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THE CONFORMATION OF THE MACROTETROLIDE RING SYSTEM FROM X-RAY AND MOLECULAR MECHANICS STUDIES

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Abstract—X-ray data of four compounds of nactins (nonactin, dinactin, tetranactin in free and complex forms) were analysed by molecular mechanics in order to study the stability of the conformations of the macrotetrolide antibiotics (ionophoric substance). Starting with the X-ray data, the four types of conformation were converged to the respective minimum energy structures. The complex type conformation (approximate S_4 symmetry) has the lowest initial and final steric energy. However, the vicinal H-H coupling constants of the complex type conformation, calculated for the minimum energy structure by the Karplus formula, are not in accordance with the published data for nonactin in acetone-d_6 and for tetranactin in $CDCl_3$ solutions. The dinactin type conformation (asymmetric) has the largest dipole moment, which may be the most favorable one to take the cations in the molecule.

Macrotetrolide antibiotics nactins (Fig. 1) are widely known as a neutral ion-carrier across the biological and artificial membrane.[1] Nactins can form 1:1 complex with alkali metal cations as well as with ammonium ions forming a distorted cubic coordination around the cations. In these complexes, the conformation of the backbone of the ligand molecule resembles the seam of a tennis ball (approximate S_4 symmetry; hereafter denoted as C-type).[2,3] This conformation was shown to be present in solution[4,5] of the complex as well as in crystals (Fig. 2a). On the other hand, it has been observed that the four subunits of the ion free nonactin as well as those of tetranactin are magnetically equivalent in solution by NMR spectroscopy,[5,6] suggesting the average conformations of the nactins in solution to be similar to those of the complex.

Although the molecular symmetry of nonactin crystals (C_2 with approximate S_4 symmetry; torus form; hereafter denoted as N-type; Fig. 2c)[7] was compatible with that derived from ^{1}H-NMR spectra, some of the vicinal H–H spin coupling constants (J_{vic}), calculated by Karplus formula, showed some discrepancies from the observed values, indicating the N-type conformation cannot exist in high population.[8]

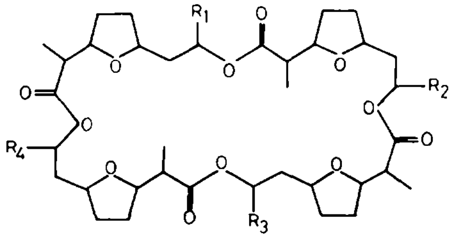

NONACTIN $R_1, R_2, R_3, R_4 = -CH_3$
MONACTIN $R_1, R_2, R_3 = -CH_3$ & $R_4 = -CH_2CH_3$
DINACTIN. $R_1, R_3 = -CH_3$ & $R_2, R_4 = -CH_2CH_3$
TETRANACTIN: $R_1, R_2, R_3, R_4 = -CH_2CH_3$

Fig. 1. Macrotetrolide antibiotics nactins.

