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Molecular Dynamics Conformational Search for the Factors that Determine Conformation of Modified Cyclodextrins

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Modified cyclodextrins (modified CDs), which have an appending moiety, form various conformations depending on its moiety. In this study we examined the factors that determine the conformation of modified CDs with *p*-dimethylaminobenzoyl and *p*-nitrobenzoyl moiety as a pendant (DMAB-β-CD and NB-β-CD, respectively) using computational chemistry. The structures and potential energies were calculated using molecular dynamics conformational search, and the relationship between conformation and energy calculated from force field was investigated. These calculations suggested that the conformation of the modified CDs is dominated by the opposing influences of the van der Waals energy, which favors locating the appending moiety inside the CD cavity, and the angle related to the bending energy, which favors the moiety outside the cavity.

Keywords: Modified cyclodextrin, molecular dynamics, molecular mechanics, conformation

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides which have six or more members of *D*-glucopyranose units. They are able to form inclusion complexes with various organic compounds in aqueous solution. On this basis, modified CDs with appropriate functional groups have been synthesized as enzyme catalysts [1] mimics or indicators of molecular recognition [2]. The conformations of these modified CDs have been studied by spectroscopic methods and the orientations of their appending moiety have been determined [3]. These studies indicate that modified CDs change their conformation depending on the appending moiety.

The conformation of 6-deoxy-6-(*p*-dimethylaminobenzoyl)amino-β-CD (DMAB-β-CD) (Fig. 1), which is a fluorescent indicator of molecular recognition, was determined by several spectroscopic methods (^{1}H-NMR, fluorescence spectra, and circular dichroism spectra) [4]. Several modern high resolution 2D NMR techniques have been used to determine its conformation. They showed that all protons of the DMAB moiety have NOE cross peaks with the protons of the inner cavity of β-CD. However, these cross peaks of DMAB-β-CD disappeared in the presence of 1-adamantanol.

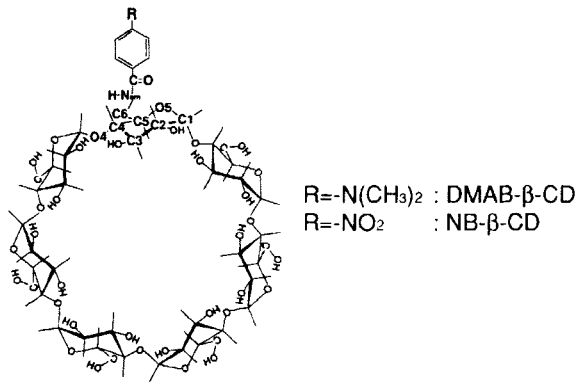

FIGURE 1 Chemical structure of DMAB-β-CD and NB-β-CD.

This result indicates that DMAB-β-CD includes its DMAB moiety in its own cavity in the absence of the guest compound (Fig. 2, form A). Similar analysis has been done to 6-deoxy-6-(*p*-nitrobenzoyl)amino-β-CD (NB-β-CD) (Fig. 1). In contrast with DMAB-β-CD, the protons of NB moiety have no cross peaks with the protons of the inner cavity of β-CD. This result indicated that the NB moiety of NB-β-CD is located outside of its CD cavity (Fig. 2, form B).

The structural difference between these two compounds resides only in the substituent group (nitro or dimethylamino) attached to the benzene ring. The experimental results indicate that the modified CDs assume different conformations depending on the difference in the chemical structure of the appending moieties. However the reason has not yet been clarified on the theoretical basis. In this study, we have examined the factors that determine such modified CDs using computational chemistry.

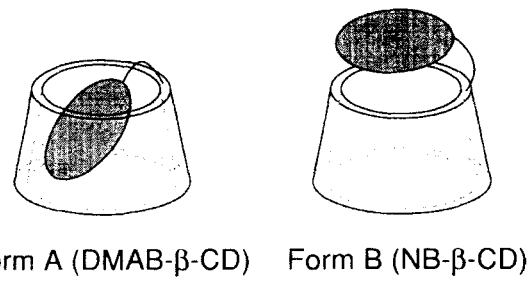

FIGURE 2 Schematic representation for two conformations of modified CDs. Spectroscopic data suggest that form A and B are preferable for DMAB-β-CD and NB-β-CD, respectively.

A Molecular mechanics (MM) calculation has been widely used in studies of molecular structures and conformational energies. In host-guest chemistry it has been used to speculate the structures of inclusion complexes or to evaluate the complex formation mechanisms [5]. One of the important aspects of computational studies of modified CDs is predicting the most stable form from several possible forms on the clear theoretical basis. We know that simple gradient minimization of one initial structure would not be adequate for sampling correct conformational spaces. Therefore we have explored the energy surface of DMAB-β-CD and NB-β-CD in a random way using molecular dynamics (MD) conformational search [6, 7]. As a result, we report that the MD conformational search gives conformations that are in agreement with those obtained experimentally.

