Struct Chem (2010) 21:245–254
DOI 10.1007/s11224-009-9570-5

ORIGINAL RESEARCH

X-ray crystal structures of halogen containing nucleobase derivatives in unsolvated and DMSO solvated forms

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Received: 13 July 2009 / Accepted: 27 November 2009 / Published online: 11 December 2009

Abstract A series of halogenated nucleobase derivatives **1**–**4** is reported to yield solvent-free (**2**) and DMSO solvated crystals (**1**, **3**, **4**) on the crystallization from DMSO with one of them (**4**) containing an additional molecule of water. The molecular and crystal structures are described and comparatively discussed with reference to previous results on related compounds. The molecule of **1** is planar, molecules of **2** and **3** show *syn* alignment with reference to the heterocyclic ring and common C2′-*endo* conformation of the ribose residue, while **4** is also *syn* aligned but C4′-*exo* in the sugar conformation. The packing structures reveal typical aggregations created via networks of hydrogen bonds. These involve conventional N–H···N, N–H···O and O–H···O interactions between nucleobase and ribose units as well as solvent molecules, additionally supported by weak C–H···O contacts but excluding the participation of halogen···halogen interactions as well as halogen···heteroatom contacts in the supramolecular structure formation.

Keywords Nucleobase derivatives · Halogen compounds · DMSO solvates · X-ray analysis · Hydrogen bonding

Introduction

The pairing of nucleobases via hydrogen bonding is a fundamental process in many biological events, such as genetic coding, biological information storage and protein biosynthesis [1, 2]. In addition, the ability of nucleobases to form duplexes and other secondary structures [3] is becoming more and more widespread in the construction of new materials for potential nanotechnological applications [4–9]. With reference to this behavior, the hybridization of nucleobases with fluorophores [10, 11] or metal complexes [12] has led to the creation of programmable supramolecular devices and architectures [13–16], all showing the particular interaction property of nucleobases as an important principle [17, 18].

In order to make chemical systems of this type accessible, halogenated nucleobase derivatives are suitable basic compounds or intermediates in a respective synthesis. A particular advantage of these halogenated compounds is that they can be used for a variety of modern C–C couplings, including the reactions originally developed by Sonogashira-Hagihara [19], Suzuki-Miyaura [20] or Stille [21] as being the methods most frequently practiced [22–27]. These halogen derivatives are easily prepared via simple halogenation of the respective parent compound. Hence, halogenated derivatives of nucleobases and nucleosides have been known for a long time [28–30], involving the description of crystal structures in several cases of compounds of this kind [31–34]. However, all the crystals for the structural analysis have been obtained from aqueous solution, frequently giving rise to hydrate formation [31, 32], while structures of crystals that were grown from non-aqueous solution are, as far as we know, not mentioned in the literature, although one may expect the crystal structure to be influenced by the solvent. From among the rather rare cases of organic solvents that dissolve nucleobases and nucleosides to a sufficient extent, DMSO was selected which is a highly polar solvent and strong acceptor in hydrogen bonding but only a weak

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hydrogen bonding donor [35]. Nevertheless, solvated aggregate structures could be formed that might exhibit interesting modes of interaction between particular nucleobase derivatives and DMSO. It was also a challenge to study potential halogen contacts [36–38] emanating from the halogen substituent.

Following this approach, here we present the results of an X-ray structural analysis performed on the crystals of 5-iodocytosine (**1**) and of three different derivatives of bromo substituted nucleosides (**2**–**4**), as specified in Fig. 1, which were obtained from DMSO solution. These structures are discussed in comparison with reported data of the structures produced from aqueous solution [31, 32, 34].

Experimental

5-Iodocytosine (**1**) was obtained by iodination of cytosine with iodine in aqueous KOH [30]. 8-Bromoadenosine (**2**) was synthesized from adenosine and bromine in a buffered aqueous solution (NaOAc/HOAc) [39]; 8-bromoguanosine (**3**) was analogously prepared from guanosine but with the bromination carried out in water [40]. Reaction of 8-bromoguanosine with *i*-butyryl chloride in pyridine was used to yield 2-*i*-butyramido-8-bromo-9-(2′,3′,5′-tri-*O*-*i*-butyryl-*β*-D-ribofuranosyl)purin-6-one (**4**) [26].

Crystals of the compounds suitable for X-ray analysis were formed by slow evaporation of corresponding solutions of **1**–**4** in DMSO. The X-ray diffraction intensities were recorded on a Bruker Kappa diffractometer equipped with an APEX II CCD area detector and graphite-monochromatized MoK_α radiation ($\lambda = 0.71073$ Å) employing φ and ω scan modes. The data were corrected for Lorentz and polarization effects. Semiempirical absorption corrections were applied using the SADABS program [41] and the SAINT program was utilized for integration of the diffraction profiles [42]. The crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement against F^2 using SHELXL-97 [43]. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were generated at ideal geometrical positions and refined with the appropriate riding model or positioned by Difference Fourier synthesis. Geometrical calculations were performed using PLATON [44] and molecular graphics were generated using SHELXTL [45].

Results and discussion

Crystallization of the halogenated nucleobase or nucleoside derivatives **1**–**4** (Fig. 1) from DMSO solution yielded solvated species of compounds **1**, **3** and **4**. In the cases of **1** and **3**, they were shown to be 1:1 stoichiometric solvates with DMSO, while **4** crystallized as a mixed hydrate solvate containing **4**, water and DMSO in a stoichiometric 1:1:1 ratio, which corresponds with NMR integrations and elemental analyses of the particular species. Remarkably, the halogenated nucleoside **2** was obtained in solvent-free crystals. Crystal data and details of the refinement of the structures, **1**·DMSO, **2**, **3**·DMSO and **4**·H_2O·DMSO, are summarized in Table 1. Selected torsion angles for the nucleoside derivatives that define the principal molecular conformations are listed in Table 2. Parameters of the hydrogen bonding interactions are specified in Table 3, whereas Fig. 2 shows the molecular structures, including atom labeling schemes. Packing illustrations and diagrams involving specific modes of hydrogen bonding are given in Figs. 3–7.

