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Investigation of macrocyclization sites for the synthesis of dendroamide A—an approach from a conformational search

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Dedicated to Professor Hisashi Yamamoto in celebration of his winning the Tetrahedron Prize

Abstract—The systematic conformational analysis of three linear precursors for the synthesis of dendroamide A has revealed that these three precursors have the distance between the N- and C-terminal in the range of 3.43–3.93 Å, which suggests the possibility of macrocyclization. This result coincides with the results of the actual synthesis of dendroamide A, but contradicts the reported calculated results.

1. Introduction

The total syntheses of cyclic peptides and depsipeptides have been playing an important role in the structural determination for several decades.[1,2] For the total synthesis of cyclic peptides and depsipeptides, the selection of a suitable cyclization site is necessary to prevent epimerization due to the activation of the C-terminal carboxyl group, because there are some synthetic problems regarding a macrocyclization of linear precursors. In particular, glycine has features of no epimerization and a higher reactivity. Proline and amino acids, including thiazole or oxazole[3] also have features of no epimerization and a fixed conformation. Less hindered amino acids should be selected when there are no glycine, proline, and azole amino acids in the cyclic peptides and depsipeptides. Therefore, it is quite important and problematic as how to select suitable cyclization sites for the efficient synthesis of cyclic peptides and depsipeptides.

Dendroamide A (**1**) was isolated by Moore et al. from the terrestrial cyanobacterium *Stigonema dendroideum* Fremy in 1996,[4] which is a cyclic peptide composed of oxazole and thiazole derivatives (Fig. 1). The peptide **1** reverses multiple drug resistance in tumor cells by acting as a P-glycoprotein and MRP1 antagonist at noncytotoxic doses.[5] Because of these interesting biological activities, **1** and its derivatives are being investigated from the viewpoint of a structure–activity analysis.[6] In 2000, Bertram and Pattenden succeeded in the first total synthesis of **1**.[7] The groups of Smith,[8] Kelly,[9] and Shin[10] then also achieved the total synthesis. The difference in the total synthesis that the four groups accomplished is the final cyclization position. As shown in Figure 1, Pattenden et al.[7] carried out the cyclization at position A. Smith et al.[8] and Kelly et al.[9] selected the cyclization at position B, while Shin et al.[10] did the cyclization at position C. Bertram and Pattenden also succeeded in the one-pot synthesis from three amino acids including thiazole and oxazole.[11]

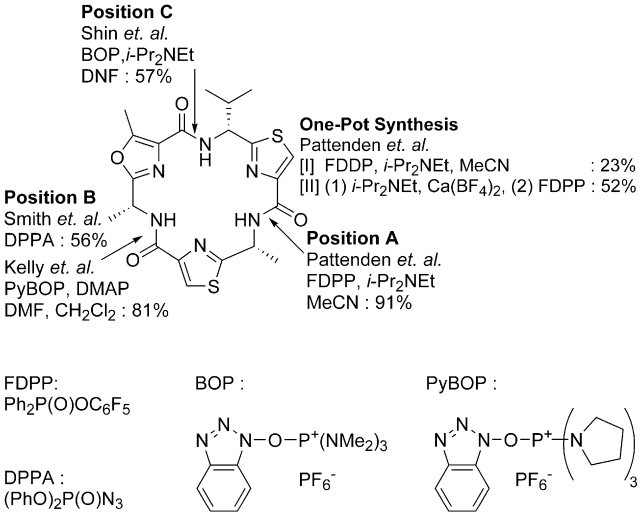

Figure 1. The structure of dendroamide A (**1**) and the macrocyclization point under a reaction condition reported by each group.

Keywords: Dendroamide A; Cyclic peptide; Macrocyclization; Rational synthetic strategy; Conformational analysis.
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Table 1. Estimation of distances between the N-terminal nitrogen and C-terminal carbon in the cyclization intermediates[8]

Cyclization point	MM2 (Å)	MOPAC (Å)
A	12.76	13.85
B	3.56	6.14
C	8.03	10.25

These results show that three final cyclization points can allow effectively the total synthesis of **1**.

