Fluorinated enamines of nucleobases as precursors of nucleoside analogues. Synthesis, spectroscopic and structural studies†‡

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The ^{1}H and ^{19}F NMR spectra of *N*-α-fluoro-β-trifluoromethylenamines and isostructural *N*-β-fluoro-β-trifluoromethylenamines of nucleobases dissolved in $CDCl_3$ and DMSO-d_6 have shown distinct differences associated with the conformational conversion between the *Z* and *E* stereoisomers. In the *E* stereoisomer the tetrafluoropropenyl group is rotated relative to the heteroring plane, whereas the *Z* stereoisomer assumes the most planar structure. The flat conformation of the *Z* stereoisomer is stabilised by internal hydrogen bonding between C^{α}–H and the carbonyl oxygen (pyrimidinic bases) or the endocyclic nitrogen (purinic bases). Large variations in the magnitudes of the chemical shifts of C^{β}–H, C^{α}–F, C^{6}–H and C^{8}–H were observed, *i.e.* the chemical shift increased with increasing polarity and ability of DMSO-d_6 to establish intermolecular hydrogen bonds in competition with intramolecular hydrogen bonds. The (*Z*)-N^4-benzoyl-N^1-(1,3,3,3-tetrafluoroprop-1-enyl)cytosine crystals undergo a phase transition at 230 K induced by the tetrafluoropropenyl substituent reorientations. Between 300 and 230 K the molecules are present in two conformations, and below 230 K the molecules gradually assume five conformations, remaining in a stable equilibrium with intermolecular forces, evidenced by single-crystal X-ray diffraction.

Introduction

N-Vinyl derivatives of nucleobases are important starting materials for the synthesis of polymeric analogues of nucleic acids.[1] In a recent approach to modified nucleosides, the furanose ring was replaced with *N*,*O*-containing five-membered heterocycles, in particular isoxazolidine and isoxazoline derivatives. The 1,2-dipolar cycloaddition of nitrones to enamines is the most straightforward way to these derivatives.[2] However, the literature gives only a few examples of syntheses of enamines of nucleobases with fluorine and fluorine substituents in the enamine moiety.[3] Selective introduction of fluorine into biologically active molecules can substantially change their physical, chemical and biological properties, converting them into effective agents in many areas of biology and biochemistry. In the context of nucleic acids derivatives the carbohydrate-modified fluoronucleosides exhibit modulated pharmacological properties,[4] and fluorinated aromatic nucleoside analogues incorporated into oligonucleotides can be employed as a selective approach to pairing in DNA.[5] The role of fluorine substitution in bioorganic substrates is often discussed in terms of the ability of fluorine to act as a hydrogen or hydroxyl mimic.[6] Fluorine is a relatively close steric replacement for hydrogen and is capable of producing significant electronic changes in a molecule with minimal steric perturbation. Fluorine is also an isopolar and isosteric replacement for the hydroxyl group, since the C–F bond length (1.35 Å) is very similar to the C–O length (1.43 Å) and because fluorine is a weak hydrogen bond acceptor.

We have recently synthesized a new series of *N*-α,β-difluoro-β-trifluoromethyl enamines and *N*-α-fluoro-β-trifluoromethyl enamines of uracil (**2**), thymine (**3**), 5-fluorouracil (**4**), cytosine (**5** and **9**), adenine (**6**) and guanine (**7**) (Fig. 1). The compounds were obtained with high regioselectivity for N^9 (for purines) and N^1 (for pyrimidines), as mixtures of *E* and *Z* stereoisomers.[7]

We expected that *N*-α-fluoro-β-trifluoromethylenamines would undergo lithiation at low temperatures to give the corresponding products with electrophiles. Interestingly, the reaction of compound **2b** with excess of *t*-BuLi followed different courses for the *E* and *Z* stereoisomers. To explain this, we assumed that the *Z* stereoisomer could produce a weak hydrogen bond between C^{β}–H and C^{2}=O. Stereoisomer *E*, with the hydrogen atom C^{β}–H not involved in a hypothetical weak hydrogen bond, reacted as expected, so as a result of proton abstraction it gave a lithiated derivative that was quenched by CD_3OD to give a product of lithium–deuterium exchange. In the *Z* stereoisomer, whose hydrogen atom is engaged in the interaction with carbonyl, *t*-BuLi behaves as a typical nucleophile, giving as a result of the reaction with CD_3OD a mixture of addition–elimination products. The intermolecular hydrogen-type interactions have been earlier observed in heterocyclic *N*-vinyl derivatives,

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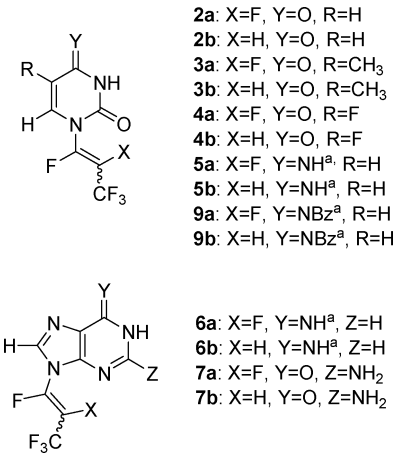

Fig. 1 *N*-α,β-Difluoro-β-trifluoromethyl enamines and *N*-α-fluoro-β-trifluoromethyl enamines of nucleic acid bases. [a] Compounds given in their imino forms.

where the β-*cis* hydrogen atom of the vinyl group participated in specific C–H···X interactions with an endocyclic or exocyclic heteroatom.[8] According to G. R. Desiraju, who addressed some questions related to the now well-established C–H···X hydrogen bonds, the observed interactions could belong to this category.[9]

The hydrogen bond plays an essential role in chemistry and biochemistry.[10] It generally has the form X–H···Y, where X and Y are highly electronegative atoms such as O or N. The idea that the less electronegative carbon can also behave as a proton donor to form C–H···Y hydrogen bonds has been the subject of controversy for many years, but it is now well accepted and has been identified in many biological systems[11] and crystal engineering.[12] Most of the C–H···Y hydrogen bonds have been observed for the activated C atom, where the hydrogen C atom is attached to electronegative groups such as halogen atoms or NH groups in proteins. Despite the importance of the C–H···X hydrogen bonds and extensive theoretical studies,[13] its nature is still being debated and there has been no experimental characterization of its strength to date.[14]

We present here the results of some ^{1}H NMR, ^{19}F NMR and IR measurements and crystallographic data along with a discussion of the possible factors determining different stabilities of the *Z* and *E* stereoisomers of the enamines studied.

