Propeller-twisted Adenin.Thymine and Guanine.Cytosine Base Pairs Tend to Buckle and Stagger in Opposite Directions

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Abstract. Base pairs are propeller-twisted, buckled and staggered in DNA fragment crystals. These deformations were analyzed with isolated Watson-Crick base pairs using empirical potentials and buckle was found to almost linearly correlate with propeller. Interestingly, the thymine.adenine pair favours negative buckling for propellers mostly observed in DNA crystals while positive buckling is preferred by the cytosine.guanine pair. The propeller also induces opposite staggers in the adenine.thymine and guanine.cytosine base pairs.

Introduction

The base pairs are not planar in DNA but rather propeller-twisted (Wing et al. 1980). The extent of propeller-twist moves between $-2°$ and $-25°$ (Cambridge convention, Dickerson 1989), depending on the type of base pair (C.G or T.A), sequence context and other as yet unknown factors (Dickerson 1988). Furthermore, the base pairs are non-negligibly buckled in DNA crystal structures (Šponer and Kypr 1990; Yanagi et al. 1991). It is interesting that nucleic acid bases form nonplanar hydrogen-bonded complexes in crystals even on the monomer level (Wilson 1987; 1988). Consequently, it is appealing to study mutual dispositions of complementary Watson-Crick bases and energies necessary for their hydrogen bond deformations observed in DNA crystal structures. The deformations of hydrogen bonds between complementary bases are analyzed here as a continuation of our effort to study separately forces which contribute to stability of DNA double-helical conformations. Our previous studies along this line concerned base stacking (Šponer and Kypr 1989; 1990; 1991), mutual interphosphate interactions in DNA

backbone at high-salt concentrations (Jursa and Kypr 1990), and high salt-induced
DNA bending (Jursa and Kypr 1991).

Materials and Methods

Calculations were performed with the aid of an IBM-AT personal computer with a math-
ematical co-processor, using the AMBER joint atom potential (Weiner et al. 1984). Base
pair energies were calculated using the formula

$$E = \sum_{i,j} \left(e_i e_j / \epsilon r_{ij} + A_{ij} r_{ij}^{-12} - B_{ij} r_{ij}^{-6} + C_{ij} r_{ij}^{-12} - D_{ij} r_{ij}^{-10} \right), \tag{1}$$

where e_i, e_j are partial atomic charges, ϵ is dielectric permitivity, r_{ij} are distances between
atoms i and j, each of which belongs to one base in the pair. A_{ij}, B_{ij} and C_{ij}, D_{ij} are
constants describing van der Waals and hydrogen bonding interactions, respectively. The
base bond lengths and angles were kept constant in the calculations. We tested the
adenine, cytosine and guanine amino group rotations and found their effects on base pair
energy and geometry negligible. Consequently, the amino group hydrogen atoms were
fixed in the base planes in all calculations reported herein.

The coordinate system connected with a base pair was defined according to the
Cambridge convention (Dickerson 1989). The N1 atom of pyrimidine base and N9 atom of
purine base are symmetry-related by the x-axis, and the y-axis goes through the C6 atom
of pyrimidine and C8 atom of purine. The energy optimized base pair configurations were
obtained using simulated annealing minimization procedure (the software kindly provided
by J. Dřímal) with all the six base pair parameters (propeller, buckle, opening, S_x, S_y,
S_z) as variables (Dickerson 1989). Each configuration analyzed was created from a planar
base pair arrangement, first adjusting propeller, then buckle, opening, and finally the three
translational parameters. Dielectric permitivity equal to the interatomic distance was used
in the electrostatic energy calculations because this assignment mimics the polarization
effect in attractive interactions by giving a higher weight to short range forces. It also
compensates for the lack of explicit consideration of solvation by damping long range
charge interactions more than the short range interactions (Weiner et al. 1984). Owing
to the relatively small dimensions of the base pairs, it was not necessary to introduce the
cut-off distance beyond which the dielectric permitivity is constant.

Results and Discussion

First, we searched optimum geometries for the base pair (C.G or T.A) by energy
minimization when all the six parameters specifying the relative position of the
bases in the pair were free to vary. The optimization was repeated several times