In order to probe the possibility of the cyclization of three acyl-azide precursors at the disconnections A–C, Smith et al.[8] calculated the most stable conformers using MM2 and MOPAC in Chem 3D before the total synthesis of **1**. As shown in Table 1, the calculations clearly indicated that the disconnection B was the most suitable point because the distance between the N-terminal nitrogen and C-terminal carbon was the closest. The disconnections A and C were found to be far from both the terminal atoms. The concept indicated by Smith et al. was definitely unique and rational. However, the fact that any of the three final cyclization positions were used for the total synthesis and that the one-pot synthesis was accomplished questioned the reported distance between the N- and C-terminal atoms. Therefore, we performed a full conformational analysis of the three linear precursors in detail.

2. Experimental section

As shown in Figure 2, the N- and C-terminal of the three linear precursors as a target is an amine and a carboxylic acid, respectively. To obtain the initial 3D molecular coordinates of the three precursors, CS Chem 3D version 7.0 was used. In order to obtain all conformational isomers of the three flexible linear precursors, CONFLEX 5[12] was used. All geometrical optimizations were fully carried out by MMFF94[13] in CONFLEX 5. These calculations were performed on Linux PC-Cluster computers; IBM xSeries 335 (xenon, 3.06 GHz). Distributions of these three flexible precursors were obtained from the Boltzmann distribution based on the Gibbs free energies calculated by a vibrational analysis.

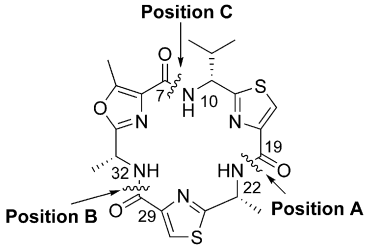

Figure 2. The macrocyclization positions of **1**.

3. Results and discussion

3.1. The case of each precursor

First, the conformational analysis for the precursor **2** that is derived from the cyclization position A shown in Figure 2 was carried out in detail. Based on the Gibbs free energy shown in Figure 3(a), the number of conformers reaches a peak of 26 kcal mol^{-1} and the distribution for the ranges over 8 kcal mol^{-1} became 0%. On the one hand, according to the distance between the N- and C-terminal in Figure 3(b), the wide distribution to extend over 18.63 Å