Results and discussion

In order to examine the intramolecular hydrogen bonding and to evaluate the sensitivity of the ^{1}H and ^{19}F shift values on the conformations of molecules, the ^{1}H and ^{19}F NMR spectra of tetrafluoropropenyl enamines of nucleobases have been investigated. A scheme depicting the postulated hydrogen bond interactions and atom numbering for selected compounds **2b** and **6b** is given in Fig. 2.

NMR spectra

The ^{1}H and ^{19}F NMR experiments were carried out in $CDCl_3$ and DMSO-d_6. The choice of the NMR solvents was based upon their hydrogen bond profile. $CDCl_3$ can be considered as

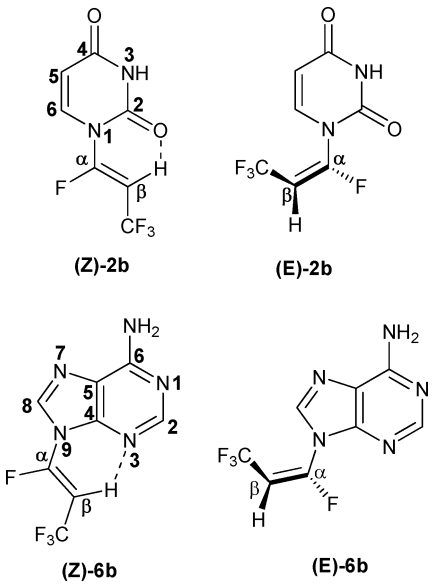

Fig. 2 The *E* and *Z* stereoisomers and the atom numbering for pyrimidinic and purinic enamines.

apolar and practically without specific hydrogen bond properties, whereas DMSO is a hydrogen bond acceptor. The ^{1}H NMR spectra taken in $CDCl_3$ and DMSO-d_6 provided the evidence of the interactions between C^{β}–H···O=C^{2} and C^{β}–H···N^{3} in the *Z* stereoisomers of compounds **2b–7b** and **9b**. Table 1 shows that a change in the solvent causes large variations in the values of chemical shift of C^{β}–H; *i.e.* its value increases with increasing polarity and ability of DMSO-d_6 to establish intermolecular hydrogen bonds in competition with intramolecular hydrogen bonds.

In general, the chemical shifts of the intramolecularly bonded C^{β}–H hydrogen atoms in the *Z* stereoisomers in $CDCl_3$ are shifted downfield relative to those of the C^{β}–H hydrogen atoms in the *E* stereoisomers. In DMSO-d_6 (a strong proton acceptor) the situation is reversed, and the hydrogen atoms of C^{β}–H in the *E* stereoisomers are not involved in any intramolecular interactions, and are stronger-downfield shifted than those in the *Z* stereoisomers.

The C^{β}–H hydrogen atoms of the tetrafluoropropenyl group of the *Z* stereoisomer of compounds **2b–4b** and **9b** are involved in the stereospecific intramolecular C–H···O=C interaction. Accordingly, the signals of C^{β}–H of stereoisomers *Z* are shifted in DMSO downfield by 0.20–0.47 ppm as compared to the spectra taken in $CDCl_3$, while those of stereoisomers *E* are shifted downfield by 0.91–0.98 ppm. Also the C^{β}–H of the *Z* stereoisomer of compound **6b** is similarly affected by the specific intermolecular C–H···N interaction, and the signal of H^{β} for the *Z* stereoisomer is shifted in DMSO shifted downfield only by 0.09 ppm, whereas the signal of H^{β} for the *E* stereoisomer is shifted downfield by 1.03 ppm. This relatively low susceptibility of H^{β} to the change in the solvent in the *Z* stereoisomer and much greater susceptibility in the *E* stereoisomer indicates that in the former in DMSO there is a strong competition between the intramolecular hydrogen bond type interaction and the intermolecular interactions with the solvent. It seems that the solvents like DMSO diminish but do not destroy the intramolecular C–H···O=C and C–H···N

Table 1 Chemical shifts (δ/ppm) of C^{β}–H and C^{α}–F of compounds **2b–9b** in $CDCl_3$ and DMSO-d_6

	Z stereoisomer				*E* stereoisomer			
	$CDCl_3$		DMSO-d_6		$CDCl_3$		DMSO-d_6	
Compound	C^{β}–H	C^{α}–F	C^{β}–H	C^{α}–F	C^{β}–H	C^{α}–F	C^{β}–H	C^{α}–F
Ura-(1,3,3,3-TFP) (**2b**)	5.97	−86.30	6.40	−76.51	5.91	−74.38	6.82	−72.82
Thy-(1,3,3,3-TFP) (**3b**)	5.89	−86.76	6.36	−76.80	5.83	−74.56	6.78	−72.95
5-FUra-(1,3,3,3-TFP) (**4b**)	5.97	−88.05	6.34	−77.40	5.88	−75.47	6.83	−73.95
Cyt-(1,3,3,3-TFP) (**5b**)	—[a]	—[a]	6.31	−76.26	—[a]	—[a]	6.56	−70.48
Ade-(1,3,3,3-TFP) (**6b**)	6.77	−96.29	6.68	−90.48	5.99	−73.78	7.02	−70.86
Gua-(1,3,3,3-TFP) (**7b**)	—[a]	—[a]	6.60	−89.11	—[a]	—[a]	6.80	−70.26
BzCyt-(1,3,3,3-TFP) (**9b**)	6.36	−90.23	6.56	−78.48	5.87	−75.19	6.85	−74.01

[a] Data not available in this solvent.

interactions by participating *via* the solute–solvent hydrogen bond. A particularly small $\Delta\delta$ ($= \delta H^{\beta}(Z_{CDCl_3}) - \delta H^{\beta}(Z_{DMSO})$) for compound **6b** suggests that in this compound the intermolecular interaction with the solvent plays a secondary role.

In the enamines studied the π-system of the tetrafluoropropenyl group and the purine or pyrimidine ring efficiently interact with each other *via* a p–π conjugation mechanism. The differences in the behaviour of the *E* and *Z* stereoisomers can be analysed in terms of the distortion of coplanarity between the tetrafluoropropenyl group and pyrimidine and purine rings, and thus a greater or smaller disruption of the p–π conjugation. The intermolecular interaction of the hydrogen bond type taking place in the *Z* stereoisomers and the related conformation stabilisation of these isomers should reduce the distortion of coplanarity and be manifested in the ^{19}F NMR parameters, including the deshielding/shielding effect on the F atoms.

According to the literature, the chemical shift of F^{α} in *Z*-perfluoropropenyl and *E*-perfluoropropenyl aromatic derivatives is very sensitive to the steric structure. In aromatic perfluoroalkene systems, the distortion of the planar structure induces a strong deshielding effect on C^{α}–F. It can be explained by the diamagnetic anisotropy appearing due to the aromatic π–electron system.[15] Thus, ^{19}F NMR spectroscopy can be a very effective tool in investigation of conformations of the systems in which the fluoroalkenyl substituent can assume a coplanar or out-of-plane conformation with respect to the other part of the molecule, depending on the intra- and intermolecular interactions.

