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# Determinants of the Unexpected Stability of RNA Fluorobenzene Self Pairs

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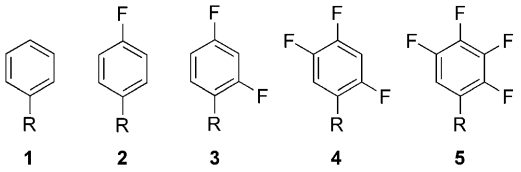
Fluorine-substituted base analogues have proven invaluable as "nonpolar nucleoside isosteres"[1] to probe the physical forces that govern the stabilities of nucleic acids.[2–4] When paired against natural bases, fluorinated analogues destabilize DNA and RNA helices and exhibit little binding sequence specificity.[2,5] These observations make Watson–Crick base pairing involving hydrogen bonds to fluorine unlikely.[2,6] When paired opposite one another, however, a considerable degree of stability is regained, and a selective pairing of fluorinated bases in the context of nucleic acids is observed.[2,5] Weak C–F···H–C dipolar interactions have been implicated as acting as stabilizing forces in this case.[5]

Apparently, the role of fluorine in molecular recognition strongly depends on the surrounding molecular environment. Similar effects have been observed in the fields of medicinal chemistry and protein design, in which the fluorophilicity/fluorophobicity of the protein environment affects the affinity of fluorine-substituted ligands[7–9] or the stabilizing influence of fluorine-containing artificial amino acids.[10,11] With the goal of addressing the influence of the environment on the molecular recognition thermodynamics of organic fluorine, we have undertaken a combined experimental/computational study of fluorobenzene self-pairing in the context of duplex RNA. We report here the first systematic study of the determinants of the surprising stability of fluorobenzene-based self-pairs with increasing fluorine-substitution.

Motivated by preliminary modeling results, we synthesized novel ribonucleoside analogues in which the nucleobases are replaced by benzene or fluorine-substituted benzenes, respectively[2,12,13] (Scheme 1 and in the Supporting Information). The modified nucleosides were tested in a defined 12-mer RNA duplex (5′-CUU UUC XUU CUU paired with 3′-GAA AAG YAA GAA). The nucleoside analogues were introduced at positions X and Y, respectively, to form a base pair in the duplex. We anticipated that this supramolecular system should be particularly apt for investigation of the molecular recognition properties of organic fluorine. Here we focus on results obtained for homo-self-pairs (that is, positions X and Y were occupied by the same nucleotide) of **1**–**5**. The 2,4,6-trifluorobenzene-substituted nucleoside analogue and the pentafluorinated species




**Scheme 1.** Structures of the base analogues that form self pairs. R is always the ribosephosphate moiety. **1** = benzene; **2** = 4-fluorobenzene; **3** = 2,4-difluorobenzene; **4** = 2,4,5-trifluorobenzene; **5** = 2,3,4,5-tetrafluorobenzene.

were omitted, as steric effects due to bis-*ortho* substitution result in large destabilization.[3,14] Likewise, we restrict ourselves to the homologous set of benzene derivatives **1**–**5** instead of also considering, for example, indole- or benzimidazole-based base analogues.[2,15] That way we can minimize any influence due to variation in shape or size of the base analogues[16,17] or stacking interactions[2,18] (see also below) on the observed stabilities. The CD spectra of the RNA duplexes with the modified bases follow the typical curves for an A-type helix (Figure S2 in the Supporting Information). Thus, the structure of the duplex RNA is not disturbed by incorporation of our modified nucleosides, in agreement with previous findings.[2,19]

The thermodynamic stabilities of the modified RNA duplexes were determined by thermal denaturation as monitored by UV absorbance in a phosphate buffer (20 mM, pH 7.0) containing NaCl (140 mM).[20] The thermodynamic data were extracted from the melting curves by means of a two-state model for the transition from duplex to single strand.[21]