Energy / kJ/mol
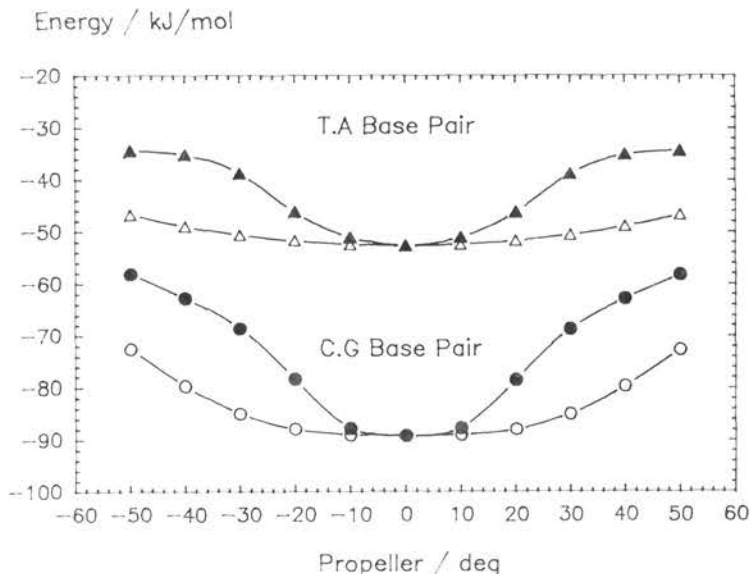
Figure 1. Energy dependences of Watson-Crick C.G (circles) and T.A (triangles) pairs on propeller. The propeller was fixed at the indicated values (open symbols), then the remaining parameters (buckle, opening, S_x, S_y and S_z) were optimized by simulated annealing using the AMBER joint atom force-field. Control calculations were performed (closed symbols) when, besides propeller, buckle was fixed at the optimum absolute values but with opposite sign.

starting from different initial base pair configurations. As expected, nearly planar Watson-Crick geometries of base pairs were found to be the most stable ones.

Next, our interest was focused on the energy changes caused by propeller, which significantly deviates from zero in DNA crystal structures. It is furthermore a very interesting general observation that negative propellers dominate over positive ones in DNA (Dickerson 1988). We set the propeller to a number of fixed values within −50° and +50° in Watson-Crick C.G and T.A base pairs and run the simulated annealing procedure to minimize their energies, letting the five remaining base pair parameters, i.e. buckle, opening, S_x, S_y and S_z, variable. The energy dependences were found to be very flat for propellers in absolute values smaller than 25°, while the flatness was much more pronounced with the T.A than C.G base pair (Fig. 1), obviously because in the former case two hydrogen bonds are only deformed by the propeller. Poltev and Shulyupina (1986) have arrived at similar results using other type of empirical potential. Consequently, the base pairs, and particularly the T.A pair, are sufficiently flexible to be propeller-twisted
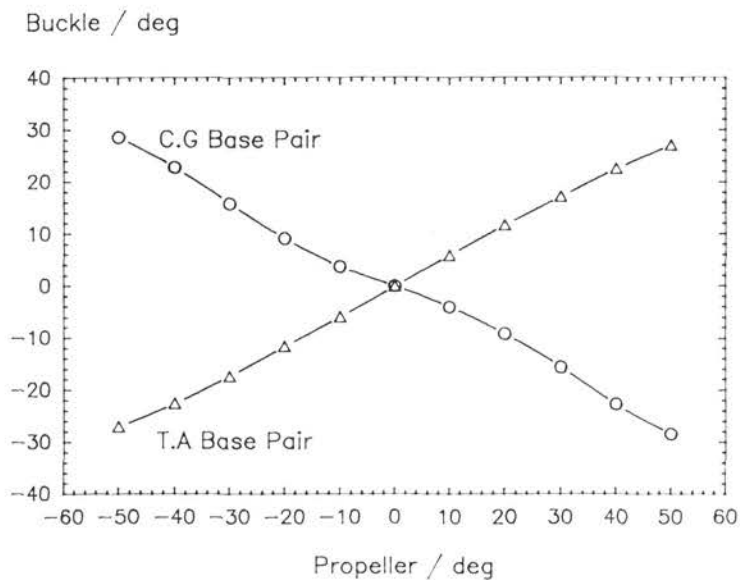
Buckle / deg

Figure 2. Correlation of buckle with propeller in the energy minima as in Fig. 1 for C.G (*circles*) and T.A (*triangles*) base pairs.
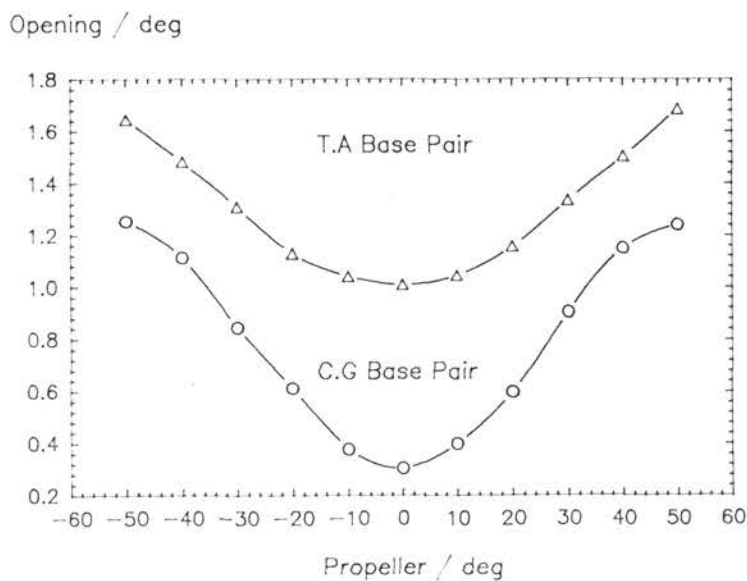
Opening / deg