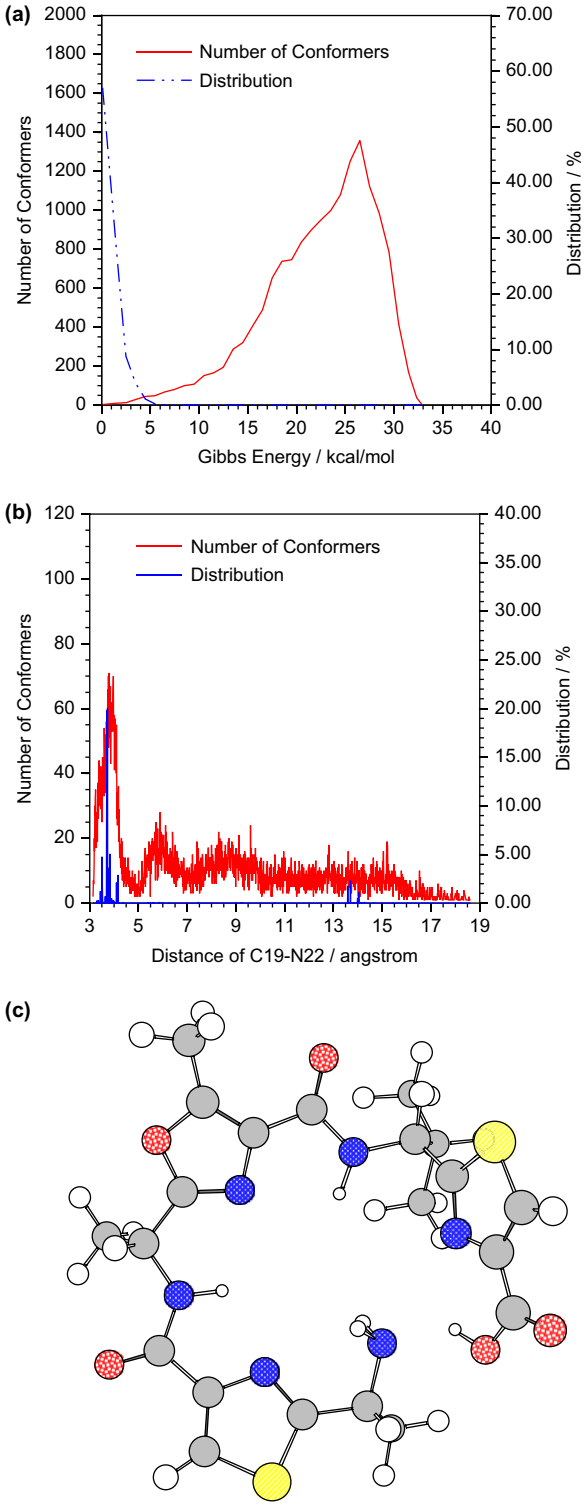

Figure 3. (a) Plots of number of conformers and distribution against Gibbs energy, (b) plots of number of conformers and distribution against the distance of C19–N22, and (c) the most stable conformer (**5**) of **2** at cyclization position A.

was confirmed and the maximum point for the number of conformers was a peak of 3.80 Å. However, in the other range relatively no distinguishing peaks appeared. The most stable conformer **5** shown in Figure 3(c) belongs to a conformational group of 3.73 Å. The range of 3.51–3.83 Å reached 81.24% of the total. The 1600 conformers in this range occupied 10.29% of the found 15,548 ones.

The conformational analysis for the precursor **3** that is derived from the cyclization position B shown in Figure 2 was also carried out. According to the rank classification based on the Gibbs free energy shown in Figure 4(a), the number of conformers reaches a peak of 26 kcal mol^{-1} and the distribution for the ranges over 7 kcal mol^{-1} got 0%. On the one hand, according to the distance between the N- and C-terminal in Figure 4(b), the wide distribution that extended over 18.34 Å was confirmed and the maximum point for the number of conformers was the peak of 3.81 Å. However, in the other range relatively no distinguishing peaks appeared. The most stable conformer **6** shown in Figure 3(c) belongs to a conformational group of 3.93 Å. The range of 3.43–3.93 Å reached 68.96% of the total. The 3275 conformers in this range also occupied 16.37% of the found 20,009 ones.

The precursor **4** that is derived from the cyclization position C shown in Figure 2 was also subjected to the conformational analysis. According to the rank classification based on the Gibbs free energy shown in Figure 5(a), the number of conformers reaches a peak of 25 kcal mol^{-1} and the distribution for the ranges over 9 kcal mol^{-1} got 0%. On the one hand, according to the distance between the N- and C-terminal in Figure 5(b), the wide distribution to extend over 18.09 Å was confirmed and the maximum point for the number of conformers was a peak of 3.72 Å. However, in the other range relatively no distinguishing peaks appeared. The most stable conformer **7** shown in Figure 3(c) belongs to a conformational group of 3.70 Å. The range of 3.68–3.72 Å reached 80.96% of the total. The 299 conformers in this range also occupied 1.78% of the found 16,795 ones.

The above-mentioned results are summarized in Table 2. The distance between the N- and C-terminal limits the particular ranges in the three precursors. In addition, the distribution of the peak area also has a similar value. The numbers of conformers in the peak area and the ratio are different, especially at position C.

3.2. Comparison between the two results

As shown in Table 3, the distance between the N- and C-terminal of the cyclization precursors showed specific ranges (3.43–3.94 Å) and the distances for the most stable conformers also seemed very similar. These values would seem suitable to accomplish the cyclization from the viewpoint of organic chemistry. Therefore, the calculated result that any precursor can cyclize agrees with the fact that four research groups succeeded in the total synthesis of **1**.[7–10] Moreover, the result corresponds with the fact that Bertram and Pattenden[11] succeeded in the one-pot synthesis by mixing only three amino acids. On the other hand, Smith et al.[8] showed that the distance between the N- and