METHOD

Model buildings of initial starting conformations of DMAB-β-CD and NB-β-CD were performed with the aid of interactive molecular graphics. Two types of initial conformations were prepared for each of DMAB-β-CD and NB-β-CD. The first one is the conformation with the appending moiety included in its CD cavity (form A) and the second one is that with the appending moiety located outside of the CD cavity (form B). In order to obtain the partial atomic charges for appending moieties the AM1 hamiltonian [8] of Ampac ver. 2.10 was used. The charges for the CD ring were obtained from parameterized sets with consistent valence force field (CVFF) [7]. All parameters

were used as implemented in generic parameter set of CVFF.

The initial conformations of the two compounds were subjected to energy minimization with the aid of CVFF until the maximum derivative became less than 0.5 kcal/mol. Starting with the minimized conformations, MD at 500 K was carried out for 200 ps after an initial 10 ps equilibration time using an integration step of 1 femto second. During the calculation, a structure is stored every 1 ps and subsequently energy is minimized until the maximum derivatives became less than 0.01 kcal/mol. To maintain the structure of the pyranose ring in $^4C_1$ form during the MD calculation, the torsion angles of each pyranose ring were constrained to initial values by using the constant of 20 kcal/mol as the coefficient of the harmonic potential, and then these restrictions were removed in subsequent energy minimization. There was no cut-off radius for non-bond interaction and a distance (r)-dependent dielectric constant of $2.5r$ was used. These procedures of calculations were applied to two compounds with initial structures of A and B forms. During the 200 ps MD conformational search, no conformational change between A and B forms occurred, so the 200 minimized structures with A and B forms were gained, starting from A and B forms, respectively. The structure numbers for 200 minimized structures were defined as the order of time.

All calculations were performed on a Silicon Graphics Personal Iris 4D/35 workstation. For model building and MD calculations, the programs Insight II ver. 2.20 and Discover ver. 2.90 from Biosym, Inc., were used.

RESULT AND DISCUSSION

Optimized Structural Features of Modified CDs Gained from MD Conformational Search

First we will discuss the structural features of each modified CD gained from the MD conformational search. In order to compare the conformations sampled during the 200 ps MD conformational search, cluster graphs and graphs of the total energy calculated from the CVFF potential function were prepared. On the other hand, in order to investigate the orientations of the appending moiety, the graph of dihedral angle of O5-C5-C6-Nam was also prepared where Nam is the nitrogen atom of amide bond. As the dihedral angles, the three orientations GG, GT, and TG were adopted (GG; O5-C5-C6-Nam=−60°, GT; O5-C5-C6-Nam= 60°, TG; O5-C5-C6-Nam=180°).

On this basis, we have performed a molecular dynamics conformational search for DMAB-β-CD and NB-β-CD starting from form A and B of each compound, and the results are as follows.

DMAB-β-CD (form A)

The cluster graph of DMAB-β-CD in form A is shown in Figure 3 (a). The distinct clusters are the ones with the structure number extending from 80 to 110 and from 170 to 190 (each of these areas is enclosed by a square). It is indicated that the conformations included in these two squares are similar to each other. As indicated by the comparison of Figure 3 (a) with (b), in these areas, dihedral angles of O5-C5-C6-Nam fell in about 150°, and consequently, the appending moiety is suggested to be oriented with the angle of the TG range. The other cluster is the one with the structure number extending from 60 to 75 (this area was also enclosed by a square). The conformations included in this area are different from the previous ones because the orientations of O5-C5-C6-Nam fell into a range of GT (O5-C5-C6-Nam=60°). Figures 4 (a) and (b) shows snap shots, each corresponding to GT (structure number 63) and TG (structure number 161) form.

DMAB-β-CD (form B)

The cluster graph of DMAB-β-CD in form B is shown in Figure 5 (a). These plots, extending in

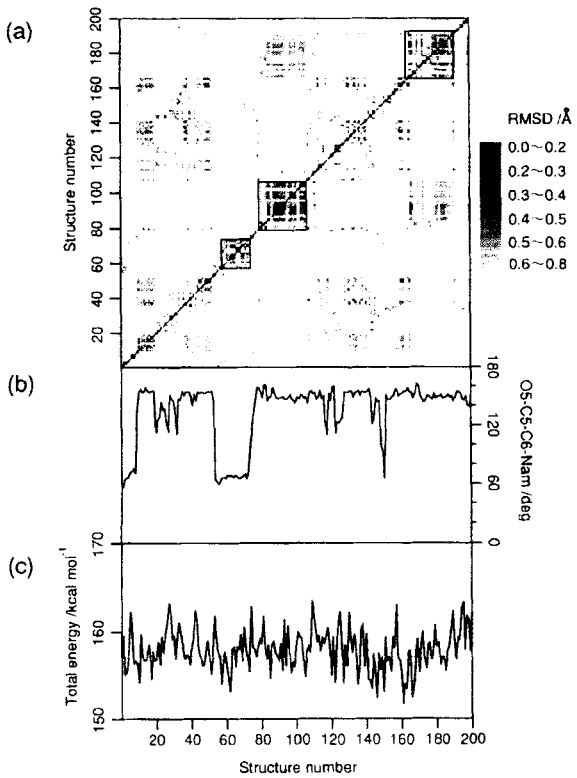

FIGURE 3 Mutual RMSD (root mean square deviation) of 200 minimized structures of DMAB-β-CD (form A) sampled during 200 ps MD conformational search (a). The RMSD values are mapped reduced data (RMSD < 0.8). Dihedral angle of O5-C5-C6-Nam (b) and total energy (c) are also shown.