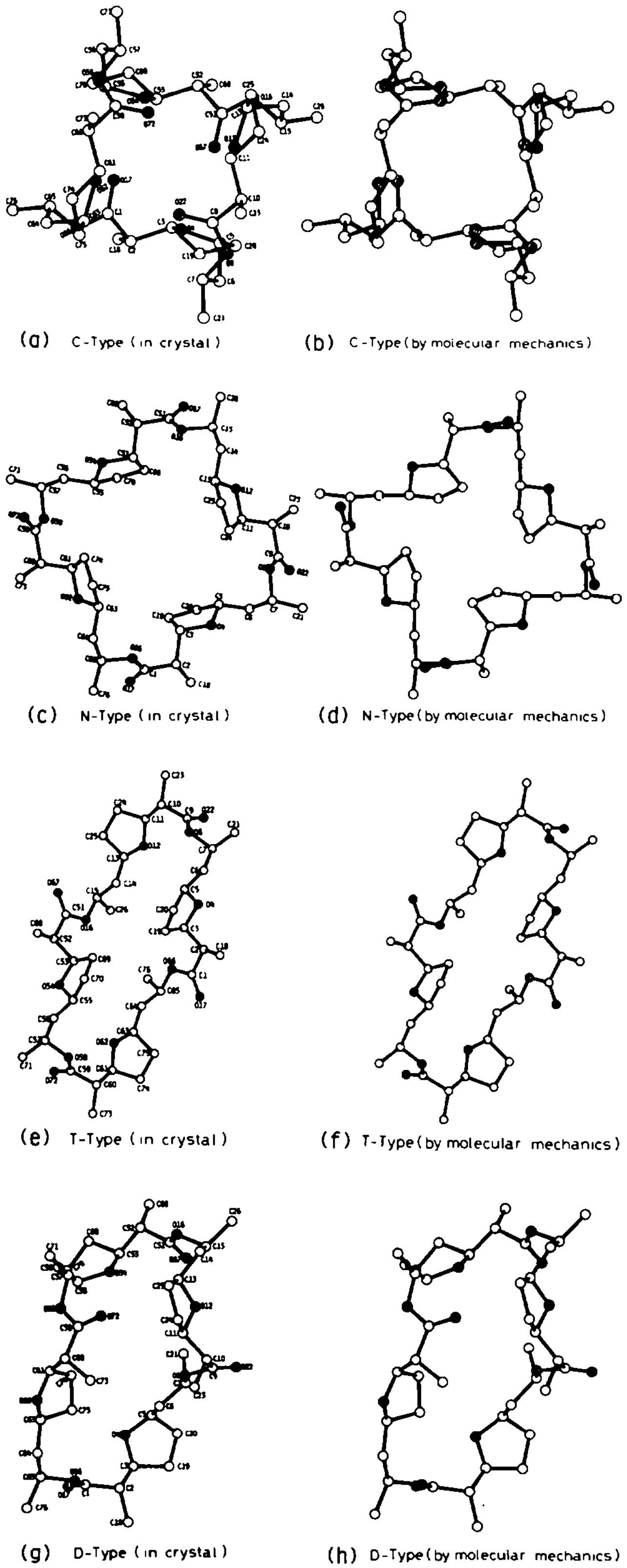
The molecular structure of tetranactin in the crystal is elongated and twisted just as propeller with C_2 symmetry (hereafter denoted as T-type; Fig. 2e).[9] In the T-type structure, the conformations of the four subunits are classified into two types (T_1 and T_2).[8]

The molecular structure of dinactin in the crystal is elongated but curled up on one end and looks like a deformed cradle with an asymmetric conformation (hereafter denoted as D-type; Fig. 2g).[8] In this molecule, the conformations of the four sub-units are different from each other.

If we consider the molecular conformations of the nactins in solution to be in equilibrium through rapid molecular motion, NMR spectra may be averaged out resulting in the magnetical equivalence of the four subunits. Actually, the observed J_{vic} values of nactins are closer to the calculated values of tetranactin and dinactin than those for nonactin. Therefore we thought that both the T-type and the D-type conformers might be predominant intermediates in solution. In order to study the stability of the conformations of nactins, X-ray data of nonactin,[7] dinactin, tetranactin[9] and K$^+$-tetranactin complex[10] are analysed by the molecular mechanics.

ANALYSIS OF THE DATA AND DISCUSSION

Crystal data of the nactins are summarized in Table 1. The crystal structure of nonactin contains a stacking disorder which made a detailed diffraction analysis difficult. Consequently, an unusual intramolecular short contact was observed between C14 and H'26 (2.05 Å). The crystal structure analysis of dinactin has been carried out on a mixed crystal of dinactin ($C_{42}H_{68}O_{12}$) and monactin ($C_{41}H_{66}O_{12}$) (approximate molar ratio = 7:3), and the Et groups in both molecules were presumed to



(a) C-Type (in crystal) (b) C-Type (by molecular mechanics)

(c) N-Type (in crystal) (d) N-Type (by molecular mechanics)

(e) T-Type (in crystal) (f) T-Type (by molecular mechanics)

(g) D-Type (in crystal) (h) D-Type (by molecular mechanics)

Fig. 2. ORTEP[15] drawings of the four conformers of nactins. Atomic parameters of minimum energy conformers, used for plottings, are those obtained by energy minimization with the parameters given in MMPI program. For clarity the hydrogen atoms are omitted and the oxygen atoms are shaded: (a) C-type conformer of K^+-tetranactin complex,[10] (b) C-type minimum energy conformer (without cation), (c) N-type conformer in the crystal structure of nonactin,[7] (d) N-type minimum energy conformer, (e) T-type conformer in the crystal structure of tetranactin,[9] (f) T-type minimum energy conformer, (g) D-type conformer in the crystal structure of dinactin,[8] and (h) D-type minimum energy conformer.