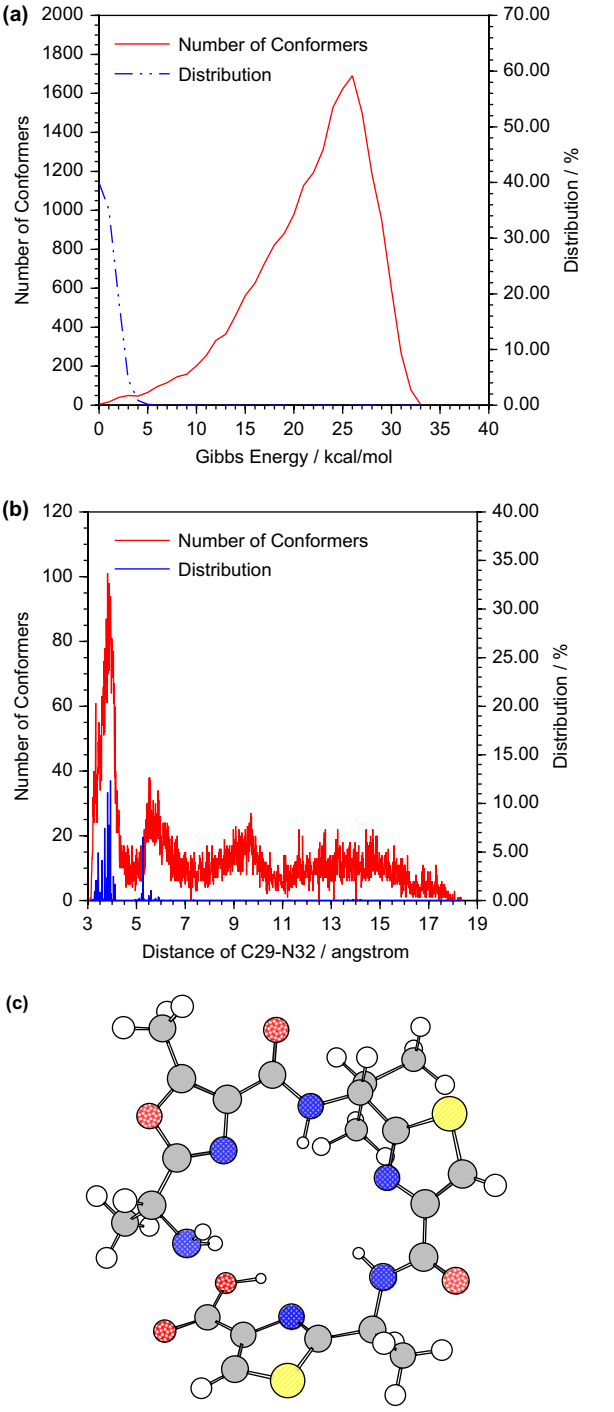

Figure 4. (a) Plots of number of conformers and distribution against Gibbs energy, (b) plots of number of conformers and distribution against the distance of C29–N32, and (c) the most stable conformer (**6**) of **3** at cyclization position B.

C-terminal of position B was the closest based on the most stable conformers using MM2 and MOPAC in Chem 3D, as shown in Table 3. However, their calculated distance did not correspond to the experiments. This result reveals that Smith et al. cannot correctly search all the conformational isomers of three precursors. However, the concept of planning the final cyclization indicated by Smith et al. seems definitely unique and rational from a strategically synthetic viewpoint.