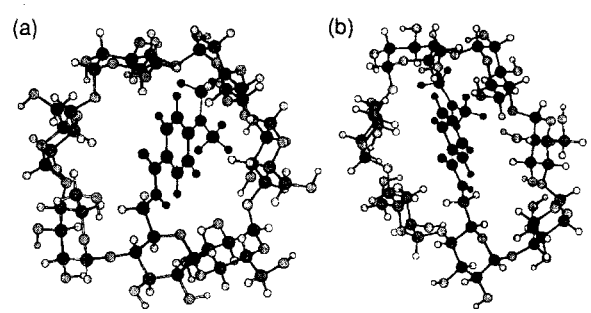

FIGURE 4 The structures of DMAB-β-CD (form A) with structure number 63 (a) (GT) and 161 (TG) (b).

the cluster graph, reveal that one kind of conformation was preferably gained from the MD conformational search with a few exceptions included. The dihedral angle of O5-C5-C6-Nam of the conformation fell in about 60°,

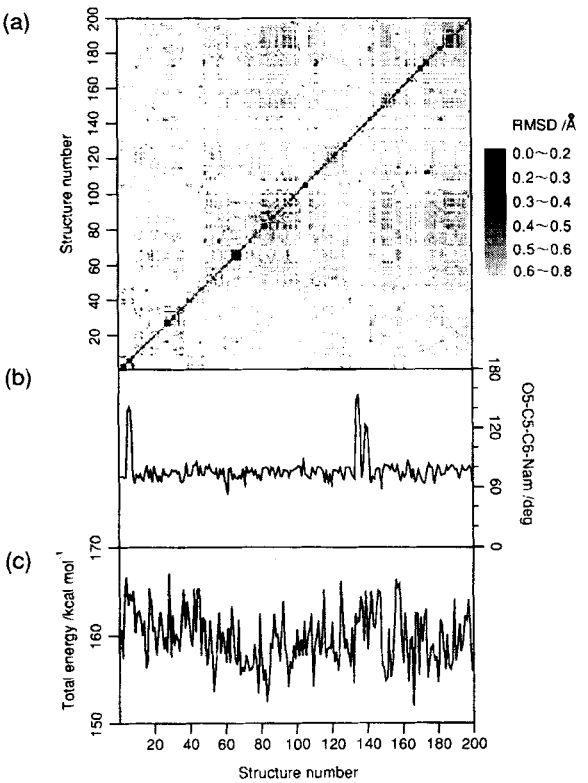

FIGURE 5 Mutual RMSD (root mean square deviation) of 200 minimized structures of DMAB-β-CD (form B) sampled during 200 ps MD conformational search (a). The RMSD values are mapped reduced data (RMSD < 0.8). Dihedral angle of O5-C5-C6-Nam (b) and total energy (c) are also shown.

indicating that the appending moiety is oriented with the angle of GT. In the exceptional cases, the moiety is oriented with the angle of the TG range. Figure 6 shows a snap shot corresponding to GT form (structure number 166).

NB-β-CD (form A)

The Cluster graph and the graph of the dihedral angles are shown in Figures 7 (a) and (b). The Cluster graph indicates that two kinds of conformations are gained from the MD conformational search. The first conformation is extending from structure number 70 to 150. In this area the dihedral angle of O5-C5-C6-Nam fell in about 60° so the appending moiety is oriented with the angle of the GT range. The

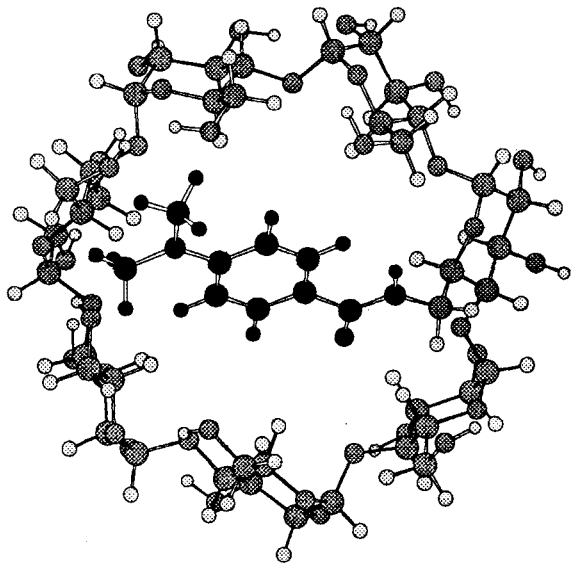

FIGURE 6 The structure of DMAB-β-CD (form B) with structure number 166.

