
The influence of terminal 3', 5' phosphates on conformations of dApdA*

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ABSTRACT

Addition of 3' and 5' terminal phosphates to dApdA causes a decrease in conformational flexibility. pdApdAp has much fewer conformers with energies below 2.5 kcal./mole than dApdA. The A, B and Watson-Crick (34) helices are the most preferred forms. Other important conformations are in the trans domain of ψ . Thus, flexibility in ψ as well as in ω' and ω , and in the sugar pucker is indicated. The transformation from the B helix to the Watson-Crick helix follows a low energy path. This is significant since Watson-Crick conformations may be important for intercalation into nucleic acid polymers (40-42) above the dimer level. The B helix is preferred over the A form in these larger DNA subunits.

INTRODUCTION

The conformations of deoxy- and ribodinucleoside monophosphates have been under investigation for some years because these are the smallest subunits of DNA and RNA that possess all the conformational degrees of freedom of the larger polymer. Theoretical studies have revealed the conformational domains accessible to the backbones of these molecules (1-4) and some studies have investigated the influence of the bases on conformation (5-10). The conformations of 3',5' mononucleotide diphosphates were extensively investigated by Olson and Flory (12-13). Extension of the dinucleoside monophosphate molecules by addition of 3', and 5' terminal phosphates has been investigated in absence of the bases for DNAs (14) and RNAs (4,15), while bases were included in studies of the ribodinucleotide triphosphates pApAp (16), poly (8,2'-5-cycloadenylic acid) (16) and poly 8-bromoadenylic acid (17). In the present work we investigate the conformational influence of 3',5' phosphorylation on the deoxydinucleoside monophosphate conformations calculated previously (10-18), employing dApdA as a representative example. As in earlier work (10), our calculations minimize the potential energy as a function of conformation, with the in-chain torsion angles and the deoxyribose pucker as flexible parameters.

METHODS

Figure 1 shows the structure of pdApdAp and the torsion angle definitions for the variable parameters. The potential energy calculations were carried out as detailed previously (10), including Van der Waals, E_{nb} , electrostatic, E_{el} , torsional, E_{tor} , and deoxyribose strain, E_{st} , contributions to the energy, E .

$$E = E_{nb} + E_{el} + E_{tor} + E_{st} \quad (1)$$

$$E_{nb} = \sum_{i < j} (a_{ij} r_{ij}^{-6} + b_{ij} r_{ij}^{-12}) \quad (2)$$

$$E_{el} = \sum_{i < j} 332 q_i q_j r_{ij}^{-1} e^{-1} \quad (3)$$

$$E_{tor} = \sum_{k=1}^8 \frac{V_{0,k}}{2} (1 + \cos 3\theta_k) \quad (4)$$

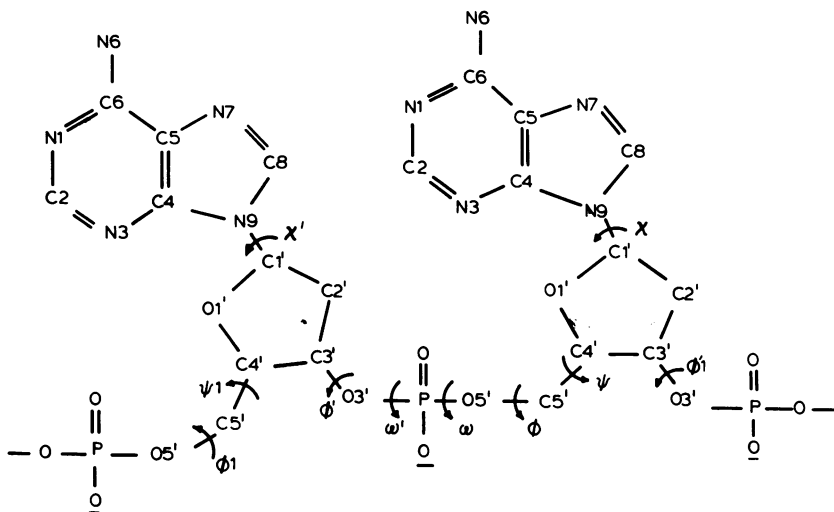


Figure 1

Structure, numbering scheme and variable conformational angle designations for pdApdAp. The dihedral angles A-B-C-D are defined as follows:

