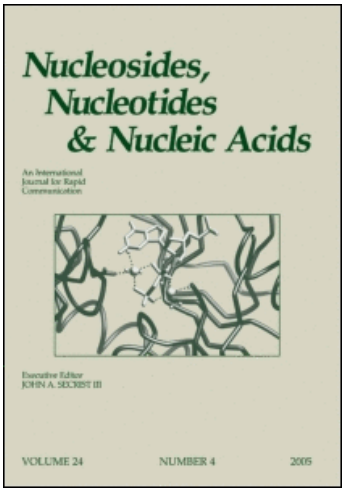

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Configuration and Conformation Studies of Nucleoside Analogues Based on the Benzo[*c*]furan Core

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CONFIGURATION AND CONFORMATION STUDIES OF NUCLEOSIDE ANALOGUES BASED ON THE BENZO[*c*]FURAN CORE

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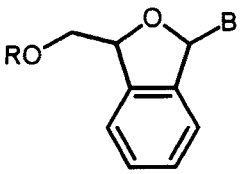
The glycone 1,3-dihydro-1-hydroxy-3-hydroxymethylbenzo[*c*]furan (**1**, R =H, B =OH) has been coupled to the regular nucleoside bases to a series of novel nucleoside analogues (**1**, B = thymine, adenine). Both *cis* and *trans* forms of these compounds have been obtained and the configuration



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is unequivocally established by NMR. The assignment of stereochemistry for each isomer of the compounds was initially based on the magnitude of the coupling between the dihydrofuran ring protons. The NMR spectra of the 1,3-dihydrobenzo[*c*]furan system have been investigated for several compounds with one or no substituent in the dihydrofuran ring. The observed coupling between H-1 and H-3 in a *cis* arrangement is in the range 0–2 Hz and the corresponding *trans* coupling is in the range 2.0–3.4 Hz. The data in Table 1 indicate that there are several spectral features which taken together strongly support the assignment of a common configuration to the compounds with a measurable cross-ring coupling. Further support is found in the NOESY spectrum of the

TABLE 1. Comparative NMR data for the dihydrobenzo[*c*]furan stereoisomers

Compound 1		*cis* isomer			*trans* isomer			
R	B	δ(H-1)	δ(H-3)	$J_{1,3}$	δ(H-1)	δ(H-3)	$J_{1,3}$	ratio *cis/trans*[a]
Bn	OH	6.30	5.29	<0.5	6.52	5.54	2.1	1.5
Bn	OMe	6.12	5.33	<0.5	6.22	5.54	2.2	0.6
Bn	T	7.49	5.40	*b*	7.55	5.66	2.6	1.5
H	T	7.28	5.23	*b*	7.33	5.55	2.8	

[a] From crude reaction products. [b] Not accessible.

mixed isomers of **1** (R = Bn, B = T). This spectrum showed a strong contact between the thymine proton, H-6, and H-3' in the *trans* isomer (protons on the same side of the furan ring) but no analogous contact in the *cis* isomer (protons on the opposite side of the furan ring).

Molecular modelling

In order to confirm the assignment of structure the relative energies of the diastereoisomers of glycone **1** and its derivatives have been examined by molecular modelling using the Nemesis programme. For the purposes of calculation the benzyl group in **1** was replaced by methyl. This reduces the computing time without prejudicing the evaluation of the energetics of the ring. These dihyrobenzo[*c*]furan compounds exists in a puckered form with the oxygen atom of the dihydrofuran ring either above or below the plane containing the benzene ring and carbons C-1 and C-3 (envelope conformation). The substituents at the 1,3 positions adopt pseudo axial or pseudo equatorial orientations. The *cis* isomer can thus exist in *ee* or *aa* forms and the trans isomer in *ea* and *ae* forms (Fig 1). In all cases the energies are likely to be similar.

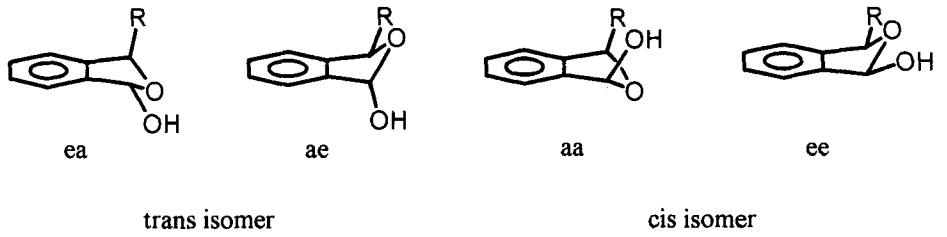

Fig. 1 Conformational forms of 1,3-disubstituted benzo[*c*]furans.

For both the *trans* and *cis* isomers of **1** (B = T), the form with the thymine group in an axial position was unstable. Thus each isomer has only one stable ring conformation, such that the thymine substituent is in equatorial orientation. The *cis* isomer adopts an *ee* form in which, depending on the conformation of the CH_2OH group, the ring oxygen is 10 – 30° below the ring plane (*i.e.* the dihedral angle between the two planes of the envelope form). In the minimum energy form this angle is 28° and the C8 oxygen is trans to the benzene ring. The plane of the *anti* thymine group is nearly orthogonal to the benzo[*c*]furan ring plane (notional dihedral angle *ca.* 102°).