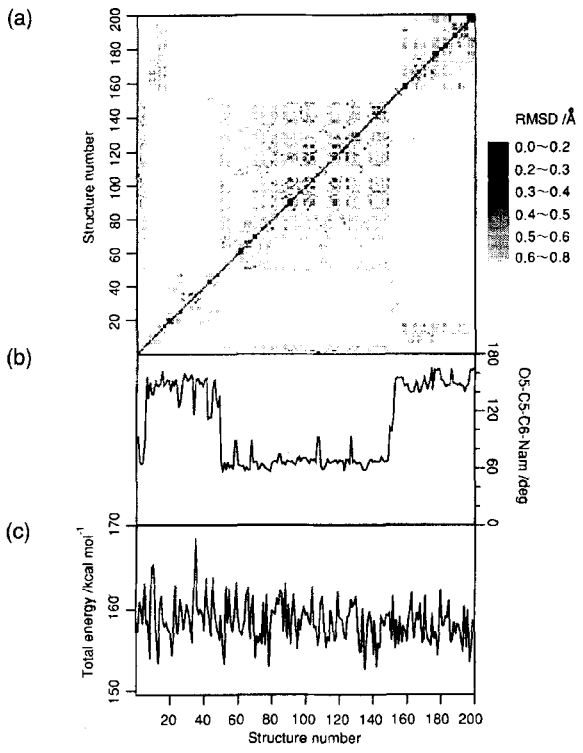

FIGURE 7 Mutual RMSD (root mean square deviation) of 200 minimized structures of NB-β-CD (form A) sampled during 200 ps MD conformational search (a). The RMSD values are mapped reduced data (RMSD < 0.8). Dihedral angle of O5-C5-C6-Nam (b) and total energy (c) are also shown.

second conformation is included in the area of structure number from 160 to 200. Here, the dihedral angle of O5-C5-C6-Nam fell in 150°, indicating that this conformation nearly adopts the TG form. The result demonstrates that the conformational difference between the two areas can be induced by variation in the orientation of the appending moiety. Figures 8 (a) and (b) shows snap shots corresponding to the GT (structure number 78) and TG (structure number 197) forms.

NB-β-CD (form B)

The Cluster graph and the graph of the dihedral angle are shown in Figures 9 (a) and (b). One kind of conformation extending from structure number 10 to 200 and was gained from the MD conformational search. The appending moiety fell in the GT form. The snap shot is shown in Figure 10 (structure number 21).

Some interesting conformational features of the modified CDs emerge from this search. When the modified CDs take form A the appending moiety may adopt two orientations (GT and TG forms), but when they take form B it adopts one orientation (GT form). Lipkowitz *et al.* reported that, in the solid structure of CDs, primary hydroxyl orientation fell in the GT and GG ranges and no structure in the TG range exists because of steric hindrance between the primary hydroxyl group and the CD ring [9]. However, in our calculations structures in the

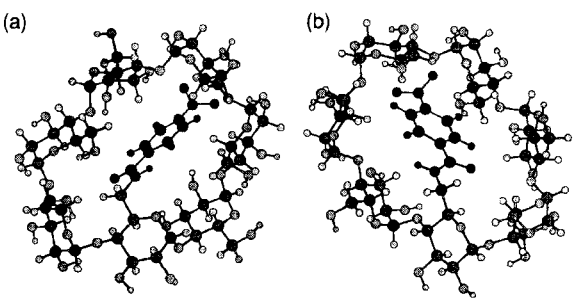

FIGURE 8 The structures of NB-β-CD (form A) with structure number 78 (a) (GT) and 197 (b) (TG).

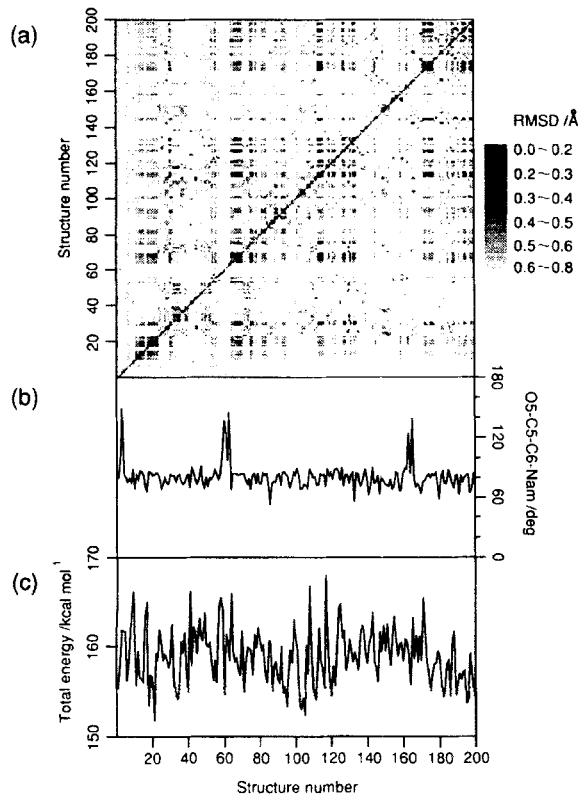

FIGURE 9 Mutual RMSD (root mean square deviation) of 200 minimized structures of NB-β-CD (form B) sampled during 200 ps MD conformational search (a). The RMSD values are mapped reduced data (RMSD < 0.8). Dihedral angle of O5-C5-C6-Nam (b) and total energy (c) are also shown.