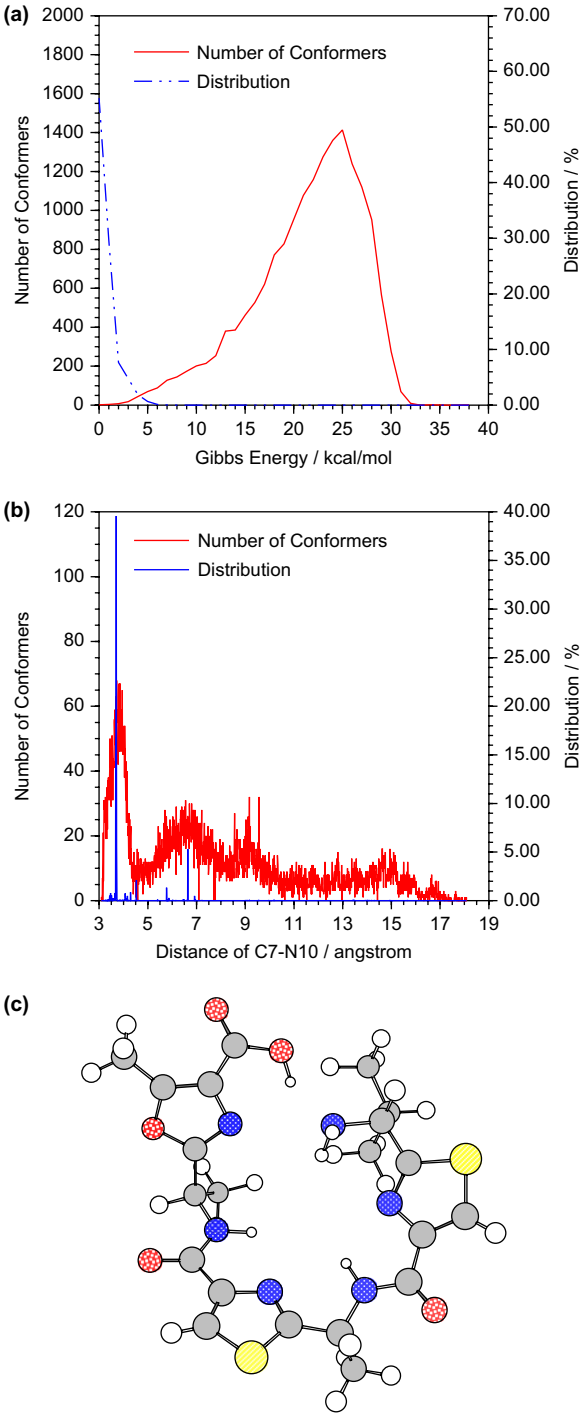

Figure 5. (a) Plots of number of conformers and distribution against Gibbs energy, (b) plots of number of conformers and distribution against the distance of C7–N10, and (c) the most stable conformer (**7**) of **4** at cyclization position C.

Table 2. Results for conformational analysis of each precursor

	Position A	Position B	Position C
Total numbers of found conformers (A)	15,548	20,009	16,795
Range of the peak area	3.51–3.83 Å	3.43–3.93 Å	3.68–3.72 Å
Distribution of the peak area	81.24%	68.96%	80.96%
Numbers of conformers in the peak area (B)	1600	3275	299
The ratio of (B)/(A)	10.29%	16.37%	1.78%

Table 3. Distances between the N-terminal nitrogen and C-terminal carbon in the cyclization intermediates

Cyclization Point	MM2 (Å)	MOPAC (Å)	This work (Å)
Precursor A: **2**	12.76	13.85	3.51–3.83 (3.73)[a]
Precursor B: **3**	3.56	6.14	3.43–3.93 (3.93)[a]
Precursor C: **4**	8.03	10.25	3.68–3.72 (3.70)[a]

[a] A value in the brackets means the distance for the most stable conformer of each precursor.

4. Conclusion

In conclusion, based on a full conformational analysis on the three linear precursors, the possibility of the final cyclization for all precursors was clarified. The results are summarized as follows. (1) Based on the correctly calculated distances between the N- and C-terminal in Table 3, any linear precursors have a potential positional relation to finally cyclize. (2) The obtained result agrees with the success of the total synthesis of **1** and the one-pot synthesis. (3) The concept Smith et al. proposed[8] seems definitely unique and rational, except for the results they calculated. Therefore, it is important to correctly calculate all the conformational isomers of a precursor in order to determine a synthetic strategy of a cyclic peptide and to examine whether the final cyclization of a precursor can be carried out. Work is now underway to elucidate the effect of protecting groups on the cyclic peptides.

Supplementary data

The supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.04.096.