- χ, χ' : O1'-C1'-N9-C8;
- ψ, ψ' : C3'-C4'-C5'-O5';
- ϕ, ϕ' : P-O3'-C3'-C4';
- ϕ, ϕ' : C4'-C5'-O5'-P;
- ω, ω' : O5'-P-O3'-C3';
- ω, ω' : C5'-O5'-P-O3';

The angle A-B-C-D is measured by a clockwise rotation of D with respect to A, looking down the B-C bond. A eclipsing D is 0°. Sugar pucker is described by the pseudorotation parameter, P (44).

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$$E_{st} = \sum_{\ell=1}^5 K_{\tau_{\ell}} (\tau_{\ell} - \tau_{o,\ell})^2 \quad (5)$$

r_{ij} is the distance in angstroms between atoms i and j , q_i is the partial charge assigned to atom i , ϵ is the dielectric constant, $V_{o,k}$ is the barrier to internal rotation for the k th dihedral angle and θ_k is the value of that angle, $K_{\tau_{\ell}}$ is a force constant, τ_{ℓ} is the (strained) deoxyribose bond angle, and $\tau_{o,\ell}$ is the value that angle adopts at equilibrium. Also, k denotes the eight independent dihedral angles and ℓ , the five deoxyribose bond angles. Partial charges for the terminal phosphates, as for the rest of the molecule, were taken from Renugopalakrishnan, et al. (19). The dielectric constant was assigned a value of 4 and the torsional barriers were taken from Lakshminarayanan and Sasisekharan (20). Parameters in equation (5), originally obtained by Dr. T. Sato, are given in reference 10. In the first set of runs the parameters a_{ij} and b_{ij} were those employed previously (10), calculated from reference 20. However, we found that the 2 additional negatively charged phosphates caused some low energy conformers to be calculated which had close contacts due to overwhelming coulombic interactions. This problem is obviously much more serious in the dinucleoside triphosphates than in dinucleoside monophosphates. Therefore, following Olson (21), we also minimized the energy such that the closest approach between two atoms exceeds the sum of the Van der Waals radii. In our case 0.3 Å was added to each Van der Waals distance of reference 20; these were then used to calculate another set of a 's and b 's in equation (2). The new parameters produced mean perpendicular distances between adjacent base planes in our stacked helical conformers of pdApdAp (A, B and Watson-Crick types) of 3.31 to 3.62 Å; the unaltered Van der Waals radii yielded distances of 3.07 to 3.26 Å.

The calculated dihedral angles of deoxydinucleoside monophosphates are generally satisfactory for minimizations at the sum of the Van der Waals radii (10). Evidence for this is the good agreement between calculated helix geometries of single strand A and B forms and experiment. Minimizing at the Van der Waals distance, we previously obtained theoretical single-stranded A and B forms with 4-9 nucleotides per turn, depending on base sequence, for ribo- and deoxydinucleoside monophosphates (22,23). This agrees with fiber diffraction studies on single-stranded poly rC which has 6 nucleotides per turn (24) and poly 2'OMe-C which has 6 or 7 nucleotides per turn (25) depending on environmental conditions. We also calculate, for the alternating A and B form helical portions in the crystal of dApdTpdApdT (26,27) (the dApdT segments with