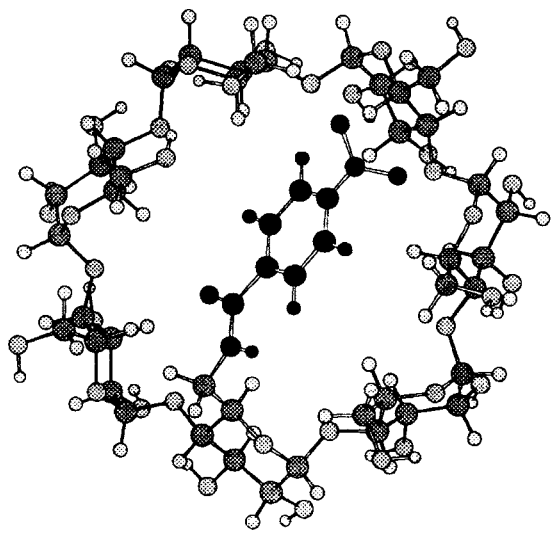

FIGURE 10 The structures of DMAB-β-CD (form A) with structure number 63 (GT) and 161 (TG).

TG range are found in modified CDs when they take A form. The steric hindrance is dissolved in the modified CDs when the bulky appending moiety is included in the CD cavity.

Although the appending moiety can exist in the GG range when it is located outside of the CD cavity, we found no structures in the GG range in our MD conformational searches. If the appending moiety fell in the structure of the GG range it would be oriented so as to seperate from the CD residue. Therefore it is preferable that the appending moiety falls in the GT range, locating near the rim of the primary side of the CD ring. This situation seems to be reflected in the results of our MD conformational search.

Total Energy Difference Between A and B Forms

The plots of total energy obtained by the MD conformational search were shown in Figures 3(c), 5(c), 7(c), and 9(c). The values fluctuate around 160 kcal/mol, and no clear distinction in the total energy is found between the different conformations of GT, TG, and others. On this basis, we examined the total energy difference between A and B forms for all the structures gained from the MD conformational search.

In order to compare the total energies between the A and B forms, the structures were re-arranged in the order of the magnitude of total energies and then the structure numbers were given newly in accordance with the order of the total energies.

Figures 11(a) and 12(a) show the total energies for DMAB-β-CD and NB-β-CD. The broad line indicates the energies calculated from form A and the narrow line indicates those calculated from form B. Figure 11(a) reveals that the total energies of form A are lower than those of form B in DMAB-β-CD, indicating that DMAB-β-CD is more stable when it forms a self-inclusion complex. This calculated result is in good agreement with the experimental result. In the case of NB-β-CD, the total energies of the A and