Not unexpectedly,[2,5] our measurements demonstrate that the pairing preference of fluorinated bases is higher in self-pairs (Figure 1; Table 1) than in pairs with natural bases.[2] In both cases, the stability increases incrementally with the number of fluorine substituents in the base analogue, with the largest gain in stability observed in the first two fluorination steps (**1**→**2**: $\Delta\Delta G^0 = 1.7$ kcal mol$^{-1}$, **2**→**3**: 1.4 kcal mol$^{-1}$). Surprisingly, this leads to RNA duplex stabilities with self-paired bases **3**, **4**, and **5** (11.6, 11.8 and 12.2 kcal mol$^{-1}$, respectively) that are similar to or exceed that of the natural AU base pair (11.9 kcal mol$^{-1}$).[2] In stark contrast, in the case of a 12-mer DNA double helix, the presence of two self-pairs of **5** bases resulted in an overall destabilization of the duplex by 4.6 kcal mol$^{-1}$ compared to the natural AT base pairs, and the stability increase observed on going from two self-pairs of **1** bases to two self-pairs of **5** bases is much less pronounced ($\Delta\Delta G^0 = 0.6$ kcal mol$^{-1}$).[5] What is the molecular origin of the stepwise stability increase and the unexpected overall stability in the RNA case?

To address this question, we performed 10 ns molecular dynamics (MD) simulations and free energy calculations together with a structural component analysis for RNA duplexes containing homo-self-pairs of **1**–**5**, including solvent and consider-

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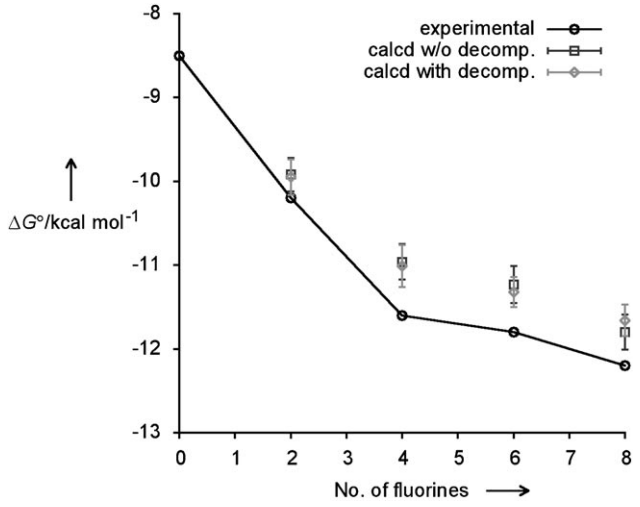


**Figure 1.** Stabilities of the modified RNA duplexes with respect to the number of fluorine atoms in the homo-self-pairs. Black circles show experimentally determined values, dark gray rectangles show computed stabilities, and light gray diamonds show computed stabilities obtained as the sum of RNA and solvent contributions as determined by the free energy analysis. To obtain absolute stabilities, the computed relative values were added cumulatively to the experimental value of the RNA duplex with the **1** homo-self-pair.

**Table 1.** Experimentally measured and calculated relative RNA duplex stabilities, decomposition of the calculated free energies into contributions from RNA and solvent, and differences in the buried solvent-accessible surface area regions contributed by fluorine atoms.

| Transition | $\Delta\Delta G_{exp}$[a] | $\Delta\Delta G_{calcd}$[b] | $\Delta\Delta G_{RNA}$[a] | $\Delta\Delta G_{solv}$[a] | $\Delta\Delta SASA_F$[e] |
|---|---|---|---|---|---|
| **1**→**2** | −1.7 (0.3) | −1.5 (0.2) | 4.1 (0.2) | −5.5 (0.6) | 13.7 (0.2) |
| **2**→**3** | −1.4 (0.3) | −1.1 (0.3) | −1.5 (0.3) | 0.4 (0.5) | 2.2 (0.4) |
| **3**→**4** | −0.2 (0.3) | −0.3 (0.2) | −0.6 (0.3) | 0.3 (0.8) | 1.5 (0.5) |
| **4**→**5** | −0.4 (0.3) | −0.3 (0.2) | 3.7 (0.3) | −4.1 (0.4) | 15.4 (0.7) |
| **1**→**5**[c] | −3.7 (0.6) | −3.2 (0.4) | 5.7 (0.6) | −8.8 (1.2) | –[f] |
| **1**→**5**[d] | −3.7 (0.3) | −3.3 (0.5) | 3.4 (0.5) | −6.7 (1.1) | 32.8 (0.5) |

