

The A and B Conformations of DNA and RNA Subunits. Potential Energy Calculations for dGpdC

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Synopsis

In order to obtain a molecular picture of the A and B forms of a DNA subunit, potential energy calculations have been made for dGpdC with C(3')-endo and C(2')-endo [or C(3')-exo] sugar puckerings. These are compared with results for GpC. The global minima for dGpdC and GpC are almost identical. They are like A-form duplex DNA and RNA, respectively, with bases *anti*, the ω' , ω angle pair near 300° , 280° , and sugar pucker C(3')-endo. For dGpdC, a B-form helical conformer, with sugar pucker C(2')-endo and $\omega' = 257^\circ$, $\omega = 298^\circ$, is found only 0.4 kcal/mol above the global minimum. A second low-energy conformation (2.3 kcal/mol) has $\omega' = 263^\circ$, $\omega = 158^\circ$ and ψ near 180° . This has dihedral angles like the original Watson-Crick model of the double helix. In contrast, for GpC, the C(2')-endo B form is 6.9 kcal/mol above the global minimum. These theoretical results are consistent with experimental studies on DNA and RNA fibers. DNA fibers exist in both A and B forms, while RNA fibers generally assume only the A form. A low-energy conformation unlike the A or B forms was found for both dGpdC and GpC when the sugars were C(3')-endo. This conformation— ω' , ω near 20° , 80° —was not observed for C(2')-endo dGpdC. Energy surface maps in the ω' , ω plane showed that C(2')-endo dGpdC has one low-energy valley. It is in the B-form helical region ($\omega' \sim 260^\circ$, $\omega \sim 300^\circ$). When the sugar pucker is C(3')-endo, dGpdC has two low-energy regions: the A-form helical region and the region with the minimum at $\omega' = 16^\circ$, $\omega = 85^\circ$.

INTRODUCTION

The deoxyribonucleic acids have long been known to exist in either an A or a B helical conformation,¹ depending on ionic conditions and/or relative humidity.^{2,3} The RNA's on the other hand, almost always occur in the A form.⁴ Fiber diffraction studies have shown that these forms differ in the puckering of the ribose: the A-type conformations have the ribose pucker in the vicinity of C(3')-endo^{5,6} while the B-type pucker is C(2')-endo⁷ or the neighboring C(3')-exo.⁸ (For details on the puckering nomenclature, see Altona and Sundaralingam.⁹)

The ability of DNA's to assume both A and B forms is likely to be of importance *in vivo*. It has been proposed that DNA must be in the A form during transcription,¹⁰ and that the transition to this form is

primed by interaction with RNA.¹¹ Furthermore, it is possible that drugs and site-specific proteins bind only to one or the other form. To understand better the biological roles of the A and B forms, pictures of these conformations in atomic detail are needed. Crystal structures of these forms at or above the dimer level have been solved for a few molecules: UpA;^{12,13} the iodo-UpA-ethidium bromide co-crystal¹⁴ GpC;¹⁵⁻¹⁷ ApU;¹⁸ the ApU-9-amino acridine co-crystal;¹⁹ the iodo-CpG-ethidium bromide co-crystal²⁰ dTpdTp;²¹ and ApApA.²² GpC, ApU, and part of ApApA crystallized in the A-form helical conformation. Iodo-UpA in the co-crystal with ethidium bromide had the 5' ribose C(2')-endo and the 3' ribose C(3')-endo, to accommodate the drug. dTpdTp and the 3' ribose in the ApU-9-amino acridine co-crystals crystallized with C(2')-endo sugar pucker (the B-form sugar pucker) but the bases were not stacked in a helical conformation. At present, there are no reported crystal structures of the same molecule in both the A and B form. Nor do we have crystal structures for the A forms of deoxy and ribonucleic acid subunits of the same base sequence.

In order to obtain a molecular picture of the A and the B forms of DNA's, we have made potential energy calculations for dGpdC. Previous work has examined GpC.¹⁶ Additional calculations on GpC have been made in the present study for the C(2')-endo sugar pucker. The earlier calculations for GpC¹⁶ gave a lowest energy conformation like A-RNA. The second lowest energy conformation for GpC also had a C(3')-endo pucker but the ω', ω angle pair was near 20°, 80° (notation in Table I). A third low-energy region, $\omega' \sim 340^\circ$, $\omega \sim 150^\circ$, has been calculated for other ribodinucleoside phosphate base sequences.²³ The above three ω', ω regions were studied for dGpdC with the sugar pucker C(3')-endo. More extensive calculations were made for dGpdC and GpC with the C(2')-endo pucker. The conformation space available to the A and B forms of dGpdC was evaluated by constructing energy contour maps.