Structure of 5-iodocytosine·DMSO (**1**·DMSO)

The compound crystallizes in the monoclinic space group $P2_1/c$ with one molecule of **1** and one DMSO molecule in the asymmetric unit. The molecular structure of the nucleobase largely agrees with an already known solvent-free structure of compound **1** [34]. The pyrimidine ring is nearly planar with the exocyclic amino group not deviating significantly from the least-squares plane of the ring atoms.

The crystal is predominantly stabilized by hydrogen bonding, including both nucleobase and DMSO molecules (Table 3). They form a tape structure with the tapes located parallel to the Miller plane *101* and the individual tapes elongating in direction of the *b*-axis to yield an ABAB layer structure parallel to the *bc*-plane (Fig. 3a). Within a single tape, eight-membered hydrogen bonded rings that link the nucleobase molecules are found (Fig. 3b) involving

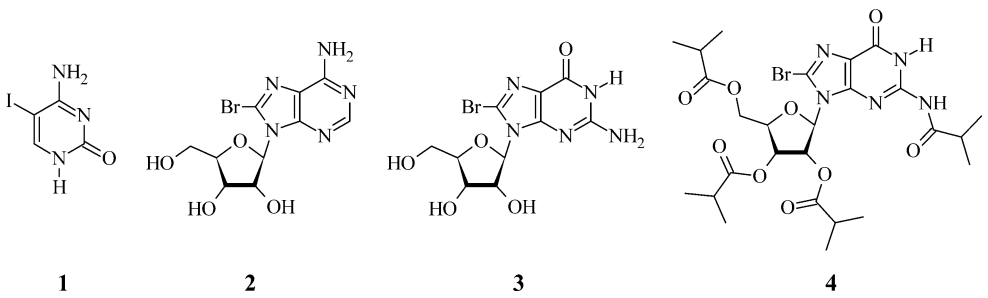

Fig. 1 Chemical structures of the nucleobase derivatives studied in this paper

Table 1 Crystallographic data for the compounds studied

Compound	**1**·DMSO	**2**	**3**·DMSO	**4**·H_2O·DMSO
Empirical formula	$C_4H_4INO_3 \cdot C_2H_6OS$	$C_{10}H_{12}BrN_5O_4$	$C_{10}H_{12}BrN_5O_5 \cdot C_2H_6OS$	$C_{26}H_{36}BrN_5O_9 \cdot H_2O \cdot C_2H_6OS$
Formula weight (g mol^{-1})	315.13	346.16	440.28	738.65
Temperature (K)	173(2)	296(2)	296(2)	90(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1$	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$
Unit cell dimensions				
a (Å)	11.3335(3)	5.11690(10)	6.6841(6)	9.7254(3)
b (Å)	9.4638(2)	17.8949(4)	10.9379(11)	11.4087(4)
c (Å)	9.8621(3)	6.9879(2)	22.977(2)	31.2293(10)
α (°)	90	90	90	90
β (°)	105.1790(10)	98.984(2)	90	90
γ (°)	90	90	90	90
V ($Å^3$)	1020.89(5)	632.01(3)	1679.9(3)	3465.0(2)
Z	4	2	4	4
Calculated density (g cm^{-3})	2.050	1.819	1.741	1.416
Absorption coefficient (mm^{-1})	3.315	3.275	2.613	1.309
$F(000)$	608	348	896	1544
Crystal size (mm^3)	0.22 × 0.37 × 0.43	0.04 × 0.14 × 0.23	0.12 × 0.14 × 0.32	0.13 × 0.20 × 0.55
θ range for data collection (°)	2.85–25.99	2.95–27.99	2.06–25.49	2.19–30.50
Limiting indices	$-13 \le h \le 13$	$-6 \le h \le 6$	$-8 \le h \le 5$	$-13 \le h \le 13$
	$-11 \le k \le 11$	$-23 \le k \le 23$	$-13 \le k \le 12$	$-16 \le k \le 16$
	$-12 \le l \le 12$	$-9 \le l \le 9$	$-27 \le l \le 27$	$-44 \le l \le 44$
Reflections collected/unique	27458/1996 [R(int) = 0.0204]	16271/3050 [R(int) = 0.0401]	12165/3106 [R(int) = 0.0541]	50172/10563 [R(int) = 0.0411]
Completeness to θ (%)	99.8	99.9	99.4	99.9
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	1996/0/120	3050/1/184	3106/0/234	10563/2/472
Goodness-of-fit on F^2	1.147	1.019	0.974	1.047
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0147$, $wR_2 = 0.0354$	$R_1 = 0.0242$, $wR_2 = 0.0555$	$R_1 = 0.0316$, $wR_2 = 0.0374$	$R_1 = 0.0352$, $wR_2 = 0.0752$
R indices (all data)	$R_1 = 0.0151$, $wR_2 = 0.0356$	$R_1 = 0.0291$, $wR_2 = 0.0571$	$R_1 = 0.0402$, $wR_2 = 0.0694$	$R_1 = 0.0616$, $wR_2 = 0.0825$
Largest diff. peak and hole (e $Å^{-3}$)	0.345 and −0.318	0.392 and −0.193	0.767 and −0.399	0.584 and −0.559

conventional N–H···N and N–H···O contacts as the characteristic feature. The tape structure is not completely planar, because the nucleobase molecules are slightly rotated to each other (interplanar angle between the least-squares planes of two pyrimidine rings of 9.27(12)°). This specific hydrogen bonding pattern seems to be a rather robust supramolecular synthon [46] since it is also present both in the structures of the solvent-free compound **1** [34] and 5-bromocytosine [33]. The DMSO molecules are also components of the tapes. They are located in longitudinal direction at both sides of the tape, operating as hydrogen bonding acceptors as well as hydrogen bonding donors to create another type of eight-membered hydrogen bonded cyclic pattern formed by means of N–H···O and weaker C–H···O contacts [47], with the carbonyl oxygen of the nucleobase being the acceptor of a three-centered hydrogen bond. Between the single tapes, there are weak C–H···N interactions [47, 48] including nucleobase and DMSO molecules as well as offset face-to-face π–π stacking interactions [49] between pyrimidine rings. However, the iodine atom of **1** is not engaged in any contact relevant to the packing structure. Nevertheless, it acts as an acceptor for an intramolecular hydrogen bond with the neighboring N–H group of the pyrimidine ring (N4-H4B···I5).

