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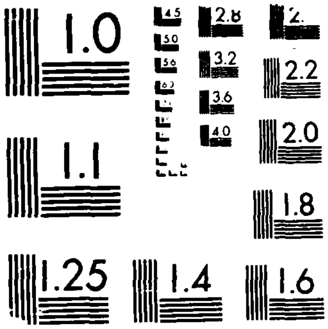

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Normal Mode Calculation for Methylated Z-DNA poly(dG-m^5dC)·(dG-m^5dC)

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Abstract

[illegible]

Normal modes of methylated Z-DNA poly(dG-m^5dC)·(dG-m^5dC) are computed by helix lattice dynamics. Good agreement with Raman spectral data is obtained. We discuss improvements in the formulation of the problem which allow us to greatly reduce the size of the matrix used. This leads to greatly reduced calculation times. The improvements come from using knowledge of the C_2^- and time reversal symmetries. → [illegible]

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I. Introduction

Currently DNA methylation is an interesting topic in biopolymer research. Behe and Felsenfeld[1] discovered that the B-Z transition of poly(dG-m^5dC)·(dG-m^5dC) occurs at low salt concentration, close to usual physiological conditions. Möller et al.[2] methylated poly(dG-dC)·(dG-dC) at the N-7 position of guanine. They confirmed that at 100% methylation of the guanine residues, poly(m^7dG-dC).(m^7dG-dC) is fully converted to Z form in a physiological salt solution. Thus methylation could efficiently affect genetic activities of DNA. In particular, the sequence m^5dC-dG is associated with systems which have decreased transcription levels.[3,4]

Crystal structure of (m^5dC-dG)$_3$ Z-DNA[5] and (GCm^5 CCGGCC) A-DNA[6] have been solved by x-ray diffraction. Slight structural differences between methylated and unmethylated DNA have been observed[5-6] and have been used to explain the electrostatic stability of methylated Z-DNA.[5,7] Structural information of the poly(dG-m^5dC) molecule in solution have been obtained in both B- and Z-conformations from electric dichroism measurements.[8] Raman spectroscopy has been employed to investigate the temperature dependence of the B-Z transition in poly(dG-m^5dC).[9] Vaccuum UV CD spectrum were also obtained experimentally. The results are consistent with the suggestion that the low- and high-salt Z-forms are comprised of different proportions of Z_I- and Z_{II}-conformations.[10]

Lattice dynamics has been used to quantitatively explore the far-infrared absorption spectrum and Raman scattering spectrum of A-, B- and Z-form DNA.[11] In this calculation we use lattice dynamics to compute the normal modes of methylated Z-DNA poly(dG-m^{5}dC)·(dG-m^{5}dC). The internal force constant formalism is rearranged and Coulomb potential energy is reformulated in a precise fashion. The C_2 symmetry of Z-form poly(dG-m^{5}dC)·(dG-m^{5}dC) is emphasized. A brief discussion about C_2 symmetry is given. This rearrangement helps us to greatly reduce the computer run time. The results of a normal mode analysis and assignments are compared with experimental data.[9] A reasonably good agreement between them is obtained.

II. Theoretical Formalism

Let us consider an infinite double-helical molecule. The helical symmetry axis is taken as Z axis in cartesian coordinates. Helical symmetry implies that each unit cell is transformed geometrically into the next by the operation $H(p,\overset{\text{Psi}}{\psi})$ where p is the pitch along Z-axis and $\overset{\text{Psi}}{\psi}$ is the pitch angle about Z-axis. $H(p,\overset{\text{Psi}}{\psi})$ is thus a translation through p plus rotation through ψ.

In helix lattice dynamics all interactions between atoms are characterized by effective force constants which are appropriate second derivatives of the true potential with respect to pairs of degrees of freedom of the system. These are most concisely expressed as functions of the difference in positions of pairs of atoms and we call this difference of positions the internal coordinate system. These internal coordinate force constants can be further broken down into valence force constants, hydrogen bond force constants, and non-bonded force constants which are due to Van der Wall and electrostatic interactions. The electrostatic forces dominate our non-bonded interactions.[11] The potential energy in internal coordinates is

$$U_i = \frac{1}{2} \sum_{mt} S_t^m f_t^m S_t^m \quad , \qquad (2.1)$$

where S_t^m is the internal coordinate, m labels what we will call the unit set of internal coordinates and t labels the individual internal coordinate in the unit set. Since atoms in one unit cell of the repeating helix interact directly with atoms in other unit cells the unit set of internal coordinates involves atoms in more than one unit cell and the unit set is distinct from the coordinate of a unit cell. In particular one needs to pay attention to the force constants of atoms that cross the boundaries of the unit cells.