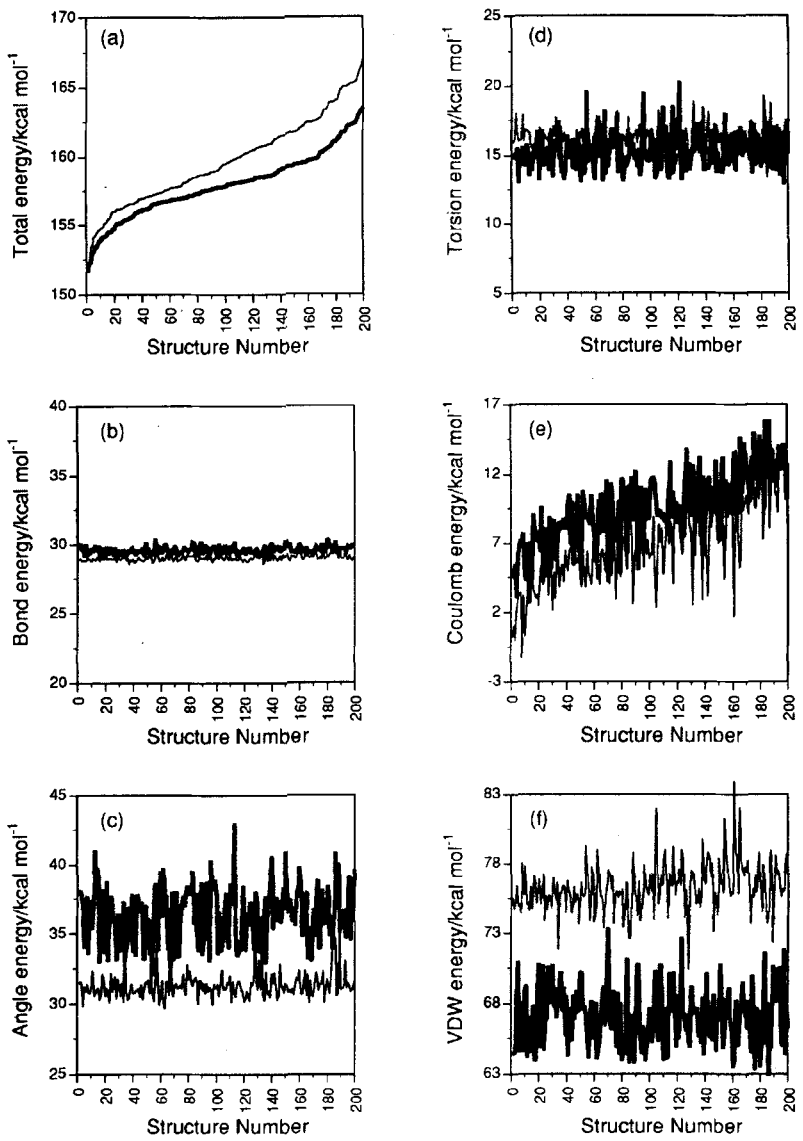

FIGURE 11 Total energy of DMAB-β-CD (a) for A (—) and B (—) forms. The values of total energy are rearranged in the order of their magnitudes and broken down into bond energy (b), angle energy (c), torsion energy (d), coulomb energy (e), and van der Waals energy (f).

B forms are similar at all points of the structure number, indicating that NB-β-CD is not appreciably stable even if it forms a self-inclusion complex.

It is very difficult to know how the energy hyper surface of a molecule will be changed when the solvent water exists, so the calculations in this study were carried out under pseudo vacuum conditions, using distance-dependent-dielectric conditions to compensate the lack of explicit water. Nevertheless this method, using molecular dynamics in pseudo vacuum, indicated the correct conformational features of modified CDs.

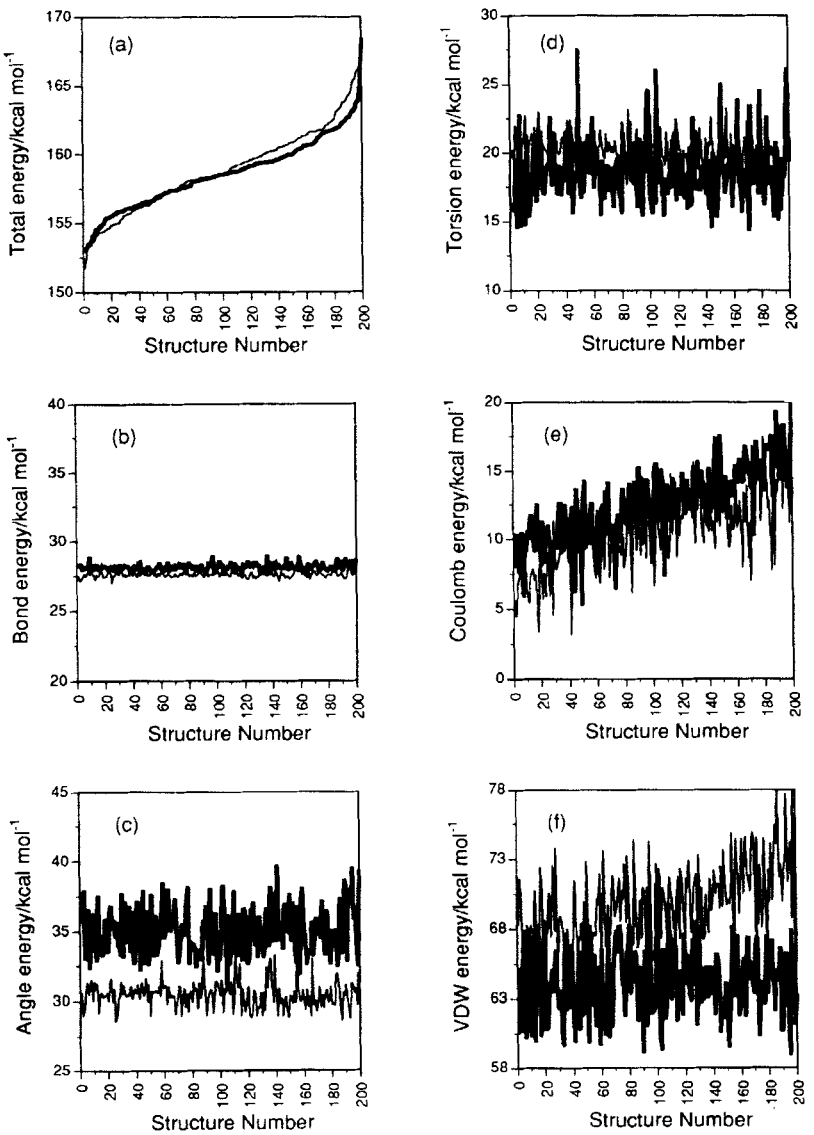

FIGURE 12 Total energy of NB-β-CD (a) for A (—) and B (—) forms. The values of total energy are rearranged in the order of their magnitudes and broken down into bond energy (b), angle energy (c), torsion energy (d), coulomb energy (e), and van der Waals energy (f).

