JOC *Article*

Relative Stabilities of Some Synthetically Useful 2,3-*cis*-Disubstituted Aziridines and Their 2,3-Trans Isomers

Norio Mimura,[*,†] Yoshihisa Miwa, and Toshiro Ibuka[‡]

Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

Yoshinori Yamamoto

Department of Chemistry, Graduate School of Science, Tohoku University,
Sendai, Miyagi 980-8578, Japan

Norio.Mimura@pharma.novartis.com

Received March 30, 2002

The relative stabilities of synthetically useful 2,3-cis/trans pairs of 2,3-disubstituted aziridines were investigated theoretically by performing molecular orbital calculations at the MP2/6-31G**/RHF/6-31G** level of theory. The results showed clearly that a functional group on the nitrogen atom of the aziridine ring plays a very important role in conjunction with the relative stabilities of these pairs of isomers. There is a tendency that the 2,3-cis isomer bearing tetrahedral structure on the aziridine nitrogen is preferable. Bulky substituents such as a phenyl group on aziridine atoms can also affect the relative stability sterically.

Introduction

The aziridine ring framework can be frequently found in natural and synthetic compounds of biological importance.[1] 2,3-Disubstituted aziridines are versatile synthetic intermediates for the synthesis of many important compounds such as β-lactams,[2] azinomycin,[3] azacycles such as 2,6-disubstituted tetrahydropyridines,[4] indolizidine and pyrrolizidine alkaloids,[5] allylic amines,[6] and 2*H*-azirines,[7] amino acids,[8] and alkene dipeptide isosteres.[9] Recent literature afforded a variety of methods for the synthesis of 2,3-disubstituted aziridines in racemic and enantiomerically enriched forms.[10]

In the reactions of 2,3-disubstituted aziridines with various reagents, the importance of 2,3-cis or 2,3-trans

---

[†] Present address: Novartis Tsukuba Research Institute, 8 Okubo, Tsukuba, Ibaraki 300-2611, Japan.

[‡] This article is dedicated to Professor Toshiro Ibuka, who died in 2000.

(1) (a) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 7, Part 5, p 47. (b) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 5287. (c) Kasai, M.; Kono, M. *Synlett* **1992**, 778. (d) Naylor, M. A.; Threadgill, M. D.; Webb, P.; Stratford, I. J.; Stephens, M. A.; Fielden, E. M.; Adams, G. E. *J. Med. Chem.* **1992**, *35*, 3573. (e) Tanner, D.; He, H. M. *Tetrahedron* **1992**, *48*, 6079. (f) Carreaux, F.; Duréault, A.; Depezay, J. C. *Synlett* **1992**, 527. (g) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1992**, *57*, 5813. (h) Armstrong, R. W.; Moran, E. J. *J. Am. Chem. Soc.* **1992**, *114*, 371. (i) Bergmeier, S. C.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019. (j) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (k) Korn, A.; Rudolph-Böhner, S.; Moroder, L. *Tetrahedron* **1994**, *50*, 1717. (l) Arai, H.; Kanda, Y.; Ashizawa, T.; Morimoto, M.; Gomi, K.; Kono, M.; Kasai, M. *J. Med. Chem.* **1994**, *37*, 1794. (m) Arai, H.; Ashizawa, T.; Gomi, K.; Kono, M.; Saito, H.; Kasai, M. *J. Med. Chem.* **1995**, *38*, 3025. (n) Atkinson, R. S.; Williams, P. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1951.

(2) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91. Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2415.

(3) Moran, E. J.; Tellew, J. E.; Zhao, Z.; Armstrong, R. W. *J. Org. Chem.* **1993**, *58*, 7096.

(4) Åhman, J.; Javevang, T.; Somfai, P. *J. Org. Chem.* **1996**, *61*, 8148. Åhman, J.; Somfai, P. *J. Am. Chem. Soc.* **1994**, *116*, 9781−9782. Åhman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747. Åhman, J.; Somfai, P. *Tetrahedron Lett.* **1996**, *37*, 2495.

(5) Indolizidine alkaloid: Åhman, J.; Somfai, P. *Tetrahedron Lett.* **1995**, *36*, 303. Pyrrolizidine alkaloids: Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3527. Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755. Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683.

(6) Åhman, J.; Somfai, P. *Tetrahedron Lett.* **1995**, *36*, 303. Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc., Chem. Commun.* **1994**, 2785. Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K.-C.; Poon, Y.-F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5719.

(7) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651.