ω' , $\omega = g^-, g^-$) only six nucleotides per turn. [The methods previously used (22) were amended for this calculation. The building block for generating the larger polymer is composed of two residues, one A type and the adjacent B type. We then have 3 building blocks per turn or 6 nucleotides. This 6-fold single strand is necessarily different from the 9-fold double-stranded model (26,27) due to the required geometrical factors in double helix formation (22)]. However, for pdApdAp some calculated dihedral angles are less satisfactory. Using normal parameters, Van der Waals radii may be violated, as mentioned above. With 0.3 Å added to the Van der Waals radii, the calculated A form is 13-fold while the A form of dApdA, obtained with the unaltered parameters, is 6-fold. (B forms of the two molecules have similar calculated helix geometries.) The A form, whose phosphates are about 1 Å closer than the B form, is more affected by coulombic forces. Helix geometries are extremely sensitive to small changes in dihedral angles (22,23). Thus, neither set of parameters produces entirely satisfactory dihedral angles for pdApdAp. It is probably necessary to incorporate the neutralizing counter ion near the ionized phosphates to avoid this problem. The calculated conformational regions and their associated energies are, however, reasonable.

Bond lengths and bond angles assigned to the appended phosphates are the same as for the in chain phosphates (10,31). The dihedral angles C4'-C5'-O5'-P, ϕ_1 , and P-O3'-C3'-C4', ϕ'_1 , of the added phosphates were varied in tandem with their in chain counterparts ϕ and ϕ' . The terminal C5'-O5'-P-O and C3'-O3'-P-O were fixed in the staggered conformation. Since charges on the terminal phosphates are not identical (19) this is an approximation, employed to keep the number of variables tractable.

The modified Powell algorithm (32) was used for the minimizations. The convergence criterion required that successive iterations produced no change greater than 0.1 degree in all 9 parameters. At times 50 or more iterations may be required to meet this criterion. It is hazardous to cut off the minimizations earlier, as the routine can slowly work its way out of a valley to find a lower minimum. As starting parameters, we employed all the low energy conformers previously obtained for dApdA (10,18). This is reasonable in view of the recent NMR findings on dTpdTpdT and dTpdTp dC (33) that deoxydinucleoside phosphates essentially conserve their intrinsic conformational features when incorporated into oligomers. Some trials were also made from the conventional staggered starting positions. These tended to yield higher energy forms, a reflection of the diminished flexibility of the 3',5' triphosphates.

RESULTS AND DISCUSSION

Low energy forms. Tables I and II present a summary of low energy conformations of pdApdAp. The energies of the analogous dApdA conformers (10,18) are also given, for comparison. Results are shown for two sets of the parameters a and b of equation (2). For $\Delta E(1)$ the Van der Waals distances of reference 20 were employed, while for $\Delta E(2)$ these were increased by 0.3 Å. The C-3'-endo g^+,t conformer of pdApdAp whose $\Delta E(1)$ was 0 has close contacts which warrant its elimination as the calculated lowest energy conformation. It was no longer the lowest energy form in $\Delta E(2)$. This aside, we observe that both sets of parameters yield the following most important conformers: in the C-3'-endo domain with $\psi = g^+$, the A helix, and with $\psi = \text{trans}$ the Watson-Crick helix (34) ($\omega', \omega = g^-,t$) and an $\omega', \omega = g^+,g^+$ conformation. In the C-2'-endo domain with $\psi = g^+$ the B helix, and with $\psi = \text{trans}$ the Watson-Crick type helix and a conformer with $\omega', \omega = t,g^+$ (skewed). Other low energy dApdA conformers are at or above 2.5 kcal./mole. Earlier studies of the polynucleotide backbone by Olson (35) and by Yathindra and Sundaralingam (1,2) have noted that the $\omega', \omega = g^+,g^+$ and g^+,t conformers, with $\psi = g^+$ and C-3'-endo pucker, are disfavored in the larger polymers. We observe that the dApdA low energy forms, except for those cited above, are all less favored in the larger pdApdAp. The g^+,t conformer (C-3'-endo, $\psi = g^+$) was not highly preferred in dApdA, and it remains about the same [$\Delta E(2) = 3.0$] in pdApdAp. These results imply a generally diminished conformational flexibility in the 3',5' triphosphates. It is worth mentioning, however, that even a 5 kcal./mole energy barrier is not an overwhelming obstacle when intermolecular interactions are present. This is evidenced in the recent crystal structure of ApA-proflavine (36), wherein the ApA adopts conformations that are less preferred in the isolated molecule.