Evaluation of Various Energy Terms

Subsequently we have examined the reasons, why form A is more stable than form B in DMAB-β-CD and why the energy difference between forms A and B is small in NB-β-CD. To explain the reason, total energy was broken down into bond energy, angle energy, torsion energy, coulomb energy, and van der Waals (VDW) energy. The CVFF potential function, which was used in these calculations, has the following form.

$$E_{\text{pot}} = \sum_b \mathbf{D}_b(\mathbf{b} - \mathbf{b}_0)^2 + \sum_\theta \mathbf{H}_\theta(\theta - \theta_0)^2 \quad (1) \qquad (2)$$

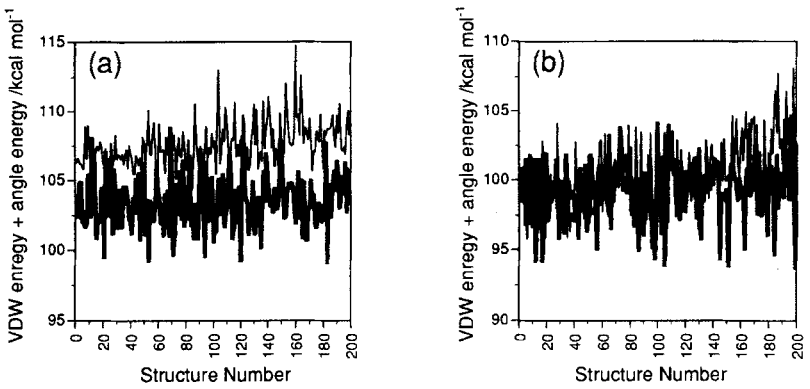

FIGURE 13 The sum of van der Waals energy and angle energy for DMAB-β-CD (a) and NB-β-CD (b) in A (—) and B (—) forms.

$$+\sum_{\phi}\mathbf{H}_{\phi}(1+\mathbf{s}\cos(\mathbf{n}\phi))+\sum_{\chi}\mathbf{H}_{\chi}\chi^{2}$$

(3) (4)

$$+\sum\varepsilon\left[\left(\frac{\mathbf{r}^{*}}{\mathbf{r}}\right)^{12}-2\left(\frac{\mathbf{r}^{*}}{\mathbf{r}}\right)^{6}\right]+\sum\frac{\mathbf{q}_{i}\mathbf{q}_{j}}{\varepsilon\mathbf{r}_{ij}}$$

(5) (6)

Terms (1)–(4) represent the energy deformation of bond length, bond angle, torsion angle, and out-of-plane interactions, respectively. The out-of-plane energies are too small to compare with total energy, so we neglected them. Terms (5) and (6) are related with non bond interactions. Term (5) represents the van der Waals interactions with a Lennard-Jones function while term (6) is the Coulombic representation of electrostatic interactions.

The plots of each term are shown in Figures 11 (b) to (f) for DMAB-β-CD and Figures 12 (b) to (f) for NB-β-CD. It was found that angle energies of form A are larger than those of form B, however VDW energies of form A are smaller than those of form B. The result implies that VDW interaction increases the stability of modified CDs while angle bending interaction decreases their stability.

For further examination of these opposing energies, the graphs of structure number vs. sum of VDW energy and angle bending energy were prepared (Figs. 12(a) and 12(b)). The values of energy summation are smaller for form A than for form B in DMAB-β-CD but are similar for forms A and B in NB-β-CD. The result implies that in DMAB-β-CD the gain of VDW energy which stabilizes the molecule is larger than the loss of angle bending energy which makes the molecule unstable. In the case of NB-β-CD, the gain of VDW energy is almost the same as the loss of angle bending energy. Accordingly, it has become obvious that the total energy differences between the two forms are reflected in these opposing energies, suggesting that the gain and the loss of these two energies are determination factors for the conformations of the modified CDs.

The values of the averaged energies are shown in Table I. It reveals that the energy differences between forms A and B are −9.17 kcal/mol and 5.07 kcal/mol for VDW and angle bending energies, respectively, for DMAB-β-CD, while they are −5.65 kcal/mol and 4.54 kcal/mol for VDW and angle bending energies, respectively, for NB-β-CD. These values of averaged energies also support the previous result.

The Relationship Between Angle Bending Energy and Distortion of the CD Ring

The gain of VDW energy may arise from the fact that the appending moiety interacts with the

TABLE I Averaged potential energies[a] calculated by MD comformational searches[b]

	Bond Energy	Angle Energy	Torsion Energy	VDW Energy	Coulomb Energy	Total Energy
DMAB-β-CD (form A)	29.59	36.41	18.27	67.09	9.57	157.92
DMAB-β-CD (form B)	29.00	31.34	16.09	76.26	6.99	159.68
ΔE[c]	0.23	5.07	2.18	−9.17	2.58	−1.76
NB-β-CD (form A)	28.15	35.02	18.61	64.23	12.58	158.58
NB-β-CD (form B)	27.60	30.48	20.13	69.88	10.78	158.87
ΔE[c]	0.55	4.54	−1.52	−5.65	1.80	−0.29

[a] Energies in kcal mol $^{-1}$.
[b] Total energy is broken down into bond, angle, torsion, van der Waals, and coulomb energy.
[c] The energy difference between forms A and B.