Table 1. Crystal data of nactins

Compound	nonactin	dinactin*	tetranactin	KSCN-tetranactin complex
Conformation	N-type	D-type	T-type	C-type
Chemical formula	$C_{40}H_{64}O_{12}$	$(C_{41.7}H_{67.4}O_{12})$	$C_{44}H_{72}O_{12}$	$C_{44}H_{72}O_{12}\cdot KSCN$
Formula weight	737	(760.8)	792	889.6
Crystal system	orthorhombic	triclinic	monoclinic	monoclinic
Space group	Pbam	$P\bar{1}$	C2/c	C2/c
Cell dimensions				
a (Å)	47.57/2	10.531(5)	25.44(3)	27.455(6)
b (Å)	31.40/2	25.230(10)	9.46(1)	12.420(1)
c (Å)	5.69	9.422(4)	24.52(3)	30.211(6)
α (°)	90.0	91.18(4)	90.0	90.0
β (°)	90.0	116.07(5)	129.83(8)	97.15(2)
γ (°)	90.0	96.84(5)	90.0	90.0
Number of molecules in a unit cell	2	2	4	8
R-factor (%)	10.3 [#1] (anisotropic non-H atoms)	8.2 [#2] (anisotropic non-H atoms & isotropic H atoms)	5.9 (anisotropic non-H atoms & isotropic H atoms)	11.1 [#3] (anisotropic non-H atoms)
E.s.d.'s for bond lengths(Å)	0.011~0.025	0.008	0.006	0.022
Reference	7	8	9	10

*Crystal structure analysis of dinactin has been carried out on a mixed crystal of dinactin ($C_{42}H_{68}O_{12}$) and monactin ($C_{41}H_{66}O_{12}$) (approximate molar ratio = 7:3).

No. 1 Crystal structure of nonactin contains a stacking disorder.

No. 2 In the crystal structure of dinactin, the ethyl groups are randomly distributed over the four positions.

No. 3 In the crystal structure of KSCN–tetranactin complex, SCN^- group is disordered.

be randomly distributed over the four positions (C7, C15, C57 and C65). The crystallographic refinement showed that the thermal parameters of the terminal Me carbon atoms in the Et groups are extraordinarily large (B_{eq}: 14.3 ~ 28.5 $Å^2$), and the C–C bond distances in the Et groups become apparently shorter than those observed in the tetranactin molecule. For this reason, four Et groups in the dinactin molecule were replaced by the Me groups, respectively, before the steric energy calculation.

In the dinactin molecule, several intramolecular short contacts between the O atoms and the alkyl groups, stabilize the elongated molecular conformation. The intramolecular short contacts are also observed in tetranactin between the alkyl groups which are related by the crystallographic two fold axis.

Raman spectroscopic studies on these nactins revealed that the molecular conformations of the nactins in solution are quite similar.[13] Accordingly, prior to the molecular mechanics calculations on the nactins, the Et groups in tetranactin and K^+-tetranactin complex were replaced by the Me groups, respectively. In addition, the K^+ cation was excluded from the complex. These modification of the molecular structures made comparison between the steric energies of the four skeletal conformations possible. Steric energy minimization was carried out by the use of the program MMPI[14] without the restriction of molecular symmetries which were observed in the crystals. The minimum energy bond lengths and angles, given in the program MMPI, may be somewhat different from the actual bond lengths and angles observed for the nactins. Accordingly, the averaged values found in the crystal structure of tetranactin[9] were employed: $C(sp^3)$–$C(sp^3) = 1.524$, $C(sp^3)$–$C(sp^2) = 1.512$, $C(sp^3)$–$O' = 1.444$, $C(sp^2)$–$O' = 1.338$ and $C(sp^2)$=$O = 1.202$ (Å), $\angle C(sp^3)$–$C(sp^3)$–$C(sp^3) = 110.51$, $\angle C(sp^3)$–$C(sp^3)$–$C(sp^2) = 110.53$, $\angle C(sp^3)$–$C(sp^3)$–$O' = 106.53$, $\angle C(sp^3)$–$C(sp^2)$=$O = 124.30$ and $\angle C(sp^3)$–O–$C(sp^3) = 106.95$ (°).