[a] In kcal mol$^{-1}$. [b] Free energies computed by use of the FED scheme. In kcal mol$^{-1}$. [c] Calculated as the sum of the single steps. [d] Calculated for the transition **1**→**5**. [e] In Å$^2$. [f] Same values as if calculated for the transition **1**→**5**.

ing long-range electrostatic effects. For the free energy calculations, the thermodynamic integration (TI)[22,23] method was used and standard thermodynamic cycles were applied (Figure S1). Both TI and MD simulations were performed with the AMBER 8 suite[24] and the force field of Cornell et al.,[25] which has a very good balance of intermolecular interaction terms for nucleobases.[26–28] Computational details are described in the Supporting Information.

We first calculated relative binding free energies for the modified RNA duplexes containing homo-self-pairs of **1**–**5**. Our calculations show an excellent agreement with experiment (Figure 1; Table 1), with deviations between experimentally measured and computed values $< 0.4$ kcal mol$^{-1}$. The trend of the computed free energies closely follows that of the experimentally measured ones ($r^2 = 0.97$ for the series without free energy decomposition (FED), $r^2 = 0.99$ for the series with FED; Figure S4). Overall, these findings give us confidence in the quality of the applied force field. Finally, the free energy change computed for the **1**→**5** transition is in close agreement with the sum of changes obtained for stepwise transitions (Table 1). Likewise, the free energy profiles (Figure S3) are smooth and without discontinuities, which could indicate the existence of hysteresis. These findings demonstrate the statistical quality of these estimates.

We next performed a structural decomposition of the calculated relative binding free energies into contributions from single nucleotides and an overall contribution of the solvent. Although the validity of FED in general has been debated,[29] expressing free energies as a sum of components that correspond to different parts of the system is of particular interest for interpreting macroscopic data in terms of microscopic interactions.[30] With the FED applied, the relative binding free energies calculated as the sums of the single contributions agree with the free energies reported above to within the statistical uncertainty (Figure 1).

In a congeneric series of fluorine-substituted benzenes such as **1**–**5** one would intuitively expect that similar macroscopic observations, such as the observed stability increments, should correspondingly arise from similar microscopic origins. Surprisingly, this is not the case, as demonstrated by the FED results (Table 1). For the transitions **1**→**2** and **4**→**5**, the binding free energy changes are dominated by favorable solvent contributions (−5.5 and −4.1 kcal mol$^{-1}$). Contributions due to changes of interactions within the RNA, in contrast, are unfavorable. Opposite trends are revealed for the transitions **2**→**3** and **3**→**4**: changes of interactions within the RNA contribute favorably to the stability gain (−1.5 and −0.6 kcal mol$^{-1}$), whereas the solvent contributions are negligible. The FED thus reveals that it is indirect (solvent) contributions that stabilize **2** and **5** over **1** and **4**, respectively. In contrast, direct (RNA) contributions stabilize the **2**→**3** and **3**→**4** cases. Notably, the indirect (solvent) contributions dominate over the direct (RNA) contributions. These trends are in perfect agreement with experimentally determined contributions to duplex RNA stability for **1**, **2**, or **3** paired against uridine (Table 4 in ref. [2]), which corroborates our calculations.

How can one explain that the solvent strongly contributes to RNA duplex stability in two of the cases while it shows negligible effects in the other ones? Obviously, it is not sufficient to consider the overall lipophilicity of the base analogues, because this property increases generally with increasing fluorination of aromatic compounds.[32] Accordingly, the log *P* values of nucleosides containing **1**–**5** are 1.05, 1.50, 1.70, 1.83, and 1.92, respectively.[13] Likewise, no correlation with the molecular dipole moment can be seen. This remains essentially constant for the fluorinated base analogues **2** to **4** (**1**: 0.3 D; **2**: 2.4 D; **3**: 2.2 D; **4**: 2.0 D; **5**: 4.0 D),[3] whereas it strongly increases on going from **1** to **2** and from **4** to **5** (in which cases one would anticipate a favorable solvent contribution for the **2**→**1** and

  

the **5**→**4** transitions, but not for **1**→**2** and **4**→**5** as found above).