Table 2 Selected torsion angles for the nucleoside derivatives

Denotation[a]	Torsion angles (°)		
	2	**3**·DMSO	**4**·H_2O·DMSO
χ	59.77(30)	66.06(38)	64.79(26)
ν_0	−22.01(23)	−28.17(31)	−23.34(18)
ν_1	35.40(20)	39.95(29)	−4.13(18)
ν_2	−34.75(20)	−35.92(30)	27.92(19)
ν_3	23.35(23)	21.00(32)	−42.37(18)
ν_4	−1.03(25)	4.24(32)	41.46(18)

[a] *Definition*: χ (C4–N9–C11–O10), ν_0 (C14–O10–C11–C12), ν_1 (O10–C11–C12–C13), ν_2 (C11–C12–C13–C14), ν_3 (C12–C13–C14–O10), ν_4 (C11–O10–C14–C13)

Structure of 8-bromoadenosine (**2**)

The crystal structure of this solvent-free compound, crystallizing in the non-centrosymmetric space group $P2_1$, has already been published in 1970 [32]. In order to lead to more precise structural parameters, the structure solution was reconsidered using modern technical equipment. Moreover, in the previous paper, the structure of **2** is reported only rather briefly with an emphasis on the conformational property of the molecule rather than on current aspects of supramolecular behavior.

The bond parameters of the previous [32] and the present data are in reasonable agreement (Fig. 2b). The purine ring is planar to within experimental error, while the plane of the ribose unit, defined by C11, C13, C14 and O10, is rotated about 76.02(6)° towards the plane of the nucleobase. The distance of 1.3340(33) Å between the atoms C6 and N6 suggests a double bond, giving rise to a planar structure of the amino group. The torsion angle of the atom sequence C4–N9–C11–O10 with $\chi = 59.77(30)°$ (Table 2) indicates a *syn* alignment of the sugar moiety. This means that the sterical hindrance caused by the purine ring is less significant than the hindrance caused by the bromo substituent of C8. Furthermore, this conformation is stabilized by a strong intramolecular hydrogen bond between O15 and N3 and a weaker one between C12 and N3. Additional stabilization results from an intramolecular O–H···O contact (O12–H17···O13) and a weak C–H···Br interaction (C11–H11···Br8). The ribose sugar residue shows a so-called C2′-*endo* conformation, explained in more depth in the earlier paper [32].

Irrespective of the solvent used for recrystallization—water in the previous and DMSO in the present study—compound **2** was obtained in crystals free from solvent. This may indicate that the molecule is rather well suited to yield a balanced packing structure without the help of additional solvent molecules. In a more detailed description, due to their planar structure, the purine moieties give rise to the formation of molecular layers (Fig. 4). They exhibit a specific zig-zag pattern which is defined by the dihedral angle of 21.18(6)° between the planes of two neighboring purines. Within an individual layer, the sequence is ABAB, with the layers differing in the orientation of the ribose units. This enables molecules within the layer to form N–H···O (N6, O15) and O–H···N (O13, N7) hydrogen bonds between the purine and ribose moieties of neighboring molecules. These layers are linked through strong O–H···O hydrogen bonding interactions that include O12 and O15 atoms of two ribose units, completing the network structure of hydrogen bonds. Although the bromine substituent affects the molecular conformation of **2**, the halogen atom is not involved in a definite intermolecular contact, as before.

Structure of 8-bromoguanosine·DMSO (**3**·DMSO)

Unlike 8-bromoadenosine (**2**), described above, the present 8-bromoguanosine (**3**) yields a DMSO solvate on crystallization from this solvent. The crystals belong to the non-centrosymmetric space group $P2_12_12_1$ which was also found for the reported structure of the 1:2 stoichiometric hydrate of **3** [32], obtained from aqueous solution. This allows an interesting comparison of the crystal structures not only between the brominated nucleosides **2** and **3** but also between **3** in DMSO solvated and hydrated forms.

A specific feature of the molecular structure of compound **3** is the intramolecular hydrogen bond connecting the O15 hydroxyl proton with the N3 atom of the guanine ring (Fig. 2c). The molecular conformation is furthermore stabilized both by weaker hydrogen bonding interactions as shown in the structure of 8-bromoadenosine (**2**) (O12–H17···O13, C12–H12···N3 and C11–H11···Br8) and additional intramolecular O–H···O and C–H···O contacts (O15–H19···O10 and C12–H12···O15) (Fig. 2c). Considering these particular interactions and the bulk of the bromo substituent, the *syn* orientation of the ribose moiety with reference to the purine unit is an obvious fact. The corresponding torsion angle χ of the glycosidic bond is 66.06(38)° (Table 2). The purine ring is planar to within experimental error. The ribose sugar residue is C2′-*endo* (relating to C12 in Fig. 2). This atom deviates 0.610(3) Å from the least-squares plane of the other four ribose ring atoms. Concerning that, the structural parameters of the 8-bromoguanosine molecule in **3**·DMSO are very similar to the corresponding ones in the adenosine derivative **2** and also to those in the known dihydrate of **3** [32]. In particular, the latter finding shows that the different solvents in the crystals do not significantly affect the molecular structure of **3**.