Figure 3. Dependences of the base pair opening on propeller in the energy minima as in Fig. 1 for C.G (circles) and T.A (triangles) base pairs.
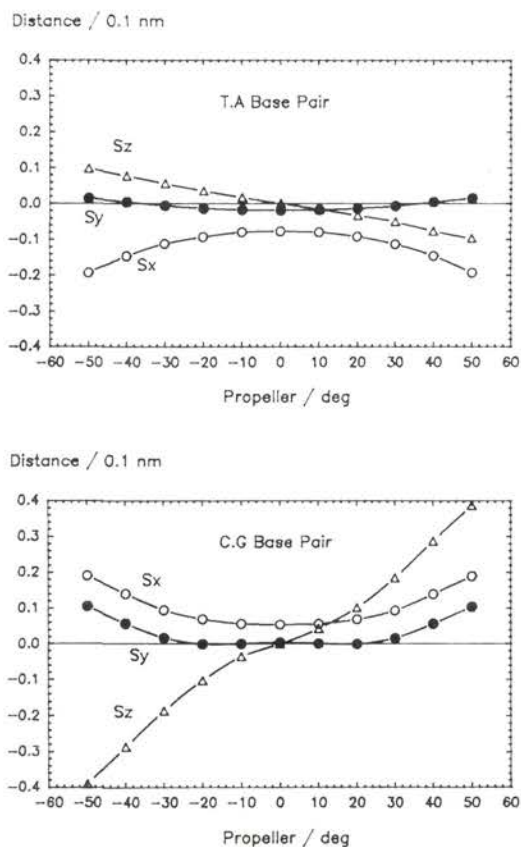
Distance / 0.1 nm

Distance / 0.1 nm

Figure 4. Dependences of the optimum S_x, S_y and S_z values on propeller, corresponding to the energy minima as in Fig. 1 for T.A (top) and C.G (bottom) base pairs.

in DNA crystal structures. However, it is not clear which force causes the propeller to be mostly negative in DNA because base stacking can only account for a part, if at all, of the observed propeller (Šponer and Kypr, unpublished data).

The key result of the present work is that the optimum base pair geometries having predetermined propellers contain non-negligible buckles which, however, have opposite signs in C.G and T.A pairs (Fig. 2). Deviations of base pair opening from the optimum values are less than 1° in the propeller region investigated (**Fig. 3**). Shifts along the coordinate axes (S_x, S_y, S_z) are generally smaller than 0.02 nm with an exception of S_z (stagger) of the C.G pair reaching 0.04 nm (**Fig. 4**). Propeller-induced changes in stagger are almost linear but have opposite slopes with C.G and T.A pairs, again (Fig. 4).

Hydrogen Bond Length / 0.1nm

Hydrogen Bond Length / 0.1nm
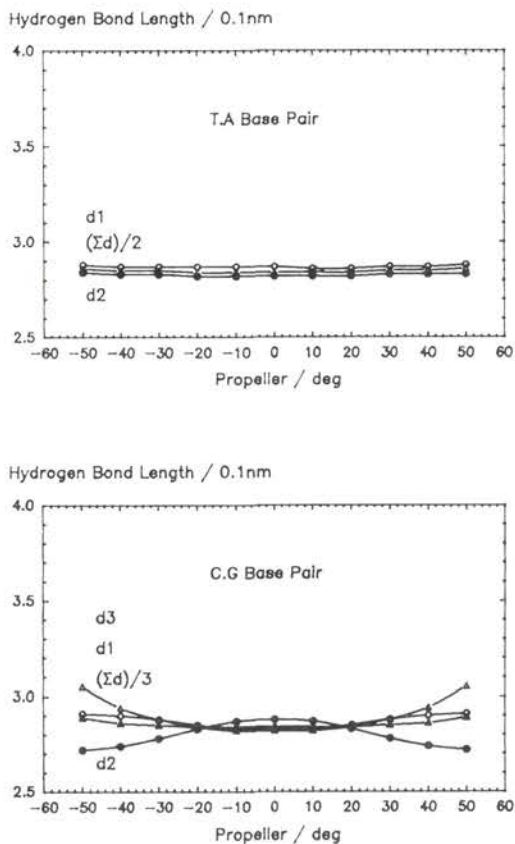
Figure 5. Dependences of hydrogen bond lengths (distances of the participating non-hydrogen atoms) on propeller at energy minima as in Fig. 1. Hydrogen bonds are denoted d1, d2, d3 (from the major towards the minor groove base pair side). $(\Sigma d)/2$ and $(\Sigma d)/3$ are the average values of hydrogen bonds in T.A (top) and C.G (bottom) base pairs, respectively.