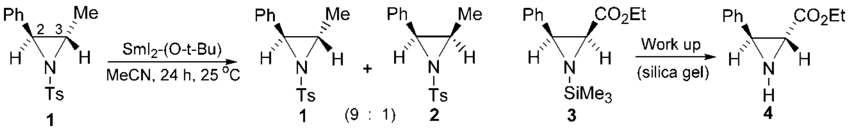
(8) Carreaux, F.; Duréault, A.; Depezay, J. C. *Synlett* **1992**, 527. Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. *J. Chem. Soc., Chem. Commun.* **1987**, 153. Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073. Church, N. J.; Young, D. W. *Tetrahedron Lett.* **1995**, *36*, 151.

(9) (a) Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1359. (b) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 652. (c) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (d) Satake, A.; Shimizu, I.; Yamamoto, A. *Synlett* **1995**, 64. (e) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586.

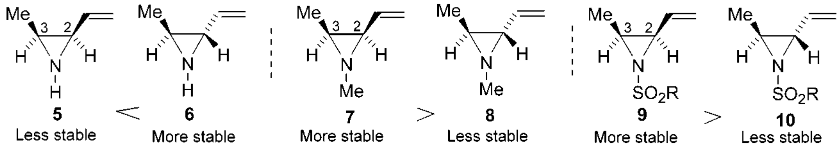
(10) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (b) Fujii, N.; Nakai, K.; Habashita, H.; Hotta, Y.; Tamamura, H.; Otaka, A.; Ibuka, T. *Chem. Pharm. Bull.* **1994**, *42*, 2241. (c) Atkinson, R. S.; Fawcett, J.; Russell, D. R.; Williams, P. J. *Tetrahedron Lett.* **1995**, *36*, 3241 and references therein. (d) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676. (e) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Otaka, A.; Tamamura, H.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Chounan, Y.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 2044. (f) Willems, J. G. H.; Dommerholt, F. J.; Hammink, J. B.; Vaarhorst, A. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 603. (g) Åhman, J.; Jarevång, T.; Somfai, P. *J. Org. Chem.* **1996**, *61*, 8148. (h) Willems, J. G. H.; Hersmis, M. C.; de Gelder, R.; Smits, J. M. M.; Hammink, J. B.; Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 963. (i) For a recent review, see: Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693.

10.1021/jo025777k CCC: $22.00

SCHEME 1



SCHEME 2



stereochemistry in controlling stereoselectivity has been reported.[9,11] Evans and co-workers reported that exposure of *N*-tosyl-2-phenyl-3-methylaziridine **1** to 5 mol % of $\mathrm{SmI_2}$ (O-*t*-Bu) gave a 9:1 mixture of the 2,3-*trans*- and 2,3-*cis*-aziridines **1** and **2** (Scheme 1). Independently, treatment of the pure 2,3-*cis*-aziridine **2** under identical conditions failed to promote any isomerization.[12] Surprisingly, Rasmussen and Jørgensen demonstrated that the *N*-trimethylsilyl-2,3-*cis*-aziridine **3** was isomerized to the 2,3-*trans*-aziridine **4** under a work-up condition (Scheme 1).[13]

Although the relative stabilities of 2,3-*cis*-disubstituted aziridines and their 2,3-trans isomers would be dependent on the nature of the substituents at the C-2 and C-3-positions, and the *N*-protecting group, except for a few cases,[14−16] little is known about the relative stabilities of 2,3-cis/trans pairs of 2,3-disubstituted aziridines. We reported based on theoretical calculations that whereas *N*-unsubstituted 2,3-*trans*-2-vinylaziridine **6** was predicted to be more stable than its 2,3-cis isomer **5**, 2,3-*cis*-aziridines **7** and **9** bearing a methyl and methanesulfonyl group, respectively, on the nitrogen atom were predicted to be more stable than the corresponding 2,3-trans isomers **8** and **10**.[16] In addition, prediction of the relative stabilities of **9** and **10** has been proven to be quite close to the experimental results in solution (Scheme 2).[17,18]

In continuation of our interest in small-ring chemistry, we wish to report our results on the relative stabilities of some 2,3-cis/trans pairs of *N*-unsubstituted and *N*-substituted aziridines that have been the subject of much synthetic interest.[8,19]

Results and Discussion

Relative Energetic Stabilities of 10 Selected 2,3-Cis/Trans Pairs of 2,3-Disubstituted Aziridines. As described above, despite their potential usefulness for the synthesis of various biologically important compounds, 2,3-disubstituted aziridines have scarcely been studied from the viewpoint of relative energetic stabilities to date.