The internal coordinates are then expanded in mass weighted Cartesian (MWC) coordinates as

$$S_t^m = \sum_{Ki} \frac{1}{\sqrt{m_i}} \vec{B}_{ti}^{mk} \cdot \vec{q}_i^{\,k} \quad , \qquad (2.2)$$

where $\vec{q}_i^{\,k} = \sqrt{m_i}\, \vec{u}_i^{\,K}$, m_i is the mass of i^{th} atom and $\vec{u}_i^{\,k}$ is the displacement of i^{th} atom in K^{th} unit cell. $\vec{B}_{ti}^{mk}$ is a vector whose form depends on the character of the internal coordinate[12] (stretch...etc.). The double super and subscripts of $\vec{B}_{ti}^{mk}$ emphasize that $\vec{B}_{ti}^{mk}$ is assigned to i^{th} atom in k^{th} unit cell and t^{th} internal coordinate in m^{th} unit set.

It has been proved[13] that

$$\vec{B}_{ti}^{mk} = R^m \vec{B}_{t\;\,i}^{0\;k-m} \quad , \qquad (2.3)$$

where R is the rotation through helical angle ψ,

$$R = \begin{pmatrix} \cos\psi & -\sin\psi & 0 \\ \sin\psi & \cos\psi & 0 \\ 0 & 0 & 1 \end{pmatrix} \quad . \qquad (2.4)$$

Using the Born-Von Karman boundary condition one could write

$$\vec{q}_i^{\,k} = \frac{1}{\sqrt{2\pi}} \int_{-\pi}^{\pi} d\theta R^k \, \vec{q}_i(\theta) \; e^{-ik\theta} \tag{2.5}$$

and

$$\vec{q}_i(-\theta) = \vec{q}_i^{\,*}(\theta) \tag{2.6}$$

Substituting (2.3) and (2.5) into (2.1) and noting that

$$\frac{1}{2\pi} \sum_m e^{im(\theta-\theta')} = \delta(\theta-\theta') \tag{2.7}$$

one can formulate U_i as

$$U_i = \frac{1}{2} \sum_{k\ell} \sum_{ij} \sum_t \int_{-\pi}^{\pi} d\theta \{ \vec{q}_i^{\,+} (\theta) \cdot R^{-k} \frac{1}{\sqrt{m_i}} \vec{B}_i^k {}^0_t \, f_t^0 \, \vec{B}_t^0 {}^\ell_j \frac{1}{\sqrt{m_j}} R^\ell \cdot \vec{q}_j(\theta) e^{i(k-\ell)\theta} \} \tag{2.8}$$

With the condition k,ℓ = 0, ± 1 and k-ℓ = 0, ± 1 which results from the local properties of internal forces.

In previous work the electrostatic forces were treated as simple stretch forces. It is possible to treat them more exactly without this implicit simplification as follows. In the harmonic approximation the Coulomb potential energy could be written as

$$U_c = \frac{1}{4} \sum_{k\ell} \sum_{ij} \{ (\vec{u}_i^{\,k} - \vec{u}_j^{\,\ell}) \cdot \nabla\nabla \frac{e_i e_j}{\sqrt{\varepsilon_i \varepsilon_j}} \frac{1}{|\vec{r}_i^{\,k} - \vec{r}_j^{\,\ell}|} \Bigg|_0 \cdot (\vec{u}_i^{\,k} - \vec{u}_j^{\,\ell}) \} \tag{2.9}$$

where $\vec{r}_i^{\,k} = \vec{R}_i^k - \vec{u}_i^{\,k}$ is the position of i^{th} atom in k^{th} unit cell provided $\vec{R}_i^k$ is the equilibrium position and $\vec{u}_i^{\,k}$ is the displacement. e_i is atomic partial charge assigned to atom i and ε_i is local dielectric function in the neighborhood of atom i.

