Conformational Flexibility of Dihydropyrimidinone and Tetrahydropyrimidine-2,4-dione Rings in DNA Bases

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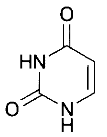
Dihydropyrimidinone and tetrahydropyrimidine-2,4-dione rings in the DNA bases are not conformationally rigid.

Base stacking[1,2] and hydrogen bonding[3,4] interactions between the DNA bases represent an important source of conformational variability in DNA molecules. For many years, isolated DNA bases were expected to be planar[5–7] and conformationally rigid.[8] Recently,[9] it was shown that the amino groups of these molecules can adopt a non-planar geometry. However, the pyrimidine rings of the bases were considered to be planar and rigid.

Systematic investigation of the conformational flexibility of six-membered nitrogen-containing dihydroheterocycles (for example[10–12]) has shown that these rings possess a degree of conformational flexibility. The transition from a planar equilibrium conformation to a non-planar one increases the energy of the molecules less 1 kcal mol^{-1} (1 cal = 4.184 J) at a bend angle *ca.* 15–20°. The type of non-planar conformation is determined by number and mutual arrangement of the double bonds in the ring.



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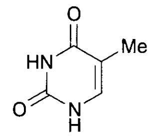

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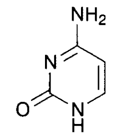

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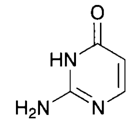

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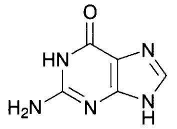

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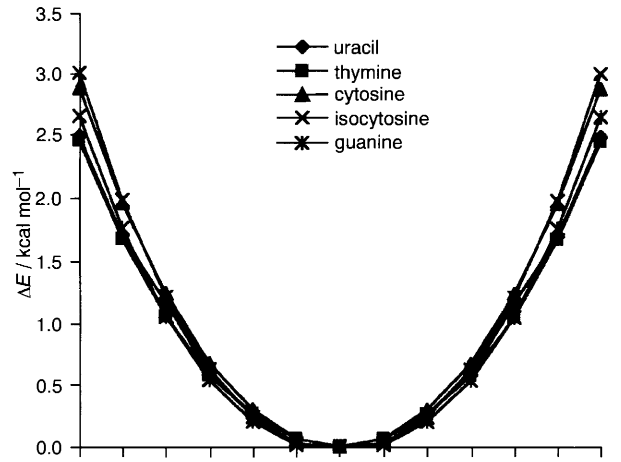

Fig. 1 Dependence of energy changes from the N–C(=O)–N–C(=O) torsion angle for the uracil and thymine molecules, the C–N–C(=O) angle for the cytosine molecule and the C–N–C–(=O)–C angle for the isocytosine and guanine molecules

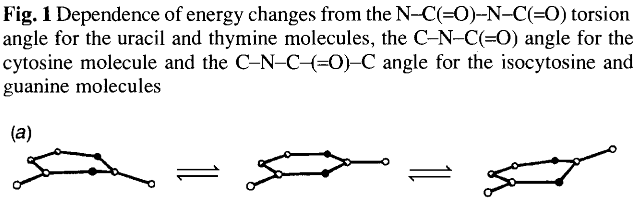

Fig. 2 Changes of conformation of the pyrimidine ring (a) uracil; (b) guanine

The majority of DNA base molecules contain partially hydrogenated pyrimidine rings. However, consideration of these rings as rigid entails some doubt, which stems from the high conformational flexibility of other dihydropyrimidinone rings mentioned above.

The structure of the uracil **1**, thymine **2**, cytosine **3**, isocytosine **4** and guanine **5** molecules was calculated by a semi-empirical quantum chemical method AM1.[13] Conformational flexibility was studied by scan of the N–C(=O)–N–C(=O) torsion angle in the uracil and thymine molecules, the C–N–C(=O)–N angle in the cytosine molecule and the C–N–C(=O)–C angle in the isocytosine and guanine molecules in the range of 0–30° with 5° steps. The dependence of energy changes on the relevant torsion angle is shown in Fig. 1.

The equilibrium conformation of the molecules **1**–**5** is planar. The aminogroups in molecules **3**–**5** have a trigonal-pyramidal configuration which agrees with non-empirical calculations using 6-31G** basis.[9]

Changing the above-mentioned endocyclic torsion angles in the pyrimidinone ring leads to transition of this cycle to a distorted sofa conformation with displacement of the carbonyl groups from plane of other atoms of the ring. (Fig. 2). Results of the calculation have shown that changing the relevant torsion angles of dihydropyrimidinone and tetrahydropyrimidine-2,4-dione ring in the range ±15° causes an energy increase of less than 1 kcal mol^{-1}. The most flexibility is observed for the uracil and thyme molecules. The dihydropyrimidinone ring in the isocytosine molecule is the most rigid.

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