To gain an understanding of the relative stabilities of 2,3-*cis*- and 2,3-*trans*-disubstituted aziridines, we undertook ab initio molecular orbital calculations involving full optimizations using the GAUSSIAN 94 quantum mechanical package (Revision D).[20a,21] All geometries were fully optimized with the HF/6-31G**,[22] and a harmonic frequency analysis was done for every optimized geometry. All calculated frequencies are positive for the optimized geometries, which is an indication of a true minimum on the potential surface. Each transition state structure was also confirmed by a harmonic frequency analysis, and only one imaginary frequency appeared in

---

(11) Aoyama, H.; Mimura, N.; Ohno, H.; Ishii, K.; Toda, A.; Tamamura, H.; Otaka, A.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1997**, *38*, 7383.

(12) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742.

(13) (a) Rasmussen, K. G.; Jørgensen, K. A. *Chem. Commun.* **1995**, 1401. (b) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368.

(14) Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753. Huisgen, R.; Scheer, W.; Mäder, H. *Angew. Chem.* **1969**, *81*, 619.

(15) Cromwell, N. H.; Graff, M. A. *J. Org. Chem.* **1952**, *17*, 414.

(16) Coutrot, P.; Elgadi, A.; Grison, C. *Heterocycles* **1989**, *28*, 1179.

(17) (a) Mimura, N.; Ibuka, T.; Akaji, M.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Chem. Commun.* **1996**, 351 and 1399. (b) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999.

(18) (a) Ibuka, T.; Akaji, M.; Mimura, N.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 2849. (b) Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2982.

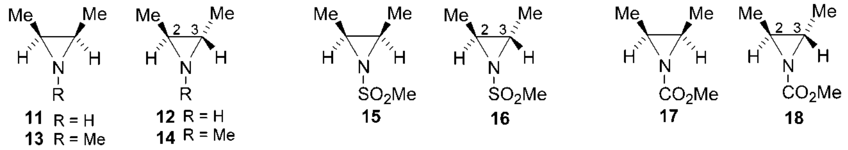
(19) (a) Kuyl-Yeheskiely, E.; Loddeer, M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1992**, *33*, 3013. (b) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243. (c) Casarrubios, L.; Pérez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358. (d) Mohan, J. M.; Uphade, B. S.; Choudhary, V. R.; Ravindranathan, T.; Sudalai, A. *Chem. Commun.* **1997**, 1429. (e) Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5909.

(20) (a) All ab initio calculations were performed with the program GAUSSIAN 94 on a Cray T94/4128 at the Supercomputer Laboratory, Institute for Chemical Research, Kyoto University. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, Revision D.3; Gaussian, Inc.: Pittsburgh, PA, 1995.

(21) For ab initio calculations of some aziridines derivatives, see: Rauk, A. *J. Am. Chem. Soc.* **1981**, *103*, 1023. Shustov, G. V.; Kadorkina, G. K.; Kostyanovsky, R. J.; Rauk, A. *J. Am. Chem. Soc.* **1988**, *110*, 1719. Shustov, G. V.; Kachanov, A. V.; Kadorkina, G. K.; Kostyanovsky, R. G.; Rauk, A. *J. Am. Chem. Soc.* **1992**, *114*, 8257. Shustov, G. V.; Kadorkina, G. K.; Varlamov, S. V.; Kachanov, A. V.; Kostyanovsky, R. G.; Rauk, A. *J. Am. Chem. Soc.* **1992**, *114*, 1616. Shustov, G. V.; Rauk, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1669. Shustov, G. V.; Kachanov, A. V.; Korneev, V. A.; Kostyanovsky, R. G.; Rauk, A. *J. Am. Chem. Soc.* **1993**, *115*, 10267.

(22) For references dealing with the 6-31G** basis set and Møller−Plesset perturbation theory, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. In *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986.

SCHEME 3



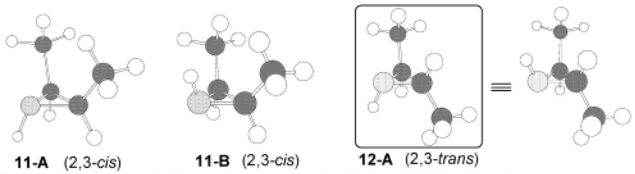
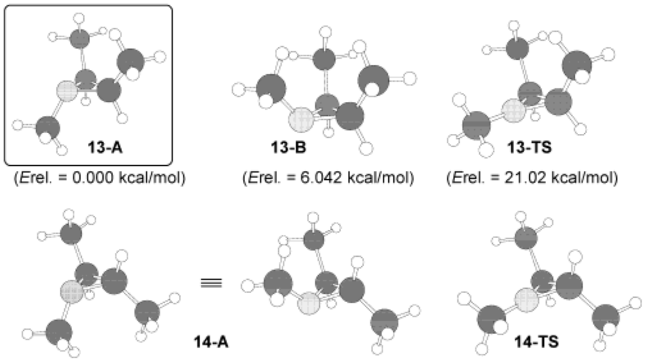