Table 1 gives ^{19}F NMR data for compounds **2b–7b** and **9b** in the above-mentioned solvents. As expected, there are some differences in the chemical shift of C^{α}–F in the *E* and *Z* stereoisomers; the signal of C^{α}–F in the *E* stereoisomer is usually more deshielded than in C^{α}–F in the *Z* stereoisomer because of the stronger interaction of the *E*-CF_3 group with the heteroring, and thus stronger steric repulsion.

The solvent change in the spectra of the *E* stereoisomers results in only a small change in the position of the signal assigned to C^{α}–F. The difference in the chemical shifts, $\Delta\delta = \delta F^{\alpha}(E_{CDCl_3}) - \delta F^{\alpha}(E_{DMSO})$, is 1.18–1.56 ppm and only for compound **6b** does it increase to 2.93 ppm. The intermolecular hydrogen bond between C^{β}–H and DMSO does not significantly change the geometry of the molecule and has no effect on the p–π conjugation of the tetrafluoropropenyl substituent and purine or pyrimidine ring. In both solvents, $CDCl_3$ and DMSO-d_6, the *E* stereoisomer adopts the same or very similar conformation. The situation is drastically changed for the *Z* stereoisomers in which the solvent change disturbs the weak intramolecular hydrogen bond, which must affect the geometry of the molecule. Increasing non-planarity must cause a stronger deshielding effect which is clearly visible in all pyrimidinic *Z* enamines. In DMSO-d_6 the signal assigned to C^{α}–F is shifted downfield by 9.79–11.75 ppm in comparison with its position in the spectrum recorded in $CDCl_3$. Only in compound **6b** the effect of deshielding is much smaller, and $\Delta\delta$ ($= \delta F^{\alpha}(Z_{CDCl_3}) - \delta F^{\alpha}(Z_{DMSO})$) is 5.81 ppm. This observation confirms the earlier supposition based on the ^1H NMR results that in compound **6b** the intramolecular C–H···N hydrogen bond becomes competitive with that with the solvent, or that its breaking gives a smaller distortion of coplanarity. Clearly, the compounds studied have structures of different planarity following from their different thermodynamic stability. The *Z* stereoisomers are engaged in the hydrogen bond type interaction and tend to be as planar as possible, which is not true for the *E*stereoisomers. As mentioned above, the *Z* stereoisomers tend to assume the most planar conformation possible in $CHCl_3$, this conformation being distorted in DMSO-d_6, which has high hydrogen bond accepting capability and polarity.

To understand the effect of the solvent on the behaviour of similar systems, the positional isomers of compounds **2b–4b**, **6b** and **9b** were synthesised (Fig. 3). The reaction of uracil (**2**), thymine (**3**), 5-fluorouracil (**4**), adenine (**6**) and benzoylocytosine (**9**) with 1,2,3,3,3-pentafluoropropene gave tetrafluoropropenyl derivatives of compounds **2c**, **3c**, **4c**, **6c** and **9c** with the C^{α}–H hydrogen atom and C^{β}–F fluorine in the exocyclic olefin part of the moiety. In contrast to compounds **2b–9b**, the synthesis of these compounds are highly stereoselective, giving the *Z* stereoisomer in great excess. The differences in the polarity of the *E* and *Z* stereoisomers were sufficiently distinct to permit their separation by standard column chromatography.

Table 2 gives a selection of ^{19}F NMR and ^1H NMR data for the compounds **2c–4c**, **6c** and **9c**, namely the chemical shifts of C^{α}–H and C^{β}–F in $CDCl_3$ and DMSO-d_6.

The chemical shifts of C^{α}–H were expected to change considerably for both *Z* and *E* isomers on changing the solvent, which would be a consequence of much less engagement of this hydrogen atom in the intramolecular interactions. We expected that the strength of this interaction and its overall consequences in the rest of the molecule should

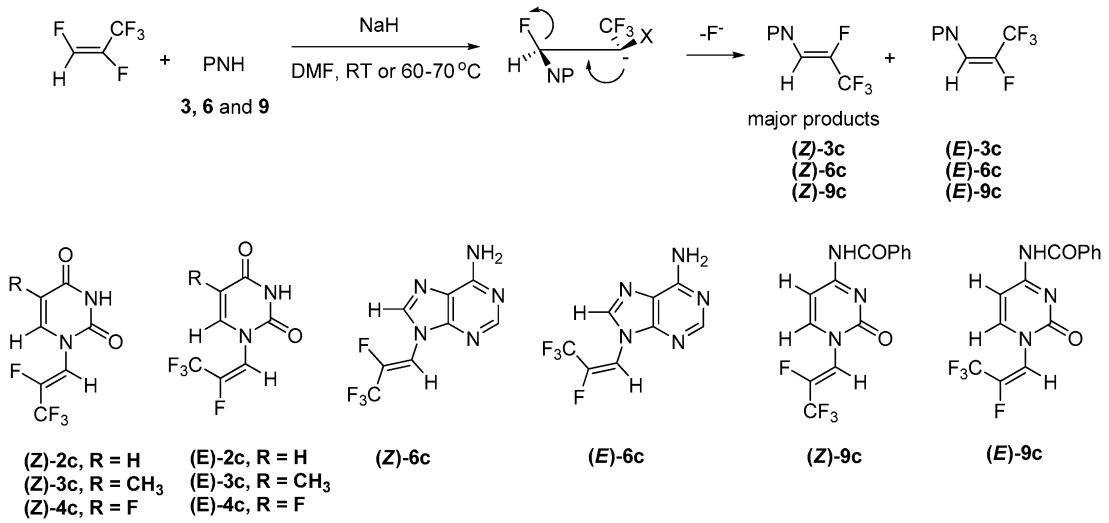

Fig. 3 *N*-β-Fluoro-β-trifluoromethylenamines of nucleobases.