Flexibility in ψ : Watson-Crick, g^+,g^+ and t,g^+ (skewed) ω',ω conformers with $\psi = \text{trans}$. Previous theoretical work has emphasized that the primary source of flexibility in polynucleotides is in ω' and ω (37-39). In addition it is apparent from these low energy forms that there is also flexibility in ψ . This was found earlier for deoxydonucleoside monophosphates. The added phosphates appear to enhance the importance of the trans domain of ψ .

The Watson-Crick conformations with $\omega', \omega = g^-,t$, $\psi = \text{trans}$ are particularly favored. Although these conformers have not been observed at this writing, theoretical considerations indicate that they may occur when larger DNA or RNA polymers are intercalated by planar aromatic molecules, either at the intercalation site (40,41) or adjacent to it (42). In view of this, we

TABLE I
Comparison of dApdA and pdApdAp Minimum Energy Conformations
C(3')-endo - C(2')-exo Region

ω^-, ω	ΔE dApdA	ΔE (1) pdApdAp	ΔE (2) pdApdAp
		$\psi \sim 60^\circ$	
g^-, t	0.	3.1	5.6
g^-, g^- (A)	0.2	1.6	0.7
g^+, g^+	0.5	5.9	4.4
t, g^-	1.3	3.5	5.9
g^+, t	3.1	a	3.0
		$\psi \sim 180^\circ$	
t, g^+	1.7	6.1	3.8
g^-, t (W-C)	2.7	0.7	0.
g^+, g^+	3.4	0.	1.7
		$\psi \sim 300^\circ$	
g^+, t	1.6	8.5	14.7
g^-, g^-	4.6	b	19.7
g^-, g^+	4.6	15.9	b

a = minimum has steric close contacts
b = no local minimum found

Energies, in kcal./mole, are relative to the lowest energy form in this puckering domain.

TABLE II
Comparison of dApdA and pdApdAp Minimum Energy Conformations
C(2')-endo - C(3')-exo Region

ω^-, ω	ΔE dApdA	ΔE (1) pdApdAp	ΔE (2) pdApdAp
		$\psi \sim 60^\circ$	
g^-, g^- (B)	0.	0.	2.1
g^+, t	0.7	3.7	4.9
g^-, t	2.3	6.0	6.4
t, g^-	a	5.1	7.2
		$\psi \sim 180^\circ$	
t, g^+	0.4	0.9	2.4
g^-, t (W-C)	0.8	1.1	0.
		$\psi \sim 300^\circ$	
g^-, g^-	1.3	2.5	6.1
t, g^+	3.3	7.1	13.8

a = no local minimum found

Energies, in kcal./mole, are relative to the lowest energy form in this puckering domain.

have investigated the energetics of the transition from the B form to the C-2'-endo Watson-Crick conformer. Figure 2 shows an energy contour map in the ω, ψ plane. The interesting feature of this map is the diagonal low energy strip within the 8 kcal/mole contour connecting the B form with the Watson-Crick form. A low energy path from the B form is indicated; it involves a tandem decrease in ω with an increase in ψ . The two opposite rotations compensate for one another to produce conformers that are very much alike in overall appearance. Model building shows that the Watson-Crick helix can be incorporated in the B helix with little strain or change in helix direction.

The added flexibility in ψ is also evidenced by the accessibility of the $\omega', \omega = g^+, g^+$, C-3'-endo conformation when ψ is trans. This domain is of