Although the minimization proceeded accompaned by the remarkable displacements of relative atomic positions (Table 2), the four conformations were not converged to the same structure with the lowest steric energy, but to the respective minimum energy structures, in which the approximate molecular symmetries observed in the crystals were preserved. The largest displacement of the atoms was observed for the N-type conformation, for which the conformational changes were also the largest. The tetrahydrofuran (THF) rings of nonactin in the crystal were approximately parallel to the symmetry axis of S_4 (4), but in the minimum energy

Table 2. Initial and minimized steric energies of the four conformations of nactins

Conformation type	D-type		T-type		N-type		C-type	
Symmetry	asymmetric		C_2	pseudo C_2	pseudo S_4		pseudo S_4	
Cycles	1	215	1	165	1	745	1	240
Compression (Kcal/mol)	17.86	5.70	14.67	5.78	77.44	5.57	26.74	5.70
Bending (Kcal/mol)	47.80*	25.81	34.27*	23.55	51.52*	25.64	44.81*	24.79
Stretch-bend (Kcal/mol)	-0.51	1.20	-0.04	1.13	-3.05	1.15	-0.35	0.91
van der Waals 1,4 energy (Kcal/mol)	63.20	46.56	67.39	47.37	88.34	47.96	50.11	46.19
other (Kcal/mol)	-17.72	-24.35	-15.24	-22.46	-11.13	-22.47	-19.46	-23.46
Torsion (Kcal/mol)	4.70	-1.17	7.17	2.53	9.44	-3.04	-3.44	-0.10
Torsion-bend (Kcal/mol)	-0.31	0.04	0.67	0.61	0.45	0.17	-0.30	0.19
Dipole (Kcal/mol)	2.83	-1.46	3.24	-0.46	4.22	1.40	12.62	-4.24
STERIC ENERGY (Kcal/mol)	117.86*	52.33	112.12*	58.05	217.23*	56.39	110.71*	49.97
Dipole moment (D)	3.133	4.299	0.513	0.531	0.033	0.117	0.226	0.186
Displacements** of relative atomic positions (Å)	av. 0.154 (0.032 ~ 0.509)		av. 0.150 (0.026 ~ 0.486)		av. 0.622 (0.169 ~ 1.381)		av. 0.267 (0.066 ~ 1.023)	
Changes*** in torsional angles (°)	av. 4.8 (0.6 ~ 15.5)		av. 3.4 (0.2 ~ 11.0)		av. 6.4 (0.3 ~ 32.8)		av. 12.9 (0.1 ~ 36.3)	
Differences**** in torsional angles (°)	av. 1.5 (0.0 ~ 3.6)		av. 1.3 (0.1 ~ 3.8)		av. 1.7 (0.0 ~ 3.7)		av. 1.7 (0.0 ~ 4.6)	

*The contribution of the lone paired orbitals to bending energy was substracted.

**These were estimated by the least-squares fitting of the initial and the minimized energy structures, using the program ORIENTN written by Dr. T. Akimoto.

***These are the absolute values of the differences in the torsional angles along the 32-membered ring between the initial and the minimized energy structures.

****These are the absolute values of the differences in the torsional angles along the 32-membered ring between the two minimized energy structures, calculated with the parameters given in MMPI program and with those observed in the crystal.

structure (Fig. 2d) they were arranged almost perpendicular to that and came close to each other diminishing the size of the central cavity of the molecule; the approximate size of the cavity was 2.9 × 3.0 Å in the crystal but it diminished to 0.8 × 1.2 Å in the minimum energy structure. On the other hand, the conformational changes of both the T-type and the D-type structures by the energy minimization were small, although intramolecular short contacts observed in the both structures were further shortened by the energy minimization; especially the distance between C11 and O72. In the latter it was diminished by 0.24 Å, probably due to the replacement of the Et groups by the Me groups.

The displacements of the relative atomic positions were also remarkable in the C-type conformation when the cation was removed; the carbonyl O atoms, related by a pseudo symmetry axis of C_2, kept away from each other to decrease the repulsive intramolecular dipole-dipole interactions: the average distance (3.80 Å in the crystal) was lengthened to 4.62 Å in the minimum energy structure. On the other hand, the displacements of the ether O atoms were moderate (Table 3). This is consistent with the observation that in a series of alkaline metal-tetranactin complex, the metal-carbonyl O distance varies according to the ionic radius of the metal ions.[3] Thus the conformational changes in this structure were distinct around the bonds adjacent to the CO groups, and the changes in torsional angles were the largest among the four types of conformation.

