**Supplementary Figure S1.** The distributions of $\omega$ angles in the results of gREST in water solution with CHARMM force field containing CMAP terms of N-methyl amino acids. In these panels $\omega$ angles of N-methyl amino acids are shown red captions. Here, cis- and trans-form are around 0 and 180 degree, respectively.
Supplementary Figure S2. The distributions of $\omega$ angles in the results of gREST in water solution with CHARMM force field containing no CMAP terms of N-methyl amino acids. In these panels $\omega$ angles of N-methyl amino acids are shown red captions. Here, cis- and trans-form are around 0 and 180 degree, respectively.
Supplementary Figure S3. The distributions of \( \omega \) angles in the results of gREST in chloroform solution with CHARMM force field containing CMAP terms of N-methyl amino acids. In these panels \( \omega \) angles of N-methyl amino acids are shown red captions. Here, \textit{cis}- and \textit{trans}-form are around 0 and 180 degree, respectively.
Supplementary Figure S4. The distributions of \( \omega \) angles in the results of gREST in chloroform solution with CHARMM force field containing no CMAP terms of N-methyl amino acids. In these panels \( \omega \) angles of N-methyl amino acids are shown red captions. Here, cis- and trans-form are around 0 and 180 degree, respectively.
Supplementary Figure S5. The distributions of ω angles in the results of conventional MD in water solution started from the closed form structure. In these panels ω angles of N-methyl amino acids are shown red captions. Here, cis- and trans-form are around 0 and 180 degree, respectively.
Supplementary Figure S6. The distributions of ω angles in the results of conventional MD in water solution started from the open form structure. In these panels ω angles of N-methyl amino acids are shown red captions. Here, cis- and trans-form are around 0 and 180 degree, respectively.
Supplementary Figure S7. The heat maps of the free energy from the results of gREST sampling in chloroform (panel A) and in water (panel B and C) solution with CHARMM force field with CMAP term of N-methyl amino acids. These panels are shown the distributions on PC1-PC2 plane of conformations whose \( \omega \) angles between MLE2-MLE3 are cis (panel A and B) and trans form (panel C). Here, cis and trans conformations were selected from trajectories whose \( \omega \) angle are 0° \( \pm \) 30° and 180° \( \pm \) 30°, respectively. The principal component axis are calculated from C\( \alpha \) atoms of the normal MD simulations of CsA in aqueous solutions. In these panels, the position of the crystal structure of open form (PDB_ID 1CWA) and closed form (CDC_ID DEKSAN) are shown by black circle and black square, respectively. Here, we did not show the heat map of trans form in chloroform because of there was absence of trans conformation in the results of gREST sampling.
Supplementary Figure S8. The heat maps of the free energy from the results of gREST sampling in chloroform (panel A and B) and in water (panel C and D) solution with CHARMM force field with no CMAP term of N-methyl amino acids. These panels are shown the distributions on PC1-PC2 plane of conformations whose ω angles between MLE2-MLE3 are cis (panel A and C) and trans form (panel B and D). Here, cis and trans conformations were selected from trajectories whose ω angle are 0º ± 30º and 180º ± 30º, respectively. The principal component axis are calculated from Cα atoms of the normal MD simulations of CsA in aqueous solutions. In these panels, the position of the crystal structure of open form (PDB_ID 1CWA) and closed form (CDC_ID DEKSDAN) are shown by black circle and black square, respectively.
Supplementary Figure S9. Structural clustering of ensembles obtained by gREST simulation of cyclosporin A in chloroform solvent using CHARMM force field containing CMAP terms of N-methyl amino acid. (A) Structural distribution projected to the PC1-PC2 plane. In this panel, cluster centers by K-means are shown by black dots and cluster numbers. (B) Representative structure of cluster 1. These structures are indicated by stacking the ten structures closest to the center of the cluster, and the number of structures constituting this cluster is shown in parentheses.
Supplementary Figure S10. Structural clustering of ensembles obtained by gREST simulation of cyclosporine A in chloroform solvent using CHARMM force field without CMAP terms of N-methyl amino acid. (A) Structural distribution projected to the PC1-PC2 plane. In this panel, cluster centers by K-means are shown by black dots and cluster numbers. (B) Representative structures of each clusters. These structures are indicated by stacking the ten structures closest to the center of the cluster, and the number of structures constituting this cluster is shown in parentheses.
Supplementary Figure S11. Structural clustering of ensembles obtained by gREST simulation of cyclosporine A in water solvent using CHARMM force field containing CMAP terms of N-methyl amino acid. (A) Structural distribution projected to the PC1-PC2 plane. In this panel, cluster centers by K-means are shown by black dots and cluster numbers. (B) Representative structure of each of clusters. These structures are indicated by stacking the ten structures closest to the center of the cluster, and the number of structures constituting this cluster is shown in parentheses.
Supplementary Figure S12. Structural clustering of ensembles obtained by gREST simulation of cyclosporine A in water solvent using CHARMM force field without CMAP terms of N-methyl amino acid.

(A) Structural distribution projected to the PC1-PC2 plane. In this panel, cluster centers by K-means are shown by black dots and cluster numbers. (B) Representative structures of each of clusters. These structures are indicated by stacking the ten structures closest to the center of the cluster, and the number of structures constituting this cluster is shown in parentheses.
Supplementary Figure S13. Backbone-backbone hydrogen bond map
(A) Hydrogen bond map of closed form crystal structure (DEKSAN). (B-D) Hydrogen bond maps of clusters obtained from gREST simulations in chloroform by using CHARMM force field with CMAP terms of N-methyl amino acid (B) and no CMAP terms of them (C, D). These clusters are the closest the position of closed form crystal structure on the PC1-PC2 plane.
Supplementary Table S1. The average number of hydrogen bonds in each clusters obtained from gREST simulations.

| Cluster ID | \( N_{\text{H-bonds}}^* \)       |
|------------|----------------------------------|
|            |                                  |
| gREST-CHCL3-w-CMAP                   |
| 1          | 1.70 (1.60)                      |
| gREST-CHCL3-wo-CMAP                  |
| 1          | 0.75 (0.13)                      |
| 2          | 0.21 (0.13)                      |
| 3          | 0.81 (0.06)                      |
| 4          | 0.51 (0.14)                      |
| 5          | 2.90 (2.82)                      |
| 6          | 1.70 (1.45)                      |
| gREST-water-w-CMAP                   |
| 1          | 0.26 (0.01)                      |
| 2          | 0.09 (0.09)                      |
| 3          | 0.01 (0.00)                      |
| 4          | 0.01 (0.00)                      |
| 5          | 0.01 (0.00)                      |
| 6          | 0.01 (0.00)                      |
| 7          | 0.01 (0.00)                      |
| 8          | 0.84 (0.00)                      |
| 9          | 0.78 (0.01)                      |
| 10         | 0.04 (0.00)                      |
| 11         | 0.15 (0.13)                      |
| 12         | 0.10 (0.01)                      |
| gREST-water-wo-CMAP                  |
| 1          | 0.22 (0.03)                      |
| 2          | 0.24 (0.13)                      |
| 3          | 0.23 (0.03)                      |
| 4          | 0.40 (0.15)                      |
| 5          | 0.29 (0.02)                      |
| 6          | 0.29 (0.01)                      |
| 7          | 0.20 (0.01)                      |

*The average number of backbone-to-backbone hydrogen bonds is shown in parentheses.