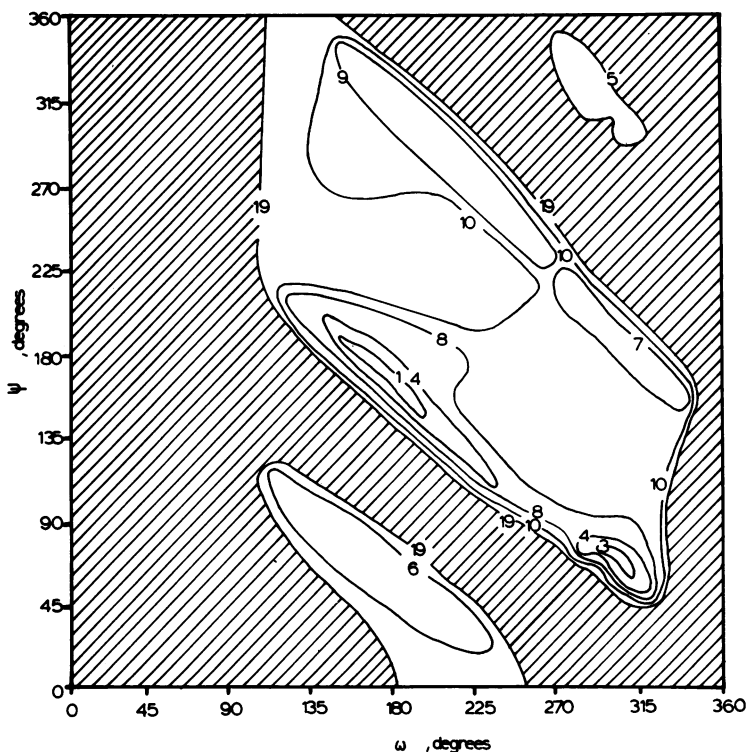


Figure 2

Energy contour map in the ω, ψ plane for pdApdAp. Other torsion angles fixed at $\chi' = 55^\circ$, $\psi_1 = 60^\circ$, ϕ' , $\phi'_1 = 193^\circ$, $\omega' = 250^\circ$, $\phi, \phi_1 = 176^\circ$, $\chi = 65^\circ$, $P = 172^\circ$.

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diminished importance in the 3',5' triphosphate with $\psi = g^+$. The close approach of the terminal phosphates, which causes the $\omega', \omega = g^+, g^+$, $\psi = g^+$ conformation to be disfavored, is alleviated by rotating ψ to the trans region. In fact, stabilizing interactions between the 5' linked base and 5' terminal phosphate seem to be in effect.

The $\omega', \omega = t, g^+$ (skewed) $\psi = \text{trans}$, C-2'-endo low energy conformer of dApdA also remains favorable in the 3',5' diphosphate. Because of its extension, this conformation may play a role in the coil form of poly (dA) (18).

The g^- region of ψ is, however, further disfavored in the 3',5' triphosphate as compared to dApdA itself.

Base stacking. Figure 3 shows ORTEP (43) drawings of the most favored conformers of pdApdAp. The proclivity of the low energy forms to have bases stacked and near planar is apparent. This was previously observed for the dApdA preferred conformers (10,18).

A and B forms. dApdA had an in vacuo calculated preference for the A over the B helix by $\Delta E(1)_{B-A} = 2.1$ kcal./mole (10). For pdApdAp on the other hand, the B form is preferred over the A by an absolute energy difference $\Delta E(1)_{B-A} = -2.9$ kcal./mole. With the parameters yielding $\Delta E(2)$ (see Methods Section) the B form is slightly preferred by $\Delta E(2)_{B-A} = -0.2$ kcal./mole. Clearly, the added phosphates cause an increase in the population of the C-2'-endo puckering domain, although specific interactions with water and salt, not included in our calculations, may further stabilize the C-2'-endo region in these media. NMR studies have previously revealed an increased preference for C-2'-endo pucker in solution as deoxynucleotides are incorporated in larger subunits (44).

Energy contour maps. Energy contour maps in the ω', ω plane for the A, B and Watson-Crick helices are shown in Figures 4 and 5. As mentioned in earlier work (10) the shape of conformation space in the maps is very dependent on the exact choice of the torsion angles that are not varied in the map calculation. (This problem is evidently less severe in calculations where the bases are absent, as these moieties do impose steric restrictions on the backbone.) However, a very approximate view of ω', ω space in the $\psi = g^+$ and $\psi = \text{trans}$ domains is afforded. A significant difference between these maps and those for dApdA is the diminished area within the 1 kcal./mole contour, pointing again to the diminished flexibility of these conformers in the 3',5' triphosphates.

