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^{1}H and ^{13}C NMR conformational study of 2-(benzotriazol-1-yl)-substituted tetrahydrofurans

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ABSTRACT: Assignments of the proton and carbon NMR signals for 2-(benzotriazol-1-yl)tetrahydrofurans **1–6** are based on ^{1}H–^{1}H COSY, NOESY, ^{1}H–^{13}C heteronuclear HETCOR, ^{1}H–^{13}C heteronuclear long-range HETCOR-LR and nuclear Overhauser enhancement experiments, and supported by selective spin decoupling experiments. The electronic and steric effects of the 2-benzotriazolyl substituent on the ^{1}H and ^{13}C NMR chemical shifts are evaluated and discussed. Conformational isomers *cis* and *trans* are distinguished by the magnitude of the $J_{(H-2,H-3)}$ coupling constant, by one-bond $^{1}J_{(C-2,\ H-2)}$ coupling constants and by ^{13}C chemical shifts of the C-2 anomeric carbon. The benzotriazol-1-yl group prefers the pseudo-axial orientation in each of **1–6**. The stereochemistry and conformation of **6** are rigorously demonstrated by an x-ray structure. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: tetrahydrofurans; conformation; ^{1}H NMR; nuclear Overhauser effect; benzotriazolyl; anomeric effect

INTRODUCTION

The tetrahydrofuran ring is the core of various sugars, which are known to play important roles as fundamental structural units of nucleic acids. This ring system is responsible in part for the structure, conformation and dynamics of nucleic acids.

The conformational properties of tetrahydrofurans have been extensively studied by both theoretical[1] and experimental methods.[2a–e] Frequently, interpretation of the NMR spectra of tetrahydrofurans is complicated as a time-averaged spectrum of all conformers is obtained owing to pseudorotation: a single three-bond coupling constant $^{3}J_{(H-2,H-3)}$ observed value may correspond to several different pseudorotamers.[3] The anomeric effect in tetrahydrofurans[4] and furanosides[5] and its influence on their conformational preferences have been reviewed.[6] The NMR technique has also been applied to the determination of the activation energy for pseudorotation of a tetrahydrofuran ring and for calculation of the relative energies of the potential puckered forms.[7,8a] Extensive studies on pseudorotation and anomeric effects in a series of furanosides in the solid state have been carried out by Sundaralingam and co-workers.[8b–d]

2-Substituted tetrahydrofurans and particularly 2-substituted furanoses have a similar stereoelectronic interaction between an anomeric substituent and lone pairs of the oxygen for both α- and β-anomers.[9] However, the $^{1}J_{(C-2,H-2)}$ and $^{3}J_{(H-2,H-3)}$ values depend significantly on the orientation of a substituent at C-2 and can therefore provide valuable information about the conformations of furanosides.[2c,10]

Stereochemical analysis of the interactions in nucleosides between the lone pair (LP) of the furanose oxygen and the aromatic nitrogen of the purine (N9) or pyrimidine (N1) base in different conformations suggests that the oxygen lone pair interactions should be minimized in the O-*exo* (W type) conformations (owing to the favorable *anti* disposition of the endocyclic oxygen lone pair and the nitrogen atom), but have an energy maximum in O-4 *endo* (E type) conformations.[6]

^{1}H NMR studies on 2-halo- or 2,3-dihalo-5-aryltetrahydrofurans demonstrated that the aryl group favors the pseudo-equatorial and the halogen group the pseudo-axial position,[2e] while the conformation of the 2,5-diaryl analogs depends strongly on the bulk of the substituents.[8] For more sterically hindered tetrahydrofurans with an additional substituent in the 5-position, the conformation is determined by the relative configuration of the substituents: with two *cis* polar groups in the 2- and 3-positions, the anomeric group is always pseudo-axial. However, *trans*-2,3-dihalo analogs can exist either in the pure anomeric conformation (2ax, 3eq), pure anti-anomeric conformation (2eq, 3ax), or as a mixture of the two.[4] The anomeric form is more stabilized by a bromine or a chlorine substituent at the 3-position than by a methoxy group.[2d,4]

^{13}C NMR spectra of mono- and disubstituted tetra-

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hydrofurans[11,12] and furanosides[13,14] have also been extensively analyzed. The anomeric effect has been studied on an example of *cis*- and *trans*-2,5-dimethyltetrahydrofurans.[11] In the ^{13}C NMR spectra of these compounds, the anomeric C-2 signal of the *cis* isomer is shifted downfield by 0.7 ppm compared with that of the corresponding *trans* isomer, whereas for the C-3 and C-4 ring carbon atoms the opposite effect is observed.

The $^{1}J_{(C-2,H-2)}$ coupling constant values show a clear dependence on the orientation of the substituent at C-2 and therefore provide information about the conformation of the anomeric structures. Thus, $^{1}J_{(C-2,H-2)}$ values for methyl glycosides with the H-2 axial are lower (158–162 Hz) than those for the analogs with the H-2 equatorial (169–172 Hz).[13]

Benzotriazole-substituted tetrahydrofurans and tetrahydropyrans and especially benzotriazolylfuranosides have recently received much attention as modified analogs of purine nucleosides from the points of view of both their chemical reactivity to achieve access to more elaborate derivatives and their biological activity. Thus, a series of benzotriazolyltetrahydrofurans and -tetrahydropyrans has been screened for antitumor and anti-HIV activity.[15a] The significant influence of substituent conformation on the biological activities of five-membered heterocycles[15b] and also on the reactivity (e.g. the hydrolysis rate[15c]) is well known. Hence studying the effect of an electron-withdrawing heteroaromatic benzotriazolyl substituent on the preferred conformation of a furanoid ring is of practical importance.