We find that the global minimum for dGpdC is the C(3')-endo helical conformation, with ω', ω near 300°, 280°. A C(2')-endo helical conformation, with ω', ω close to 260°, 300° is only 0.4 kcal/mol above it. In contrast, the C(2')-endo helix for GpC is 6.9 kcal/mol above the C(3')-endo GpC helical conformation. dGpdC also has another C(2')-endo low-energy conformation at 2.3 kcal/mol, which has $\omega' \sim 260^\circ$, $\omega \sim 160^\circ$ and ψ near 170°. This conformer has dihedral angles similar to those in the B-form DNA model proposed by Crick and Watson.²⁴ (Dihedral angles are presented in Ref. 12.) It is noted, however, that this original model had the sugar pucker C(3')-endo, where our dGpdC conformation is C(2')-endo.

METHODS

Figure 1 gives the structure and conformational angles for dGpdC and GpC. The angles, defined in Table I, follow Sussman et al.¹²

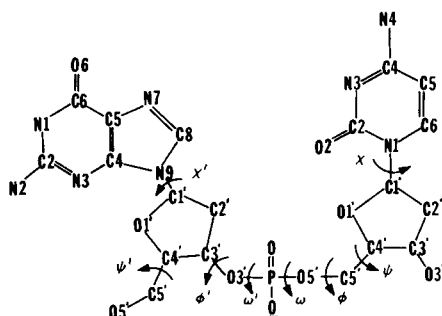


Fig. 1. Structure, numbering convention, and conformational angles for dGpdC. For GpC Substitute O2'-H for H2'.

The calculations were made in the same fashion as described earlier.^{16,25} The Scott and Scheraga equation^{26,27} [Eq. (1) below] was used to calculate the potential energy:

$$E = \sum_{i < j} \sum (a_{ij} r_{ij}^{-6} + b_{ij} r_{ij}^{-12}) + \sum_{i < j} \sum 332 q_i q_j r_{ij}^{-1} \epsilon^{-1} + \sum_{k=1}^8 \frac{V_{0,k}}{2} (1 + \cos 3\theta_k) \quad (1)$$

The double sums extend over all atom pairs whose distance varies with the dihedral angles; r_{ij} is the distance between atom pairs, q_i is the charge on atom i , a_{ij} and b_{ij} are parameters in the 6-12 potential, and ϵ is the dielectric constant. The single summation extends over all eight flexible dihedral angles, where θ_k is the k th dihedral angle, and $V_{0,k}$ is the rotational barrier height for that rotation. Values for a_{ij} , b_{ij} , q_i , $V_{0,k}$, and ϵ were taken from Refs. 28-30.

The energy was minimized with the eight dihedral angles as simultaneously variable parameters, using the Powell algorithm.³¹ Three sugar puckers were examined: C(3')-endo, corresponding to the A form of polynucleotides, and C(2')-endo and C(3')-exo, corresponding to the B form. Starting conformations for the torsional angles were χ' , $\chi = 15^\circ$

TABLE I
Definition of Dihedral Angles for dGpdC

Angle	Bonds
χ'	O1'-C1'-N9-C8
ψ'	C3'-C4'-C5'-O5'
ϕ'	P-O3'-C3'-C4'
ω'	O5'-P-O3'-C3'
ω	C5'-O5'-P-O3'
ϕ	C4'-C5'-O5'-P
ψ	C3'-C4'-C5'-O5'
χ	C6-N1-C1'-O1'

[C(3')-endo], 55° [C(2')-endo, C(3')-exo]; $\psi' = 60^\circ, 180^\circ, 300^\circ$; $\phi' = 200^\circ, \phi = 180^\circ$; $\psi = 60^\circ$; $\omega', \omega = 60^\circ, 60^\circ; 290^\circ, 180^\circ; 290^\circ, 290^\circ$.

The following additional trials were made for dGpdC and GpC, with C(2')-endo pucker: $\omega', \omega = 60^\circ, 180^\circ; 60^\circ, 290^\circ; 180^\circ, 60^\circ; 180^\circ, 300^\circ; 290^\circ, 60^\circ; \psi = 180^\circ$.