In the crystal packing structure, the nucleobase and DMSO molecules are held together by a complex network

Table 3 Hydrogen bonding interactions

Atoms involved	Symmetry	Distance (Å)		Angle (°)
		D(D···A)	*d*(H···A)	*θ*(D–H···A)
1·DMSO				
N1–H1···N3	$-x+1, y-1/2, -z+3/2$	2.821(2)	1.97	163.1
N4–H4A···O2	$-x+1, y+1/2, -z+3/2$	2.913(2)	2.03	178.0
N4–H4B···O21	$x, y+1, z$	3.019(2)	2.37	131.0
C21–H21A···N4	$x, -y+3/2, z+1/2$	3.293(3)	2.75	115.7
N4–H4B···I5	x, y, z	3.2958(17)	2.82	115.2
C22–H22A···O2	$-x+1, y-1/2, -z+3/2$	3.381(3)	2.41	173.9
2				
O12–H17···O13	x, y, z	2.701(3)	2.31	109.9
O15–H19···N3	x, y, z	2.761(3)	1.95	169.7
O13–H18···N7	$-x+1, y+1/2, -z+1$	2.788(3)	1.99	162.8
O12–H17···O15	$x, y, z+1$	2.881(2)	2.16	146.8
N6–H6A···O15	$-x+2, y-1/2, -z$	3.032(3)	2.28	145.8
C12–H12···N3	x, y, z	3.273(3)	2.60	126.3
C2–H2···O12	$x, y, z-1$	3.332(3)	2.58	138.3
C11–H11···Br8	x, y, z	3.347	2.84	112.9
3·DMSO				
O12–H17···O15	$x-1, y, z$	2.645(3)	1.90	151.2
O13–H18···O21	x, y, z	2.662(3)	1.84	174.3
O12–H17···O13	x, y, z	2.714(3)	2.31	111.1
N1–H1···O6	$x+1/2, -y-1/2, -z$	2.755(3)	1.91	165.3
O15–H19···O10	x, y, z	2.850(3)	2.56(4)	100(3)
O15–H19···N3	x, y, z	2.899(4)	2.03(4)	167(3)
N2–H3···O12	$x+1, y, z$	2.937(3)	2.12	159.2
N2–H2···O6	$x+1/2, -y-1/2, -z$	3.108(3)	2.39	141.3
C12–H12···O15	x, y, z	3.114(4)	2.57	114.7
C21–H21C···O6	$-x+3/2, -y, z+1/2$	3.154(4)	2.53	122.6
N2–H2···O21	$-x+2, y-1/2, -z+1/2$	3.163(4)	2.48	137.2
C21–H21B···O10	$-x+1, y-1/2, -z+1/2$	3.232(4)	2.54	129.4
C12–H12···N3	x, y, z	3.241(4)	2.57	125.9
C11–H11···Br8	x, y, z	3.293(3)	2.76	114.9
C14–H14···O12	$-x+1, y+1/2, -z+1/2$	3.448(4)	2.56	150.7
C22–H22C···O15	$x-1, y, z$	3.470(5)	2.60	151.0
4·H_2O·DMSO				
O61–H61A···O51	$x-1/2, -y+1/2, -z+2$	2.565(8)	1.745(16)	165(4)
N1–H1···O16	x, y, z	2.664(2)	1.98	133.3
N2–H2···O61	x, y, z	2.739(2)	1.88	165.7
O61–H61A···O41	$x-1/2, -y+1/2, -z+2$	2.812(4)	1.979(12)	171(4)
C51–H51B···O41	$x-1/2, -y+1/2, -z+2$	2.819(9)	2.01	137.8
O61–H61B···N7	$x-1, y, z$	2.8866(19)	2.076(13)	165(3)
C52–H52B···O41	$x-1/2, -y+1/2, -z+2$	3.024(9)	2.17	144.4
C41–H41A···O28	$x+1/2, -y+1/2, -z+2$	3.179(5)	2.26	156.6
C52–H52A···N3	x, y, z	3.194(9)	2.62	117.3
C41–H41B···O41	$x-1/2, -y+1/2, -z+2$	3.219(5)	2.38	142.9
C42–H42A···O41	$x-1/2, -y+1/2, -z+2$	3.273(5)	2.39	149.4
C11–H11···Br8	x, y, z	3.2871(5)	2.74	115.0
C51–H51B···O51	$x-1/2, -y+1/2, -z+2$	3.388(11)	2.55	143.6
C51–H51A···O6	$x-1/2, -y+1/2, -z+2$	3.411(9)	2.56	145.1

Table 3 continued

Atoms involved	Symmetry	Distance (Å)		Angle (°)
		D(D···A)	*d*(H···A)	*θ*(D–H···A)
C30–H30C···O6	$x - 1/2, -y + 1/2, -z + 2$	3.412(3)	2.45	165.6
C15–H15B···O41	$x - 1/2, -y + 1/2, -z + 2$	3.441(5)	2.50	159.4
C52–H52B···O51	$x - 1/2, -y + 1/2, -z + 2$	3.469(10)	2.56	154.5
C13–H13···O61	x, y, z	3.501(2)	2.54	161.2