Table 2 C^{α}–H and C^{β}–F ^{19}F NMR and ^{1}H NMR chemical shifts (δ/ppm) for the exocyclic tetrafluoropropenyl substituents of compounds **2c–4c**, **6c** and **9c**

	Z stereoisomer				*E* stereoisomer			
	$CDCl_3$		DMSO-d_6		$CDCl_3$		DMSO-d_6	
Compound	C^{β}–F	C^{α}–H	C^{β}–F	C^{α}–H	C^{β}–F	C^{α}–H	C^{β}–F	C^{α}–H
Ura-(2,3,3,3-TFP) (**2c**)	−144.51	7.27	−144.92	7.27	−137.04	7.00	−141.23	7.38
Thy-(2,3,3,3-TFP) (**3c**)	−145.37	7.26	−145.52	7.25	−138.22	6.99	−141.86	7.35
5-FUra-(2,3,3,3-TFP) (**4c**)	−144.43	7.26	−143.78	7.24	−136.05	6.96	−140.76	7.30
Ade-(2,3,3,3-TFP) (**6c**)	−141.63	7.55	−142.42	7.69	−137.72	7.43	−139.84	7.99
BzCyt-(2,3,3,3-TFP) (**9c**)	−143.77	7.48	−143.04	7.44	−137.31	7.23	−141.01	—[a]

[a] The H^{α} signal overlaps with those of the aromatic protons.

be less pronounced in the systems where the hydrogen bond occurs in five-membered rings than in six-membered ones. However, for the *Z* stereoisomers the replacement of $CDCl_3$ by strongly hydrogen bond accepting DMSO-d_6 has no (or a very small) effect on the chemical shift of C^{α}–H, while for the *E* stereoisomers this replacement results in a significant chemical shift of C^{α}–H towards lower fields. The signals of C^{α}–H of the *E* stereoisomers taken in DMSO-d_6 are shifted downfield by 0.36–0.56 ppm in comparison with $CDCl_3$. This result is surprising, but suggests that the intermolecular interaction with the solvent is no longer able to disturb the intramolecular interactions in the *Z* isomers. In compounds **2c–4c**, **6c** and **9c** the hydrogen atom C^{α}–H is at the highly electrophilic carbon, as the strongly electron-withdrawing CF_3 group is responsible for large electron deficit in the double bond. This situation should enhance the acidity of the C^{α}–H hydrogen atom, which can strengthen the C–H···O and C–H···N intramolecular interactions, despite the poorer geometrical parameters of the five-membered system. The fluorine atom C^{β}–F is not so sensitive to the steric structure as C^{α}–F. The signal assigned to C^{β}–F in both the *Z* and *E* stereoisomers are slightly shielded in DMSO-d_6 relative to $CDCl_3$, and the chemical shift difference $\Delta\delta$ is 0.15–0.79 ppm for the *Z* isomers and 2.12–3.64 ppm for the *E* isomers.

For *N*-α,β-difluoro-β-trifluoromethyl enamines **2a–7a** the C^{8}–H purine hydrogen atoms and C^{6}–H pyrimidine hydrogen atoms have practically the same chemical shift for both stereoisomers – the differences between *E* and *Z* do not exceed 0.04 ppm. For enamines **2b–7b** and **2c–6c** the differences in the chemical shifts of C^{6}–H (or C^{8}–H) between *Z* and *E* are clearly pronounced and accompanied by unexpected long-range spin–spin J_{HF} couplings.

The chemical shifts of C^{6}–H and C^{8}–H in $CDCl_3$ and DMSO-d_6 solutions and the observed values of $^{4}J_{HF}$ and $^{5}J_{HF}$ are collected in Table 3.

The couplings observed are the result of interactions over four and five bonds which are transferred through the zigzag fragment in the molecules. Similar long-range coupling constants for a β hydrogen atom in the vinyl group and ring hydrogen atoms have been observed in the ^{1}H NMR spectra of 2-substituted 1-vinylimidazoles.[16]

As follows from the above-discussed ^{1}H NMR and ^{19}F NMR data, in the *Z* stereoisomers of compounds **2b–6b** and **9b** the interactions C–H···O=C and C–H···N induce their planar or near planar conformation. The *Z* stereoisomers tend to assume the conformation with the tetrafluoropropenyl substituent in a *syn* position with respect to the C=O group of the heteroring in pyrimidinic bases or the pyrimidinic ring in purinic bases. In the *E* stereoisomers the lack of interactions of this type together with the repulsion between the C^{β}–CF_3 group and the carbonyl group or the rest of the purinic moiety leads to the complete deviation of the tetrafluoropropenyl

Table 3 ^{1}H NMR chemical shifts (δ/ppm) for C^6–H (for pyrimidines) and C^8–H (for purines), and heteronuclear coupling constants J_{HF}($J_{F,C^6–H}$ and $J_{F,C^8–H}$) of compounds **2a–7a**, **2b–7b** and **2c–6c** in $CDCl_3$ and DMSO-d_6

	Z stereoisomer		*E* stereoisomer	
Compound	$CDCl_3$	DMSO-d_6	$CDCl_3$	DMSO-d_6
Ura-PFP (**2a**)	—	7.96	—	7.96
Thy-PFP (**3a**)	7.01	—	7.01	—
5-FUra-PFP(**4a**)	7.43	—	7.39	—
Cyt-PFP (**5a**)	—	7.83	—	7.83
Ade-PFP (**6a**)	—	8.58	—	8.58
Gua-PFP (**7a**)	—	8.10	—	8.10
Ura-(1,3,3,3-TFP) (**2b**)	7.41	7.84	7.19	7.90
Thy-(1,3,3,3-TFP) (**3b**)	7.25, m, J = 0.55 Hz[b]	7.73, m, J = 0.37 Hz[b]	7.00	7.77
5-FUra-(1,3,3,3-TFP) (**4b**)	7.54, dd, J = 0.55 Hz[b]	8.35, dm, J = 0.55 Hz[b]	7.29	8.45
Cyt-(1,3,3,3-TFP) (**5b**)	—[a]	7.72	—[a]	7.71
Ade-(1,3,3,3-TFP) (**6b**)	8.14, d, J = 0.8 2 Hz	8.58	7.89	8.51
Gua-(1,3,3,3-TFP) (**7b**)	—[a]	8.10, d, J = 0.55 Hz	—[a]	8.01
Ura-(2,3,3,3-TFP) (**2c**)	7.72, dd, J = 1.2 Hz[b]	7.85	7.08, dd, J = 1.1 Hz[b]	7.62
Thy-(2,3,3,3 TFP) (**3c**)	7.56, m, J = 1.1 Hz[b]	7.74, m	6.99, m, J = 1.1 Hz[b]	7.50
5-FUra-(2,3,3,3-TFP) (**4c**)	7.86, dd, J = 1.9 Hz[b]	8.24	7.20, m, J = 0.8 Hz[b]	8.16
Ade-(2,3,3,3-TFP) (**6c**)	8.36, d, J = 2.0 Hz	8.54, d, J = 2.4 Hz	7.82	8.23

[a] Data not available in this solvent. [b] Only J_{HF} couplings ($J_{F,C^6–H}$ and $J_{F,C^8–H}$) are given.

group from the heteroring plane. In **(*Z*)-2c–(*Z*)-6c** and **(*Z*)-9c**, these stabilizing interactions force the *anti* conformation of the tetrafluoropropenyl substituent. In the *E* stereoisomers the molecules lose these conformations as a result of the existence of repulsive intramolecular interactions.