Energy contour maps were calculated for dGpdC with deoxyribose pucker either C(3')-endo or C(2')-endo. In these calculations, the other angles were fixed at values at or near the global minimum for each sugar pucker. For C(3')-endo these were $\chi' = 15^\circ$; $\psi' = 60^\circ$; $\phi' = 185^\circ$; $\phi = 190^\circ$; $\psi = 55^\circ$; $\chi = 25^\circ$. For C(2')-endo the other angles were set at $\chi' = 63^\circ$; $\psi' = 60^\circ$; $\phi = 172^\circ$; $\phi = 188^\circ$; $\psi = 50^\circ$; $\chi = 63^\circ$. Energies were evaluated at 18° intervals for ω' and ω , for a total of 400 points.

The calculations were made on the Univac 1108 computer system at the Georgia Institute of Technology. The program ORTEP written at Oak Ridge National Laboratories was kindly provided to us by Dr. Paul Mackie of the School of Physics, Georgia Institute of Technology, and was used to draw the calculated conformation.

RESULTS

Minimum Energy Conformations

A selection of minima obtained for dGpdC is given in Table II. The A-form helical DNA conformation is the global minimum. It has the ω', ω angle pair at 302°, 283°, bases *anti*, and the sugar pucker is C(3')-endo. The B-form conformation of dGpdC, with sugar pucker C(2')-endo and ω', ω at 257°, 298°, is only 0.4 kcal/mol above the global minimum. The B-form helix differs from the A helix primarily in the glycosidic torsion angles and in ω' . χ' and χ for the B helix are in a higher *anti* range than when in the A form, and ω' is 45° lower than when in

TABLE II
Selected Minimum Energy Conformations for dGpdC
Starting Conformation/Final Conformation Dihedral Angles (degrees)

χ'	ψ'	ϕ'	ω'	ω	ϕ	ψ	χ	ΔE (kcal/ mole)
<i>Sugar Pucker all C(3')-endo</i>								
15/9	60/63	200/197	290/302	290/283	180/187	60/49	25/31	0.0
15/19	60/58	200/176	60/16	60/85	180/192	60/64	25/32	1.9
15/0	180/181	200/160	290/277	180/173	180/218	60/62	25/2	8.3
<i>Sugar Pucker all C(2')-endo</i>								
55/63	60/60	200/172	180/257	290/298	180/188	60/50	55/63	0.4
55/47	180/180	200/180	290/263	180/158	180/180	180/173	55/37	2.3
55/119	180/181	200/173	290/270	180/193	180/171	60/64	55/32	8.7
55/-15	300/299	200/197	60/53	60/56	180/191	60/60	55/43	14.0
<i>Sugar Pucker all C(3')-exo</i>								
55/18	180/178	200/227	290/310	290/181	180/160	60/55	55/18	6.3
55/70	180/172	200/175	290/247	180/330	180/199	60/14	55/74	6.4
55/77	180/178	200/190	290/282	180/168	180/197	180/150	55/72	9.5
55/75	300/296	180/183	60/55	60/59	180/172	60/13	55/67	16.6

the A form. Next in energy is the C(3')-endo conformation at 1.9 kcal/mol, which has ω', ω at $16^\circ, 85^\circ$. A C(2')-endo conformer with $\psi = 173^\circ$ and ω', ω at $263^\circ, 158^\circ$ is at 2.3 kcal/mol. This is a B-form helical conformation with dihedral angles like those of the original Watson-Crick model.²⁴ Other conformations not shown in the table are above 8 kcal/mol.

Table III presents, for comparison, selected minimum energy conformations obtained for GpC. The A-form helical RNA conformation is the global minimum, and it is nearly identical to that of dGpdC. Next in energy are two C(3')-endo conformations: one at 1.7 kcal/mol with $\omega' = 16^\circ, \omega = 83^\circ$; the other at 3.6 kcal/mol with $\omega' = 337^\circ, \omega = 130^\circ$. No conformations are found at less than 5.8 kcal/mol for the C(2')-endo pucker. The B-form conformation is at 6.9 kcal/mol. Other conformations, not shown in the table, are of higher energy.

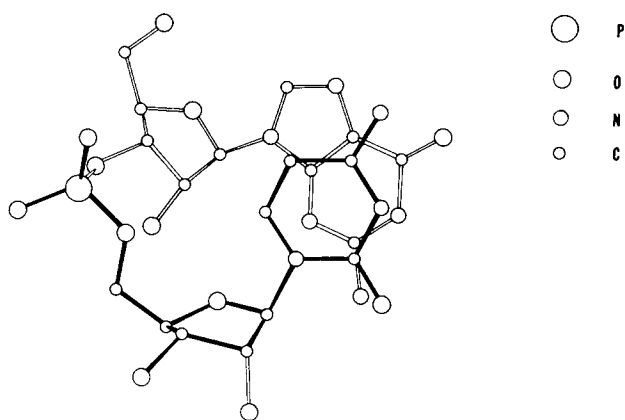
Figure 2 shows the C(3')-endo (A form) and C(2')-endo (B form) helices of GpC. It can be seen that the B-form helix is disfavored largely due to close contacts between the 2' OH of the guanosine ribose with the cytidine base. (O2' is 3.08 Å from cytidine C6.) The stacking of six-membered rings shows that the A helix has more base overlap than the B.