Eq.(2.8) could be expressed in MWC coordinate as

$$U_c = \frac{1}{2} \sum_{ki} \vec{q}_i^{\,k} \cdot \Big[\sum_{\ell h} \frac{e_i e_h}{m_i \sqrt{\varepsilon_i \varepsilon_h}} \frac{-\overleftrightarrow{I} + 3\vec{B}_{ih}^{k\ell}\, \vec{B}_{ih}^{k\ell}}{|\vec{R}_{ih}^{k\ell}|^3} \Big] \cdot \vec{q}_i^{\,k}$$

$$- \frac{1}{2} \sum_{k\ell} \sum_{ij} \vec{q}_i^{\,k} \cdot \frac{e_i e_j}{\sqrt{m_i m_j \varepsilon_i \varepsilon_j}} \frac{-\overleftrightarrow{I} + 3\vec{B}_{ij}^{k\ell} \vec{B}_{ij}^{k\ell}}{|\vec{R}_{ij}^{k\ell}|^3} \cdot \vec{q}_j^{\,\ell} \quad , \tag{2.10}$$

where

$$\vec{B}_{ij}^{k\ell} = \frac{\vec{R}_i^k - \vec{R}_j^\ell}{|\vec{R}_i^k - R_j^\ell|} = \frac{\vec{R}_i^k - \vec{R}_j^\ell}{|\vec{R}_{ij}^{k\ell}|} \quad . \tag{2.11}$$

Using (2.3)-(2.6) leads to

$$U_c = \frac{1}{2} \sum_i \int_{-\pi}^{\pi} d\theta \; \vec{q}_i^{\,\dagger} (\theta) \cdot \Big\{ \sum_{\ell h} \frac{e_i e_h}{m_i \sqrt{\varepsilon_i \varepsilon_h}} \frac{-\overleftrightarrow{I} + 3\vec{B}_{ih}^{o\ell}\, \vec{B}_{ih}^{o\ell}}{|\vec{R}_{ih}^{o\ell}|^3} \delta_{ij}$$

$$- \sum_{\ell j} \frac{e_i e_j}{\sqrt{m_i m_j \varepsilon_i \varepsilon_j}} \frac{-\overleftrightarrow{I} + 3\vec{B}_{ij}^{o\ell}\, \vec{B}_{ij}^{o\ell}\; R^\ell}{|\vec{R}_{ij}^{o\ell}|^3} e^{-i\ell\theta} \Big\} \cdot \vec{q}_j (\theta) \quad . \tag{2.12}$$

The kinetic energy T is

$$T = \frac{1}{2} \sum_i \int_{\pi}^{\pi} d\theta \; \dot{\vec{q}}_i^{\,\dagger} (\theta) \cdot \dot{\vec{q}}_i (\theta) \tag{2.13}$$

The Lagrangian

$$L = T - (U_i + U_c)$$

leads to the secular equation:

$$\sum_j \overleftrightarrow{D}_{ij} \cdot \vec{q}_j = \omega^2 \vec{q}_i \quad , \tag{2.14}$$

where the harmonic behavior $e^{-i\omega t}$ is assumed and the dynamical matrix $\overleftrightarrow{D}_{ij}$ is given by

$$\overleftrightarrow{D}_{ij} = \sum_{k\ell t} R^{-k} \frac{1}{\sqrt{m_i}} \vec{B}^{ko}_{ti} f_t \vec{B}^{o\ell}_{tj} \frac{1}{\sqrt{m_j}} R^{\ell} e^{i(k-\ell)\theta}$$
$$+ \sum_{\ell h} \frac{e_i e_h}{m_i \sqrt{\varepsilon_i \varepsilon_h}} \frac{-\overleftrightarrow{I} + 3 \vec{B}^{o\ell}_{ih} \vec{B}^{o\ell}_{ih}}{|\vec{R}^{o\ell}_{ih}|^3} \delta_{ij}$$
$$+ \sum_{\ell} \frac{e_i e_j}{\sqrt{m_i m_j \varepsilon_i \varepsilon_j}} \frac{-\overleftrightarrow{I} + 3 \vec{B}^{o\ell}_{ij} \vec{B}^{o\ell}_{ij} R^{\ell}}{|\vec{R}^{o\ell}_{ij}|^3} e^{-i\ell\theta} \quad . \tag{2.15}$$

Since potential energy is a real quantity, D_{ij} should be hermitian:

$$D_{ij} = D^{\dagger}_{ji} \quad . \tag{2.16}$$

III. Solution of Secular Equation

We are dealing with a double helical molecule with C_2 symmetry. Once we pick the 0th unit cell by convention the x-axis is chosen as the C_2 symmetry axis. Even for those double helical molecules without C_2 symmetry the backbone atoms still have C_2 symmetry and the x-axis is the same. In such a cartesian coordinate system the C_2 symmetry implies that if the equilibrium position of i^{th} atom on one strand in N^{th} unit cell is (x,y,z), then the corresponding atom on the antiparallel strand in $-N^{th}$ unit cell is at (x,-y,-z).