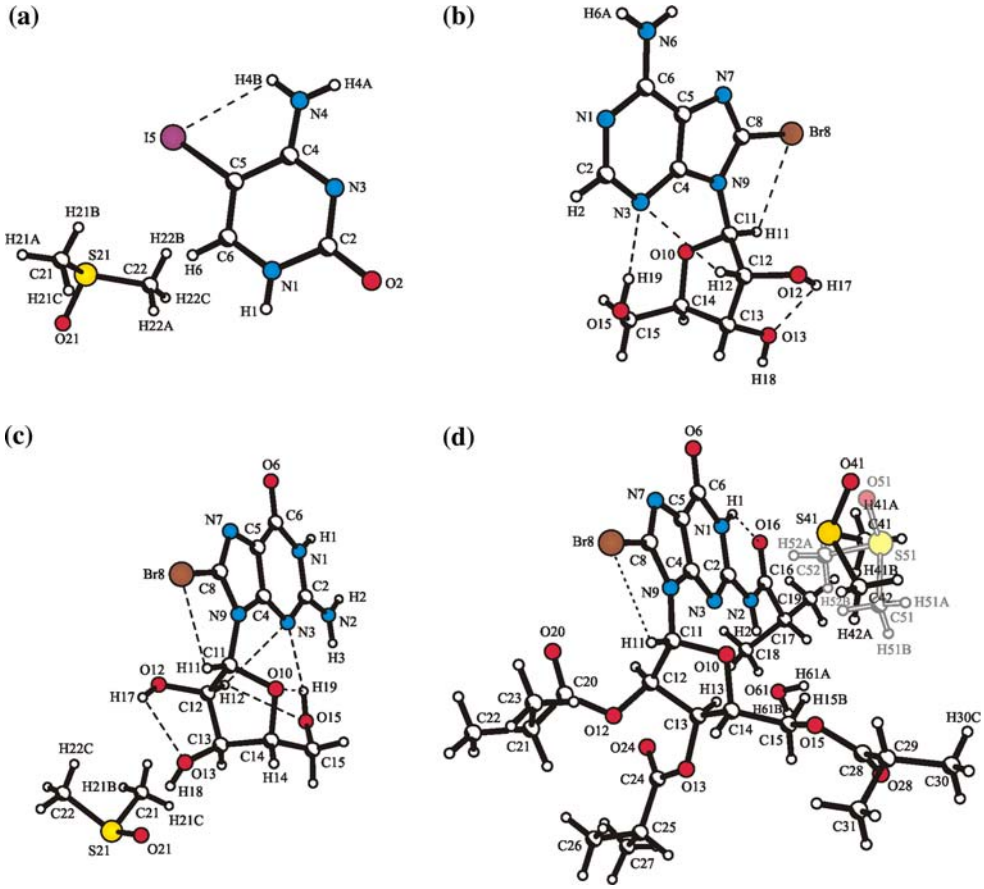

Fig. 2 Molecular structures and atomic labeling schemes for **a 1**·DMSO, **b 2**, **c 3**·DMSO and **d 4**·H_2O·DMSO

of strong and weaker hydrogen bonds (Fig. 5) involving guanine–guanine, guanine–solvent, ribofuranosyl–ribofuranosyl and ribofuranosyl–solvent interactions (Table 3). The most prominent interaction between adjacent guanine moieties is an N–H···O type hydrogen bond including the N1 ring proton in one and the O6 carbonyl oxygen atom in a symmetry related residue, creating an eight-membered hydrogen bonded ring as a specific supramolecular pattern. This particular mode of interaction is also shown in the structure of the hydrated compound **3** [32]. The guanine oxygen atom O6 is also involved in an N–H···O hydrogen bond to the NH_2 group of an adjacent guanine moiety, and in addition to this forms a weak C–H···O contact [47] to H21C of the solvent molecule, thus giving rise to an inverse trifurcated system of hydrogen bonds around O6. Furthermore, there is an N–H···O contact between the guanine N2 atom and the oxygen atom of the DMSO. As expected for the ribofuranosyl moiety, possessing several hydrogen bonding donor and acceptor sites, this group contributes substantially to the stabilization of the crystal structure. Different conventional O–H···O and N–H···O hydrogen bonds as well as a weaker C–H···O contact are formed that link the ribofuranosyl unit to solvent molecules, to the guanine moiety and to the ribofuranosyl residue of a neighboring molecule (Table 3). However, a significant contact involving the bromine atom, such as an interaction of Br···Br type [50] or between Br and another heteroatom [36, 37], is not detectable in the structure.

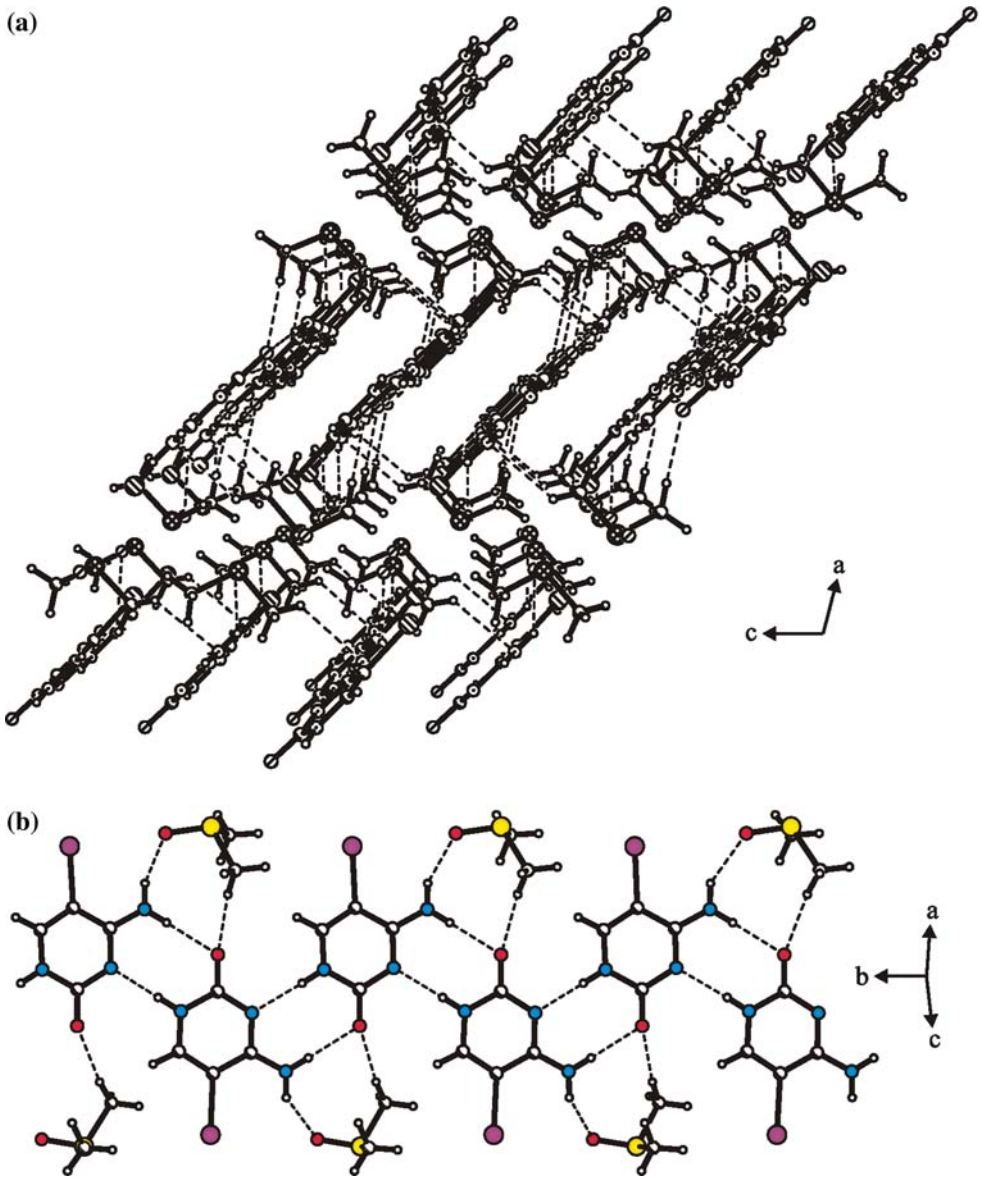

Fig. 3 Packing structure of **1**·DMSO: **a** view down the *b*-axis; **b** excerpt showing the tape formation. Hydrogen bond interactions are represented as *broken lines*

