

Theoretical Evaluation of the Reaction Intermediate Complex for an Asymmetric Reaction Using a Chiral Lithium Amide by the Molecular Mechanics (MM3) Calculations

Takashi Yoshida, Kazuhisa Sakakibara,* and Masatoshi Asami

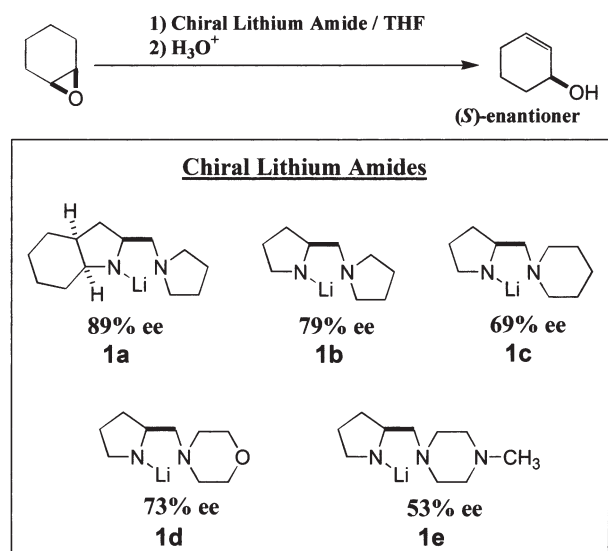
Department of Applied Chemistry, Graduate School of Engineering, Yokohama National University,
79-5 Tokiwadai, Hodogaya-ku, Yokohama 240-8501

(Received October 28, 2002; CL-020916)

The structures and conformational energies of the reaction intermediate complex for an asymmetric reaction, in which cyclohexene oxide is transformed to chiral (*S*)-2-cyclohexen-1-ol with high enantioselectivity by various chiral lithium amide in tetrahydrofuran (THF), were evaluated well by the extended Allinger's MM3 force field calculations.

Chiral lithium amide molecules are used widely as useful reagents for asymmetric syntheses.¹ The chiral lithium amides, prepared from (*S*)-2-(disubstituted aminomethyl)pyrrolidines and butyllithium, have been reported as effective reagents for the asymmetric transformation reaction where cyclohexene oxide can be transformed to (*S*)-2-cyclohexen-1-ol with high enantioselectivity (Scheme 1).² It seems worthwhile to try to design an efficient chiral lithium amide for asymmetric syntheses by computational methods. Though the computational approach using the quantum mechanical (QM) calculations has already been reported by Ahlberg's³ group, the molecular mechanics (MM) calculations can be another useful and efficient method to organic chemists for the purpose of a molecular design of good and efficient asymmetric lithium amide because the MM3⁴ calculation has the advantage of the calculation speed and the size of the systems to be handled over QM calculations. In this paper, we report the MM3 calculations on the reaction intermediate complexes stated above, and show the MM3 approach is useful to design an efficient chiral lithium amide with high enantioselectivity.

As this asymmetric reaction using the chiral lithium amide can



Scheme 1. Experimentally determined enantioselectivity for formation of (*S*)-2-cyclohexen-1-ol using chiral lithium amide reagents (1a-e).²

be thought to proceed as kinetic control, the structure and energy of the transition state should be calculated appropriately by a theoretical approach to estimate the enantioselectivity. However, current MM3 force field calculations usually predict the energy local minima rather than local maxima (transition state). Therefore, we have tried to find a reaction intermediate (local minimum) which is located closely to the transition state by the MM3 assuming that Hammond's postulate⁵ is valid. In order to search for appropriate reaction intermediates neighbored on the transition state, the transition state structure was first evaluated by MP2/6-31+G* geometry optimization calculations⁶ on the model system comprising lithium amide (LiNH₂) and propene oxide where 2-propen-1-ol is prepared. Then, the MM3 input data for the actual asymmetric synthesis system was constructed by fixing the essential geometrical parameters⁷ obtained for the transition state of the reaction of LiNH₂ and propene oxide with regard to the reaction center as shown in Figure 1a, and then the other remaining parts of the actual substrate and the chiral lithium amide are added to complete the input data. When an initial reaction intermediate structure is constructed, we have assumed that the substrate cyclohexene oxide is coordinated with a chiral lithium amide (as shown in Scheme 1) and the solvent molecule (tetrahydrofuran: THF) is incorporated into the complex on the basis of the NMR and X-ray experimental results.⁸ The structures of the (*S*)- and (*R*)- intermediate complexes constructed from the critical geometrical parameters of the transition state are shown in Figure 1b.⁹ It can be recognized easily that the strongly basic nitrogen atom bonded to lithium atom is