The lowest energy conformations of the A and B forms of dGpdC are shown in Figure 3. The similarity between A-dGpdC (Figure 3a) and A-GpC (Figure 2a) is apparent. Comparing B-dGpdC (Figure 3b) with B-GpC (Figure 2b), one can readily see that the steric hindrance is relieved when the 2' OH is replaced by H at the guanosine ribose. This makes the low-energy B conformation possible for dGpdC. Figure 3c shows the C(2')-endo helix with ω', ω at $263^\circ, 158^\circ$ and $\psi = 173^\circ$. It is striking how the overall appearance of this conformation resembles Figure 3b.

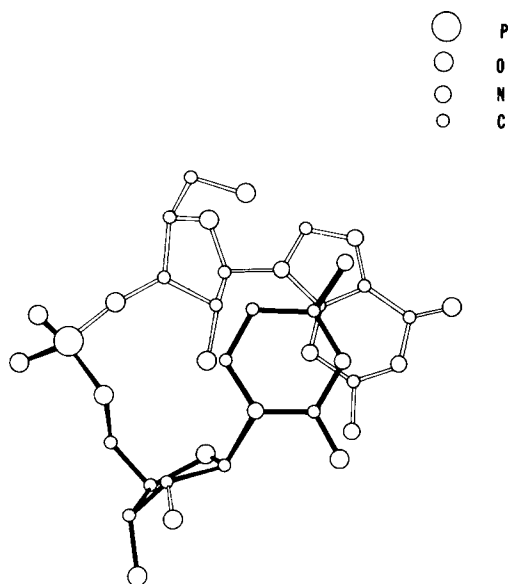
TABLE III^a
Selected Minimum Energy Conformations for GpC
Starting Conformation/Final Conformation Dihedral Angles (degrees)

χ'	ψ'	ϕ'	ω'	ω	ϕ	ψ	χ	ΔE (kcal/mol)
<i>Sugar Pucker all C(3')-endo</i>								
15/5	60/63	200/203	290/298	290/279	180/182	60/57	25/27	0.0
15/11	60/61	200/181	60/16	60/83	180/192	60/62	25/39	1.7
15/29	180/180	200/198	290/337	180/130	180/189	60/59	25/27	3.6
<i>Sugar Pucker all C(2')-endo</i>								
55/43	180/179	200/197	290/253	180/152	180/177	180/171	55/55	5.8
55/149	60/60	200/277	60/78	290/247	180/170	60/60	55/68	6.6
55/-32	60/57	200/227	290/297	290/269	180/179	60/59	55/68	6.9
55/25	60/56	200/218	60/44	60/58	180/188	60/60	55/43	14.9

^a There are small differences for the minimum energy conformations of GpC C(3')-endo in the present paper and Ref. 16. These are due to changes in the fixed orientations of H(O5') and H(O3'), which produced a lower energy global minimum. The C(2')-endo conformations reported in Ref. 16 are incorrect due to an error in generation of this ribose pucker.



(a)



(b)

Fig. 2. A- and B-form helical conformations for GpC. (a) C(3')-endo global minimum: $\chi' = 5^\circ$, $\psi' = 63^\circ$, $\phi' = 203^\circ$, $\omega' = 298^\circ$, $\omega = 278^\circ$, $\phi = 183^\circ$, $\psi = 56^\circ$, $\chi = 27^\circ$. (b) C(2')-endo: $\chi' = -32^\circ$, $\psi' = 57^\circ$, $\phi' = 227^\circ$, $\omega' = 297^\circ$, $\omega = 269^\circ$, $\phi = 179^\circ$, $\psi = 59^\circ$, $\chi = 68^\circ$.

The C(3')-exo conformation is neighboring to C(2')-endo in the pseudorotation description of ribose puckerings.⁹ It is the sugar pucker of B-DNA fibers according to the recent model of Arnott and Hukins.⁸ However, for dGpdC, our calculations show C(3')-exo has a higher energy than C(2')-endo (Table II). Figure 3 indicates more stacking for the C(3')-endo helix than for C(2')-endo, with virtually none for C(3')-exo.