In Table 2, both the initial and the final steric energies, based on the natural bond lengths and angles found in the crystal, are listed for the four conformations of the nactins. The N-type conformation has the highest initial steric energy (approx. 1.9 times the value of T-type). This is probably due to the inaccurate molecular structure of nonactin as mentioned above. The D-type conformer has the larger dipole moment (3.133 D) than those of the other conformations of higher symmetry, and among the three conformers (excluding C-type) it also has the lowest minimized energy, in which the lowest van der Waals energy is involved (Fig. 2h). The smalles bending energy and the largest torsional energy are estimated for the minimum energy structure of the T-type conformation (Fig. 2f). Dipole interaction energy in the minimum energy structure of the N-type conformation is positive, in contrast to the negative values in the other type of conformation. The energy minimized N-type conformation has also the lowest torsional energy. On the other hand, the larger repulsive dipole interaction is observed for the C-type conformer. This energy should be compensated by the ion–dipole interaction when the K^+ cation is incorporated into the central cavity of the molecule. Minimization on the C-type structure brought a strong attractive dipole–dipole interaction, which made the minimized steric energy of this type the lowest (Table 2 and Fig. 2b). However, if the K^+ ion were placed into the central cavity, it would have less attractive ion–dipole interaction energy (−22.20 kcal/mol for a unit positive electric charge; dielectric constant = 1.0) than that (−63.85 kcal/mol) for the K^+-tetranactin complex.[10]

In connection with the conformations of the nactins in solution, J_{vic} values were calculated by the Karplus formula[11,12] using the atomic coordinates determined by the energy minimization, and compared with the observed values for nonactin in acetone-d_6 and for tetranactin in $CDCl_3$ solution.[5,6] Among the values listed in Table 3, $^3J_{H2-H3}$, $^3J_{H5-H6}$ and $^3J_{H6-H7}$ are directly related with the conformation of the 32-membered ring of the nactins. The $^3J_{H2-H3}$ values of the N-type and the C-type conformations deviate considerably from those of the observed values. Although those of the D-type and the T-type do not deviate extensively from the observed values, the rest of calculated J-values of the two are not always in good accordance with the observed values.

It is probable that the minimum energy structure of the

Table 3. The displacements of the relative atomic positions by energy minimization for C-type conformation

Atom	Displacements* (Å)	Distances (Å) from molecular center	K^+...O distances (Å) in K^+-tetranactin complex[10]
Carbonyl			
O17	0.574	3.354	2.81
O22	0.847	3.574	2.77
O67	1.023	3.696	2.75
O72	0.803	3.576	2.76
	(av. 0.812)	(av. 3.550)	(av. 2.77)
Ether			
O4	0.381	3.119	2.86
O12	0.271	3.113	2.92
O54	0.405	3.137	2.83
O62	0.329	3.160	2.88
	(av. 0.347)	(av. 3.132)	(av. 2.87)

*These were estimated by the same procedure described in the legend of Table 2 (**).

Table 4. Selected torsional angles and calculated vicinal H–H coupling constants for the minimized energy structures $J(\mathrm{Hz}) = J_o \times \cos^2 \phi - 0.28$ ($J_o = 10.9$ Hz for $90° \leq \phi \leq 180°$, $J_o = 9.9$ Hz for $0° \leq \phi \leq 90°$)[11,12]