11-A (2,3-*cis*) (*Erel.* = 0.740 kcal/mol) **11-B** (2,3-*cis*) (*Erel.* = 2.213 kcal/mol) **12-A** (2,3-*trans*) (*Erel.* = 0.000 kcal/mol)

FIGURE 1. RHF/6-31G** optimized geometries of model compounds **11** and **12**. Energies are relative to the lowest energy at the MP2/6-31G**/RHF/6-31G** level. **11-A**: The lowest energy geometry of 2,3-*cis*-2,3-dimethylaziridine (**11**). **11-B**: The lowest energy geometry of the nitrogen invertomer of **11-A**. **12-A**: The lowest energy geometry of 2,3-*trans*-2,3-dimethylaziridine (**12**).


13-A (*Erel.* = 0.000 kcal/mol) **13-B** (*Erel.* = 6.042 kcal/mol) **13-TS** (*Erel.* = 21.02 kcal/mol)

14-A (*Erel.* = 2.034 kcal/mol) **14-TS** (*Erel.* = 19.76 kcal/mol)

FIGURE 2. RHF/6-31G** optimized geometries of model compounds **13** and **14**. Energies are relative to the lowest energy at the MP2/6-31G**/RHF/6-31G** level. **13-A**: The lowest energy geometry of 2,3-*cis*-1,2,3-trimethylaziridine (**13**). **13-B**: The lowest energy geometry of the nitrogen invertomer of **13-A**. **14-A**: The lowest energy geometry of 2,3-*trans*-1,2,3-trimethylaziridine (**14**). **13-TS** and **14-TS**: The transition structures of 2,3-*cis*-1,2,3-trimethylaziridine (**13**) and 2,3-*trans*-1,2,3-trimethylaziridine (**14**).

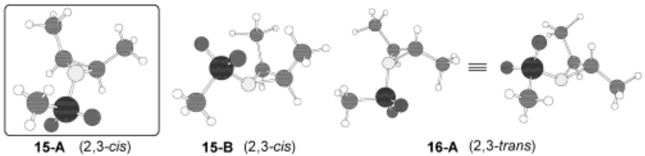

15-A (2,3-*cis*) (*Erel.* = 0.000 kcal/mol) **15-B** (2,3-*cis*) (*Erel.* = 6.897 kcal/mol) **16-A** (2,3-*trans*) (*Erel.* = 4.552 kcal/mol)

FIGURE 3. RHF/6-31G** optimized geometries of 2,3-cis and 2,3-trans model compounds **15** and **16**. Energies are relative to the lowest energy at the MP2/6-31G**/RHF/6-31G** level. **15-A** and **15-B**: The lowest energy geometry of 2,3-*cis*-*N*-mesyl-2,3-dimethylaziridine and its nitrogen invertomer, respectively. **16-A**: The lowest energy geometry of 2,3-*trans*-*N*-mesyl-2,3-dimethylaziridine.

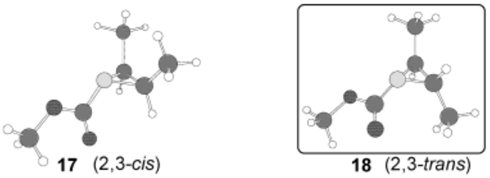

17 (2,3-*cis*) (*Erel.* = 2.218 kcal/mol) **18** (2,3-*trans*) (*Erel.* = 0.000 kcal/mol)

FIGURE 4. RHF/6-31G** optimized geometries of 2,3-cis and 2,3-trans model compounds **17** and **18**. Energies are relative to the lowest energy at the MP2/6-31G**/RHF/6-31G** level. **17**: The lowest energy geometry of 2,3-*cis*-*N*-methoxycarbonyl-2,3-dimethylaziridine and its nitrogen invertomer, respectively. **18**: The lowest energy geometry of 2,3-*trans*-*N*-methoxycarbonyl-2,3-dimethylaziridine.