Rather, the observed trend parallels the differences in solvent-accessible surface area regions contributed by fluorine atoms that are buried upon duplex formation (Table 1; $\Delta\Delta SASA_F \approx 15$ Å$^2$ for the **1**→**2** and **4**→**5** transitions; $\Delta\Delta SASA_F \approx 1.5$ Å$^2$ for the **2**→**3** and **3**→**4** transitions). Average structures of the RNA duplexes from unperturbed MD simulations confirm this result (Figure 2). Both fluorine atoms of **2** are almost

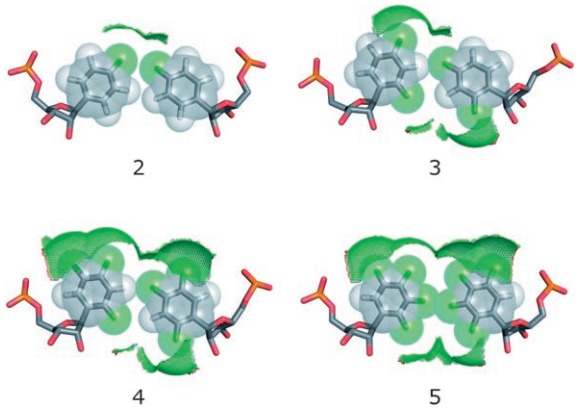


**Figure 2.** Averaged structures obtained from the MD trajectories of the self-paired fluorobenzene nucleotides in stick and van der Waals surface representations. The solvent-accessible surfaces of the fluorine atoms are depicted as green meshes. The figures were generated with PyMOL.[31]

completely buried in the duplex structure, as are the fluorines at position three in the case of **5**. In contrast, the fluorine atoms of **3** and **4** remain mostly solvent-accessible. We note with interest that the observed $\Delta\Delta SASA_F$ dependency points to a local influence of fluorine substitution on duplex stability, rather than an influence due to changes in global molecular properties. This local influence can be explained by electrostatic and, in particular, time-dependent interactions of C–F bond dipoles being of minimal importance in polar heteroatom solvents.[32,33] Poor aqueous solvation of C–F dipoles results,[34] and hence a hydrophobic character of these regions, removal of which from water is energetically favorable. Maximizing the burial of the fluorine atoms in the cases of **2** and **5** leads to base configurations that show short F···F contacts (between 2.9 and 3.0 Å, the sum of the fluorine van der Waals radii being 2.94 Å), either with an almost perpendicular orientation of the C–F bond vectors (**2**) or with a collinear orientation (**5**). Intuitively, these configurations seem unlikely because two negatively polarized sites face each other. However, ab initio calculations at the MP2 level of theory demonstrate attractive interactions between two $CF_4$ molecules at F···F distances of the above range,[35,36] even in the least favorable case of collinear orientation of the C–F bonds. Short intermolecular F···F contacts have also been observed in the crystal packings of hexafluoropropene and pentafluorobenzoic acid.[37,38] In the latter case, their occurrence has been interpreted as stacking interactions and hydrogen bonds in the crystal being very likely to be of more energetic advantage than the presumed disadvantage of the F···F contacts.[37] Likewise, we interpret our findings in the cases of **2** and **5** in terms of the solvent contributions due to the burial of fluorine atoms being favorable enough to overcompensate even energetically slightly unfavorable fluorine contacts.