IR spectra

When an inter or intramolecular hydrogen bond is present, the stretching mode frequency of the donor X–H group is typically red-shifted with respect to that of the same group without the hydrogen bond. However, some examples are known where the C–H stretching vibrations involved in the C–H···X bond are shifted to higher wavenumbers (blue-shifted hydrogen bonds). In nucleic acid bases the N–H and C–H stretching modes usually appear in the region 3000–3200 cm^{-1}. For the C–H vibration mode of $CF_3CH{=}CH_2$ and $CF_3CH{=}CF_2$ a frequency around 3150–3170 cm^{-1} is reported.[17]

Unfortunately, in the solid-state IR spectra (KBr) of compounds **2c–4c** and **9c** it is hardly possible to determine the position of the C^α–H band because it overlaps with other stretching vibration bands. In the IR spectra of compounds **(*Z*)-** and **(*E*)-6c** only one broad band assigned to two types of C^8–H and C^α–H vibrations is observed. There are significant differences between two stereoisomers; the stretching frequency of C–H in **(*Z*)-9c**, in which the C–H distinctly participates in H-bond interaction, is 3110 cm^{-1}, whereas the stretching frequency in **(*E*)-9c** appears at 3156 cm^{-1}.

However, the hydrogen bonding causes noticeable changes in the stretching frequency of the acceptor partner $C^2{=}O$. In the 1690–1750 cm^{-1} range, two intense bands of stretching vibrations $C^2{=}O$ and $C^4{=}O$ are observed adjacent to stretching vibrations of $C^\alpha{=}C^\beta$ bond. The two C=O stretching modes in the uracil type of structure are easily identified because the first band is always located at higher wavenumbers. Vibrational frequencies of $C^\alpha{=}C^\beta$ bond for the *E* and *Z* stereoisomers (1711–1737 cm^{-1}) are in good agreement with previous studies.[17–19] The vibrational frequencies of $C^2{=}O$ for separated stereoisomers of compounds **2c–4c** and **9c** are given in Table 4.

This data show that the intramolecular hydrogen bonding $C^2{=}O\cdots H–C^\alpha$ causes an evident decrease in the absorption frequency of the acceptor partner.

Temperature X-ray study

It has been revealed by X-ray diffraction that at room temperature the molecules of N^4-benzoyl-N^1-(1,3,3,3-tetrafluoroprop-1-enyl)cytosine **(*Z*)-9b** are conformationally disordered.[7] The tetrafluoropropenyl substituent assumes two positions in the molecule, rotated by *ca.* 180° about the N1–C7 bond, and the terminal fluorine atoms apparently possess freedom to additionally rotate about the C8–C9 bond, as illustrated in Fig. 4. Otherwise the **(*Z*)-9b** molecule is nearly planar in the crystal structure: the best planes fitted to the phenyl and pyrimidinone rings are inclined by 7.2(2)°, and the two sites of the tetrafluoropropenyl substituent are nearly coplanar with the pyrimindinone ring, too.

At T_c = 230 K the crystal undergoes a continuous phase transition. Below T_c the unit-cell becomes two times larger along [010], the crystal symmetry lowers to space group *Pn*, and there are four symmetry-independent molecules, labelled A, B, C and D. The progress of the structural transformations preceding the phase transition can be visualized by the intensity changes of the reflections that become extinguished at T_c[20] as shown in Fig. 5. The crystal phase above T_c will be referred to as phase α and this below T_c as phase β. The phase transition differentiates the conformation of the four symmetry-independent molecules in phase β. Two of them have different orientations of tetrafluoropropenyl substituent (molecules A and B) and in the remaining two (molecules C and D) this

Table 4 The vibrational frequencies $\nu(C^2{=}O)$ (in cm^{-1}) for *Z* and *E* isomers of compounds **2c–4c** and **9c**

Compound	*Z* stereoisomer	*E* stereoisomer
Ura-(2,3,3,3-TFP) (**2c**)	1722	1729
Thy-(2,3,3,3-TFP) (**3c**)	1719	1725
5-FUra-(2,3,3,3-TFP) (**4c**)	1724	1742
BzCyt-(2,3,3,3-TFP) (**9c**)	1718	1740

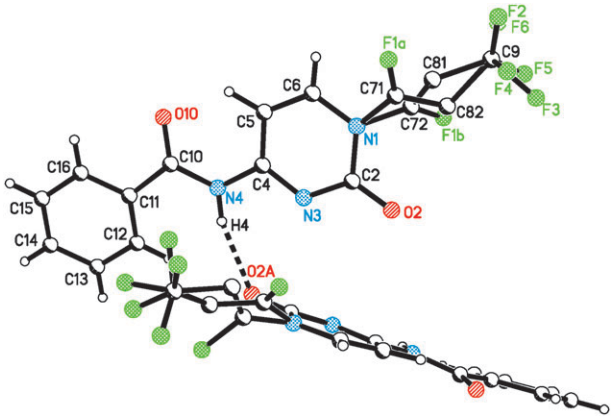

Fig. 4 Two molecules of **(*Z*)-9b** hydrogen-bonded in the structure into zigzag chains along crystal direction [010]. Both half-occupied sites of the disordered propane substituent have been included in this drawing.

substituent is orientationally disordered; however, in conformations different to those in phase α (Fig. 6).

Phases α and β are isostructural, and the projections of the crystal packing along [010] illustrate that except for small displacements of the symmetry-independent molecules in phase β (Fig. 7), these structures are nearly identical. Thus it can be argued that the main structural changes concern the tetrafluoropropenyl substituent; the progress of its temperature-controlled conformational differentiation is reproduced by the plot in Fig. 5.

The conformational differentiation of the tetrafluoropropenyl substituent is illustrated in Fig. 8. The conformations of two symmetry-independent molecules disordered in phase β (*i.e.* molecules C and D) are very similar to the conformations assumed by the molecule disordered in phase α. It is an intriguing observation that the conformations of the molecules disordered in phase β are significantly different from those of the ordered molecules. Thus at 100 K, 78% of one molecule (C) and 46% of another (molecule D) – *i.e.* 124% of symmetry-independent 400% molecules – assume the conformation with

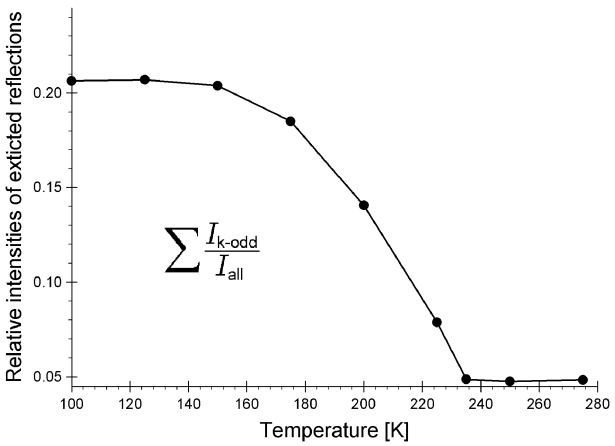

Fig. 5 The temperature dependence of the ratio $\sum I_{k\ \text{odd}} \Big/ \sum I_{\text{all}}$, where $\sum I_{k\ \text{odd}}$ is the sum of the intensities of reflections extinguished, for which Miller indices k are odd, and $\sum I_{\text{all}}$ is the sum of all measured intensities.

