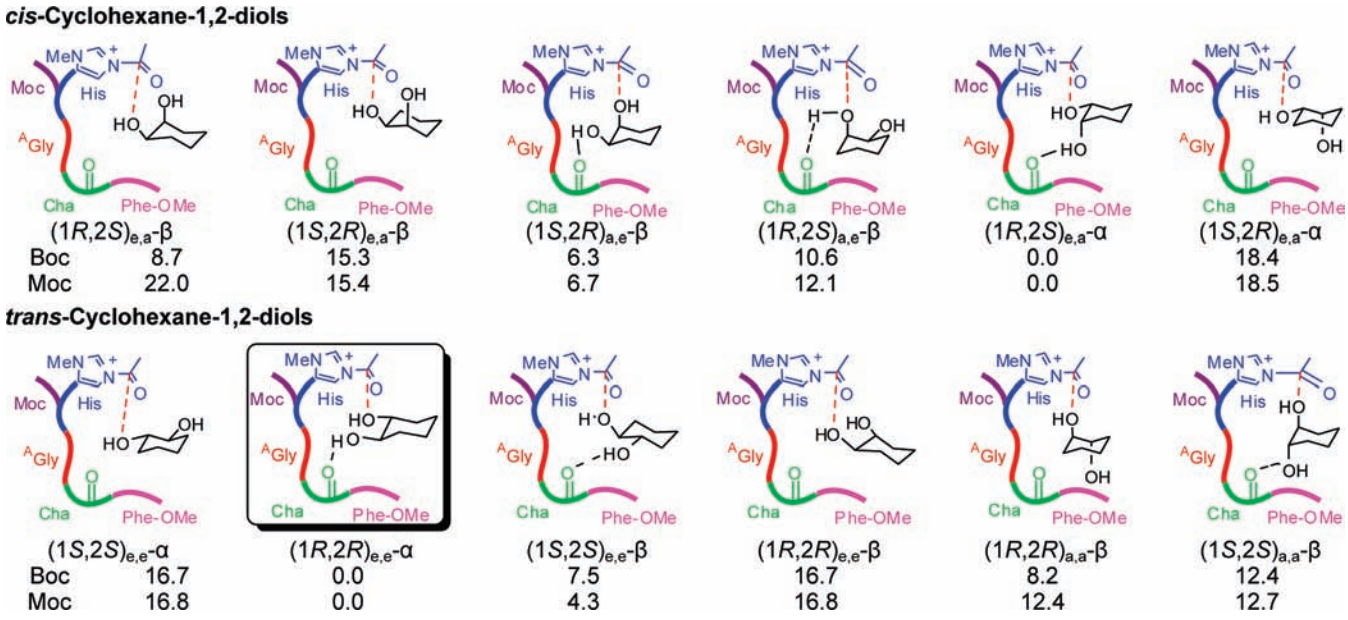


Figure 1. Computed relative energies (ΔE in kcal/mol) at the B3LYP/6-31G*//ONIOM2(B3LYP/6-31G*:PM3) level of theory for catalyst-acylium···diol complexes. The relative energies for *trans*- and *cis*-diols are reported separately, on the basis of the lowest-energy inclusion complex in each case.

envisaged to offer a congenial template for the ensuing acylation reaction. It is logical to assume that the acyl transfer reaction is more likely to take place soon after the correct inclusion complexes are generated. Next, the TSs for acyl transfer to diols are located. The relative energies with respect to the lowest-energy TS for both *trans*- and *cis*-diols are provided in Table 1. The TS for the acyl transfer reaction, $(1R,2R)_{e,e}$-$\alpha^{\ddagger}$,[12] leading to the formation of (1*R*,2*R*)-2-hydroxycyclohexyl acetate is found to be the lowest-energy TS. The enantiomeric excess calculated on the basis of relative activation energy of the next higher energy diastereomeric TS $(1S,2S)_{e,e}$-$\beta^{\ddagger}$ giving rise to the corresponding enantiomer is above 99%. The computed ee is larger than the experimentally reported value of 75%.[5] Though the calculated ee is quantitatively higher than the observed value, the predicted sense of stereoselectivity toward acylation is same as that observed experimentally. The protecting groups (Boc or Moc) do not seem to influence the stereochemical outcome, as those are farther from the reaction site.