It is interesting that no low-energy minima other than B-type helices are obtained for C(2')-endo or C(3')-exo pucker. The one B-type minimum resulted from trials with ω', ω at $60^\circ, 290^\circ$ and $180^\circ, 290^\circ$ as well as from $290^\circ, 290^\circ$.

Values of χ' and χ in the 60° – 80° range have been noted for B-DNA fibers.⁸ This range is also observed for the B-type conformations of

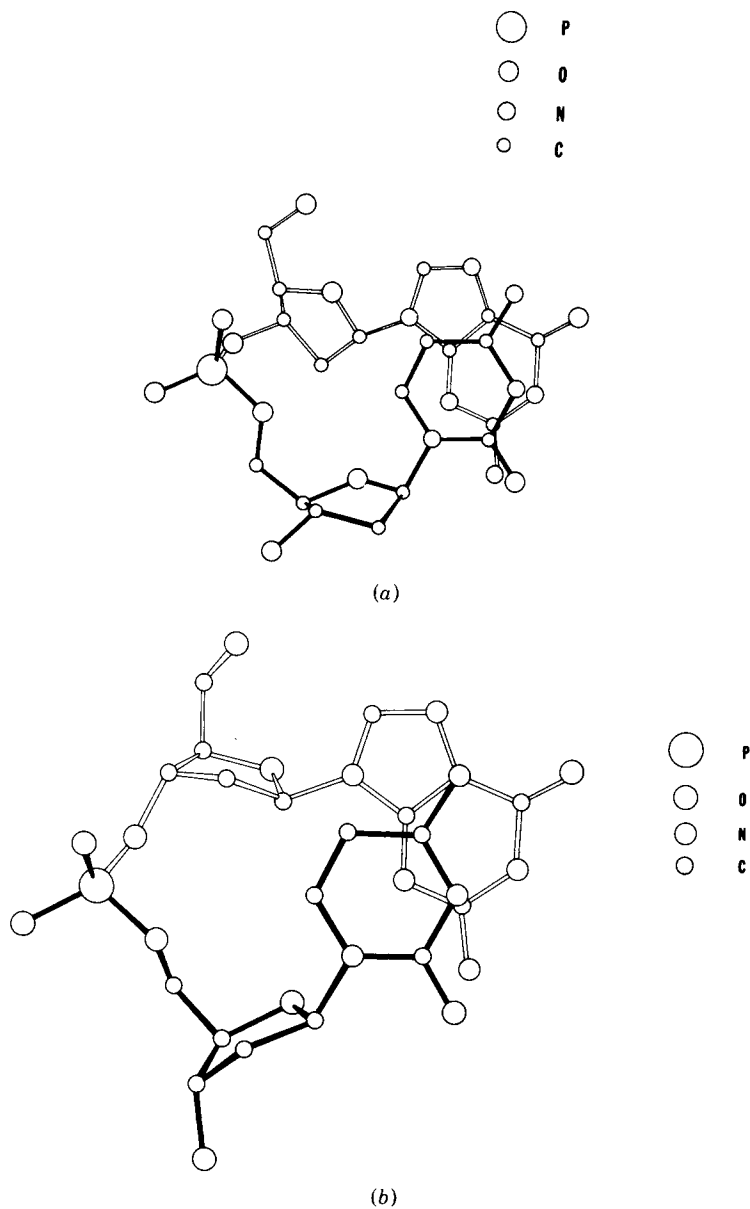


Fig. 3 (continued)