What is the molecular origin for the favorable RNA contributions to duplex stability in the **2**→**3** and **3**→**4** transitions? In addition to solvation effects, hydrogen bonding and stacking are considered predominant forces for nucleic acid stability.[39–41] With regard to stacking, when paired against uridine, a **2**→**3** substitution stabilized duplex RNA by 0.6 kcal mol$^{-1}$. This value explains less than half of the computed stabilization (1.5 kcal mol$^{-1}$) and might even overestimate stacking, due to the presence of additional interactions involving fluorine at position 2.[2] Even more compellingly, "dangling end" fluoro-substituted benzenes have been found to stabilize DNA equally well irrespective of the degree of fluorination.[3] Accordingly, we conclude that the observed stability increase for the above transitions is not related to differences in stacking.

A hint as to what might instead be the stabilizing force was provided by the frequency distributions of the distances between the H3 atom of the base at position X and the F4 atom at position Y (Figure 3). Distances of around 2.6 Å are observed in 13.0% and 14.6% of the investigated snapshots for self-pairs of **3** and **4**, respectively, but only in 9.7% in the case of **2**. Conversely, distances greater than 3.2 Å occur in 43% in the last case, but only in 16% (20%) of the **3** (**4**) self-pairs. The most populated H···F distance (2.6 Å; Figure 3) and C–H···F angle (140°; Figure S5 in the Supporting Information) thus agree perfectly with geometries reported for H···F interactions in small-molecule crystal structures.[2,42–45] Accordingly, we interpret our findings in terms of weak attractive C–F···H–C dipolar interactions, with more short-range interactions present in **3** and **4** self-pairs than in their **2** counterparts. This interpretation is corroborated by analysis of the occupancy of C–F···H–C interactions: that is, the ratio of times when the interaction is present relative to the total simulation time. Occupancies of

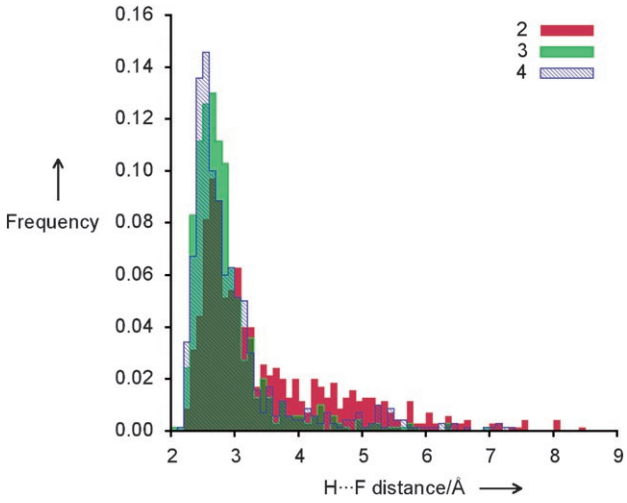


**Figure 3.** Frequency distributions of the distances between the H3 atom of the bases at position X and the F4 atom of the bases at position Y. The last 7 ns of the unperturbed MD trajectories were investigated. The bin width of the histograms is 0.1 Å. The olive color results if the red histogram is overlaid by the green one.

  

0.76 (0.70) are found in the case of **3** (**4**) self-pairs, whereas this value amounts to 0.46 in the case of **2**. Thus, C–F···H–C interactions prevail for a larger fraction of time in the **3** (**4**) case. Together with the higher frequency of interactions at shorter distances, this may well explain the gains in stability observed for **3** and **4**. Finally, we also examined the stagger between the base analogue self-pairs,[46] which describes the translational displacement between the two bases along the helix axis. The **1** (**2**) self-pair shows a large stagger of 1.3 (1.6) Å, probably due to repulsion between opposing C–H (C–F) groups. In contrast, the stagger of the **3** (**4**) self-pair is only 0.7 (0.8) Å, indicating more favorable C–F···H–C interactions in these cases. Surprisingly, the stagger of the **5** self-pair only amounts to 0.8 Å, despite a potentially repulsive interaction between C–F groups, which may be attributed to the overall stability of the RNA duplex in this case.