Recently, we investigated the conformational behavior of a number of 2-(benzotriazol-1-yl)-substituted tetrahydropyrans[16] and found that in these compounds the benzotriazol-1-yl (Bt-1) moiety occupies predominantly the equatorial position. In contrast, in the current study we have now discovered that in five-membered tetrahydrofuran analogs the opposite applies with the Bt-1 group being in quasi-axial orientation, independently of the nature of the other tetrahydrofuran ring substituents.

RESULTS AND DISCUSSION

^{1}H NMR spectroscopic studies on 2-(benzotriazol-1-yl)tetrahydrofurans 1–6

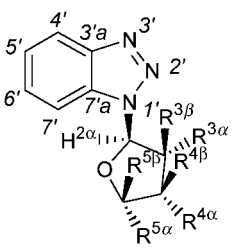
We present ^{1}H and ^{13}C NMR studies on 2-(benzotriazol-1-yl)tetrahydrofurans **1–6** (Scheme 1), bearing a variety of substituents in the 3- or 5-position, and discuss the effect of the benzotriazolyl group on the conformation of the tetrahydrofuran ring.

In the ^{1}H NMR spectrum of **1**, the H-2α anomeric proton appears at δ 6.51 as a doublet of doublets with $^{3}J_{(H-2,H-3)}$ values of 6.6 and 2.4 Hz, which is averaged owing to pseudorotation of the tetrahydrofuran ring at room temperature (Table 1). Similarly to the 2-(benzotriazol-1-yl)tetrahydropyrans,[16] a nuclear Overhauser effect (NOE) was observed between H-2 and H-7′, suggesting the preference of a rotamer favored by the *exo*-anomeric effect. The NOESY spectrum of **1** also shows a cross-peak between the protons at δ 6.51 (H-2α) and δ 7.65 (H-7′) due to their spatial proximity. In contrast to tetrahydropyrans,[16] the values of $^{3}J_{(H-2,H-3)}$ (6.6 and 2.4 Hz) found for the anomeric proton in **1** suggest the preference of a conformer with this proton in a pseudo-equatorial orientation (H-2α), while the benzotriazol-1-yl group is oriented pseudo-axial.

To confirm this conclusion, we studied the conformations of disubstituted tetrahydrofurans **2–6** using for comparison the literature data on values of $^{3}J_{(H-2,H-3)}$ for 3-chlorotetrahydrofurans bearing substituents of varying electronegativity at the 2-position.[17,18]

In the ^{1}H NMR spectrum of **1**, two distinct downfield doublets integrating for one proton each at δ 8.06 (^{3}J = 8.2 Hz) and δ 7.71 (^{3}J = 8.2 Hz) were assigned to H-4′ and H-7′ of the benzotriazolyl group, respectively. The 2D HETCOR spectrum of **1** correlates these proton signals with the corresponding carbon signals at δ 127.4 (C-4′) and δ 110.4 (C-7′). Significant long-range correlations (J = 8.0 Hz) were observed between C-3a′ (δ 146.2) and the H-7′ and H-5′ protons, and between C-7a′ (δ 132.8) and the H-4′ and H-6′ protons in the long-range ^{1}H–^{13}C heteronuclear HETCOR-LR spectrum of **1**. The corresponding signals (H-4′ and H-7′) appear in the ^{1}H NMR spectrum as doublets of the triplets with coupling constants of 8.2 Hz (*ortho* coupling constant) and 0.9 Hz [$^{4}J_{(H-4',H-6')}$ and $^{4}J_{(H-5',H-7')}$ coupling constants, respectively]. Assignment for the signals for H-5′ and H-6′ protons was made by ^{1}H–^{1}H COSY and supported by selective spin decoupling.

The assignment of proton signals of the tetrahydrofuran moiety of **1** was also based on NOE, ^{1}H–^{1}H COSY and



1: $R^{3\alpha} = R^{3\beta} = R^{4\alpha} = R^{4\beta} = R^{5\alpha} = R^{5\beta} = H$

2: $R^{3\beta} = Cl$; $R^{3\alpha} = R^{4\alpha} = R^{4\beta} = R^{5\alpha} = R^{5\beta} = H$

3: $R^{3\alpha} = Cl$; $R^{3\beta} = R^{4\alpha} = R^{4\beta} = R^{5\alpha} = R^{5\beta} = H$

4: $R^{3\beta} = CH_2\text{-}N(CH_2CH_2)_2$; $R^{3\alpha} = R^{4\beta} = R^{5\alpha} = R^{5\beta} = H$

5: $R^{3\alpha} = CH_2\text{-}N(CH_2CH_2)_2$; $R^{3\beta} = R^{4\alpha} = R^{4\beta} = R^{5\alpha} = R^{5\beta} = H$