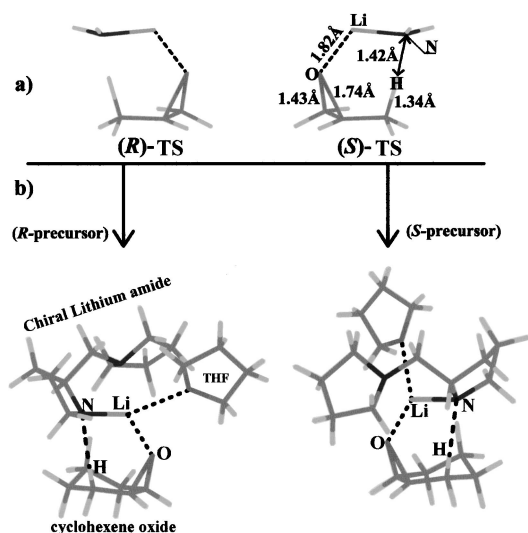


Figure 1. a) Transition state structure of the LiNH₂/propene oxide model system determined by MP2/6-31+G* calculations. b) Construction of the initial guess structures for the intermediate complexes of cyclohexene oxide + chiral Li amide (1b) + THF system for MM3 calculations.

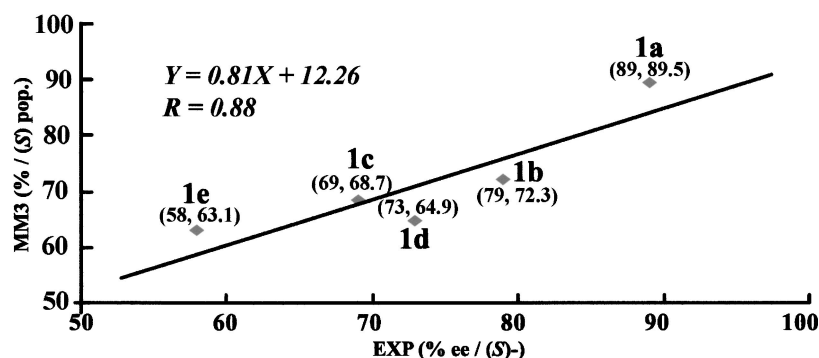


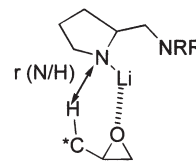
Figure 2. Correlation between the experimental %ee(S) (abscissa) and the population of (S)-intermediate complexes calculated by MM3 calculations (ordinate) with regard to the enantioselective formation of the (S)-2-cyclohexen-1-ol. The numbers in the parentheses correspond to those of the abscissa and ordinate, respectively.

oriented properly to deprotonate the β -hydrogen atom of the epoxide leading to the formation of 2-cyclohexen-1-ol.

By using these initial-guess structures for the reaction intermediate complexes stated above, the MM3 force field calculations (Full geometry optimization) extended to lithium amide¹⁰ were carried out, and the optimized stable conformations of the reaction intermediate complexes were searched by the stochastic method. The conformational energies of the dominant conformers were used to calculate the Boltzmann population at 298 K. The calculated populations of the (S)-intermediate complex for each chiral lithium amide reagent shown in Scheme 1 were plotted against the experimentally determined (S)-enantiomer excess (%ee). The plot was shown in Figure 2 (correlation coefficient $R = 0.88$). As shown in Figure 2, the enantioselectivity (%ee) for this asymmetric reaction was evaluated correctly by the MM3 force field calculations. The MM3 optimized structures of these intermediate complexes with regard to the reaction center comprising the lithium amide and the epoxide were almost as the same as those of the $\text{LiNH}_2 + \text{propene oxide}$ intermediate which was derived by the IRC (Intrinsic Reaction Coordinate) 6-31+G* QM calculations from the calculated transition state. The notable structural feature favorable to the (S)-enantiomer formation of these intermediate complexes is the distance ($\text{N} \cdots \text{H}$) between the strongly basic lithium amide nitrogen and the being deprotonated β -hydrogen atom of the epoxide. In the cases of the (S)-intermediate complexes, the $\text{N} \cdots \text{H}$ distance was shorter by $>0.1 \text{ \AA}$ than that of the corresponding (R)-intermediate complexes (Table 1). These results suggest that the MM3 force field can predict correctly the structure and conformational energy of the reaction intermediate complexes closely located at the transition state if proper initial geometries are chosen as input data.