the result. With use of these optimized geometries, further single point calculations were done by Møller–Plesset perturbation theory at the 6-31G** level of theory. All computed aziridines in their ground states are also characterized by a pyramidal configuration of the nitrogen atom.[23]

(i) Relative Stabilities of 2,3-Cis/Trans Pairs of 2,3-Dimethylaziridines. We initiated our study to determine the relative stabilities of four 2,3-cis/trans pairs of 2,3-dimethylaziridines (**11**, **12**), (**13**, **14**), (**15**, **16**), and (**17**, **18**) as model compounds.As shown in Figure 1, the calculations suggest that the energy minimum **12-A** of 2,3-*trans*-2,3-dimethylaziridine (**12**) is favored by 0.7 kcal/mol over the global energy minimum **11-A** of the cis-isomer **11** at the MP2/6-31G**/RHF/6-31G** level. In the lowest energy geometry **11-A**, a nonbonding electron pair on the aziridine nitrogen is in the cis position with respect to the methyl groups at the C-2 and C-3 positions. The energy minimum of the nitrogen invertomer **11-B** was predicted to be 1.5 kcal/mol higher in energy than the global energy minimum **11-A**. Thus, 2,3-*trans*-2,3-dimethylaziridine (**12**) is predicted to be more stable than its 2,3-cis isomer **11**.

Among *N*-substituted aziridines, the interactions between the *N*-substituent and the substituents at the C(2)- and/or C(3)-positions may have marked conformational consequences. In this context, relative energies of two cis/trans pairs of *N*-methyl- and *N*-mesyl-2,3-dimethylaziridines (**13** and **14**) and (**15** and **16**) were investigated (Figures 2 and 3).

Figure 2 shows optimized geometries and relative energies of 2,3-*cis*-1,2,3-trimethylaziridne (**13**) and its 2,3-trans isomer **14**. These calculations suggest that the energy minimum **13-A** of 2,3-*cis*-1,2,3-trimethylaziridine (**13**) is favored by ca. 2 kcal/mol over the energy minimum **14-A** of 2,3-trans isomer **14** at the MP2/6-31G**/RHF/6-31G** level. It became apparent that *N*-methylation would reverse the relative stabilities: 2,3-*cis*-1,2,3-trimethylaziridine (**13**) was predicted to be more stable than its 2,3-trans isomer **14**. The nitrogen invertomer **13-B**

---

(23) (a) Rauk, A.; Allen, L. C.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 400. (b) Carter, R. E.; Drakenberg, T.; Bergman, N.-Å. *J. Am. Chem. Soc.* **1975**, *97*, 6990. (c) Nielsen, I. M. B. *J. Phys. Chem. A* **1998**, *102*, 3193.

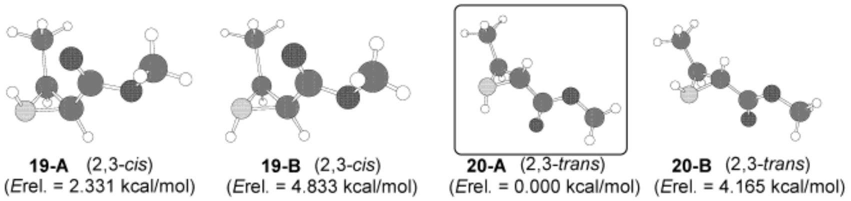
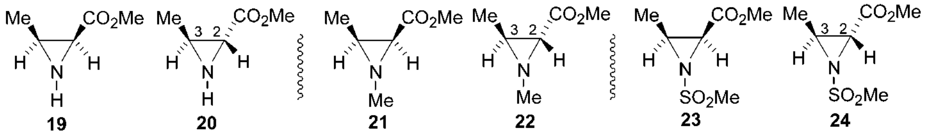


FIGURE 5. RHF/6-31G** optimized geometries of 2,3-*cis*- and 2,3-*trans*-2-methoxycarbonyl-3-methylaziridines (**19** and **20**, respectively). Energies are relative to the lowest energy at the MP2/6-31G**/RHF/6-31G** level. **19-A** and **19-B**: The lowest energy geometry of 2,3-*cis*-2-methoxycarbonyl-3-methylaziridine and its nitrogen invertomer. **20-A** and **20-B**: The lowest energy geometry of 2,3-*trans*-2-methoxycarbonyl-3-methylaziridine and its nitrogen invertomer.