6: $R^{2\alpha} = R^{3\beta} = R^{3\alpha} = R^{4\alpha} = R^{4\beta} = R^{5\beta} = H$; $R^{2\beta} = R^{5\alpha}$ = Bt-1

Scheme 1

Table 1. ^{1}H NMR chemical shifts (δ, ppm), multiplicity[a] and coupling constants[a] (J, Hz) of the tetrahydrofuran moiety for compounds **1**–**6** in $CDCl_3$ at ambient temperature

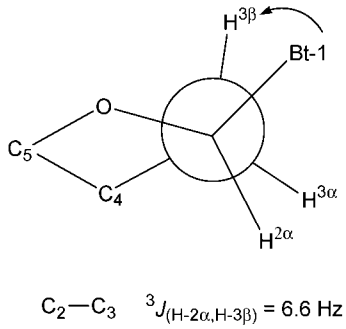
	δ (ppm) and J (Hz)					
Proton	**1**	**2**[b]	**3**[b]	**4**[b]	**5**[d]	**6**
H-2α	6.51 (dd; 6.6, 2.4)	6.62 (d; 5.1)	6.49 (br d; 1.2)	6.58 (d; 6.04)	6.56 (d; 2.6)	6.73–6.76 (m)
H-3α	3.11–3.20 (m)	4.79 (dt; 7.8, 5.1)	– –	3.01–3.14 (m)	– –	3.32–3.34 (m)
H-3β	2.46–2.60 (m)	– –	5.38 (dddd; 6.1, 2.1, 1.1, 0.5)	– –	3.60–3.71 (m)	3.32–3.34 (m)
H-4α	2.31–2.45 (m)	2.71–2.87 (m)	2.92–3.04 (m)	2.13–2.38 (m)	1.86–1.98 (m)	3.32–3.34 (m)
H-4β	2.10–2.25 (m)	2.66–2.79 (m)	2.45 (dddd; 14.0, 6.9, 3.7, 2.2)	2.23–2.38 (m)	2.58–2.64 (m)	3.32–3.34 (m)
H-5α	3.99–4.14 (m)	4.25 (pq; 8.1)	4.26 (dt; 14.2, 8.4)	4.53 (dt; 7.8, 2.6)	4.16 (dt; 7.8, 2.6)	–
H-5β	3.99–4.14 (m)	4.25 (pq; 7.2)	4.42 (pq; 8.2)	4.12–4.21 (m)	4.02 (pq; 7.8)	6.73–6.76 (m)

[a] The multiplicity and values of coupling constants are given in parentheses: dd, doublet of doublets; dt, doublet of triplets; m, multiplet; pq, pseudo-quartet.
[b] The coupling constants for **2** and **3** obtained by using selective decoupling experiments are as follows: **2**, $^2J_{(H-4\alpha,H-4\beta)} = 12.8$ Hz; $^3J_{(H-3\alpha,H-4\alpha)} = 2.1$ Hz; $^3J_{(H-3\alpha,H-4\beta)} = 7.8$ Hz; $^3J_{(H-4\alpha,H-5\alpha)} = 7.0$ Hz, $^3J_{(H-4\alpha,H-5\alpha)} = 10.9$ Hz; **3**, $^3J_{(H-3\alpha,H-4\alpha)} = 2.1$ Hz; $^3J_{(H-3\alpha,H-4\alpha)} = 5.9$ Hz; $^2J_{(H-4\alpha,H-4\alpha)} = 13.8$ Hz; $^3J_{(H-4\alpha,H-5\alpha)} = 8.5$ Hz, $^3J_{(H-4\alpha,H-5\alpha)} = 8.9$ Hz; $^2J_{(H-5\alpha,H-5\alpha)} = 8.2$ Hz.
[c] Additional signals: δ 2.05 [dd, 1H, $J = 8.8$, 12.4 Hz, C(3)–C$\underline{H}_A$H$_B$N]; 2.23 [dd, 1H, $J = 6.2$, 12.4 Hz, C(3)–CH$_A\underline{H}_B$N]; 1.62–1.72 (m, 4H, –C$\underline{H}_2$–C$\underline{H}_2$, pyrrolidine); 2.48–2.56 [m, 4H, N(C$\underline{H}_2$)$_2$, pyrrolidine].
[d] Additional signals: δ_A C(3)–C$\underline{H}_A$H$_B$: δ_A 2.91 [dd, 1H, $J = 9.9$, 12.1 Hz, C(3)–C$\underline{H}_A$H$_B$]; δ_B 2.58 [dd, $J = 6.6$, 12.1 Hz, C(3)–CH$_A\underline{H}_B$]; 2.55–2.64 [m, 4H, –N(CH$_2$)$_2$–, pyrrolidine], 1.71–1.80 [m, 4H, –(CH$_2$)$_2$–, pyrrolidine].

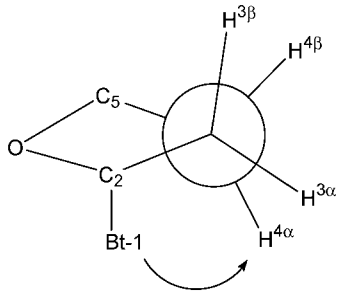
supported by selective decoupling. The H-3 protons displayed cross-peaks with H-2α in the ^{1}H–^{1}H COSY spectrum. The H-3β (multiplet centered at δ 2.53) signal appears at higher field than that of the H-3α proton (multiplet centered at about δ 3.16) owing to the shielding effect of the spatially proximate benzotriazole system (Scheme 2).