Undoubtedly, covalently bound fluorine hardly ever acts as acceptor for available Brønsted acidic sites in the presence of competing heteroatom acceptors.[47–50] Attractive H···F dipolar interactions have been described, however, for well-structured molecular environments in which heteroatom acceptors are excluded, such as the thrombin active site[7,8] or engineered crystals.[42,51] Apparently, the fluorobenzene self-pairs in the context of duplex RNA constitute a well-structured supramolecular system, which leads to favorable interactions between self-pairs of **3** and **4**. These interactions might even be under-represented in our analysis, because the Cornell et al. force field underestimates interaction energies for weak base pairs relative to reference QM data.[26]

In summary, this study demonstrates an intricate influence of the molecular environment on the molecular recognition thermodynamics of organic fluorine. In particular, as revealed for the case of fluorinated base analogues, it may generally not be sufficient to discuss the molecular recognition properties of organic fluorine in terms of global molecular properties.[3] Instead, analyses at an atomic level, as provided by combined experimental/computational approaches, are required.

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**Keywords:** fluorine · molecular dynamics · molecular recognition · RNA structures · thermodynamics

[1] B. A. Schweitzer, E. T. Kool, *J. Org. Chem.* **1994**, *59*, 7238.
[2] J. Parsch, J. W. Engels, *J. Am. Chem. Soc.* **2002**, *124*, 5664.
[3] J. S. Lai, J. Qu, E. T. Kool, *Angew. Chem.* **2003**, *115*, 6155; *Angew. Chem. Int. Ed.* **2003**, *42*, 5973.
[4] G. T. Hwang, F. E. Romesberg, *Nucleic Acids Res.* **2006**, *34*, 2037.
[5] J. S. Lai, E. T. Kool, *J. Am. Chem. Soc.* **2004**, *126*, 3040.
[6] A. Somoza, J. Chelliserrykattil, E. T. Kool, *Angew. Chem.* **2006**, *118*, 5116; *Angew. Chem. Int. Ed.* **2006**, *45*, 4994.
[7] J. A. Olsen, D. W. Banner, P. Seiler, U. O. Sander, A. D'Arcy, M. Stihle, K. Muller, F. Diederich, *Angew. Chem.* **2003**, *115*, 2611; *Angew. Chem. Int. Ed.* **2003**, *42*, 2507.
[8] J. A. Olsen, D. W. Banner, P. Seiler, B. Wagner, T. Tschopp, U. Obst-Sander, M. Kansy, K. Muller, F. Diederich, *ChemBioChem* **2004**, *5*, 666.
[9] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881.
[10] C. Jäckel, W. Seufert, S. Thust, B. Koksch, *ChemBioChem* **2004**, *5*, 717.
[11] C. Jäckel, M. Salwiczek, B. Koksch, *Angew. Chem.* **2006**, *118*, 4305; *Angew. Chem. Int. Ed.* **2006**, *45*, 4198.
[12] J. Parsch, J. W. Engels, *Helv. Chim. Acta* **2000**, *83*, 1791.
[13] A. Živković, PhD thesis, Johann Wolfgang Goethe-Universität, Frankfurt am Main (Germany), **2005**.
[14] A. Živković, J. W. Engels, *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 1023.
[15] J. Bozilovic, J. W. Bats, J. W. Engels, *Can. J. Chem.* **2007**, *85*, 283.
[16] J. C. Delaney, P. T. Henderson, S. A. Helquist, J. C. Morales, J. M. Essigmann, E. T. Kool, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 4469.
[17] H. O. Sintim, E. T. Kool, *Angew. Chem.* **2006**, *118*, 2008; *Angew. Chem. Int. Ed.* **2006**, *45*, 1974.