In addition to the calculation speed and the large size of the reaction intermediate complex system that we can deal with, the accuracy with regard to the calculated structures and energies of the MM3 force field is so high. Therefore, the computational molecular design using this MM3 force field may enable organic chemists to design systems for the purpose of carrying out asymmetric syntheses more smoothly and efficiently. The details of the characteristic features of the reaction intermediate complexes, further consideration on another kind of intermediate complexes comprising of oligomeric lithium amides, applicability of this approach to different kind of cyclic alkene oxides,¹¹ and the important factors leading to the (S)-enantiomer preference in this asymmetric reaction using these kind of chiral lithium amides will be reported elsewhere soon.

Table 1. Interatomic distances (\AA) between the lithium amide nitrogen and the enantiotopic β -proton of the cyclohexene oxide



	1a	1b	1c	1d	1e
(R)-pre	2.919	2.717	2.658	2.658	2.686
(S)-pre	2.589	2.566	2.569	2.563	2.569

This work was partially supported by a grant in aid for Scientific Research (KAKENHI) from the Ministry of Education, Culture, Sports, Science and Technology (No. 13640526).

References and Notes

- a) J. S. Sabol and R. J. Cregge, *Tetrahedron Lett.*, **30**, 3377 (1989). b) R. Hates and T. W. Wallace, *Tetrahedron Lett.*, **31**, 3355 (1990). c) K. Mori and N. Murata, *Liebigs Ann.*, **1995**, 2089. d) M. Asami, T. Ishizaki, and S. Inoue, *Tetrahedron Lett.*, **36**, 1893 (1995). e) D. Bhuniya, A. DattaGupta, and V. K. Singh, *J. Org. Chem.*, **61**, 6108 (1996). f) J. Leonard, L. Bennett, and A. Mahmood, *Tetrahedron Lett.*, **40**, 3965 (1999). g) A. Seki and M. Asami, *Tetrahedron*, **58**, 4655 (2002).
- a) M. Asami, *Chem. Lett.*, **1984**, 829. b) M. Asami and H. Kiriwara, *Chem. Lett.*, **1987**, 389. c) M. Asami, *Bull. Chem. Soc. Jpn.*, **63**, 721 (1990). d) M. Asami, T. Suga, K. Honda, and S. Inoue, *Tetrahedron Lett.*, **38**, 6425 (1997).
- S. O. N. Lill, P. I. Arvidsson, and P. Ahlberg, *Tetrahedron: Asymmetry*, **10**, 265 (1999).
- a) N. L. Allinger, Y. H. Yuh, and J.-H. Lii, *J. Am. Chem. Soc.*, **111**, 8551 (1989). b) J.-H. Lii and N. L. Allinger, *J. Am. Chem. Soc.*, **111**, 8566 (1989). c) J.-H. Lii and N. L. Allinger, *J. Am. Chem. Soc.*, **111**, 8576 (1989).
- G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 345 (1955).
- M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, "Gaussian 94 (Revision D.4)," Gaussian, Inc., Pittsburgh, PA (1995).
- J. E. Eksterowicz and K. N. Houk, *Chem. Rev.*, **93**, 2439 (1993).
- a) K. Gregory, P. v. R. Schleyer, and R. Snaith, *Adv. Inorg. Chem.*, **37**, 47 (1991). b) R. E. Mulvey, *Chem. Soc. Rev.*, **27**, 339 (1998). c) N. D. R. Barnett, W. Clegg, L. Horsburgh, D. M. Lindsay, Q.-Y. Liu, F. M. Mackenzie, R. E. Mulvey, and P. G. Williard, *J. Chem. Soc., Chem. Commun.*, **1996**, 2321.
- The other type of the reaction intermediate complex can be created for the each (S)- and (R)-precursor where the positions of the lithium amide catalyst and the solvent molecule are interchanged. However, these two complexes were not favorable ones leading to the transition states of this asymmetric reaction because the steric repulsion became larger between the lithium amide reagent and the cyclohexene oxide. The detailed discussions will be reported elsewhere.
- T. Yoshida, K. Sakakibara, M. Asami, K.-H. Chen, J.-H. Lii, and N. L. Allinger, *J. Comput. Chem.*, (2002), in press.
- S. K. Bertilson, M. J. Sodergren, and P. G. Andersson, *J. Org. Chem.*, **67**, 1567 (2002).