The multiplet centered at δ 4.08 was unambiguously assigned to the H-5α + H-5β protons on the basis of the downfield ^{1}H NMR shifts characteristic for CH—O fragments. In the ^{1}H NMR spectra of **2** and **3**, the H-2 resonance signals appear as doublets at δ 6.62 ($^3J = 5.1$ Hz) and δ 6.49 ($^3J = 1.2$ Hz), respectively. For **2**, a pseudo-equatorial orientation for the substituent at C-3 was deduced by selective decoupling from H-2α, which produced a triplet for H-3 with $^3J_{(H-3\alpha,H-4\beta)} = 7.8$ Hz; this coupling constant value demonstrates a pseudo-axial orientation of the H-3α proton. Moreover, an NOE effect was observed between the H-3α and H-5α protons (Scheme 3).

$^3J_{(H-2,H-3)}$ (*trans*) coupling constants previously reported for 2-substituted (R) 3-chlorotetrahydrofurans are 1 Hz or less for the compounds with R = OCH$_3$ and SPh[17,18] but increase to 2.0–2.5 Hz for the derivatives with a C-2 substituent of medium electronegativity (benzoyl, cyano, acyl). This indicated a *trans* configuration for compounds **3** and **5** having $^3J_{(H-2,H-3)}$ coupling constants of 1.2 and 2.6 Hz, respectively. Selective decoupling experiments carried out for the H-2 proton in **3** showed decreasing $^3J_{(H-3,H-4)}$ coupling constants of 5.9 and 2.1 Hz (compared with 7.8 Hz observed for **2**). Such a set of constants supports the pseudo-equatorial

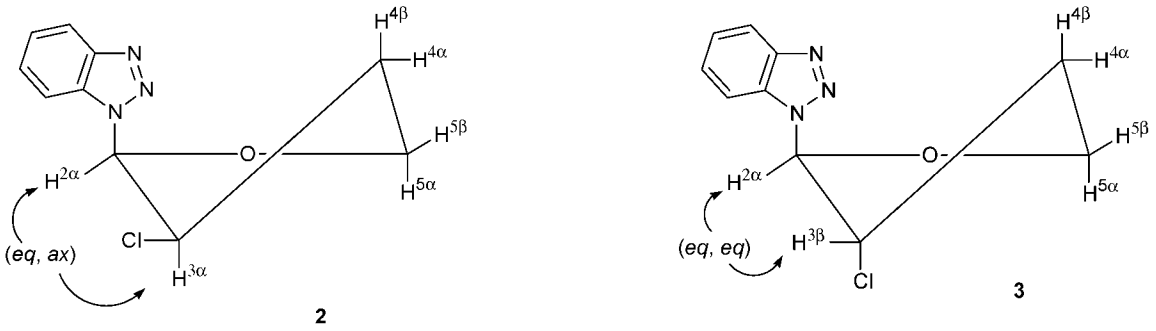


$C_2—C_3$ $^3J_{(H\text{-}2\alpha,H\text{-}3\beta)} = 6.6$ Hz



$C_3—C_4$ $^3J_{(H\text{-}2\alpha,H\text{-}3\alpha)} = 2.4$ Hz

Scheme 2



Scheme 3

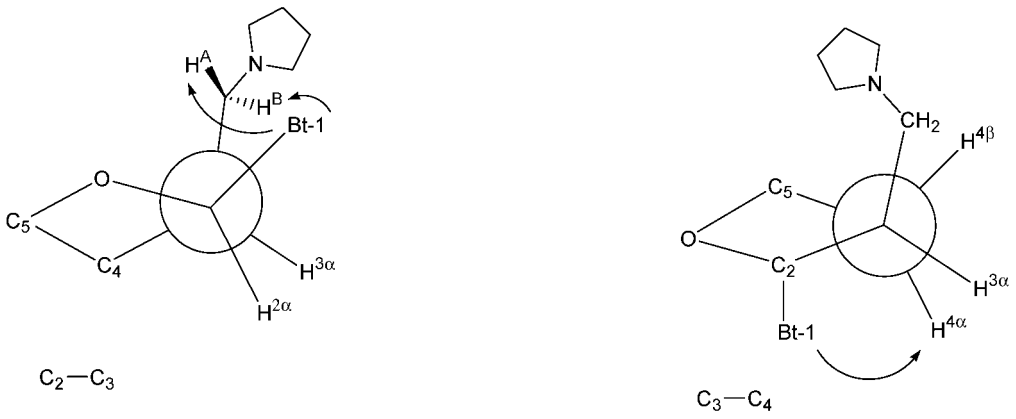
orientation of the H-3α proton in **3**. This, combined with the determined *trans* configuration, implies a pseudo-axial orientation of both the benzotriazole residue and the substituent at C-3 in **3** and **5** (see Scheme 3). However, the results of the NOE experiments were ambiguous: the signal enhancement observed for the H-3 proton on irradiation of either the H-2 or the H-5 protons makes this method inapplicable for the determination of the substituent orientation in **3** and **5**.