Structure of 2-*i*-butyramido-8-bromo-9-(2′,3′,5′-tri-*O*-*i*-butyryl-*β*-D-ribofuranosyl)purin-6-one·H_2O·DMSO (**4**·H_2O·DMSO)

Due to the *i*-butyryl substituents, this particular derivative **4** of 8-bromoguanosine (**3**) is considered to be rather hydrophobic compared to the compounds **1**–**3** discussed so far. Unexpectedly the crystals of **4** obtained from DMSO solution were isolated as a mixed solvate containing 1:1 stoichiometric amounts of water and DMSO. The crystals were found to belong to the orthorhombic space group $P2_12_12_1$. The asymmetric unit consists of one nucleoside molecule, one molecule of water and one molecule of DMSO which is twofold disordered (SOF = 0.681(2) for S41, O41, C41, C42, H41A–H41C, H42A–H42C and SOF = 0.319(2) for S51, O51, C51, C52, H51A-H51C, H52A-H52C).

Owing to the *i*-butyryl protecting group at O15, the formation of an intramolecular O15–H19···N3 hydrogen bond, as present in both **2** and **3**·DMSO, is excluded here. Instead of this, the molecular structure of **4** in **4**·H_2O·DMSO is stabilized by another intramolecular hydrogen bond between N1 of the guanine moiety and the carbonyl oxygen atom of the *N*-bound butyryl residue, additionally supported by a C11–H11···Br8 interaction similar to the molecular structures of **2** and **3** (Fig. 2d). On the other hand, in the molecular structure of **4**, the ribose unit is conformationally in a *syn* position with reference to the purine system (χ = 64.79(26)°), being in agreement with the structures of the nucleosides **2** and **3**. However, in contrast to compounds

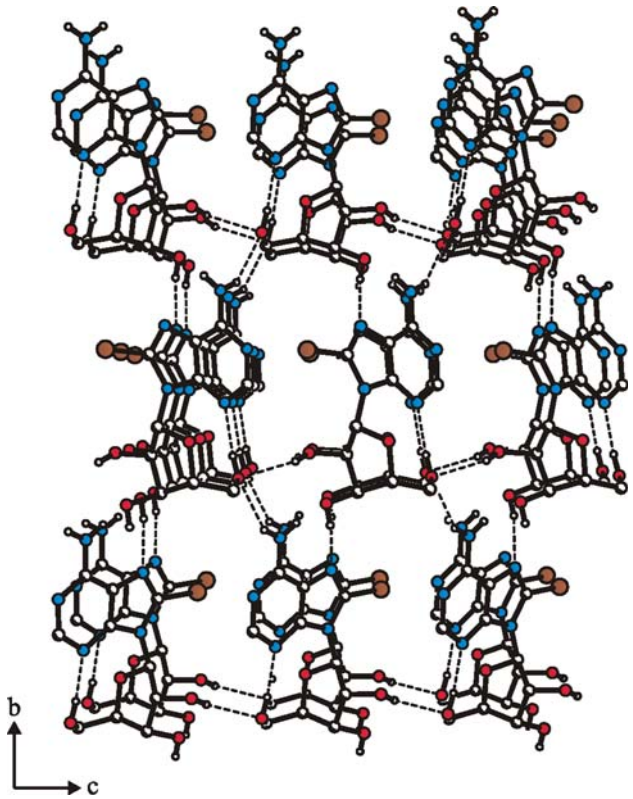

Fig. 4 Packing illustration of compound **2**, viewed down the *a*-axis, showing the supramolecular layer structure with relevant hydrogen bond interactions given as *broken lines*

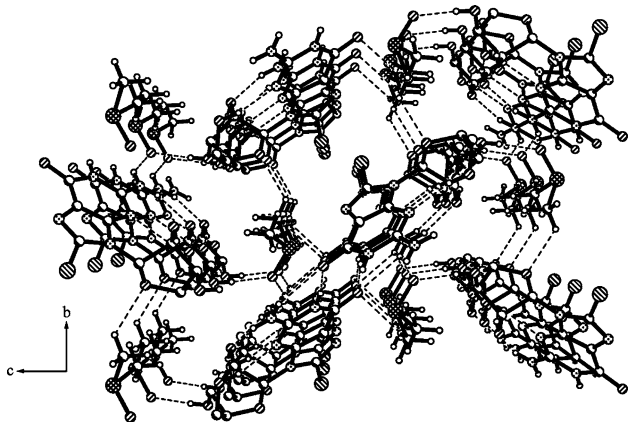

Fig. 5 Packing structure of **3**·DMSO viewed down the *a*-axis. Relevant hydrogen bond interactions are represented as *broken lines*; nonrelevant H atoms are omitted for clarity

2 and **3**, the ribofuranosyl moiety in **4** adopts a C4′-*exo* conformation (Table 2). The occurrence of this rather unusual C4′-*exo* conformation is obviously caused by the hydroxyl protecting groups. Similar unusual conformations have also been found for other hydroxyl protected