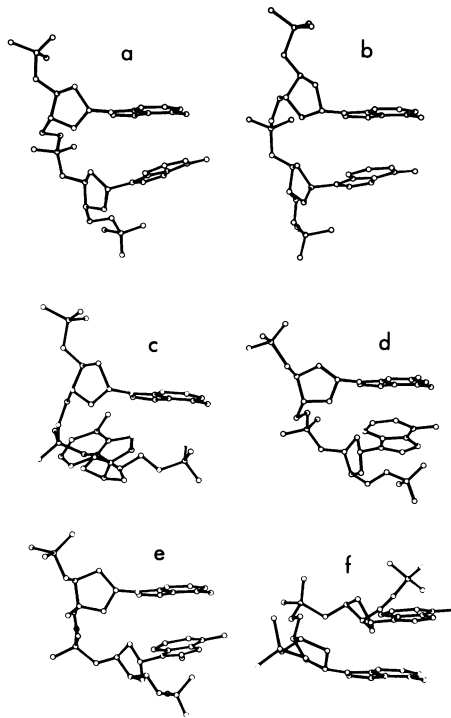


Figure 3

Low energy conformers of pdApdAp. Dihedral angles obtained from minimizations at the Van der Waals distance + 0.3 Å.

C-3'-endo region:

- (a) A helix: $\chi' = 48^\circ$, $\psi_1 = 66^\circ$, $\phi', \phi'1 = 190^\circ$, $\omega' = 290^\circ$, $\omega = 284^\circ$,
 $\phi, \phi1 = 172^\circ$, $\psi = 63^\circ$, $\chi = 48^\circ$, $\rho = 18^\circ$.
- (b) Watson-Crick helix: $\chi' = 28^\circ$, $\psi_1 = 175^\circ$, $\phi', \phi'1 = 189^\circ$, $\omega' = 287^\circ$,
 $\omega = 158^\circ$, $\phi, \phi1 = 196^\circ$, $\psi = 166^\circ$, $\chi = 14^\circ$, $\rho = 3^\circ$.
- (c) $\omega', \omega = g^+, g^+$; $\psi = t$: $\chi' = 5^\circ$, $\psi_1 = 183^\circ$, $\phi', \phi'1 = 174^\circ$, $\omega' = 24^\circ$,
 $\omega = 88^\circ$, $\phi, \phi1 = 197^\circ$, $\psi = 177^\circ$, $\chi = 41^\circ$, $\rho = 0^\circ$.

C-2'-endo region:

- (d) B helix: $\chi' = 48^\circ$, $\psi_1 = 60^\circ$, $\phi', \phi'1 = 194^\circ$, $\omega' = 265^\circ$, $\omega = 296^\circ$,
 $\phi, \phi1 = 168^\circ$, $\psi = 62^\circ$, $\chi = 82^\circ$, $\rho = 160^\circ$.
- (e) Watson-Crick helix: $\chi' = 45^\circ$, $\psi_1 = 175^\circ$, $\phi', \phi'1 = 192^\circ$, $\omega' = 266^\circ$,
 $\omega = 139^\circ$, $\phi, \phi1 = 182^\circ$, $\psi = 181^\circ$, $\chi = 60^\circ$, $\rho = 179^\circ$.
- (f) $\omega', \omega = t, g^+$ (skewed), $\psi = t$: $\chi' = 19^\circ$, $\psi_1 = 61^\circ$, $\phi', \phi'1 = 195^\circ$,
 $\omega' = 224^\circ$, $\omega = 82^\circ$, $\phi, \phi1 = 195^\circ$, $\psi = 182^\circ$, $\chi = 23^\circ$, $\rho = 183^\circ$.