Though empirical potentials are good guides through the jungle of DNA conformational space, we always try to find a simple, physically sound justification of the theoretical results. In the case of interdependence of propeller and buckle, a tendency stands obviously behind to keep the hydrogen bond lengths optimum (Fig. 5).

We wanted to understand the remarkable preferences of propeller-twisted C.G and T.A base pairs for the opposite sense of buckling. For this purpose, a series of calculations was performed with fixed propellers and buckles fixed at the optimum
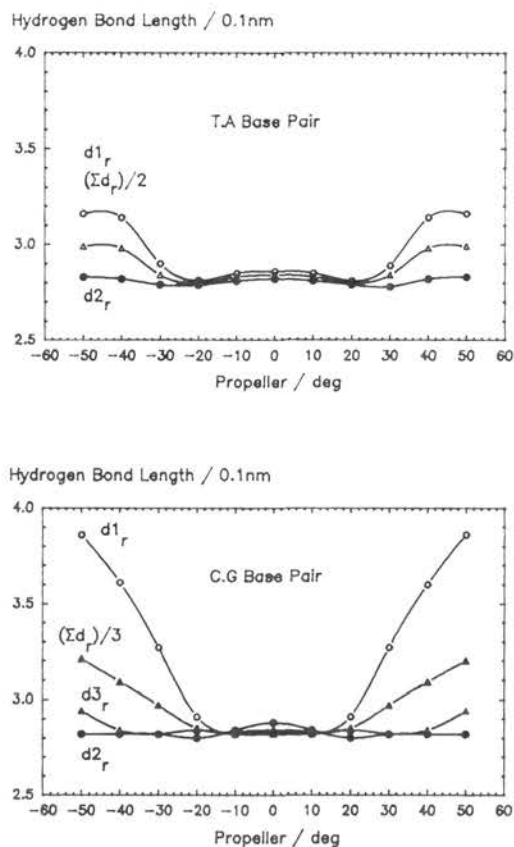
Hydrogen Bond Length / 0.1nm

Hydrogen Bond Length / 0.1nm

Figure 6. The same as in Fig. 5 but corresponding to the control calculations in Fig. 1.

absolute values following from Fig. 2 but with opposite signs. Then, the structures were energy minimized with respect to the remaining four variables (opening, S_x, S_y, S_z). The base pairs with the reversed buckles were not much destabilized at propellers lower than $\pm 10°$ but destabilization reached 4.3 and 9.6 kJ/mol for T.A and C.G pairs, respectively, at the absolute propeller values lying around 20° (compare the open and closed symbols in Fig. 1). The reversed buckling also induced a reversed stagger (not shown). Fig. 6 illustrates how the hydrogen bond lengths depend on the propeller in case of a reversed buckle.

There are two reasons for the differences in energies obtained for propeller-twisted base pairs with opposite buckles. First, the base pairs having the same propeller but opposite buckle do not have identical hydrogen bond lengths even after energy minimization over the remaining base pair variables (compare Figs.

5 and 6). This is related to the fact that the axis, the rotation around which gives the propeller, is far from coinciding with the direction of interbase hydrogen bonds. Secondly, different couples of atoms are close or far apart in case of opposite buckles. This difference influences the long range electrostatic interactions which bring about that the optimum buckles differ from zero even for small propeller values though small propellers do not change the hydrogen bond lengths (Figs. 1, 2, 5). Omitting the electrostatic term in Eq. (1) results in the energy dependences on buckle disappearing at propellers fixed between $-25°$ and $+25°$. With regard to the invariance of the conclusions of the present work with respect to the empirical potentials used, the potential of Poltev provided identical results (Poltev, personal communication). The present study was performed with constant base geometries because our computer is not fast enough to optimize the inner structures of bases in each base pair geometry during energy minimization. Nevertheless, we analyzed the effects of the base amino group rotation and found them negligible. In addition, the present work is a theoretical background of a forthcoming analysis of DNA crystal structures where the mutual positions of bases rather than their internal geometries are important.

The opposite buckling and staggering tendencies of propeller-twisted C.G and T.A pairs are interesting because they may significantly affect sequence-dependent properties of DNA conformation. However, our preliminary analysis of DNA crystal structures reveals neither a strong correlation between propeller and buckle nor opposite buckling tendencies of A.T and G.C base pairs. If these preliminary conclusions are confirmed by a complete analysis of DNA crystal structures, then energies of the hydrogen bond deformations analyzed here are obviously too small to significantly influence the base pair geometries within the DNA double helix framework in single crystals.

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