SCHEME 4



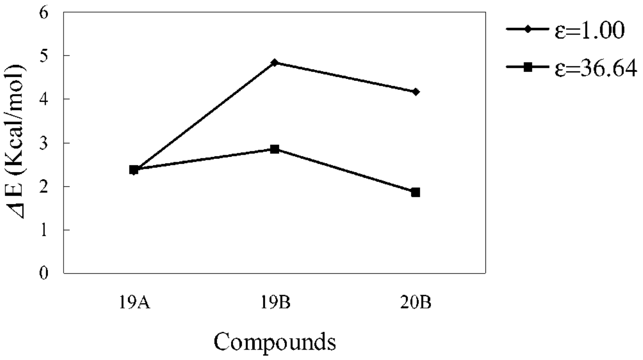


FIGURE 6. Relative energy profile between 2,3-*cis*- and 2,3-*trans*-2-methoxycarbonyl-3-methylaziridines **19** and **20**. Energies are relative to the lowest energy conformer **20-A** at the RHF/6-31G** level.

bearing three methyl groups on the same side of the plane of the aziridine ring should be destabilized to a greater degree from mere steric reasons. Energy barriers of nitrogen pyramidal inversion[23] at the transition state (TS) in aziridines **13** and **14** were also investigated. The barriers of the nitrogen inversion in **13** and **14** were predicted to be 21.0 and 19.8 kcal/mol, respectively, as shown in Figure 2. These values for free energy of activation (ca. 20 kcal/mol) are in good agreement with available experimental and calculated data for related compounds.[23]

In 2,3-cis/trans pairs of *N*-activated aziridines,[24] would 2,3-*cis*-*N*-mesyl-2,3-substituted aziridines or their 2,3-trans isomers be expected to be more stable? We examined the relative stabilities of model compounds **15** and **16** bearing an *N*-mesyl group (Figure 3). The optimized geometries **15-A** and **15-B** (the nitrogen invertomer of **15-A**) of 2,3-*cis*-*N*-mesyl-2,3-dimethylaziridine (**15**) and the optimized structure **16-A** of 2,3-*trans*-*N*-mesyl-2,3-dimethylaziridine (**16**) are shown in Figure 3. Calculations suggest that the energy minimum **15-A** is favored by 4.6 kcal/mol over the global energy minimum **16-A** at the MP2/6-31G**/RHF/6-31G** level.

In a similar manner, we also investigated the relative stabilities of model compounds **17** and **18** bearing an *N*-methoxycarbonyl group (Figure 4). Contrary to the above results, 2,3-*trans*-*N*-methoxycarbonyl-2,3-dimethylaziridine (**18**) was predicted to be favored by 2.2 kcal/mol over the energy minimum of the 2,3-cis isomer **17** at the MP2/6-31G**/RHF/6-31G** level. Both optimized geometries are shown in Figure 4.

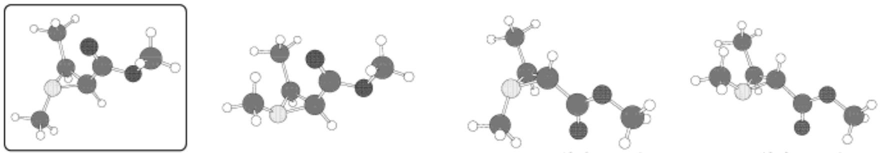
From the above calculations and assuming compounds were in the gas phase, it became clear that 2,3-*cis*-2,3-dimethylaziridines (**13** and **15**), in which substituents on the aziridine nitrogen atom have tetrahedral structures, namely, a methyl or a methanesulfonyl group, were predicted to be more stable than their 2,3-trans isomers (**14** and **16**). On the contrary, compounds in which substituents on the aziridine nitrogen atom do not have such structures, 2,3-*trans*-2,3-dimethylaziridine (**11**) and 2,3-*trans*-*N*-methoxycarbonyl-2,3-dimethylaziridine (**18**), were predicted to be more stable than their 2,3-cis isomers (**12** and **17**).

(ii) Relative Stabilities of 2,3-Cis/Trans Pairs of 2-Methoxycarbonyl-3-methylaziridines. Next, relative stabilities of 2,3-cis/trans pairs of 2-methoxycarbonyl-3-methylaziridines (**19**, **20**), (**21**, **22**), and (**23**, **24**) that could be easily prepared from (L)-threonine and (D)-*allo*threonine were investigated.[10b]The geometries of 2,3-*cis*-aziridine **19-A** and its nitrogen invertomer **19-B** as well as 2,3-trans isomer **20-A** and its nitrogen invertomer **20-B** were located by full optimizations at the RHF/6-31G** level. It was found that the energy minimum **20-A** of the 2,3-*trans*-aziridine **20** was predicted to be 2.3 kcal/mol lower than the energy minimum **19-A** of the 2,3-*cis*-aziridine **19**.