For the molecule $(dG\text{-}m^5dC)\cdot(dG\text{-}m^5dC)$ the number of atoms on one strand in a unit cell is 42 (without counting the Hydrogen atoms). The dynamical matrix D_{ij} in (2.14) is a 252×252 matrix. In the following we show how to use C_2 symmetry to simplify the calculation. Only the main procedures will be mentioned here. The mathematical circumstances are referred to in a later manuscript.[14]

It is convenient for C_2 symmetry discussion to rewrite the secular equation as the following:

$$\sum_j \overleftrightarrow{D}_{ij}\cdot\vec{q}_j(\theta) + \sum_\ell \overleftrightarrow{D}_{i\ell}\cdot\vec{q}_\ell(\theta) = \omega^2\vec{q}_i(\theta) \quad , \tag{3.1a}$$

$$\sum_k \overleftrightarrow{D}_{kj}\cdot\vec{q}_j(\theta) + \sum_\ell \overleftrightarrow{D}_{k\ell}\cdot\vec{q}_\ell(\theta) = \omega^2\vec{q}_k(\theta) \quad , \tag{3.1b}$$

where $i,j = 1, n$; $k = i+n$, $\ell = j+n$ and n is the number of atoms on one strand in a unit cell. For methylated Z-DNA (dG-m^{5}dC)·(dG-m^{5}dC) n = 42, for unmethylated Z-DNA (dG-dC)·(dG-dC) n = 41.

The invariance of the potential energy under a C_2 operation implies that the dynamical matrix should have the following property

$$\text{if} \quad D_{ij} = \begin{pmatrix} x & x & x \\ x & x & x \\ x & x & x \end{pmatrix} , \qquad \text{then} \quad D_{k\ell} = \begin{pmatrix} x^* & -x^* & -x^* \\ -x^* & x^* & x^* \\ -x^* & x^* & x^* \end{pmatrix} \tag{3.2a}$$

and

$$\text{if} \quad D_{i\ell} = \begin{pmatrix} x & x & x \\ x & x & x \\ x & x & x \end{pmatrix} , \qquad \text{then} \quad D_{kj} = \begin{pmatrix} x^* & -x^* & -x^* \\ -x^* & x^* & x^* \\ -x^* & x^* & x^* \end{pmatrix} \tag{3.2b}$$

At Brillouin zone center ($\theta = 0$) both $\overleftrightarrow{D}$ and $\vec{q}$ are real. Two independent types of eigenvector exist, they are either symmetric or antisymmetric under the C_2 operation. The symmetric eigenvector has the same structure as the system:

$$\text{if } \vec{q}_i = (q_{ix}, q_{iy}, q_{iz}), \quad \text{then } \vec{q}_k = (q_{ix}, -q_{iy}, -q_{iz}). \tag{3.3a}$$

And the antisymmetric eigenvector has the opposite structure:

$$\text{if } \vec{q}_i = (q_{ix}, q_{iy}, q_{iz}), \quad \text{then } \vec{q}_k = (-q_{ix}, q_{iy}, q_{iz}). \tag{3.3b}$$

That (3.3a) and (3.3b) are solutions of (3.1) can be seen by inserting (3.3) into (3.1), and confirming that (3.1a) and (3.1b) are the same equations.