The *trans* isomer has very similar stereochemical features. It adopts a minimum energy (*ea)* conformation which has the ring oxygen 27° out of the plane, the thymine ring in an equatorial position with its ring plane nearly orthogonal to the benzo[c]furan ring plane (100°) and the C8 oxygen trans to the benzene ring. It is evident that the two substituents in a nucleoside analogue based on a benzo[c]furan core have negligible interaction and hence quasi α and β configurations will behave similarly. The relative energies for all conformers of the isomers of **1** (R = H, B = T) were calculated. There are eleven of these confirming that the conformation of the C3 substituent is little influenced by the thymine group. The normalised populations for the pair of isomers of **1** (R = H, B = T), assuming these are in thermodynamic equilibrium, indicate a *cis:trans* ratio of 1.7:1, in excellent agreement with the observed isomeric ratio of 1.5:1 for ring closure reaction.

The cis isomer of **1** (R = H, B = T) is the analogue of d4T and could be expected to behave similarly *in vivo*. Comparison of the molecular shape of *cis*-**1** (R = H, B = T) with d4T shows that these molecules have essentially the same shape. With the CH_2OH group in an all-trans arrangement with respect to the ring oxygen atom (as would be the case for the end residue of an oligonucleotide) the distance between N1 and O8' in *cis*-**1** (R = H, B = T) is 5.80Å compared to 5.75Å in d4T. The relationship of the thymine ring plane to the CH_2OH group is indicated by the notional dihedral angle C8'–C3'–C1'–C5 which is 6.2° in *cis*-**1** (R = H, B = T) and 1.7° in d4T.. This close spatial similarity of these two compounds suggests that the benzo[*c*]furan system has chemotherapeutic potential.

In each of these four forms there are three rotatable bonds allowing 27 possible conformations. An attempt was made to determine the energy of every rotamer but many are

unstable and convert to a lower energy conformation during the minimisation procedure. (This sometimes involved inversion of the furan ring. The energy barrier for inversion of the *trans* isomer between *ae* and *ea* conformations is less than 1 kcal mol^{-1}). A complete mapping of the conformational space revealed only 32 minima in the *trans* compound and 31 in the *cis* compound, but in nearly all cases the energies are too high for the corresponding conformers to be significantly populated. Only four conformations had a population of 5% or greater and the energies and population distribution is shown in Table 2. All other forms contribute 2% or less. Perhaps not surprisingly, these four conformations correspond to the most stable conformer of each of the general types shown in Fig. 1.

The cis isomer of compound **1** (R = Bn, B = OH) exists mainly (population *ca.* 75%) as the *aa* form with the OH group at C1 directed over the ring to form a hydrogen bond to the oxygen atom of the CH_2OR group at C3. The only other significant conformation is the *ee* form (16%, 0.9 kcal mol^{-1} higher in energy) with the OH group directed over the ring but with the C3 substituent arranged all-trans with respect to the ring oxygen. No hydrogen bonding is possible between the substituents in the *trans* form of **1** (R = Bn, B = OH) but the two lowest energy forms are the *ae* and *ea* conformations each with the hydroxy group pointing over the ring to the C3 substituent which adopts an all-trans relationship to the ring oxygen. These two forms differ by only 0.14 kcal mol^{-1} and account for about 66% of the population of this diastereoisomer. If the selectivity of the ring closure step is evidence of thermodynamic control then the expected ratio *cis:trans* should reflect the overall population distribution shown in Table 2. The *cis* isomer clearly predominates (87%) but the predicted diastereoisomeric excess (0.74) is greater than that observed (0.2).

Similar calculations were carried out for the thymine derivative **1** (R = H, B = T). In this case the threefold potentials for the C3'–C8' and C8'–O8' bonds were combined with a twofold potential for the C1'–N1 bond (*syn* and *anti*). Every conformation was investigated and it was found in all cases that the *syn* orientation of the thymine group led to a higher that calculated for the *anti* orientation. The energy difference was 3 – 4 kcal mol^{-1} in most cases and the *syn* conformation does not contribute.

TABLE 2 Conformational energies and populations of the isomers of compounds **1** (R = Bn, B = OH) and **1** (R = H, B = T).

	Isomer	Relative conformer energy[a]/kcal mol^{-1}	Relative conformer populations for each isomer[b]	Overall relative population[c]
1, R = Me B = OH	*cis* (aa)	0	75%	71%
	cis (ee)	0.89	16%	16%
	trans (ea)	1.32	37%	7%
	trans (ae)	1.46	29%	6%
1[d] R = H B = T	*cis*(ee)	0	29%	18%
	cis(ee)	0.07	26%	16%
	cis(ee)	0.24	19%	12%
	cis(ee)	0.51	12%	8%
	cis(ee)	0.78	8%	5%
	cis(ee)	0.91	6%	4%
	trans(ea)	0.04	46%	17%
	trans(ea)	0.50	21%	8%
	trans(ea)	0.54	20%	7%
	trans(ea)	1.11	8%	3%
	trans(ea)	1.35	5%	2%

[a] Expressed relative to the global minimum for each isomer pair. [b] Calculated on the basis of excluding all forms with less than 2% population for **1** (R = Me, B = OH), or 4% for **1** (R = H, B = T). [c] Calculated by including both *cis* and *trans* contributing forms. [d] Data are listed for the set of conformers corresponding to rotational variation about the C3'–C8' and C8'–O8' bonds.

For both the *trans* and *cis* isomers of **1** (R = H, B = T) , the form with the thymine group in an axial position was unstable. Thus each isomer has only one stable ring conformation, such that the thymine substituent is in equatorial orientation. The *cis* isomer adopts an *ee* form in which, depending on the conformation of the CH_2OH group, the ring oxygen is 10 – 30° below the ring plane (*i.e.* the dihedral angle between the two planes of the envelope form). In the minimum energy form this angle is 28° and the C8 oxygen is trans to the benzene ring. The plane of the *anti* thymine group is nearly orthogonal to the benzo[*c*]furan ring plane (notional dihedral angle *ca.* 102°).

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