[18] K. M. Guckian, B. A. Schweitzer, R. X. F. Ren, C. J. Sheils, P. L. Paris, D. C. Tahmassebi, E. T. Kool, *J. Am. Chem. Soc.* **1996**, *118*, 8182.
[19] M. Zacharias, J. W. Engels, *Nucleic Acids Res.* **2004**, *32*, 6304.
[20] M. Schweitzer, J. W. Engels in *Antisense: From Technology to Therapy, Vol. 6* (Eds.: R. Schlingensiepen, W. Brysch, K.-H. Schlingensiepen), Blackwell, Cambridge, MA, **1997**, pp. 78.
[21] L. A. Marky, K. J. Breslauer, *Biopolymers* **1987**, *26*, 1601.
[22] J. G. Kirkwood, *J. Chem. Phys.* **1935**, *3*, 300.
[23] D. L. Beveridge, F. M. Dicapua, *Annu. Rev. Biophys. Biophys. Chem.* **1989**, *18*, 431.
[24] D. A. Case, T. E. Cheatham, T. Darden, H. Gohlke, R. Luo, K. M. Merz, A. Onufriev, C. Simmerling, B. Wang, R. J. Woods, *J. Comput. Chem.* **2005**, *26*, 1668.
[25] W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell, P. A. Kollman, *J. Am. Chem. Soc.* **1995**, *117*, 5179.
[26] J. Sponer, P. Jurecka, P. Hobza, *J. Am. Chem. Soc.* **2004**, *126*, 10142.
[27] J. E. Sponer, N. Spackova, P. Kulhanek, J. Leszczynski, J. Sponer, *J. Phys. Chem. A* **2005**, *109*, 2292.
[28] J. E. Sponer, N. Spackova, J. Leszczynski, J. Sponer, *J. Phys. Chem. B* **2005**, *109*, 11399.
[29] A. E. Mark, W. F. van Gunsteren, *J. Mol. Biol.* **1994**, *240*, 167.
[30] S. Boresch, M. Karplus, *J. Mol. Biol.* **1995**, *254*, 801.
[31] W. L. DeLano, PyMOL, DeLano Scientific, Palo Alto, CA, USA, **2002**.
[32] S. G. DiMagno, H. R. Sun, *Curr. Top. Med. Chem.* **2006**, *6*, 1473.
[33] J. C. Biffinger, H. W. Kim, S. G. DiMagno, *ChemBioChem* **2004**, *5*, 622.
[34] C. Fonseca Guerra, F. M. Bickelhaupt, *J. Chem. Phys.* **2003**, *119*, 4262.
[35] R. D. Parra, X. C. Zeng, *THEOCHEM* **2000**, *503*, 213.
[36] F. T. T. Huque, K. Jones, R. A. Saunders, J. A. Platts, *J. Fluorine Chem.* **2002**, *115*, 119.
[37] A. Bach, D. Lentz, P. Luger, *J. Phys. Chem. A* **2001**, *105*, 7405.
[38] A. Bach, J. Buschmann, D. Lentz, P. Luger, *Z. Kristallogr.* **2000**, *215*, 518.
[39] I. Tinoco, O. C. Uhlenbeck, M. D. Levine, *Nature* **1971**, *230*, 362.
[40] K. J. Breslauer, R. Frank, H. Blöcker, L. A. Marky, *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 3746.
[41] M. Petersheim, D. H. Turner, *Biochemistry* **1983**, *22*, 256.
[42] G. R. Desiraju, *Acc. Chem. Res.* **2002**, *35*, 565.
[43] L. Shimoni, J. P. Glusker, *Struct. Chem.* **1994**, *5*, 383.
[44] V. R. Thalladi, H. C. Weiss, D. Bläser, R. Boese, A. Nangia, G. R. Desiraju, *J. Am. Chem. Soc.* **1998**, *120*, 8702.
[45] J. W. Bats, J. Parsch, J. W. Engels, *Acta Crystallogr. Sect. C* **2000**, *56*, 201.
[46] R. E. Dickerson, *Nucleic Acids Res.* **1989**, *17*, 1797.
[47] P. Murray-Rust, W. C. Stallings, C. T. Monti, R. K. Preston, J. P. Glusker, *J. Am. Chem. Soc.* **1983**, *105*, 3206.
[48] J. D. Dunitz, R. Taylor, *Chem. Eur. J.* **1997**, *3*, 89.
[49] J. D. Dunitz, *ChemBioChem* **2004**, *5*, 614.
[50] E. T. Kool, H. O. Sintim, *Chem. Commun.* **2006**, 3665.
[51] K. Reichenbächer, H. I. Süss, J. Hulliger, *Chem. Soc. Rev.* **2005**, *34*, 22.

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