A benzotriazole substituent effect was observed on the vicinal coupling constant $^3J_{(H-H)}$ for **1**. On comparison of 2-phenyltetrahydrofuran with **1** (the electronegativity of phenyl is known to be less than that of a benzotriazol-1-yl moiety), the coupling constants $^3J_{(H-2\alpha,H-3\alpha)}$ and $^3J_{(H-2\alpha,H-3\beta)}$ decrease from 7.0 and 7.5 Hz for the former compound to 6.6 (*cis*) and 2.4 Hz (*trans*), respectively, for **1**. The polar substituents OMe, Cl at the 2- and 3-positions of the tetrahydrofuran moiety showed lower vicinal coupling constants $^3J_{(H-2,H-3)}$: for *cis* ca 4.0 Hz and for *trans* <2 Hz.[2e] In the case of **3**, the $^3J_{(H-2\alpha,H-3\beta)}$ is 1.2 Hz when Bt-1 and Cl occupy pseudo-axial positions. Introduction of an electronegative atom such as Cl at C-3 of the tetrahydrofuran ring (**2** and **3**) decreased the magnitudes of $^3J_{(H-2\alpha,H-3\alpha)}$ and $^3J_{(H-3\alpha,H-4\beta)}$ and $^3J_{(H-4\alpha,H-3\beta)}$ compared with 2-phenyltetrahydrofuran, e.g. the magnitudes of the vicinal coupling constant $^3J_{(H-3\beta,H-4\beta)}$ are 8.5 and 7.8 Hz for 2-phenyltetrahydrofuran and **2**, respectively.

The signal of the anomeric H-2 proton in **3** is slightly shifted upfield by 0.13 ppm compared with that of **2**; this could be ascribed to the deshielding effect of the Cl substituent in the latter. Similarly, the H-3β signal of **3** at δ 5.38 is significantly downfield compared with the H-3α signal of 2 owing to the spatial influence of the benzotriazole heteroaromatic system.

An analogous effect of the benzotriazolyl group is observed for the 3-(pyrrolidin-1-ylmethyl) derivative **4**: the H-3 proton of **5** is deshielded by about 0.6 ppm. The spatial proximity of the benzotriazole system to the C(3)—CH_2 methylene group in **4** (Scheme 4) results in a significant upfield shift of these methylene protons (δ 2.05 and 2.23 compared with δ 2.58 and 2.91 for the corresponding resonance signals of **5**). A similar shielding effect by aryl substituents at C-2 on *cis* methyl groups at C-3 was previously reported for several 2-aryl-3-methyltetrahydrofurans.[8]

The configurational and conformational assignments for **5** and **6** were also made on the basis of NOE difference spectra (Fig. 1). For 6 irradiation of the signals centered at δ 6.74 (H-2α + H-5β) gave a nuclear Overhauser enhancement of the H-7′ resonance signal indicating the relative *trans* configuration of the benzo-



Scheme 4

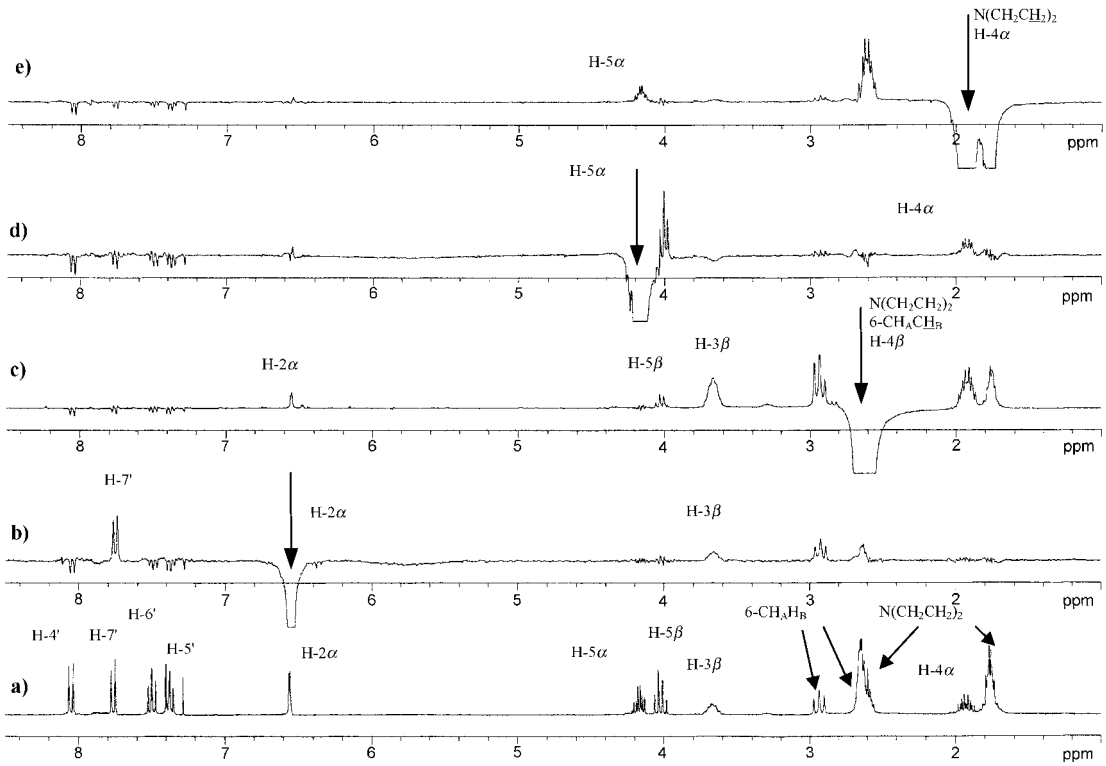


Figure 1. NOE difference spectra of **5** in $CDCl_3$. Irradiated proton peaks are indicated by arrows. (a) General spectrum; (b)–(c) NOE difference spectra