References and notes

1. Wipf, P. *Chem. Rev.* **1995**, *92*, 2115–2134 and references therein.
2. Hamada, Y.; Shioiri, T. *Chem. Rev.* **2005**, *105*, 4441–4482.
3. Thiazole (or oxazole) amino acid: 2-(1-aminoalkyl)-4-thiazole (or oxazole) carboxylic acid.
4. Ogino, J.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Nat. Prod.* **1996**, *59*, 581–586.
5. (a) Lawrence, D. S.; Copper, J. E.; Smith, C. D. *J. Med. Chem.* **2001**, *44*, 594–601; (b) Liederer, B. M.; Fuchs, T.; Velde, D. V.; Siahaan, T. J.; Borchardt, R. T. *J. Med. Chem.* **2006**, *49*, 1261–1270; (c) Dilda, P. J.; Don, A. S.; Tanabe, K. M.; Higgins, V. J.; Allen, J. D.; Dawes, I. W.; Hogg, P. J. *J. Natl. Cancer Inst.* **2005**, *97*, 1539–1547.
6. (a) Nakamura, Y.; Takeuchi, S. *QSAR Comb. Sci.* **2006**, *25*, 703–708; (b) Nakamura, Y.; Takeuchi, S. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 617–627; (c) Nakamura, Y.; Okamura, K.; Kojima, M.; Takeuchi, S. *Tetrahedron Lett.* **2006**, *47*, 239–243; (d) Molina, L.; Moreno-Vargas, A. J.; Carmona, A. T.; Robina, I. *Synlett* **2006**, 1327–1330; (e) Biron, E.; Chatterjee, J.; Kessler, H. *Org. Lett.* **2006**, *8*, 2417–2420; (f) You, S. L.; Kelly, J. W. *Tetrahedron Lett.* **2005**, *46*, 2567–2570; (g) You, S. L.; Kelly, J. W. *Tetrahedron* **2005**, *61*, 241–249; (h) You, S. L.; Deechongkit, S.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 2627–2630; (i) Shin, C.-G.; Abe, C.; Yonezawa, Y.

Chem. Lett. **2004**, *33*, 664–665; (j) You, S. L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681–1683; (k) You, S. L.; Kelly, J. W. *Chem.—Eur. J.* **2004**, *10*, 71–75; (l) Haberhauer, G.; Rominger, F. *Eur. J. Org. Chem.* **2003**, 3209–3218; (m) Rudi, A.; Chill, L.; Aknin, M.; Kashman, Y. *J. Nat. Prod.* **2003**, *66*, 575–577; (n) Bertram, A.; Blake, A. J.; de Turiso, F. G. L.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G.; Skae, M. *Tetrahedron* **2003**, *59*, 6979–6990; (o) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2002**, *4*, 3399–3401; (p) Luesch, H.; Harrigan, G. G.; Goetz, G.; Horgen, F. D. *Curr. Med. Chem.* **2002**, *9*, 1791–1806; (q) Somogyi, L.; Haberhauer, G.; Rebek, J. *Tetrahedron* **2001**, *57*, 1699–1708; (r) Boss, C.; Wartini, A. R.; Waldvogel, S. R. *Tetrahedron Lett.* **2000**, *41*, 6327–6331; (s) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826–831; (t) Prinsep, M. P.; Moore, R. E.; Levine, I. A.; Patterson, G. M. L. *J. Nat. Prod.* **1992**, *55*, 140–142; (u) Foster, M. P.; Concepcion, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671–6675.

7. Bertram, A.; Pattenden, G. *Synlett* **2000**, 1519–1521.
8. Xia, Z.; Smith, C. D. *J. Org. Chem.* **2001**, *66*, 3459–3466.
9. You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506–9509.
10. Yonezawa, Y.; Tani, N.; Shi, C.-G. *Heterocycles* **2005**, *65*, 95–105.
11. Bertram, A.; Pattenden, G. *Heterocycles* **2002**, *58*, 521–561.
12. (a) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950–8951; (b) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187–198; (c) Goto, H.; Osawa, E. *J. Mol. Struct. (THEOCHEM)* **1993**, *285*, 157–168; (d) Goto, H.; Kawashima, Y.; Kashimura, M.; Morimoto, S.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1647–1654; (e) Osawa, E.; Goto, H.; Hata, T.; Deretey, E. *J. Mol. Struct. (THEOCHEM)* **1997**, *399*, 229–236; Goto, H.; Ohta, K.; Morishita, E. *CONFLEX 5*; CONFLEX: Tokyo, Japan, 2004.
13. (a) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 720–729; (b) Halgren, T. A.; Nachbar, R. B. *J. Comput. Chem.* **1996**, *17*, 587–615; (c) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490–519; (d) Halgren, T. A. *J. Am. Chem. Soc.* **1992**, *114*, 7827–7843.