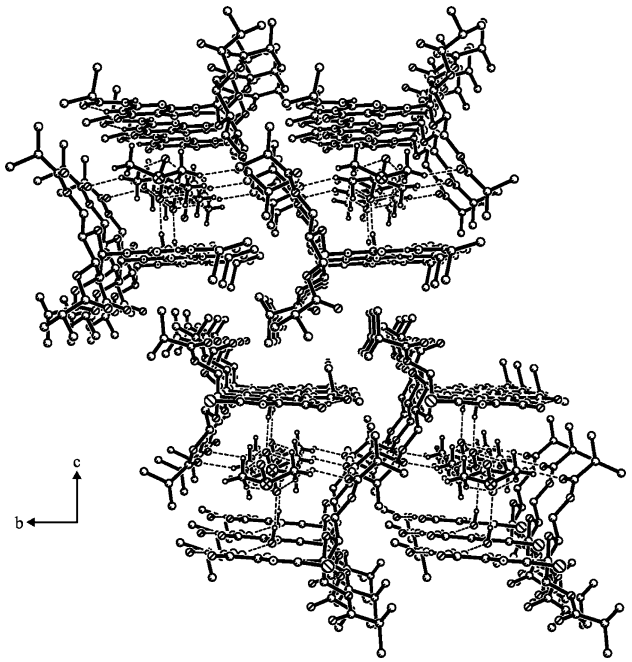

Fig. 6 Packing structure of **4**·H_2O·DMSO viewed down the *a*-axis. The second disordered position of the DMSO molecule as well as the nonrelevant H atoms are omitted. Relevant hydrogen bond interactions are represented as *broken lines*

derivatives of 8-bromoadenosine (**2**) and 8-bromoguanosine (**3**) [51, 52]. The tri-*O*-acetylated derivatives are reported to occur in a C1′-*exo* conformation in the case of 8-bromoadenosine and in a C2′-*exo* or rather a C3′-*endo*/C2′-*exo* conformation in the case of 8-bromoguanosine [52].

Although the hydrogen donor capacity of **4** is restricted by the substitution with the *i*-butyryl groups, the water and DMSO molecules, as the other components of the crystal structure, compensate for this. Hence, hydrogen bonds that involve the solvent molecules are the dominating interactions stabilizing the crystal packing (Fig. 6). In addition, there are van der Waals type contacts between the *i*-propyl residues. A particular structural feature of the packing is the strand formation of compound **4** along the *a*-axis. Within these strands, the purine bases are oriented parallel to the *ab*-plane and linked together via water molecules through N–H···O and C–H···O hydrogen bonding (Fig. 7a). The DMSO molecules are also arranged in strands along the *a*-axis. These strands are surrounded by purine bases in direction of the *c*-axis and of O15 *i*-butyryl groups in direction of the *b*-axis. Contacts between the DMSO molecules are in the form of C–H···O [35] interactions yielding an inverse bifurcated hydrogen bonding pattern (Fig. 7b). Furthermore, the DMSO molecules are involved in a C–H···O contact to the atom O28 of the proximate *i*-butyryl group as well as in a contact to H61A of the water molecule.

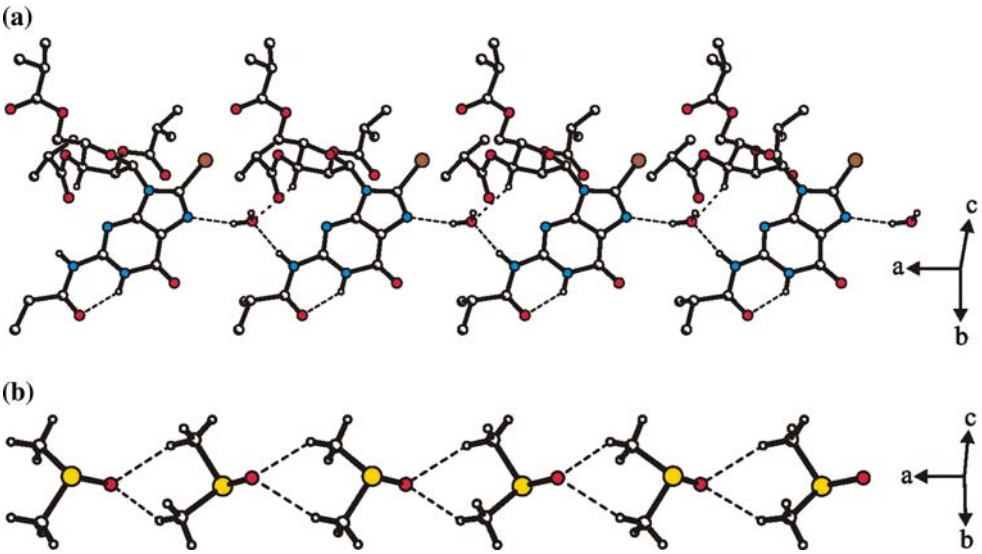

Fig. 7 Hydrogen bonded strand formation in the structure of **4**·H_2O·DMSO: **a** strand consisting of **4** and H_2O (nonrelevant H atoms are omitted); **b** strand formed of DMSO molecules (disordered position 1). Hydrogen bond interactions are represented as *broken lines*

Structural comparisons and conclusions

Considering the compounds **1** and **3**, their molecular structures are largely the same in solvent-free and DMSO solvated (**1**) or DMSO solvated and dihydrated forms (**3**), as follows from a comparison of previously reported [32, 34] and present findings. The pyrimidine and purine rings of **1**–**4** are nearly planar in structure. Both in the compounds **2** and **3**, the purine and sugar moieties are in a *syn* alignment mainly stabilized by a strong intramolecular O–H···N hydrogen bond, and the ribose sugar residues show a typical C2′-*endo* conformation. By contrast, the molecular structure of **4** differs significantly from **2** and **3**. Due to the *i*-butyryl protecting groups, the conformation of **4** is stabilized by an intramolecular N–H···O hydrogen bond involving a carbonyl oxygen atom of the *N*-bound butyryl residue and the ribofuranosyl moiety, and adopts an unusual C4′-*exo* conformation instead of C2′-*endo* as before, while the purine and sugar moieties remain in *syn* position.

Hydrogen bonded strands (**4**), tapes (**1**) and layers (**2**, **3**) are the predominant supramolecular motifs in the packing structures, mainly created by conventional N–H···N (**1**), N–H···O (**1**–**4**) and O–H···O (**2**, **3**) hydrogen bonds. They include both the nucleobase and ribose units as well as the solvent molecules. A further support stems from weak C–H···O contacts [47] involving the DMSO molecules in the cases of **1**, **3** and **4** while face-to-face π–π stacking interactions [49] are of no significant consequence, with the exception of **1**, at best. Another remarkable finding is that in none of the present crystal structures is the halogen atom engaged in any significant contact relevant to the packing, although halogen interactions are considered to form supramolecular synthons [36–38, 53]. However, the bromine atoms in **2**, **3** and **4** cooperate in the formation of the particular conformations.