Thus at $\theta = 0$ the C_2 symmetry allows us to break a (252×252) matrix into two (126×126) matrices, one for the symmetric eigenvectors

$$\sum_j \overleftrightarrow{a}_{ij} \cdot \vec{q}_j = \omega^2 \vec{q}_i \quad , \tag{3.4a}$$

And one for antisymmetric eigenvectors

$$\sum_j \overleftrightarrow{b}_{ij} \cdot \vec{q}_j = \omega^2 \vec{q}_i \quad , \tag{3.4b}$$

where

$$\overleftrightarrow{a}_{ij} = \overleftrightarrow{D}_{ij} \pm \overleftrightarrow{D}_{i\ell} \quad , \tag{3.5a}$$

and

$$\overleftrightarrow{b}_{ij} = \overleftrightarrow{D}_{ij} \mp \overleftrightarrow{D}_{i\ell} \quad . \tag{3.5b}$$

The symbol $\underline{+}$ is defined as follows

$$\overleftrightarrow{D}_{ij} \underline{+} \overleftrightarrow{D}_{i\ell} = \begin{pmatrix} D^{ij}_{xx} + D^{i\ell}_{xx} & D^{ij}_{xy} - D^{i\ell}_{xy} & D^{ij}_{xz} - D^{i\ell}_{xz} \\ D^{ij}_{yx} + D^{i\ell}_{yx} & D^{ij}_{yy} - D^{i\ell}_{yy} & D^{ij}_{yz} - D^{i\ell}_{yz} \\ D^{ij}_{zx} + D^{i\ell}_{zx} & D^{ij}_{zy} - D^{i\ell}_{zy} & D^{ij}_{zz} - D^{i\ell}_{zz} \end{pmatrix} , \quad (3.6)$$

and $\overline{+} = - \underline{+}$.

One could show that a_{ij} and b_{ij} are still symmetric matrices.

At $\theta \neq 0$ we are no longer able to separate the eigenvectors into symmetric or antisymmetric types, for if $\vec{q}$ is an eigenvector then, after multiplying by a common arbitrary phase factor $\vec{q}e^{i\phi}$ is still an eigenvector corresponding to same eigenvalue. Optionally one can show that

$$\text{if } \vec{q}_i = (q_{ix}, q_{iy}, q_{iz}), \quad \text{then } \vec{q}_k = (q^*_{ix}, -q^*_{iy}, -q^*_{iz}); \quad (3.7a)$$

or

$$\text{if } \vec{q}_i = (q_{ix}, q_{iy}, q_{iz}), \quad \text{then } \vec{q}_k = (-q^*_{ix}, q^*_{iy}, q^*_{iz}) \quad (3.7b)$$

And it is not difficult to prove that (3.7a) or (3.7b) is the solution of (3.1), but (3.7a) and (3.7b) are no longer independent. We can also choose either (3.7a) or (3.7b) as the optional solution of (3.1). C_2 symmetry allow us to transfer a hermitian matrix $\overleftrightarrow{D}$ to a real, symmetric matrix $\overleftrightarrow{G}$ and (3.1) becomes

$$\sum_j \overleftrightarrow{G}_{ij}\cdot\vec{q}\,'_j + \sum_\ell \overleftrightarrow{G}_{i\ell}\cdot\vec{q}\,'_\ell = \omega^2\vec{q}\,'_i \quad , \tag{3.8a}$$

$$\sum_k \overleftrightarrow{G}_{kj}\cdot\vec{q}\,'_j + \sum_\ell \overleftrightarrow{G}_{k\ell}\cdot\vec{q}\,'_\ell = \omega^2\vec{q}\,'_k \quad , \tag{3.8b}$$

where

$$\overleftrightarrow{G}_{ij} = \mathrm{Re}[\overleftrightarrow{D}_{ij} \pm \overleftrightarrow{D}_{i\ell}] \tag{3.9a}$$

$$\overleftrightarrow{G}_{i\ell} = -\mathrm{Im}[\overleftrightarrow{D}_{i\ell} \mp \overleftrightarrow{D}_{ij}] \tag{3.9b}$$

$$\overleftrightarrow{G}_{kj} = \mathrm{Im}[\overleftrightarrow{D}_{kj} \pm \overleftrightarrow{D}_{k\ell}] \tag{3.9c}$$

$$\overleftrightarrow{G}_{k\ell} = \mathrm{Re}\,[\overleftrightarrow{D}_{k\ell} \mp \overleftrightarrow{D}_{kj}] \tag{3.9d}$$

$$\vec{q}\,'_i = \mathrm{Re}(\vec{q}_i) \tag{3.9e}$$

$$\vec{q}\,'_k = \mathrm{Im}(\vec{q}_k) \tag{3.9f}$$

here the optional solution (3.7a) has been used.