It should be noted that the intramolecular dipole interaction between the carbonyl group and the imide group causes a great energy difference between these conformers (**19-B**, **20-B**, and **19-A**). We examined relative stabilities of these compounds in the gas phase ($\epsilon = 1.00$) and in acetonitrile solvent ($\epsilon = 36.64$[25a]) at the RHF/6-31G** level using the SCRF method.[25b,c] The energy profile (Figure 6) obviously shows that in polar solution, relative energy differences between conformers become very small. This result indicates that intramolecular

---

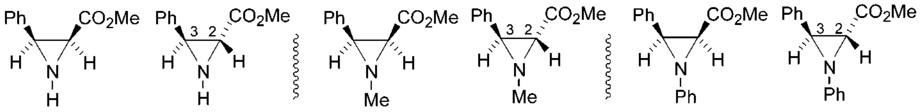
[24] For the term activated aziridines, see: Ham, G. E. *J. Org. Chem.* **1964**, *29*, 3052.



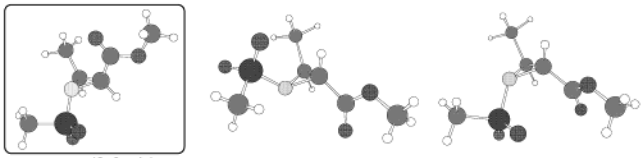
21-A (2,3-*cis*) (*E*rel. = 0.000 kcal/mol) **21-B** (2,3-*cis*) (*E*rel. = 4.101 kcal/mol) **22-A** (2,3-*trans*) (*E*rel. = 0.0352 kcal/mol) **22-B** (2,3-*trans*) (*E*rel. = 2.031 kcal/mol)

FIGURE 7. RHF/6-31G** optimized geometries of 2,3-*cis*- and 2,3-*trans*-*N*-methyl-2-methoxycarbonyl-3-methylaziridines **21** and **22**. Energies are relative to the lowest energy at the MP2/6-31G**/RHF/6-31G** level. **21-A** and **21-B**: The lowest energy geometry of 2,3-*cis*-*N*-methyl-2-methoxycarbonyl-3-methylaziridine and its nitrogen invertomer. **22-A** and **22-B**: The lowest energy geometry of 2,3-*trans*-*N*-methyl-2-methoxycarbonyl-3-methylaziridine and its nitrogen invertomer.

SCHEME 5



25 **26** **27** **28** **29** **30**



23 (2,3-*cis*) (*E*rel. = 0.000 kcal/mol) **24-A** (2,3-*trans*) (*E*rel. = 1.196 kcal/mol) **24-B** (2,3-*trans*) (*E*rel. = 2.090 kcal/mol)

FIGURE 8. RHF/6-31G** optimized geometries of 2,3-*cis*- and 2,3-*trans*-*N*-mesyl-2-methoxycarbonyl-3-methylaziridines **23** and **24**. Energies are relative to the lowest energy at the MP2/6-31G**/RHF/6-31G** level. **23**: The lowest energy geometry of 2,3-*cis*-*N*-mesyl-2-methoxycarbonyl-3-methylaziridine. **24-A** and **24-B**: The lowest energy geometry of 2,3-*trans*-*N*-mesyl-2-methoxycarbonyl-3-methylaziridine and its nitrogen invertomer.

dipole interaction makes conformers **19-B** and **20-B** more unstable in the gas phase, while in polar solutions like acetonitrile, their dipolar repulsion is released by the polar solvent.

In Figure 7, the energy minimum **21-A** of 2,3-*cis*-*N*-methyl-2-methoxycarbonyl-3-methylaziridine (**21**) was predicted to be only 0.04 kcal/mol lower than the energy minimum **22-A** of 2,3-trans isomer **22**. Since the difference between **21-A** and **22-A** in relative energies is subtle, it implies that a contribution to the relative energetic difference mainly depends on an interaction between substituents on the aziridine ring. These calculations also suggest that both nitrogen invertomers **21-B** and **22-B** are energetically unfavorable conformers.

We also investigated the relative stabilities of the 2,3-cis/trans pairs of activated aziridines, 2,3-*cis*-*N*-mesyl-2-methoxycarbonyl-3-methylaziridine (**23**) and 2,3-*trans*-*N*-mesyl-2-methoxycarbonyl-3-methylaziridine (**24**) (Figure 8). The energy minimum of the 2,3-cis isomer **23** is favored by ca. 1.2 kcal/mol over the 2,3-trans isomer **24-A**. This result is in quite good agreement with synthetic results.[13b] It can be seen that the nitrogen invertomer **24-B** is energetically unfavorable by more than 1 kcal/mol. The mesyl group on the aziridine nitrogen is expected to be at the opposite position to the methoxycarbonyl group by calculations.