triazolyl substituents. The chemical shifts of H-3α + H-4α and H-3β + H-4β coincide (AA′BB′-type spectrum), confirming the chemical equivalence of these pairs of protons and thus the uniform effect of the benzotriazolyl groups (Scheme 5).

Single-crystal x-ray crystallography of **6** (crystalline compounds were not obtained for **1**–**5**) confirmed the *trans* relationship of two benzotriazole substituents (Fig. 2). In agreement with the NOE results (Scheme 5) for **6** in solution, the solid-state structure shows that the two benzotriazole substituents occupy axial positions. Furthermore, they both exist with conformations about the C—N bond which have the N—N bonds almost eclipsed with the C—C bonds [N—N—C—C torsional angles 17.4(2) and 27.2(2)° for the two Bt groups]. In contrast to our recent study[19] that provided convincing crystallographic evidence for a vinylogous anomeric effect in benzotriazole-substituted heterocycles, no definitive evidence for anomeric bonding distortions was found in the x-ray structure of **6**. Specifically, the C—N bond lengths [1.454(2) and 1.452(2) Å] were typical for systems lacking an anomeric bond elongation,

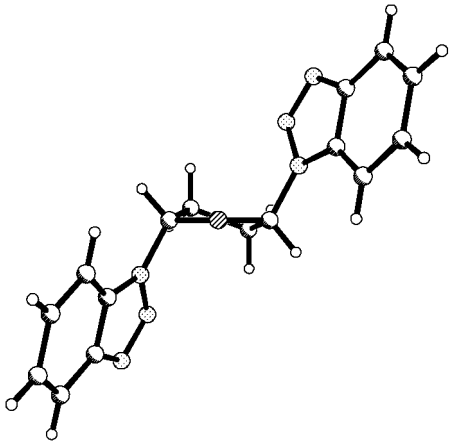
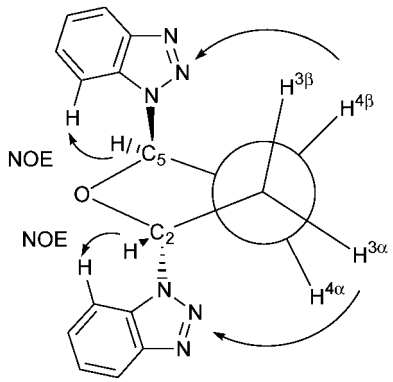


Figure 2. ORTEP projection of bis(benzotriazol-1-yl)tetrahydrofuran (**6**)



Scheme 5

Table 2. ^{13}C NMR chemical shifts (δ, ppm) and one-bond coupling constants [$^{1}J_{(C-2,H-2)}$, Hz] of 2-(benzotriazol-1-yl)tetrahydrofurans **1–6**

		Tetrahydrofuran carbons				Benzotriazole carbons					
Compound	$^{1}J_{(C-2,\ H-2)}$ (Hz)	C-2	C-3	C-4	C-5	C-4′	C-5′	C-6′	C-7′	C-3′a	C-7′a
1	167.8	87.9	30.8	24.3	69.3	119.8	124.1	127.4	110.4	146.2	132.8
2	165.5	88.8	57.8	33.3	68.3	119.8	124.0	127.6	110.3	145.4	133.4
3	172.6	93.6	59.8	34.9	68.9	119.9	124.4	128.1	109.9	145.9	132.7
4[a]	164.5	88.3	44.2	28.4	69.8	119.5	123.8	126.9	110.1	145.1	133.2
5[b]	166.6	90.6	43.0	29.6	68.6	119.7	124.1	127.4	110.6	146.2	132.9
6	172.8	87.6	30.2	30.2	87.5	120.1	124.4	128.0	109.6	146.2	132.8

[a] Additional signals: δ[C(3)–$\underline{C}H_2N$] = 54.0 ppm; δ(N$\underline{C}H_2CH_2$ of pyrrolidine) = 54.4 ppm; δ(NCH$_2\underline{C}H_2$ of pyrrolidine) = 23.3 ppm.
[b] Additional signals: δ[C(3)–$\underline{C}H_2N$] = 58.6 ppm; δ(N$\underline{C}H_2CH_2$ of pyrrolidine) = 54.1 ppm; δ(NCH$_2\underline{C}H_2$ of pyrrolidine) = 23.3 ppm.

and the C—O bonds of the ring [1.422(2) and 1.436(2) Å] showed no evidence of bond shortening.

The ^{1}H NMR spectra of **1–6** in CD_2Cl_2 solution show no changes on decreasing the recording temperature, except for line broadening at −94 °C.