In summary, it is suggested by this study that, aside from water, DMSO as a cocrystallizing solvent molecule is also capable of stabilizing the solid state structure of halogenated nucleobase and nucleoside derivatives without appreciable change of the molecular conformation.

Supplementary data

CCDC 739698 (**1**·DMSO), 739699 (**2**), 739700 (**3**·DMSO) and 739697 (**4**·H_2O·DMSO) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk].

References

1. Voet D, Voet JG (2004) Biochemistry, 3rd edn. Wiley, New York
2. Blackburne GM, Gait MJ, Loakes D (2006) Nucleic acids in chemistry and biology, 3rd edn. Royal Society of Chemistry, Cambridge
3. Bloomfield VA, Crothers DM, Tinoco J (2000) Nucleic acids—structures, properties and functions. University Science Books, Sausalito
4. Wagenknecht HA (2009) Angew Chem 121:2878
5. Wagenknecht HA (2009) Angew Chem Int Ed 48:2838
6. Park SH, Pistol C, Alm SJ, Reif JH, Lebeck AR, Dwyer C, LaBean TH (2006) Angew Chem 118:749
7. Park SH, Pistol C, Alm SJ, Reif JH, Lebeck AR, Dwyer C, LaBean TH (2006) Angew Chem Int Ed 45:735
8. Wengel J (2004) Org Biomol Chem 2:277
9. Seeman NC (2003) Nature 421:427
10. Printz M, Richert C (2009) Chem Eur J 15:3390

11. Lindegaard D, Madsen AS, Astakhova IV, Malakhov AD, Babu BR, Korshun VA, Wengel J (2008) Bioorg Med Chem 16:94
12. Kalek M, Madsen AS, Wengel J (2007) J Am Chem Soc 129:9392
13. Ogasawara S, Maeda M (2008) Angew Chem 120:8971
14. Ogasawara S, Maeda M (2008) Angew Chem Int Ed 47:8839
15. Feldkamp U, Niemeyer CM (2006) Angew Chem 118:1888
16. Feldkamp U, Niemeyer CM (2006) Angew Chem Int Ed 45:1856
17. Sessler JL, Lawrence CM, Jayawickramarajah J (2007) Chem Soc Rev 36:314
18. Sivakova S, Rowan SJ (2005) Chem Soc Rev 34:9
19. Takahashi S, Kuroyama Y, Sonogashira K, Hagihara N (1980) Synthesis 627
20. Miyaura N, Suzuki A (1995) Chem Rev 95:2457
21. Milstein D, Stille JK (1978) J Am Chem Soc 100:3636
22. Hudson RHE, Dambenieks AK (2006) Heterocycles 68:1325
23. Firth AG, Fairlamb IJS, Darley K, Baumann CG (2006) Tetrahedron Lett 47:3529
24. Western EC, Daft JR, Johnson EM, Gannett PM, Shaughnessy KH (2003) J Org Chem 68:6767
25. Collier A, Wagner GK (2008) Chem Commun 178
26. Sessler JL, Wang B, Harriman A (1995) J Am Chem Soc 117:704
27. Greco NJ, Tor Y (2007) Tetrahedron 63:3515
28. Fischer E, Reese L (1883) Liebigs Ann Chem 221:336
29. Bruhns G (1890) Ber Dtsch Chem Ges 23:225
30. Johnson TB, Johns CO (1906) J Biol Chem 1:305
31. Bugg CE, Thewalt AA (1969) Biochem Biophys Res Commun 37:623
32. Tavale SS, Sobell HM (1970) J Mol Biol 48:109
33. Kato M, Takenaka A, Sasada Y (1979) Bull Chem Soc Jpn 52:49
34. Okabe N, Tamaki K, Suga T (1995) Acta Crystallogr C51:2696
35. Csöregh I, Czugler M, Weber E, Sjögren A, Cserzö M (1986) J Chem Soc Perkin Trans 2:507
36. Metrangolo P, Resnati G (2004) In: Atwood JL, Steed JW (eds) Encyclopedia of supramolecular chemistry. Marcel Dekker, New York, pp 628–635
37. Metrangolo P, Meyer F, Pilati T, Resnati G, Terraneo G (2008) Angew Chem 120:6206
38. Metrangolo P, Meyer F, Pilati T, Resnati G, Terraneo G (2008) Angew Chem Int Ed 47:6114
39. Ikehara M, Kaneko M (1970) Tetrahedron 26:4251
40. Niles JC, Wishnok JS, Tannenbaum SR (2000) Chem Res Toxicol 13:390
41. Sheldrick GM (2004) SADABS: program for empirical absorption corrections. University of Göttingen, Germany
42. Bruker (2004) SAINT version 6.45a. Bruker AXS Inc., Madison, WI
43. Sheldrick GM (2008) Acta Crystallogr A64:112
44. Spek AL (2009) Acta Crystallogr D65:148
45. Sheldrick GM (1999) SHELXTL version 5.1: program for the solution and refinement of crystal structures. Bruker AXS Inc., Madison, WI
46. Nangia A, Desiraju GR (1998) In: Weber E (ed) Design of organic solids. Topics in current chemistry, vol 198. Springer, Berlin-Heidelberg, pp 57–95
47. Desiraju GR, Steiner T (1999) The weak hydrogen bond in structural chemistry and biology. Oxford University Press, Oxford
48. Mazik M, Bläser D, Boese R (2001) Tetrahedron 57:5791
49. Dance I (2004) In: Atwood JL, Steed JW (eds) Encyclopedia of supramolecular chemistry. Marcel Dekker, New York, pp 1076–1092
50. Reddy CM, Kirchner MT, Gundakaram RC, Padmanabhan KA, Desiraju GR (2006) Chem Eur J 12:2222
51. Tollin P, Low JN, Howie RA (1988) Acta Crystallogr C44:185
52. Mande SS, Lalitha HN, Ramakumar S, Viswamitra MA (1992) Nucleosides Nucleotides 11:1089
53. Awwadi FF, Willett RD, Peterson KA, Twamley B (2006) Chem Eur J 12:8952