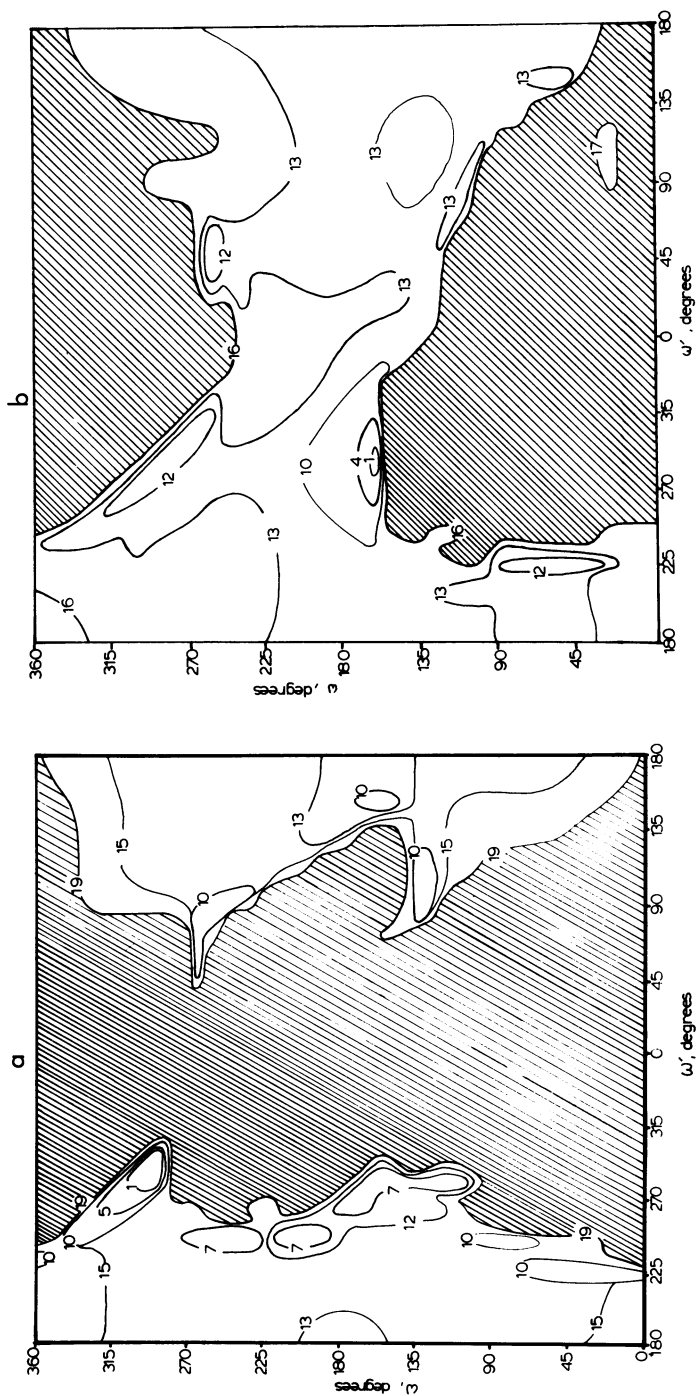


Figure 4
 Energy contour maps in the ω' , ω plane with C-3'-endo type sugar pucker. Other torsion angles fixed in (a) A form minimum energy conformation (b) Watson-Crick minimum energy conformation.