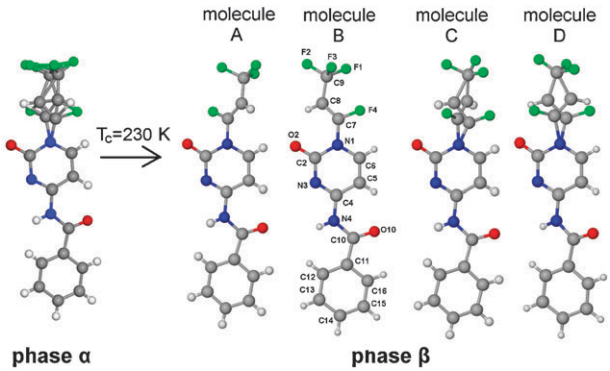

Fig. 6 Conformation of molecules of **(*Z*)-9b** at 296 K and 100 K.

the C2–N1–C7–C8 torsion about 55°, 100% (ordered molecule A) assume the conformation with the torsion about −54°, another 100% (ordered molecule B) with the torsion about 157°, and 76% (22% and 54% of molecules C and D, respectively) with the torsion about −160°. This testifies to the fact that the molecular conformation about the N1–C7 bond is very flexible, and it is most likely that the observed conformations result from the cumulative effect of the molecular preference and crystal surroundings. The disordered conformation in the crystalline state, even in the low-temperature phase, is usually an indication that the compound is also conformationally disordered in solutions. This should be reflected by broadening of the NMR peaks assigned to the protons located in the disordered group and its vicinity. However, the NMR data clearly show that the examined molecules adopt single conformations in solution.

The spectral analysis of (*Z*)-*N*-α-fluoro-β-trifluoromethylenamines of nucleobases indicates that the orientation of the tetrafluoropropenyl group is stabilized by intramolecular C–H···O interactions. The shortest intramolecular C–H···O contact in **(*Z*)-9b** is 2.278(8) Å and the C–H···O angle is 113.70° However, this hydrogen bond is clearly formed in molecule B of phase β and it also contributes to the structures of disordered molecules C and D, whereas the conformation of molecule A excludes the possibility of this hydrogen bond formation (Fig. 6).

Conclusions

Our experimental results have demonstrated that (*Z*)-*N*-α-fluoro-β-trifluoromethylenamines as well as (*Z*)-*N*-β-fluoro-β-trifluoromethylenamines, in contrast to their *E* analogues, prefer to adopt the planar conformation stabilised by stereospecific intramolecular nonbonding interactions. The formation of C–H···O=C[2] and C–H···N[3] hydrogen bonds helps anchor the planar orientation. The flat structure is stabilised in nonpolar solvents. Solvents like DMSO, with high hydrogen bonding abilities, disrupt the intramolecular hydrogen bond and weaken the p–π conjugation. Such interactions of a weak hydrogen bond type essentially affect both ^{19}F NMR and ^{1}H NMR parameters of all *Z* stereoisomers.

In X-ray study a second-order conformational phase transition exhibited by **(*Z*)-9b** illustrates the interplay between the structure of flexible molecules and intermolecular interactions.

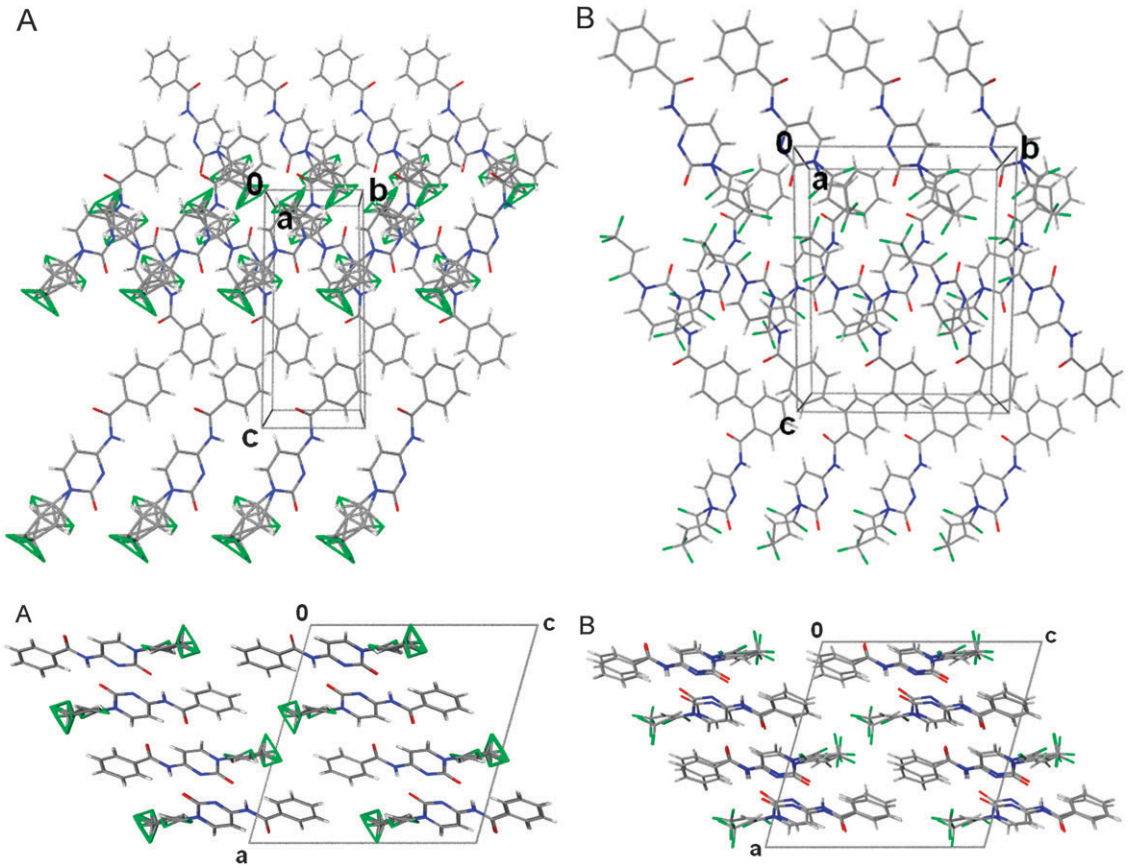

Fig. 7 Comparison of the crystal structures of **(*Z*)-9b** viewed down [100] and projected down [010]: (A) in phase α at 296 K; and (B) in phase β at 100 K.