inner wall of the CD ring. On the other hand, the increasing angle bending energy may be related to the deviation of C7 symmetry of the CD ring, as was demonstrated by the result of the MD conformational search. The deviation of the macrocycle of the CD was evaluated by assessing the distance between the center of each pyranose monomer and the center of the macrocycle. If the CD ring is perfectly symmetrical, these distortions, should have the same numerical value. We located the center of macrocycle as defined by the mean values of the coordinates of O4 linker oxygens for the CD ring and then the center of each pyran was defined by atoms C2, C3, C5, and O5. The plots of the distribution of these distances for DMAB-β-CD (forms A and B, respectively) are shown in Figure 14. For form A, the distance is spanned from approximately 4.5 to 7.8 Å, while for B the distance is spanned from 5.5 to 6.3 Å. This result indicats that the macrocycle tends to be distorted when the appending moiety is included into the CD cavity. We speculated that the distortion of the CD ring enlarges the angle bending energy, so the relationship between the magnitude of the distortion of the CD ring and the angle bending energy was investigated.

The numerical values reflecting the distortion of the CD ring were gained by the following procedure. The distance between the center of each pyranose and the center of the macrocycle was measured by the previous procedure for each structure of DMAB-β-CD sampled for the MD conformational search. After we obtained

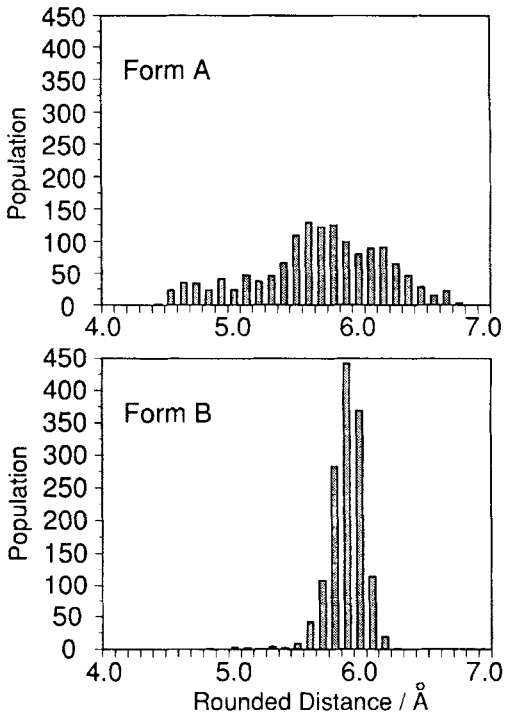

FIGURE 14 Distribution of the distances (in 0.10 Å units) from the centroid of the CD ring to the centroid of each pyran residue for DMAB-β-CD.

seven values of distance for each structure, we calculated their standard deviations. It is obvious that the value of standard deviation would be zero for C7 symmetrical CD ring but it increases with the increasing distortion of the CD ring. Figure 15 shows the relationship between the standard deviation and the angle bending energy. The gray plots, which were calculated for form B, are crowded in the range

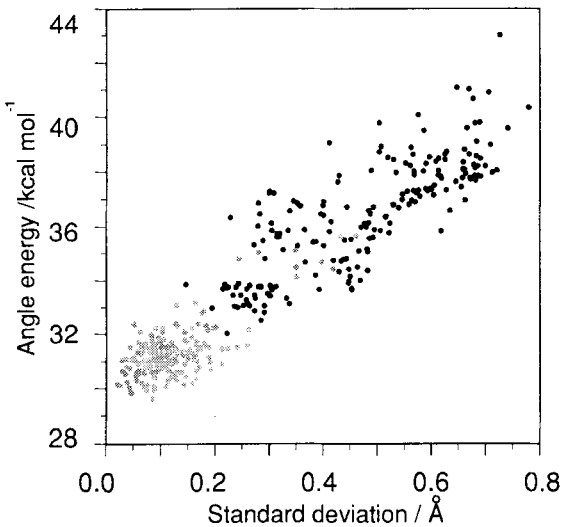

FIGURE 15 The relationship between distortion of CD ring and angle bending energy for DMAB-β-CD. The gray and black plots show calculated data for forms A and B, respectively.

of small standard deviation, indicating that these structures have a small distortion of the CD ring and the angle bending energy is not appreciably variable in the region. On the other hand, the black plots calculated for form A are widely scattered in the range of standard deviation from 0.2 to 0.8 Å and the angle energy increases with increasing standard deviation. This result confirms that distortion of the CD ring enlarges the angle bending energy, making the structure of the modified CDs unstable.

CONCLUSION

Dynamics conformational research analysis was applied to two modified CDs, DMAB-β-CD and NB-β-CD to clarify the reason why they take different conformations with the appending moiety inside the CD cavity for the former and outside the cavity for the latter. The analysis reveals that the self-inclusion structure of DMAB-β-CD is stabilized by van der Waals interaction between the appending moiety and the CD ring in spite of destabilization by the distortion of the CD ring. On the other hand, in the case of NB-β-CD, the stabilization by van der Waals interaction is invalidated by the destabilization of the distortion in the CD frameworks. These results are in agreement with the experimental results and demonstrate that the molecular dynamics conformational search is useful for explaining the experimentally determined structures as well as predicting the conformations of modified CDs.

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