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Direct Assessment of Interresidue Forces in Watson−Crick Base Pairs Using Theoretical Compliance Constants

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Though noncovalent bonds are the key to many phenomena in biochemistry,[1] the understanding of hydrogen bonds in biological macromolecules is still hampered by the fact that they are usually inferred indirectly. In the case of C−H···O═C hydrogen bonds, this indirect assessment leads to interaction strengths that range from "repulsive"[2] over "negligible"[3] in the adenine-thymine base pair to "large"[4] in supramolecular complexes. One reason for these discrepancies could be the fact that—in the case of base pairs—indirect theoretical methods refer to arbitrary conformers with partially broken hydrogen bonds ignoring, for example, π-bond cooperativity via resonance stabilization.[5] On the other hand, most experimental studies use the shift of donor-H stretching frequencies relative to the "free" molecules. These indirect experimental methods led to new and somewhat disturbing concepts such as anti- or improper-hydrogen bonds. A direct and reliable assessment of the donor−H···acceptor linkage—the hydrogen bond itself—is therefore needed. This is not only true for a general understanding of the stability of biomolecules but also for the optimization of empirical potential functions in molecular dynamic simulations, where transferability is a prerequisite for a realistic description of macromolecules. It is, for example, known that the description of DNA polymorphism is force field dependent,[6] a fact, which points to an unbalanced parameter setup.

It was recently shown that compliance constants[7] provide unique bond strengths.[8−10] In contrast to force constants, the numerical value of compliance constants do not depend on the coordinate system. Since it is possible to define interresidue donor−H··· acceptor distances as internal coordinates, compliance constants can be used for the description of interresidual forces. The physical meaning of compliance constants is deduced from their definition as a partial second derivative of the potential energy due to an external force:

$$C_{ij} = \partial^2 E/\partial f_i \partial f_j \qquad (1)$$

In other words, compliance constants measure the displacement of an internal coordinate resulting from a unit force acting on it. That means the reference state of the compliance constants method is the equilibrated complex and hence unique. Following the definition in eq 1 a *lower* numerical value of a compliance constant represents a stronger bond.

This paper presents the first calculation of interresidue potential constants based on quantum chemistry for the Watson−Crick base pairs adenine-thymine (**AT**) and guanine-cytosine (**GC**), permitting a unique quantification of individual hydrogen bond strengths. This is accomplished by calculating the interresidue compliance constants for all possible D−H···A contacts, where D is the donor atom (N, C), and A, the acceptor (O, N). We constrained the search for stationary points to C_s symmetry to save computing time even if small imaginary frequencies resulted (planar amino groups). The resulting hybrid density functional compliance constants for the adenine-thymine and the guanine-cytosine base pair are listed in Table 1 and Figure 1. To account for possible basis set superposition errors we also included compliance constant values using the counterpoise correction scheme during the geometry optimization and the computations of the second derivatives. Further, we additionally performed compliance constants calculations at the MP2 level of theory[11] since density functional theory is not the first choice when it comes to the description of dispersion forces in weak hydrogen bonds. The MP2 results are collected in Table 1 as well. All geometry optimizations and calculations of the Cartesian force constants were performed using the Gaussian03 program set.[12] The setup of nonredundant internal coordinates, as well as the transformation[13] and inversion of the Cartesian force constants, is described elsewhere.[9]

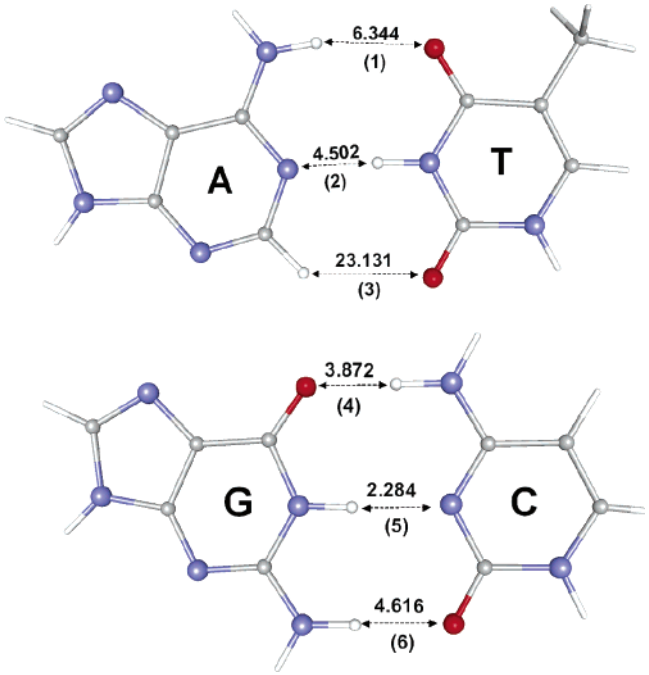

Figure 1. B3LYP[14] compliance constants C_{ij} in Å/mdyn for the hydrogen bonds in adenine-thymine and the guanine-cytosine base pair using a 6-311++G(d,p) basis set. Optimization and calculation of the energy second derivatives are counterpoise corrected. A lower numerical value indicates a stronger bond.