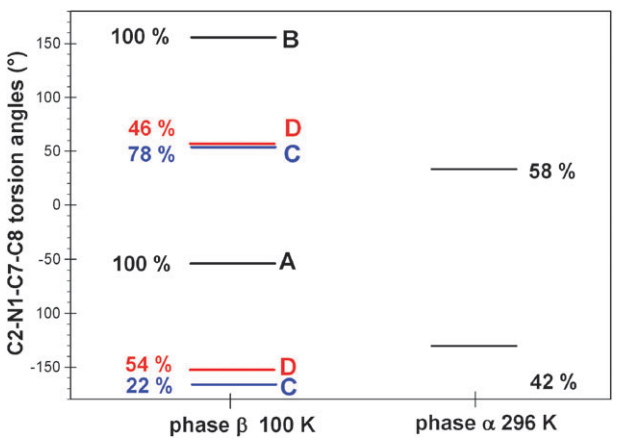

Fig. 8 Torsion angles C2–N1–C7–C8 describing the orientation of the tetrafluoropropenyl group in **(*Z*)-9b**. The torsion angles of the ordered molecules in phase β are shown in black, and those of disordered molecules C and D in blue and red, respectively.

In the low-temperature phase of this compound of four symmetry-independent molecules, only one exhibits medium length CH···O intramolecular hydrogen bond (O···H distance 2.28 Å), while in three other molecules the tetrafluoropropenyl group is either disordered or in the conformation with the oxygen and hydrogen atoms apart.

In summary, the combined spectroscopic and crystallographic approach has given us a greater understanding of the significant differences in the structure of the *Z* and *E* tetrafluoropropenyl enamines of nucleic acid bases and, in the more fundamental sense, the behaviour of related compounds.

Experimental section

^{1}H and ^{19}F NMR spectra were collected by using a Varian Gemini 300 MHz spectrometer (300.069 MHz for ^{1}H, 282.318 MHz for ^{19}F). Coupling constants are quoted in Hz. The mass spectra were recorded on a AMD 402 spectrometer under electron impact conditions. The elemental analyses were made on Perkin Elmer apparatus. The IR spectra (in KBr) were recorded on a Bruker IFS 113v spectrometer. *N*-α,β-Difluoro-β-trifluoromethylenamines (**2a–7a** and **9a**) and *N*-α-fluoro-β-trifluoromethylenamines (**2b–7b** and **9b**) were prepared and described previously.[7]

General procedure for the synthesis of 2c, 3c, 4c, 6c and 9c

The nucleobase **2**, **3**, **4**, **6**, and **9** (2 mmol) was dissolved or suspended in DMF (15 ml) at 60 °C. The solution was cooled to room temperature and NaH (60% oil suspension; 3 mmol) was added under argon. The mixture was stirred until the evolution of H_2 ceased. Then the reaction mixture was heated to 70 °C and 1,2,3,3,3-pentafluoropropene (approximately 6–8 mmol) was slowly bubbled through the reaction mixture using a Carrius tube equipped with a needle. The mixture was kept at 70 °C for 5–10 min. After cooling to room temperature the crude reaction mixture was poured into water (30 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined extracts

were washed with water and dried over Na_2SO_4. After removal of solvents under reduced pressure the residue was purified by silica gel column chromatography (silica gel, hexane–$CHCl_3$ gradient, then $CHCl_3$, then $CHCl_3$–MeOH gradient) to give a mixture of *E* and *Z* stereoisomers of enamine. Separation on a preparative plate gave pure stereoisomers.

N^1-(2,3,3,3-Tetrafluoroprop-1-enyl)uracil 2c

Compound **2** (224 mg, 2 mmol) gave (260 mg, 58%) of **2c** as a colourless solid. *Z*/*E* ratio 90 : 10.

Elemental analysis. Found: C, 37.39; H, 1.85; N, 12.30. Calc. for $C_7H_4F_4N_2O_2$ (224.08): C, 37.52; H, 1.79; N, 12.50%.

***Z* stereoisomer.** Temperature of sublimation 141–145 °C; IR (KBr) ν_{max}/cm^{-1} 1737 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 5.92 (1H, d, J_{HH} 8, C^5–H), 7.27 (1H, d, J_{HF} 27, H^{α}), 7.72 (1H, dd, J_{HH} 8 and *J* 1.2, C^6–H), 8.73 (1H, bs, N^3–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −72.01 (3F, d, J_{FF} 12, CF_3), −144.51 (1F, dq, J_{FF} 12 and J_{FH} 27, F^{β}); *m*/*z* (EI) 224 (M^+, 46%), 181 (100%).

***E* stereoisomer.** M.p. 136–140 °C; IR (KBr) ν_{max}/cm^{-1} 1713 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 5.85 (1H, d, J_{HH} 8, C^5–H), 7.00 (1H, d, J_{HF} 10, H^{α}), 7.08 (1H, dm, J_{HH} 8 and *J* 1.1, C^6–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −68.90 (3F, d, J_{FF} 10, CF_3), −137.05 (1F, dm, J_{FF} 10 and J_{FH} 11, F^{β}); *m*/*z* (EI) 224 (M^+, 52%), 181 (100%).

N^1-(2,3,3,3-Tetrafluoroprop-1-enyl)thymine 3c

Compound **3** (252 mg, 2 mmol) gave (271 mg, 57%) of **3c** as a colourless solid. *Z*/*E* ratio 88 : 12.

Elemental analysis. Found: C, 40.59; H, 2.34; N, 11.98. Calc. for $C_8H_6F_4N_2O_2$ (238.15): C, 40.35; H, 2.54; N, 11.76%.

***Z* stereoisomer.** M.p. 140–142 °C; IR (KBr) ν_{max}/cm^{-1} 1734 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.04 (3H, d, *J* 1.4, CH_3), 7.26 (1H, d, J_{HF} 27, H^{α}), 7.56 (1H, m, C^6–H), 9.50 (1H, bs, N^3–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −71.92 (3F, d, J_{FF} 12, CF_3), −145.37 (1F, m, J_{FF} 12 and J_{FH} 27, F^{β}); *m*/*z* (EI) 238 (M^+, 42%), 98 (100%).