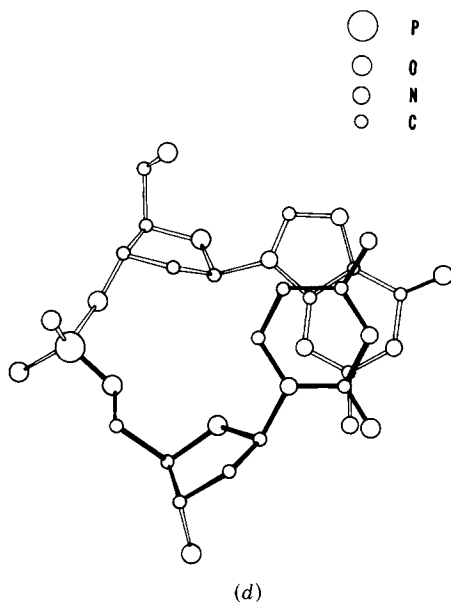
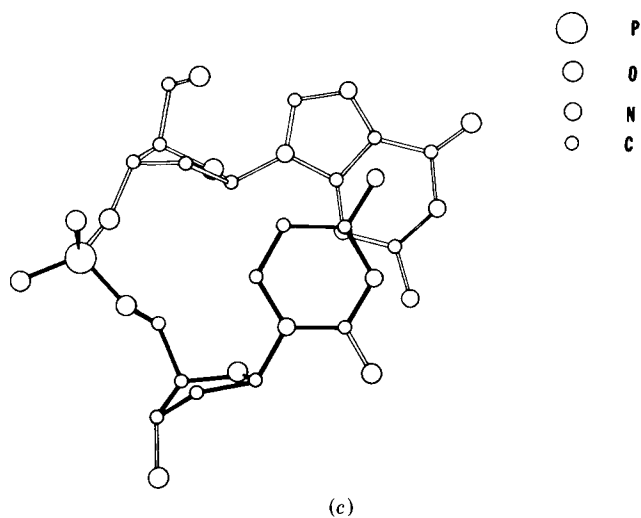


Fig. 3. A- and B-form helical conformations for dGpdC. (a) C(3')-endo global minimum: $\chi' = 9^\circ$, $\psi' = 63^\circ$, $\phi' = 197^\circ$, $\omega' = 302^\circ$, $\omega = 283^\circ$, $\phi = 187^\circ$, $\psi = 49^\circ$, $\chi = 31^\circ$. (b) C(2')-endo: $\chi' = 63^\circ$, $\psi' = 60^\circ$, $\phi' = 172^\circ$, $\omega' = 257^\circ$, $\omega = 297^\circ$, $\phi = 189^\circ$, $\psi = 50^\circ$, $\chi = 62^\circ$. (c) C(2')-endo: $\chi' = 47^\circ$, $\psi' = 180^\circ$, $\phi' = 180^\circ$, $\omega' = 263^\circ$, $\omega = 158^\circ$, $\phi = 180^\circ$, $\psi = 173^\circ$, $\chi = 37^\circ$. (d) C(3')-exo: $\chi' = 70^\circ$, $\psi' = 172^\circ$, $\phi' = 175^\circ$, $\omega' = 247^\circ$, $\omega = 330^\circ$, $\phi = 199^\circ$, $\psi = 14^\circ$, $\chi = 74^\circ$.

Table II. However, the other C(2')-endo or C(3')-exo conformations exhibit a variety of values for these angles.

We have also explored the conformational regions preferred by ψ' . We find that they depend on the ω', ω region and on the sugar pucker.

For the conformations with ω' and $\omega \sim 300^\circ$, the $\psi \sim 60^\circ$ region is of lowest energy when the sugar is either C(3')-endo or C(2')-endo, but not C(3')-exo. Differences in energy for the ψ' regions are often only a few tenths of kilocalories per mole, although occasionally 1–2 kcal/mol separate the regions. In many cases the other dihedral angles are hardly affected. Tables II and III show only the lowest energy conformations for ψ' .

ENERGY CONTOUR MAPS FOR $\omega'\omega$

Figures 4 and 5 show energy contour maps for dGpdC with the sugar pucker C(3')-endo and C(2')-endo, respectively. It is evident that the C(3')-endo A-type conformation ($\omega' \sim 280^\circ$, $\omega \sim 300^\circ$) occupies a larger region than the C(2')-endo B-type conformation. Figure 4 also shows a second low-energy region ($\omega' \sim 35^\circ$, $\omega \sim 80^\circ$) for C(3')-endo dGpdC. This region is not observed in the C(2')-endo energy map of dGpdC. Because all conformational angles are not permitted to vary in this calculation, the relative energies of the regions differ from those obtained in the eight-angle minimization. This accounts for the 0° – 70° region