The result of the reduction in size of the matrix allows a reduction in computing time by a factor of ten in normal mode calculations.

IV. Results and Discussion

We have taken atomic coordinates for our model of an infinite helix from the x-ray crystal structure analyses for the system $(m^5dC\text{-}dG)_3$ [5]. We have ignored the slight difference in pitch angles so as to impose helical symmetry on the system. The force constants used have been those refined in our previous models of DNA,[13] with the addition of force constants for the methyl group which were not present in the earlier models. The values for the force constants used for the methyl group are listed in Table I. These are the same as that used for the cytosine   group in our earlier models. After an initial calculation of the resulting frequencies we did a minimal refinement of our force constants so as to get a better fit to the experimentally observed Raman lines.[9] The refinement required only a one percent change in force constant values. The calculated frequencies displayed are the zero center ($\theta = 0$) modes.

To compare the theoretical modes with those observed and assigned experimentally we calculated the kinetic energy distribution (KED) of our modes. It is traditional to use potential energy distributions (PED) for assignment. It is far easier to calculate KED's and they are useful in assigning modes. The kinetic energy is associated with atom motion, not with energy stored in a bond between atoms. The total kinetic energy of the system is

$$T = -\frac{1}{2}\omega^2 \sum_i \vec{q}_i^{\,\dagger} \cdot \vec{q}_i$$

at $\theta = 0$, the kinetic energy of a group of atoms, say the guanine base is the kinetic energy per atom summed over the atoms in the guanine group i.e.

$$T_G = -\frac{1}{2}\omega^2 \sum_G \vec{q}_i^{\,\dagger} \cdot \vec{q}_i$$

Thus the percentage of kinetic energy stored in guanine atoms is T_G/T. If this percentage is high, the normal mode is assigned to guanine.

The results of this calculation and its comparison with experimental data[9] is displayed in Table II, where backbone 1 groups those backbone atoms that are covalently connected to guanine, and backbone 2, to m^5C

The overall agreement with experiment is fairly good and can of course be made much better by further refinement. The point to be made here is that good agreement can be found for problems in which new entities are added to the basic helix without starting from scratch and doing massive refinement of force constants to achieve a good fit. The helix lattice method is predictive of the frequencies of modified DNA on the basis of the theoretical calculations.

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Table I. Internal force constants for the methyl group.

Description		Force Constant	Unit
stretch γ	C5 - M	5.4	md/Å
bending α	C6 = C5 - M	0.7779	md/Å rad^2
bending α	C4 - C5 - M	1.484	md/Å rad^2
nonbonded	C6 ... M	0.8	md/Å
nonbonded	C4 ... M	0.65	md/Å

Table II

Theoretical frequency, cm^{-1}	Kinetic energy distribution %				Theoretical assignment	Experimental frequency, cm^{-1}	Experimental assignment
	backbone 1	G	backbone 2	m^5c			
498	33.1	62.7	3.6	0.6	G	497	G
521	2.8	0.8	21	75.4	m^5c	510	m^5c
539	46.9	4.2	43.20	5.9	backbone	538	
533	46.0	51.8	1.9	0.3	dG	576	G
590	25.9	67.8	1.4	4.9	G	621	dG-syn, c3' endo
596	4.9	3.7	26.9	64.5	m^5c	636	m^5c
626	0.4	0.0	3.1	96.5	m^5c	657	m^5c
671	26.3	73.6	0.1	0.0	G	682	dG-anti, c2' endo
731	3.9	3.2	17.5.	75.4	m^5c	754/751	m^5c
770	14.7	2.6	42.6	40.1	m^5c	795	backbone
778	56.3	8.7	13.2	21.8	backbone	805	A type backbone, c3' endo
824	9.4	16.7	63.9	10.0	backbone	835	B type backbone, c2' endo
1145	0.1	0.1	26.6	73.2	m^5c	1144/1141	m^5c
1165	44.0	56.0	0.0	0.0	dG	1176	G
1184	53.7	45.7	0.5	0.0	dG	1187	G
1210	0.2	0.0	48.1	51.7	m^5dc	1260	m^5c
1223	0.3	0.2	9.9	89.6	m^5c	1298	m^5c
1359	0.0	0.0	1.6	98.4	m^5c	1312	m^5c

END
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