***E* stereoisomer.** M.p. 120–121 °C; IR (KBr) ν_{max}/cm^{-1} 1711 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.96 (3H, d, *J* 1.4, CH_3), 6.90 (1H, m, C^6–H), 6.99 (1H, d, J_{HF} 10, H^{α}); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −68.96 (3F, d, J_{FF} 10, CF_3), −138.22 (1F, m, J_{FF} 10 and J_{FH} 10, F^{β}); *m*/*z* (EI) 238 (M^+, 61%), 98 (100%).

N^1-(2,3,3,3-Tetrafluoroprop-1-enyl)-5-fluorouracil 4c

Compound **4** (260 mg, 2 mmol) gave (281 mg, 58%) of **4c** as a colourless solid. *Z*/*E* ratio 85 : 15.

Elemental analysis. Found: C, 34.92; H, 1.19; N, 11.39. Calc. for $C_7H_3F_5N_2O_2$ (242.08): C, 34.73; H, 1.24; N. 11.57%.

***Z* stereoisomer.** M.p. 116–118 °C; IR (KBr) ν_{max}/cm^{-1} 1737 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.26 (1H, d, J_{HF} 26, H^{α}), 7.86 (1H, dd, J_{HF} 6 and J_{HF} 2, C^6–H), 9.20 (1H, bs, N^3–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −72.00 (3F, d, J_{FF} 12, CF_3), −144.43 (1F, dq, J_{FF} 12 and J_{FH} 26, F^{β}), −160.35 (1F, d, J_{FH} 6, C^5–F); *m*/*z* (EI) 242 (M^+, 87%), 140 (100%).

***E* stereoisomer.** M.p. 140–142 °C; IR (KBr) ν_{max}/cm^{-1} 1717 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.96 (1H, d, J_{HF} 10, H^{α}), 7.20 (1H, dm, J_{HF} 6 and J_{HF} 1, C^6–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −69.00 (3F, d, J_{FF} 10, CF_3), −136.05 (1F, m, J_{FF} 10 and J_{FH} 11, F^{β}), −163.22 (1F, d, J_{FH} 6, C^5–F); *m*/*z* (EI) 242 (M^+, 76%), 140 (100%).

N^9-(2,3,3,3-Tetrafluoroprop-1-enyl)adenine 6c

Compound **6** (270 mg, 2 mmol) gave (301 mg, 61%) of **6c**. **(*Z*)-6c** as colourless fine needles, **(*E*)-6c** as a colourless solid. *Z*/*E* ratio 79 : 21.

Elemental analysis. Found: C, 38.59; H, 2.33; N, 28.09. Calc. for $C_8H_5F_4N_5$ (247.16): C, 38.88; H, 2.04; N, 28.34%.

***Z* stereoisomer.** M.p. 230–233 °C; IR (KBr) ν_{max}/cm^{-1} 1738 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.55 (1H, d, J_{HF} 27, H^{α}), 5.74 (2H, s, NH_2), 8.42 (1H, s, C^2–H), 8.36 (1H, d, J_{HF} 2, 1H, C^8–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −71.76 (3F, d, J_{FF} 12, CF_3), −141.64 (1F, m, J_{FF} 12 and J_{FH} 27, F^{β}); *m*/*z* (EI) 247 (M^+, 100%).

***E* stereoisomer.** M.p. 234–235 °C; IR (KBr) ν_{max}/cm^{-1} 1710 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.43 (1H, d, J_{HF} 11, H^{α}), 5.70 (2H, s, NH_2), 7.82 (1H, s, C^8–H), 8.43 (1H, s, C^2–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −68.40 (3F, d, J_{FF} 10, CF_3), −137.72 (1F, m, J_{FF} 10 and J_{FH} 11, F^{β}); *m*/*z* (EI) 247 (M^+, 100%).

N^4-Benzoyl-N^1-(2,3,3,3-tetrafluoroprop-1-enyl)cytosine 9c

Compound **9** (430 mg, 2 mmol) gave (484 mg, 74%) of **9c** as colourless solid. *Z*/*E* ratio 88 : 12.

Elemental analysis. Found: C, 51.09; H, 2.79; N, 12.59. Calc. for $C_{14}H_9F_4N_3O_2$ (327.25): C, 51.38; H, 2.77; N, 12.84%.

***Z* stereoisomer.** Decomposition >220 °C; IR (KBr) ν_{max}/cm^{-1} 1733 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.48 (1H, m, partially overlapped with aromatic protons, H^{α}), 7.49–7.96 (6H, m, C_6H_5 and C^5–H), 8.06 (1H, d, J_{HH} 8, C^6–H), 8.83 (1H, bs, N^4–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −72.14 (3F, d, J_{FF} 12, CF_3), −143.77 (1F, m, F^{β}); *m*/*z* (EI) 327 (M^+, 10%), 105 (100%).

***E* stereoisomer.** M.p. 212–214 °C; IR (KBr) ν_{max}/cm^{-1} 1715 (C^{α}=$C^{\beta}F$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.23 (1H, d, J_{HF} 11, H^{α}), 7.50–7.96 (6H, m, C_6H_5 and C^5–H), 7.84 (1H, d, J_{HH} 8, C^6–H), 8.82 (1H, bs, N^4–H); δ_F (282 MHz; $CDCl_3$; $CFCl_3$) −68.38 (3F, d, J_{FF} 10, CF_3), −137.31 (1F, m, J_{FF} 10 and J_{FH} 11, F^{β}); *m*/*z* (EI) 327 (M^+, 15%), 105 (100%).

Crystal structure analysis

X-ray data for N^4-benzoyl-N^1-(1,3,3,3-tetrafluoroprop-1-enyl)-cytosine **(*Z*)-9b** were collected with a KUMA KM-4 CCD diffractometer. An Oxford Cryostream attachment was used for lowering the temperature. Programs used: data collection and data reduction CrysAlis[21], structure solution SHELXS-97, structure refinement SHELXL-97.[22]

X-ray crystal structure analysis for I (CCDC 716978)‡: formula $C_{14}H_9F_4N_3O_2$, M = 327.24, colourless crystal 0.50 × 0.30 × 0.10 mm, a = 15.050(2) Å, b = 12.1206(19) Å, c = 15.425(2) Å, β = 105.596(12)°, V = 2710.1(7) Å^3,

ρ_{calc} = 1.604 g cm^{-3}, μ = 0.147 mm^{-1}, Z = 8, monoclinic, space group Pn, λ = 0.71073 Å, T = 100 K, ω scans, reflections collected/independent 17 292/8467 [R(int) = 0.0404], 874 refined parameters, R = 0.0822, wR_2 = 0.2454, goodness-of-fit on F^2 = 1.140, max. residual electron density 1.750 and −0.683 e Å^{-3}; hydrogen atoms calculated and refined as riding atoms, isotropic thermal parameters for all H-atoms refined.

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