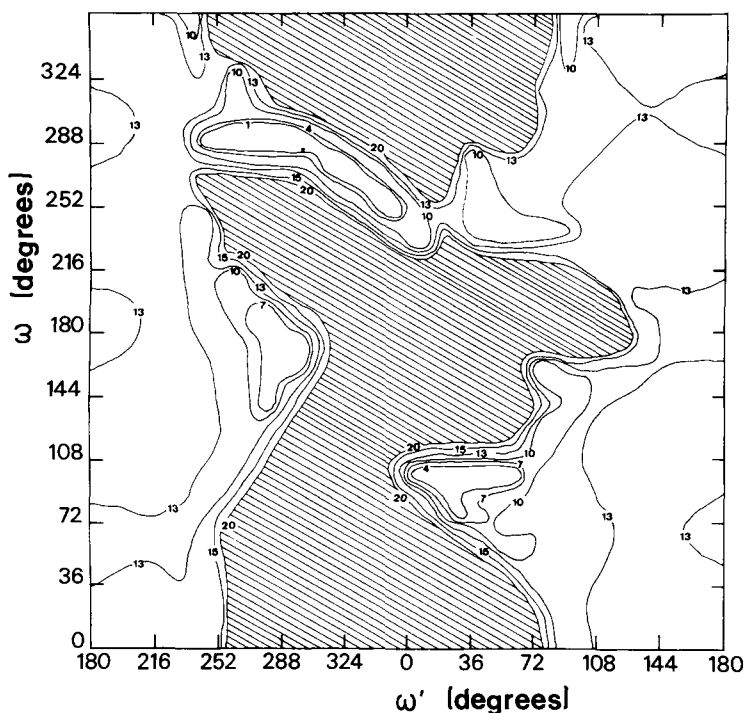


Fig. 4. Energy contour map for dGpdC, sugar pucker C(3')-endo, for the conformational angles ω' and ω . The global minimum is denoted by X. Shaded areas indicate $\Delta E \geq 20$ kcal/mol. The remaining angles were fixed at $\chi' = 15^\circ$, $\psi' = 60^\circ$, $\phi' = 185^\circ$, $\phi = 190^\circ$, $\psi = 55^\circ$, $\chi = 25^\circ$.

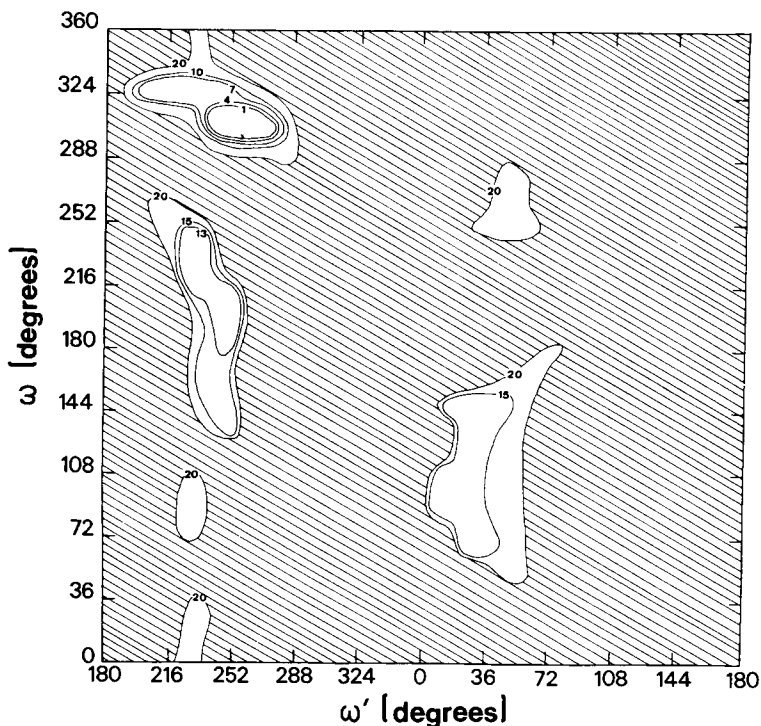


Fig. 5. Energy contour map for dGpdC, sugar pucker $C(2')$ -endo, for the conformational angles ω' and ω . The global minimum is denoted by X. Shaded areas indicate $\Delta E \geq 20$ kcal/mol. The remaining angles were fixed at $\chi' = 63^\circ$, $\psi' = 60^\circ$, $\phi' = 172^\circ$, $\phi = 189^\circ$, $\psi = 50^\circ$, $\chi = 62^\circ$.

having a minimum energy contour of 4 kcal/mol in Figure 4, while minor adjustments in the other angles bring this energy down to 1.9 kcal/mol (Table II). The other conformations shown in Table II for $C(2')$ -endo pucker, between 9 and 14 kcal/mol, are at or above 15 kcal/mol in the maps for the same reason. Nevertheless, these contour maps are the only means available to us for examining the size and shape of conformation space. Calculation of such maps with energy minimization would be more accurate, but it is at present prohibitive in terms of computer time.