Correlation of the conformation with the magnitude of the $^{1}J_{(C-2,\ H-2)}$ coupling constant

The carbon chemical shifts observed in ^{13}C NMR spectra of mono- and disubstituted tetrahydrofurans **1–6** are collected in Table 2. The chemical shift assignment of carbon atoms was made on the basis of HETCOR spectra. A representative example of the ^{1}H–^{13}C HETCOR spectra is shown for **5** in Fig. 3.

Changes in chemical shifts compared with unsubstituted tetrahydrofuran[20] (especially pronounced for the C-2 atom) are induced both by a benzotriazol-1-yl group and by a C-3 substituent. Introduction of the benzotriazolyl group into the 2-position shifts the C-2, C-3, C-4 and C-5 signals by +19.5, +5.0, −1.5, and −1.4 ppm,

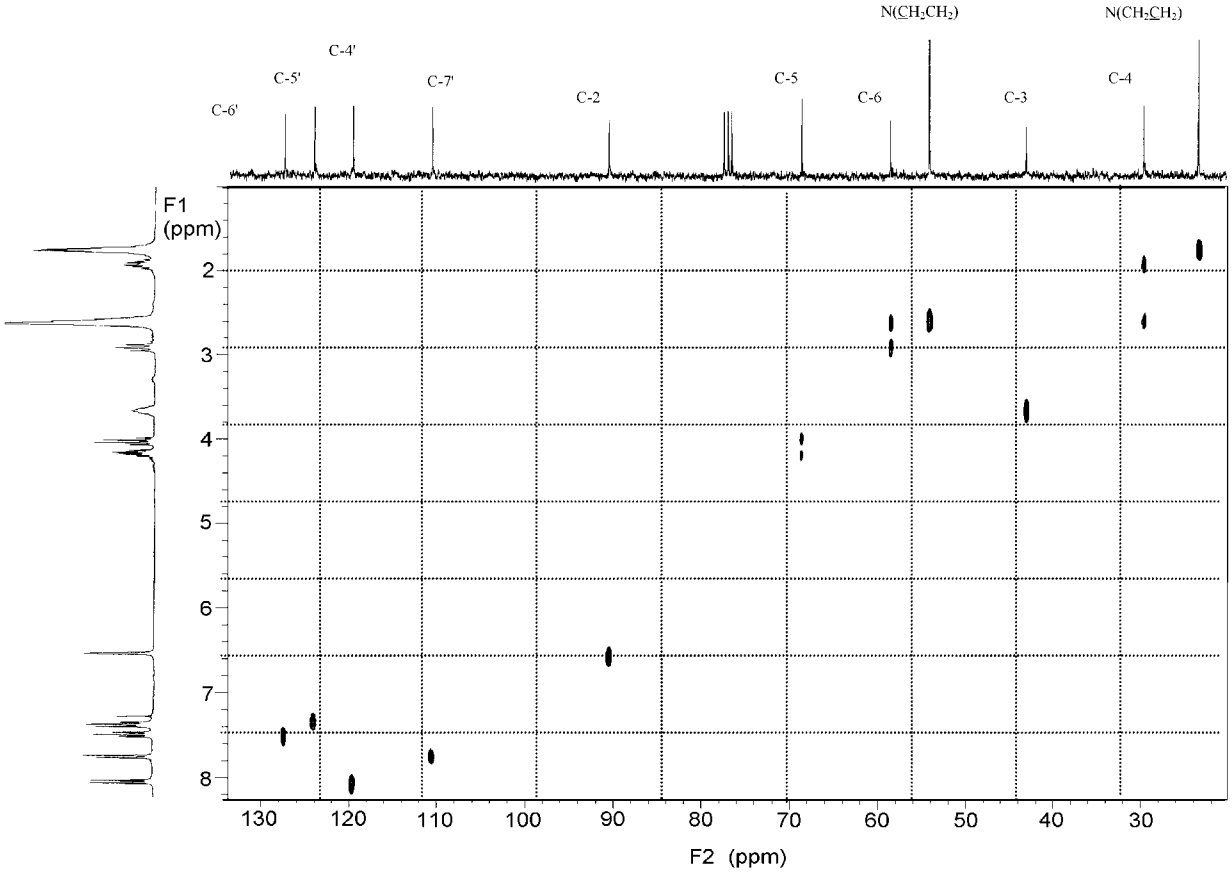
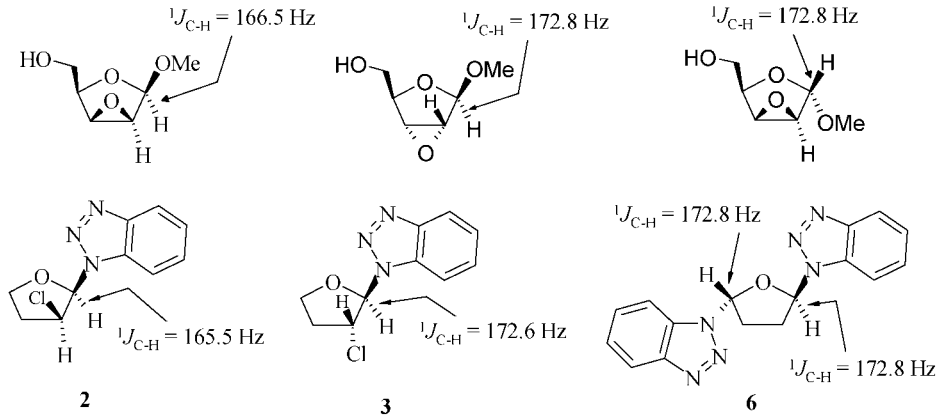


Figure 3. HETCOR spectrum of **5** in $CDCl_3$



Scheme 6

respectively, compared with those of unsubstituted tetrahydrofuran. The effect of a second benzotriazolyl group in the 5-position is the same.