Conformation type	D-type		T-type		N-type		C-type		observed J_{vic} (Hz)	
	(°)	(Hz)	(°)	(Hz)	(°)	(Hz)	(°)	(Hz)	nonactin[6]	tetranactin[5]
H2-C2-C3-H3	175.6	10.55	53.8	3.17	-53.2	3.27	-166.2	10.00		
H52-C52-C53-H53	167.4	10.10	53.7	3.19	-52.8	3.34	-164.1	9.80		
H10-C10-C11-H11	-176.6	10.58	-175.5	10.55	53.0	3.31	164.9	9.88		
H60-C60-C61-H61	-54.5	3.06	-175.5	10.55	53.0	3.31	164.3	9.82		
	av.	8.57	av.	6.87	av.	3.31	av.	9.88	7.6±0.4	7.8
H5-C5-C6-H6	-177.9	10.61	69.9	0.89	-76.4	0.27	-65.9	1.37		
H5-C5-C6-H'6	-63.5	1.69	-172.2	10.42	165.7	9.96	175.5	10.55		
H55-C55-C56-H56	66.4	1.31	69.9	0.89	-75.4	0.35	-66.2	1.33		
H55-C55-C56-H'56	-175.4	10.55	172.2	10.42	166.6	10.03	175.3	10.55		
H13-C13-C14-H14	172.6	10.44	57.7	2.55	-166.9	10.06	-174.5	10.52		
H13-C13-C14-H'14	-69.2	0.97	172.6	10.44	75.2	0.37	67.1	1.22		
H63-C63-C64-H64	56.6	2.72	57.4	2.59	-167.8	10.13	-175.4	10.55		
H63-C63-C64-H'64	172.2	10.42	172.3	10.42	74.2	0.45	66.1	1.34		
	av.	6.09	av.	6.08	av.	5.20	av.	5.93	6.2±0.4	7.0
H6-C6-C7-H7	-59.0	2.35	-172.0	10.41	171.5	10.38	170.7	10.34		
H'6-C6-C7-H7	-172.4	10.43	69.6	0.92	-69.9	0.89	-71.0	0.77		
H56-C56-C57-H57	-170.6	10.33	-172.0	10.41	171.5	10.38	169.9	10.28		
H'56-C56-C57-H57	71.7	0.70	69.7	0.91	-69.9	0.89	-71.9	0.68		
H14-C14-C15-H15	-72.2	0.65	-175.3	10.55	69.3	0.96	72.1	0.66		
H'14-C14-C15-H15	169.2	10.24	68.9	1.00	-172.1	10.41	-169.7	10.27		
H64-C64-C65-H65	-79.0	0.08	-175.2	10.54	68.7	1.03	70.6	0.81		
H'64-C64-C65-H65	164.3	9.82	69.0	0.99	-172.5	10.43	-171.1	10.36		
	av.	5.58	av.	5.72	av.	5.67	av.	5.52	6.8±0.4	6.0
H3-C3-C19-H19	38.9	5.72	-11.2	9.25	9.5	9.35	-50.8	3.67		
H3-C3-C19-H'19	159.7	9.31	108.5	0.82	-100.0	0.05	-173.3	10.47		
H53-C53-C69-H69	47.5	4.24	-11.0	9.26	9.5	9.35	-50.6	3.71		
H53-C53-C69-H'69	169.7	10.27	108.7	0.84	-110.1	1.01	-173.0	10.46		
H11-C11-C24-H24	-166.0	9.98	-156.3	8.86	110.5	1.06	173.2	10.47		
H11-C11-C24-H'24	-45.7	4.55	-37.4	5.97	-9.0	9.38	50.9	3.67		
H61-C61-C74-H74	-109.0	0.88	-155.0	8.67	110.7	1.08	173.3	10.47		
H61-C61-C74-H'74	9.7	9.34	-36.2	6.17	-8.7	9.39	50.9	3.66		
	av.	6.79	av.	6.23	av.	5.08	av.	7.07	7.0±0.4	7.0
H5-C5-C20-H20	31.3	6.95	-49.9	3.83	51.4	3.57	-10.1	9.32		
H5-C5-C20-H'20	-90.0	-0.28	-170.9	10.63	172.4	10.43	-127.6	3.78		
H55-C55-C70-H70	23.4	8.06	-49.9	3.83	51.3	3.59	-11.7	9.21		
H55-C55-C70-H'70	-97.3	-0.10	-171.0	10.35	172.3	10.42	108.0	0.76		
H13-C13-C25-H25	132.3	4.66	148.6	7.66	-172.8	10.45	-109.3	0.91		
H13-C13-C25-H'25	14.5	9.00	30.0	7.14	-51.7	3.52	10.2	9.31		
H63-C63-C75-H75	171.4	10.38	149.9	7.88	-172.8	10.45	-110.3	1.03		
H63-C63-C75-H'75	49.7	3.86	31.2	6.96	-51.7	3.52	9.1	9.37		
	av.	5.31	av.	7.29	av.	6.99	av.	5.46	6.8±0.4	6.5

D-type conformation, which has the largest dipole moment (4.299 D), is the most favorable one to draw cations strongly to the proximity of the nactins molecules in solution and to start the complex formation with the cations by ion–dipole interaction.