DISCUSSION

Relative Stability of A and B Forms of dGpdC

Our results show that the A and B forms of dGpdC are almost equally stable, the A form being only 0.4 kcal/mol lower in energy. This contrasts with the 6.9-kcal/mol difference between the A and B forms of GpC. These results are consistent with the observation that DNA fibers exist in both A and B forms while RNA fibers generally assume

only the A form. The slightly greater stability of the A form of dGpdC is probably due to favorable electrostatic interactions, which produce the increased overlap of bases in the A form.

We also find a B-form low-energy conformation of dGpdC, which is like the original Watson-Crick model, with ω', ω near 260° , 160° and ψ near 170° . It is interesting that conformations with ω', ω in this general range, but with ψ near 60° ,³² produce structures with tilted bases and sugar oxygens pointing away from one another. However, when ψ is in the 180° region a stacked conformation results, which is very similar in appearance to the helical conformations with ω', ω in the vicinity of 300° and ψ near 60° . The simultaneous changes in ω and in ψ compensate for one another. A possible inference from these calculations is that these B-type helices may have some importance.

Flexibility of A and B Forms of dGpdC

A second interesting finding is the absence of any low-energy (0–2 kcal/mol) conformation with ψ near 60° for dGpdC when the sugar pucker is C(2')-endo, while such a conformation is observed when the sugar pucker is C(3')-endo. The B helix also appears to occupy a smaller area in conformation space than the A helix. Thus, the B-type dGpdC helix appears to be less susceptible to unwinding than the A-type dGpdC helix. An examination of the base sequence dependence of this effect needs to be made, however, since dTpdTp crystallizes as a nonhelical structure with the sugar pucker C(2')-endo.²¹ Our calculations²³ have shown a base dependence of the minimum energy conformation of RNA subunits. Thus, the importance of including the bases in calculations of conformation needs to be emphasized. Potential energy calculations, both classical^{33,34} and quantum mechanical,³⁵ have been successful in delineating all the conformational regions accessible to polynucleotides, but it has been difficult to assess accurately their relative importance.^{36,37} When the bases are included and the energy is minimized with respect to the dihedral angles, the helical A-form conformation becomes the global minimum for certain sequences with no additional considerations needed.

Comparison of Calculated Conformations With Conformations in Crystals and Fibers

Table IV presents a comparison of calculated and observed conformations for A- and B-type helical nucleic acids. Comparisons are made of the theoretical dihedral angles for a given sugar pucker with experimental values of comparable nucleic acid helices. The A-form dGpdC conformation agrees very well with that of A-DNA.⁶ The close agreement between predicted GpC conformation and that observed in crystals of GpC and A-RNA fibers has been previously discussed.^{16,25} Further-

TABLE IV
Comparison of Calculated and Observed Conformations for A- and B-Form
Helical Nucleic Acids Dihedral Angles (degrees)

Molecule	Ref.	χ'	ψ'	ϕ'	ω'	ω	φ	ψ	χ
<i>Sugar Pucker all C(3')-endo</i>									
dGpdC(calc)	This work	9	63	197	302	283	187	49	31
A-DNA	6	^a	—	178	313	275	208	45	23
<i>Sugar Pucker all C(3')-exo</i>									
GpC(calc)	This work	5	60	203	298	279	182	57	37
GpC	17	1-8	53-56	216-224	288-294	283-293	167-181	47-63	21-33
GpC	15	13	—	209	291	284	186	51	25
A-RNA	5	^a	—	181	308	272	205	54	23
A'-RNA	5	^a	—	209	286	298	180	48	12
<i>Sugar Pucker all C(2')-endo</i>									
dGpdC(calc)	This work	63	60	172	257	298	188	50	63
B-DNA	8	^a	—	194	224	335	160	27	76
poly(I)	40	^a	—	185	244	290	190	51	64
<i>Sugar Pucker all C(3')-exo</i>									
dGpdC(calc)	This work	70	172	175	247	330	199	14	74
B-DNA	8	^a	—	155	264	314	213	36	80

^a Same as χ .

more, A-form GpC and dGpdC are almost identical, which is consistent with the proposed structure of DNA-RNA hybrids. These are believed to be isostructural with the RNA double-stranded A' form.^{5,38,39}

The C(3')-exo helical minimum for dGpdC is quite similar to the recent C(3')-exo B-DNA model,⁸ but it is less stable than C(2')-endo by 6 kcal/mol. The only recently described B-family nucleic acid with C(2')-endo sugar pucker is poly(I).⁴⁰ (Although all other RNA structures are of the A-type, poly(I) appears to be of the B form.) Our calculated C(2')-endo B conformation for dGpdC is very similar to poly(I) and less like the earlier C(2')-endo model of B-DNA.⁷

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