(iii) Relative Stabilities of 2,3-Cis/Trans Pairs of 2-Methoxycabonyl-3-phenylaziridines. Is the relative stability of the diastereomers of aziridines controlled only by a substituent on the aziridine nitrogen atom? To understand effects of bulky functional groups, we examined 2,3-cis/trans pairs of 2-methoxycarbonyl-3-phenylaziridines (**25**, **26**), (**27**, **28**), and (**29**, **30**) as model compounds of *N*-phenyl-2-ethoxycarbonyl-3-phenylaziridines,[19c] involving full geometry optimizations with the RHF/6-31G** level of theory.In the 2,3-cis/trans pair of 2-methoxycarbonyl-3-phenylaziridines **25** and **26**, the 2,3-trans isomer was predicted to be more stable than the 2,3-cis isomer by 5.2 kcal/mol, which is a similar result as in previous sections. Contrary to the results above, the following calculations show that in the 2,3-cis/trans pair of *N*-methyl-2-methoxycarbonyl-3-phenylaziridines **27** and **28**, the 2,3-trans isomer is favorable by 0.8 kcal/mol over the 2,3-cis isomer, even though each of this pair has a substituent on the aziridine nitrogen atom that has a tetrahedral structure. As can be seen in synthetic studies of *N*-phenyl-2-ethoxycarbonyl-3-phenylaziridines,[19c] it clearly shows that 2,3-cis isomer is favorable in this pair, despite the fact that a substituent on the aziridine nitrogen atom has a plane structure. We also found that 2,3-*trans* isomer **30** is more stable by 0.7 kcal/mol over the 2,3-cis isomer **29**. For further understanding, in the same manner as in section ii, SCRF calculations were done for this pair. According to the synthetic results, we assumed the solvent was *n*-hexane, namely, the dielectric constant was set as $\epsilon = 1.882$.[26] Surprisingly, the 2,3-cis isomer was predicted to be favored by 0.5 kcal/mol by the calculations. This result supports the synthetic results which clearly show a predominance of 2,3-cis isomer, although the predicted energy difference is relatively small. It can be said that bulky substituents on aziridine atoms sterically and the solvent electrically affect the relative stabilities of these pairs.

---

(25) (a) GAUSSIAN94 value for acetonitrile. (b) Calculations were done by the SCI-PCM method at theRHF/6-31g** level of theory, see: Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem*. **1996**, *100*, 16098. (c) During SCRF calculation with the SCI-PCM model reaction field by the GAUSSIAN 94 program, the cavity for each compound was determined self-consistently from an isodensity surface. A default value of 0.0004 was used for isodensity.

(26) Giesen, D. J.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem*. **1995**, *99*, 7137 and references cited therein.

Conclusion

These results obtained from calculations are in good agreement with experimental results. Calculations in the gas phase suggest that 2,3-*cis*-aziridine is generally favored over the 2,3-trans isomer, in cases where a substituent on the aziridine nitrogen atom is a methyl or a methansulfonyl group, which have a tetrahedral structure. This preference is consistent with our previous results,[17,18] and it also became clear that the preference depends on substituents on aziridine atoms in their steric sizes. In other words, relative stabilities of 2,3-cis/trans pairs are strongly affected by the steric hindrance of a phenyl group on atoms in the aziridine ring. Even the hydrophobic solvent that has a very small dielectric constant can affect the relative stability of the pairs. Figure 6 clearly shows that intramolecular dipole interaction can affect the relative stability of conformers, should there be strong polar functional groups on aziridine atoms. This study shows that the theoretical calculation to predict the relative stabilities is quite useful for the synthesis of the aziridines.

Acknowledgment. The authors are very grateful for the helpful discussion with Takanori Kanazawa, Novartis Tsukuba Research Institute, and for the support of Hideaki Numa and Koji Noguchi, Novartis Pharma K.K., and Simon Tye, Novartis Institute for Medical Sciences.

Supporting Information Available: SCF, MP2, and SCRF energies for compounds **11A**−**30**, Cartesian coordinates for compounds **11A**−**30**, a figure for compounds **25**−**30**, and numbers of imaginary frequencies for compounds **11A**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025777K