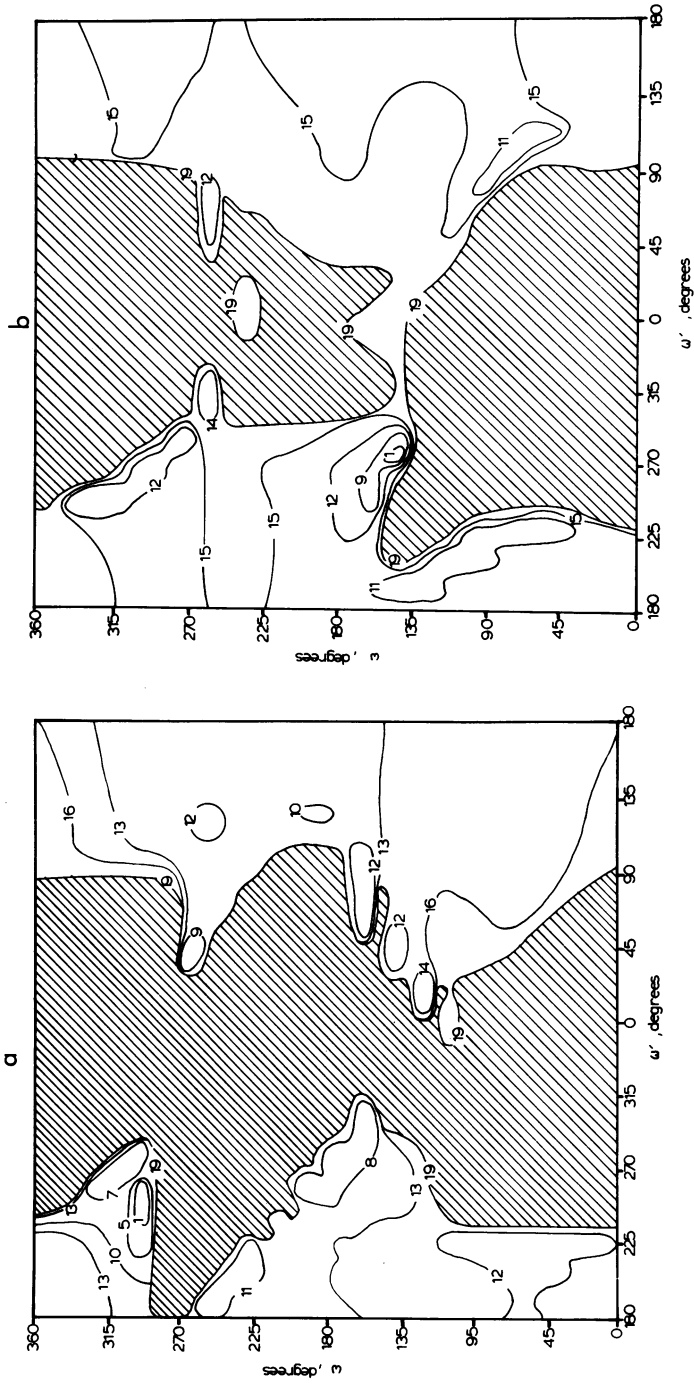


Figure 5
 Energy contour maps in the ω' , ω plane with C-2'-endo type sugar pucker. Other torsion angles fixed in (a) B form minimum energy conformation (b) Watson-Crick minimum energy conformation.

CONCLUSION

The lowest energy conformers of pdApdAp in the g^+ domain of ψ are the A and B helices. In the trans region of ψ , the Watson-Crick helices (34) are low energy, together with a C-3'-endo conformer with $\omega', \omega = g^+, g^+$ and a C-2'-endo $\omega', \omega = t, g^+$ (skewed) conformation. Terminal 3',5' phosphorylation of dApdA causes an increase in the rigidity of the molecule as manifested in the following ways: 1) Minimizations from the generalized staggered starting positions frequently lead to higher energy forms than the conformers found when starting from the dApdA minimum energy conformations indicating that the minima are narrower. 2) Fewer conformers remain in the lowest energy region, below ~ 3 kcal./mole. 3) The low energy ω', ω conformation space occupied by the A, B and Watson Crick helices is diminished. However, flexibility in ψ remains an important conformational variable, in addition to the established flexibility in the ω', ω angle pair and in the sugar pucker, which may be C-3'-endo or C-2'-endo type. The Watson-Crick helices with $\omega', \omega = g^-, t$, $\psi = t$ are important with both C-3'-endo and C-2'-endo pucker. The transformation from the A or B helix to the Watson-Crick helix follows a low energy path involving a tandem decrease in ω associated with an increase in ψ . Watson-Crick conformers have been proposed for drug intercalated polynucleotides (37-39). Another low energy conformer with ψ trans has $\omega', \omega = g^+, g^+$ (C-3'-endo) while this ω', ω region is higher energy when ψ is g^+ . A third low energy conformer with ψ trans has $\omega', \omega = t, g^+$ (skewed), C-2'-endo pucker. This extended conformer may play a role in the coil form of poly dA. The added phosphates cause an increased preference for the B helix over the A type.

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