The optimized geometries of the lower-energy TSs are provided in Figure 2. Comparison of the geometrical features of the TSs reveals that the hydrogen bonding between the diol hydroxyl groups and the C═O group of the amino acid backbone play a vital role toward stabilizing the TSs. For

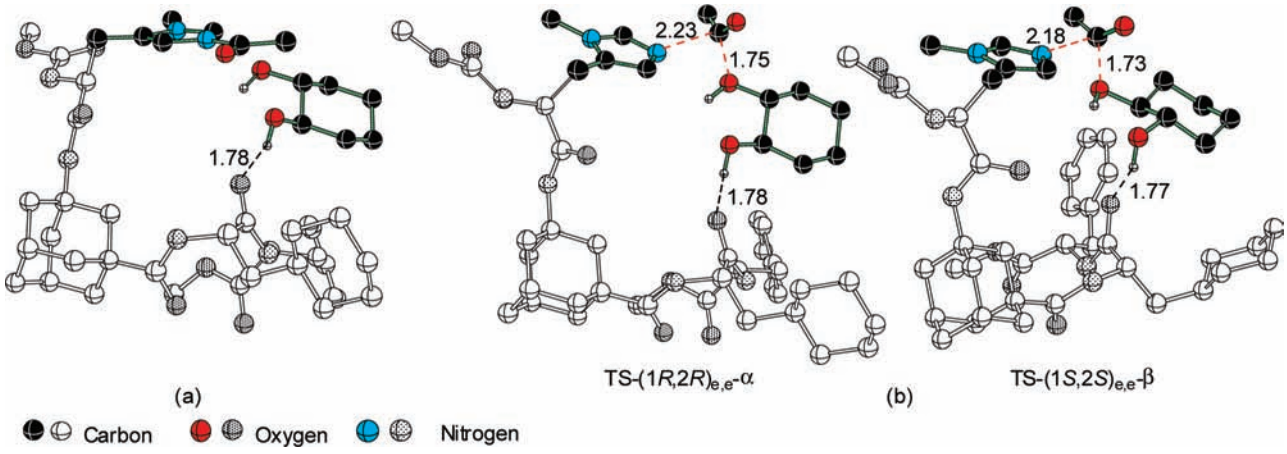


Figure 2. ONIOM2(B3LYP/6-31G*:PM3) optimized geometry of (a) $(1R,2R)_{e,e}$-cyclohexane-1,2-diol···acylium complex, and (b) the lower-energy TSs for the acetyl transfer to *trans*-diol. Only selected hydrogens are shown for improved clarity. Lighter gray and darker colored shadings, respectively, represent the lower (PM3) and higher (B3LYP) layers in the ONIOM2 partitioning. Distances are given in Å.

Table 1. Computed Relative Energies of Transition States Obtained at the B3LYP/6-31G*//ONIOM(B3LYP/6-31G*:PM3) Level of Theory for the Acyl Transfer[a]

diol	transition states	relative $\Delta E^{\ddagger}$ (in kcal/mol) Boc (**2**)	Moc (**3**)
	$(1S,2S)_{e,e}$-$\alpha^{\ddagger}$ [b]	13.5	13.4
	$(1S,2S)_{e,e}$-$\beta^{\ddagger}$	4.6	4.5
	$(1S,2S)_{a,a}$-$\beta^{\ddagger}$	7.6	7.7
	$(1R,2R)_{e,e}$-$\alpha^{\ddagger}$	**0.0**	**0.0**
	$(1R,2R)_{e,e}$-$\beta^{\ddagger}$	11.5	11.6
trans-diol	$(1R,2R)_{a,a}$-$\beta^{\ddagger}$	9.7	11.6
	$(1R,2S)_{e,a}$-$\alpha^{\ddagger}$	**0.0**	**0.0**
	$(1R,2S)_{e,a}$-$\beta^{\ddagger}$	16.1	16.3
	$(1R,2S)_{a,e}$-$\beta^{\ddagger}$	12.5	12.6
	$(1S,2R)_{e,a}$-$\alpha^{\ddagger}$	12.7	12.7
	$(1S,2R)_{e,a}$-$\beta^{\ddagger}$	14.9	15.0
cis-diol	$(1S,2R)_{a,e}$-$\beta^{\ddagger}$	4.3	4.4