Molecular mechanics calculation. The program MMPI, modified by Prof. E. Osawa, was used in the present study. The fractional atomic coordinates of nonactin, tetranactin and K^+–tetranactin complex, used in the present analysis are those taken from the literature cited above, and those of dinactin are listed in Table 5. The steric energy was very sensitive to the assumed minimum energy bond lengths and bond angles used in the calculation; namely the initial and the minimized energies listed in Table 2 are approx. 21 and 17 kcal/mol lower, respectively, than those obtained with the parameters given in the program. The conformations of the THF rings in the C-type and the N-type conformers were rather sensitive to the parameters. In the case of the former, four THF rings of envelope conformation were all deformed to twist conformation by the minimization when the parameters derived from the crystal structure were used. But one twist and three envelope conformations which are all different from those observed in

Table 5. The positional parameters ($\times 10^4$) for non-hydrogen atoms of dinactin

	X	Y	Z
C1	2875(4)	-62(2)	1943(4)
C2	4470(4)	-28(2)	2675(4)
C3	5077(4)	372(1)	1877(4)
O4	4681(3)	888(1)	2046(4)
C5	5830(4)	1299(2)	2611(5)
C6	6236(4)	1490(2)	4302(5)
C7	7408(5)	1959(2)	5054(5)
O8	7399(3)	2000(1)	6560(3)
C9	8634(5)	2298(2)	7812(5)
C10	8358(5)	2443(2)	9198(5)
C11	7290(5)	2834(2)	8803(5)
O12	7838(4)	3296(1)	8307(4)
C13	7047(6)	3718(2)	8372(6)
C14	7973(7)	4238(2)	8540(7)
C15	8283(6)	4344(2)	7151(7)
O16	6943(4)	4459(1)	5364(4)
O17	2114(3)	-149(2)	550(3)
C18	4890(5)	-587(2)	2559(6)
C19	6700(4)	464(2)	2574(5)
C20	7047(5)	1044(2)	2404(5)
C21	7313(8)	2437(2)	4200(7)
O22	9740(4)	2373(2)	7781(5)
C23	7837(7)	1940(2)	9791(7)
C24	7053(6)	3050(3)	10170(6)
C25	6681(8)	3604(3)	9776(8)
C26	9404(8)	4819(3)	7490(10)
C27	10027(29)	4922(6)	6783(38)
C28	6033(15)	2055(4)	3727(14)
C51	6623(6)	4301(5)	4383(7)
C52	5280(6)	4456(2)	3190(7)
C53	4357(7)	3957(2)	2168(7)
O54	3015(4)	3623(2)	3119(5)
C55	2455(7)	3381(2)	2248(9)
C56	1574(8)	3582(2)	2056(10)
.57	2014(7)	3485(2)	4463(10)
O58	1558(4)	2894(1)	4726(5)
C59	2406(6)	2646(2)	5090(8)
C60	1028(5)	2093(2)	5749(7)
C61	1234(5)	1820(2)	4262(7)
O62	655(3)	1275(1)	4311(4)
C63	313(4)	940(2)	3174(5)
C64	691(4)	368(2)	3610(5)
C65	357(4)	-36(2)	2516(4)
O66	2390(2)	-12(1)	3040(3)
O67	7410(5)	4062(3)	4058(6)
C68	5614(9)	4870(3)	2157(10)
C69	2942(7)	4162(3)	797(8)
C70	1982(8)	4524(3)	540(9)
C71	1238(12)	3752(3)	5574(14)
O72	3550(5)	2002(2)	7108(3)
C73	3081(8)	1702(3)	7025(10)
C74	2103(7)	1766(2)	3458(9)
C75	2234(5)	1102(2)	3237(7)
C76	243(5)	-601(2)	2500(6)
C77	265(14)	-996(5)	1471(16)
C78	1271(23)	3696(7)	6461(26)

the crystals, were obtained when the parameters given in the program were used. However, the molecular conformation was rather insensitive to the parameters; the differences in torsional angles along the 32-membered ring are less than 5° between the corresponding minimized energy structure, calculated with the different parameters.

Calculations were carried out on an ACOS 800 of Computer Center of Chugai Pharmaceutical Co. Ltd. The thermal parameters of dinactin and Cartesian atomic coordinates of the minimum energy structures of the four conformers are listed in supplementary publication No. SUP.

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