From ^{1}H coupled ^{13}C NMR spectra, the $^1J_{(C-2-H-2)}$ coupling constants (ca 164–173 Hz) (Table 2) were obtained for **1–6**. The magnitude of the $^1J_{(C-2,H-2)}$ coupling constant observed for **1–6** is comparable to those for a number of carbohydrates [$^1J_{(C-2,H-2eq)}$ = 168–172 Hz][13] and also 2,3-anhydro-*O*-furanosides [$^1J_{(C-2,H-2)}$ = 166–173 Hz],[21] supporting our conclusion on the pseudo-axial orientation of the Bt-1 group in **1–6** (Scheme 6).

CONCLUSION

The conformational behavior of a series of mono- and dibenzotriazol-1-yl-substituted tetrahydrofurans was studied, and electronic and steric effects of the benzotriazolyl groups were evaluated. The preferable quasi-axial orientation of the 2-benzotriazolyl substituent, independent of the nature of a substituent at the 3-position, was demonstrated, in contrast to our previous findings with tetrahydropyran analogs.

EXPERIMENTAL

2-(Benzotriazol-1-yl)tetrahydrofurans **1–6** were prepared according to literature procedures.[22]

^{1}H, ^{13}C and two-dimensional NMR spectra (H–H-COSY, NOESY, HETCOR, HETCOR-LR) and difference NOE experiments were recorded using a Varian GEMINI-300 MHz instrument in 5 mm NMR tubes in $CDCl_3$ solution (Cambridge Isotope Laboratories) at 25 °C. Chemical shifts (δ) are expressed in parts per million (ppm) from tetramethylsilane as an internal standard. The thermometer was calibrated using methanol and ethylene glycol standards for low and high temperatures, respectively, and the deviations in the recording temperature did not exceed $\pm$ 0.5 °C.

Two-dimensional homonuclear correlation ^{1}H–^{1}H-COSY spectra were recorded with a 1024 $\times$ 1024 data matrix and 256 time increments of each 16 scans, in magnitude mode, and processed with zero-filling in F_1 and unshifted sine-bell apodization function. For the proton composite pulse decoupled (WALTZ-16) ^{13}C NMR experiments, the conditions were as follows: spectral width 14 000 Hz (220 ppm), number of data points 65K, acquisition time 0.8 s, recycle delay 2 s and flip angle 30°. The FIDs in ^{1}H and ^{13}C experiments were apodized by an exponential windowing prior to Fourier transformation (WFT) in order to improve the signal-to-noise ratio in the NMR spectra.

Selective spin decoupling experiments were carried out with spectral width 4.5 kHz, acquisition time 3.2 s, number of data points 65K, pulse width 30° and number of scans 4, using a 300 MHz Mercury NMR instrument (Varian) with a linear amplifier. A decoupler power (dpwr) of 25 dB was used for selective decoupling.

Two-dimensional nuclear Overhauser correlation spectra (NOESY) were also recorded using a 1024 $\times$ 1024 data matrix and 256 time increments of each 16 scans (mix time 1.5 s), in phase-sensitive mode, and processed with a gauss apodization function. For the HETCOR and HETCOR-LR spectra, the conditions were as follows: spectral width ca 9900 Hz for ^{13}C and ca 2900 Hz for ^{1}H spectra, pulse width 90°, relaxation delay 1.0 s, number of increments 256 or 512, FT size 2048 $\times$ 1024 and acquisition time ca 5.25 h.

For the NOE difference experiments, the NMR sample was prepared by dissolving ca 10 mg of a compound in 0.7 ml of $CDCl_3$ in a 5 mm NMR tube. The tube was purged with argon for 1 min to remove dissolved oxygen before running NOE experiments.

X-ray crystallography. Data were collected with a Siemens SMART CCD area detector, using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). The

structure was solved by direct methods using SHELXS[23] and refined on F^2, using all data, by full-matrix least-squares procedures using SHELXL.[24] Hydrogen atoms were included in calculated positions, with isotropic displacement parameters 1.2 times the isotropic equivalent of their carrier carbons.

Crystal data for ***6***. $C_{16}H_{14}N_6O$, MW 306.33, monoclinic, $P2_1/c$, $a = 15.548(4)$, $b = 6.320(1)$, $c = 15.052(4)$ Å, $\beta = 104.255(3)°$, $V = 1433.5(6)$ Å^3, $Z = 4$, $T = -105$ °C, $F(000) = 640$, μ (Mo Kα) = 0.096 mm^{-1}, $D_{calcd} = 1.419$ g cm^{-3}, $2\theta_{max} = 53°$ (CCD area detector, 99% completeness), $wR(F^2) = 0.0972$ (all 2898 data), $R = 0.0379$ (2451 data with $I > 2\sigma I$).

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