[a] See Tables S1 and S2 in the Supporting Information, respectively, for values obtained using the 6-31G** basis set as well as the activation barriers with respect to the prereacting complexes. [b] The notations α and β refer the orientations of −OH in the diol to which the acetyl is transferred.

instance, the hydrogen bonding distance in TS $(1R,2R)_{e,e}$-$\alpha^{\ddagger}$ is found to be 1.78 Å. The separation between the cyclohexyl groups, respectively, of catalyst **2** and the diol is found to increase from the prereacting complex to the lowest-energy acyl transfer TS. The distances of the acyl group from histidine nitrogen and diol oxygen indicate a product-like TS for acyl transfer. The conformation of the peptide backbone in the higher-energy TSs is identified to exhibit larger deviations as compared to that with the lower-energy TS.[13] In particular, the orientation of the cyclohexyl group of the backbone is found to be progressively different for higher-energy TSs. In TS $(1S,2S)_{e,e}$-β, the incipient C−O bond develops 1,3-diaxial interaction with the C(β)H, which is absent in the lowest-energy TS $(1R,2R)_{e,e}$-$\alpha^{\ddagger}$. A stabilizing hydrogen bonding interaction between the acyl oxygen and cyclohexane C(α)H of the diol offers additional stabilization for $(1R,2R)_{e,e}$-$\alpha^{\ddagger}$.[14] The cumulative effects of the stereoelectronic features as noted above will help achieve the vital energy separation between the diastereomeric acyl transfer TSs. In other words, the *trans*-$(1R,2R)_{e,e}$ cyclohexane diol is predicted to undergo stereoselective acylation, leaving behind the $(1S,2S)_{e,e}$ stereoisomer amenable to KR.

After having established the molecular origins of stereoselective acylation of *trans*-diols, we became curious to learn how *cis*-diols would respond to acylation under the chiral template. Among the various acylation TSs considered for *cis*-diols, it is found that TS $(1R,2S)_{e,a}$-$\alpha^{\ddagger}$ is the lowest-energy TS. A hydrogen bonding interaction between one of the carbonyl groups of the backbone and the diol hydroxyl is found to dominate in the lower-energy TSs. An additional TS, TS $(1R,2S)_{e,a}$-$\alpha^{\ddagger}$, wherein this hydrogen bonding interaction is weaker, is found to have higher energy.[15] The next higher-energy TS leading to the opposite enantiomer, i.e., TS $(1S,2R)_{a,e}$-$\beta^{\ddagger}$, is 4.3 kcal/mol higher than the lowest-energy $(1R,2S)_{e,a}$-$\alpha^{\ddagger}$ in the case of Boc-protected peptide.[16] Such a larger difference in the activation barriers between the kinetically significant acylation step evidently suggest that the separation of *cis*-(1*R*,2*S*)-cyclohexane-1,2-diol through monoacylation using catalyst **2** appears to be a feasible option. The resulting product of desymmetrization is predicted as (1*R*,2*S*)-2-hydroxycyclohexyl acetate. We hope that the prediction would be subjected to experimental verification in the near future.

In summary, we have been able to explain the observed product stereochemistry in the kinetic resolution of *trans*-cyclohexane-1,2-diol. The predicted outcome is in concurrence with the available experimental results. The bifunctional nature of the catalyst is illustrated where one end offers nucleophilic catalysis while the backbone helps to achieve chiral recognition.

Acknowledgment. Generous computing facilities from IITB computer centre and a senior research fellowship from CSIR New Delhi (SCB) are gratefully acknowledged.

Supporting Information Available: Details on computational methods, full citation of ref 9b, optimized geometries of lower-energy transition states, and optimized coordinates of various transition states and their energies are given. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9011822

(12) In the nomenclature used for inclusion complexes and transition states, the subscripts a (axial) or e (equatorial) refer to the position of −OAc and −OH in the product and notations α and β refer to the orientations of −OH in the diol to which the acetyl group is transferred.

(13) A comprehensive comparison of such deviations is given in Figure S3 in Supporting Information.

(14) Figure S4 showing these interactions is given in Supporting Information.

(15) A comparison of these transition state features is given in Figure S2 of Supporting Information.

(16) The optimized geometries of lower-energy transition states for the acylation reaction of *cis*-cyclohexane-1,2-diol are given in Figure S1 of Supporting Information.