Analyzing the stiffness at the atomic level, all methods give the same relative hydrogen bond strengths although the hydrogen bonds in **AT** and **GC** base pairs described by the MP2 method are

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Table 1. Optimized DH···A Distances and Their Compliance Constants for the Adenine-Thymine and the Guanine-Cytosine Watson−Crick Base Pairs at the B3LYP/6-31G(d), B3LYP/6-311++G(d,p), Counterpoise Corrected B3LYP/6-311++G(d,p) and the MP2/6-31G(d,p) Levels of Theory, Denoted as DFT1, DFT2, DFT3, and MP2, Respectively

	DFT1		DFT2		DFT3		MP2	
H-bond	$R_{H\cdots A}$ (Å)	C_{ij}(Å/mdyn)	$R_{H\cdots A}$ (Å)	C_{ij}(Å/mdyn)	$R_{H\cdots A}$ (Å)	C_{ij}(Å/mdyn)	$R_{H\cdots A}$ (Å)	C_{ij}(Å/mdyn)
AT NH···OC (**1**)	1.929	5.292	1.927	5.940	1.942 Å	6.344	1.952	5.925
AT NH···N (**2**)	1.830	3.307	1.836	4.145	1.851 Å	4.502	1.807	3.242
AT CH···O (**3**)	2.853	16.974	2.888	20.891	2.905 Å	23.131	2.777	15.885
GC NH···OC (**4**)	1.780	3.247	1.767	3.676	1.782 Å	3.872	1.775	3.232
GC NH···N (**5**)	1.917	1.977	1.918	2.200	1.932 Å	2.284	1.917	1.974
GC NH···OC′ (**6**)	1.911	3.856	1.920	4.409	1.935 Å	4.616	1.911	3.676

systematically stronger in comparison with DFT results. Irrespective of the quantum chemical method, we found large differences between individual hydrogen-bond strengths. In the following, all numbers refer to the counterpoise-corrected DFT/6-311++G(d,p) results. Due to our calculated compliance constants, the central interresidue N−H···N hydrogen bond between guanine and cytosine is by far the strongest hydrogen bond in both Watson−Crick base pairs. Its perfect linear arrangement and the C_{ij} value of 2.284 Å/mdyn points to an interaction that is twice as strong as the central N−H···N hydrogen bond in **AT** (C_{ij}: 4.502 Å/mdyn), which is in line with relative energies computed indirectly by Dannenberg and co-workers.[15] Interresidue NMR $^{1H}J_{NH}$ spin−spin coupling constant measurements of a DNA 14-mer also seem to point in the same direction, even if the trend is not as strong as in our single base-pair calculations.[16] Further, due to cooperative effects, each of the two N−H···O═C hydrogen bonds in **GC** (3.872 Å/mdyn for hydrogen bond (**4**) and 4.616 Å/mdyn for hydrogen bond (**6**)) is significantly stronger than the N−H···O═C hydrogen bond (**1**) in **AT**, which has a compliance constant of 6.344 Å/mdyn. The third **AT** interresidue contact (**3**), a possible C−H···O═C hydrogen bond, produces a compliance constant of 23.131 Å/mdyn, which is in line with a week—but not negligible—interaction strength. Due to our compliance constant calculations, this C−H···O═C hydrogen bond in **AT** base pairs is 5 times weaker than a "normal" N−H···O═C or N−H···N hydrogen bond.[17] Nevertheless, the positive sign of this weak compliance constant rules out a "repulsive" interaction or an "anti-hydrogen" bond. Concerning the total stiffness with respect to base-pair stretch displacement, a recent study on DNA deformability on the base-pair level sees the **GC**-**AT** average ratio at 1.7. The study by Lankas et al.[18] was based on a unrestrained molecular dynamics simulation using an empirical potential function.[19] On the other hand, in our study the sum of computed "relaxed" force constants (reciprocal values of the compliance constants) leads to an intrinsic **GC**-**AT** stiffness ratio, which is more pronounced (2.1). Among principal differences in the two studies this could point to deficiencies in the description of hydrogen bonds between Watson−Crick base pairs by empirical force fields.

The possibility to quantify cooperative effects between individual hydrogen bonds using the compliance matrix *coupling constants* is under investigation.

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