Benzodiazepine analogues. Part 22.[1] Conformational analysis of benzodioxepine and benzoxathiepine derivatives

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^{1}H NMR spectroscopy, single crystal X-ray analysis and computer modelling have been used to explore the conformational preferences in five series of 1,5-benzodioxepine and 1,5- and 4,1-benzoxathiepine derivatives.

Keywords: 1,5-benzodioxepines, 1,5-benzoxathiepines, 4,1-benzoxathiepines, conformation, crystal structures

The detailed molecular structures of both central benzodiazepine receptors (CBRs) and peripheral benzodiazepine receptors (PBRs) have yet to be established, and the rational design of potential benzodiazepine receptor ligands has been based on the use of appropriate pharmacophore models.[2] It is reasonable to assume that conformational effects play an important role in the interaction of bioactive ligands with these receptors, and we have previously explored the conformational preferences of benzoxazepinone, benzodiazepinone and benzothiazepinone derivatives as analogues of the medicinally useful benzodiazepines.[3] As part of an ongoing investigation, we have also reported the synthesis of benzodioxepine[4] and benzoxathiepine[5] derivatives, and have investigated their receptor-binding affinities using a radio receptor assay.[6] In this paper, we discuss the results of conformational studies of these compounds based on a combination of ^{1}H NMR spectroscopic, X-ray crystallographic and computer modelling data.

The diastereotopic methylene (H_a, H_b) and methine (H_x) protons in the title compounds **1**–**5** resonate in the NMR spectral region δ *ca* 3.0–6.0 ppm (Table 1). The assignment of these signals is supported by DEPT, COSY and HETCOR data, and the relative deshielding effects of the oxygen and sulfur ring-atoms on the adjacent aliphatic protons is clearly evident. The signal multiplicities clearly reflect the geminal and vicinal couplings, while the magnitudes of the corresponding coupling constants (J_{ax} and J_{bx}) permit qualitative assessment of the dihedral geometry characteristic of each series.

1,5-Benzodioxepin-2-ones **1a**–**g**: In these systems, the relatively small vicinal coupling constants, J_{ax} and J_{bx}, are comparable [differing by *ca* 1.5 Hz (J_{ax} = 5.8±0.1 Hz; J_{bx} = 6.9±0.6 Hz)] suggesting that, in each case, the methine proton (4-H_x) is *gauche* to *both* methylene protons (3-H_a and 3-H_b). While there is no necessary correlation between solution and solid-state conformations, the X-ray crystal structure of the *p*-methoxyphenyl analogue **1e** is, at least, consistent with these deductions. Thus, inspection of the crystal structure (Fig. 1a) reveals that: (i) the methine proton (H-2) is *gauche* to *both* methylene protons (H-31, H-32); (ii) the seven-membered ring is severely puckered; and iii) the 4-phenyl substituent is quasi-equatorially disposed.

Molecular mechanics modelling of the parent system **1a**, however, suggests an equilibrium between at least two conformers (**Ia** ⇌ **Ib**; Fig. 2). The more stable conformer **Ia** (ΔE = 3.1kJ mol^{-1}) adopts a conformation in which the methine proton (4-H_x) is *anti* to one of the 3-methylene protons (ϕ = –71.5 and 168.3°). The less stable conformer (**Ib**), on the other hand, corresponds closely to the crystal structure and the *gauche* dihedral geometry (ϕ = 28.8 and –88.7°) between the methine proton (H_x) and methylene protons (3-H_a, 3-H_b) is consistent with the observed ^{1}H NMR coupling data. Of course, the modelled conformers represent *isolated* (gas phase) molecules, and the experimentally observed X-ray and NMR data may simply reflect the influence of unavoidable lattice or solvation effects, respectively. The possibility of a conformational equilibrium in solution cannot be excluded,

Table 1 Chemical shifts (ppm), signal multiplicity, and coupling constants *J* (Hz), for the methylene (H_a, H_b) and methine (H_x) protons in compounds **1–5**

Compd	R_1	R_2	H_a	H_b
1a	H	H	3.15 (dd; J_{ax} 5.8; J_{ab} 13.3)	3.10 (dd; J_{bx} 7.3; J_{ab} 13.3)
1b	Br	H	3.15 (dd; J_{ax} 5.9; J_{ab} 13.4)	2.98 (dd; J_{bx} 6.3; J_{ab} 13.3)
1c	Cl	H	3.17 (dd; J_{ax} 5.8; J_{ab} 13.4)	3.02 (dd; J_{bx} 6.9; J_{ab} 13.4)
1d	F	H	3.16 (dd; J_{ax} 5.8; J_{ab} 13.3)	3.03 (dd; J_{bx} 6.9; J_{ab} 13.3)
1e	OMe	H	3.15 (dd; J_{ax} 5.8; J_{ab} 13.3)	2.98 (dd; J_{bx} 7.3; J_{ab} 13.3)
1f	H	Br	3.16 (dd; J_{ax} 5.8; J_{ab} 13.5)	3.11 (dd; J_{bx} 7.3; J_{ab} 13.5)
1g	H	Cl	3.15 (dd; J_{ax} 5.7; J_{ab} 13.6)	3.09 (dd; J_{bx} 7.5; J_{ab} 13.5)
2a	H	H	2.99 (dd; J_{ax} 7.2; J_{ab} 12.4)	2.96 (dd; J_{bx} 9.7; J_{ab} 12.4)
2b	Br	H	3.01 (dd; J_{ax} 7.1; J_{ab} 12.5)	2.97 (dd; J_{bx} 9.5; J_{ab} 12.5)
2c	Cl	H	3.02 (dd; J_{ax} 7.1; J_{ab} 12.5)	2.98 (dd; J_{bx} 9.4; J_{ab} 12.5)
2d	F	H	3.00 (dd; J_{ax} 7.0; J_{ab} 12.5)	2.98 (dd; J_{bx} 9.5; J_{ab} 12.5)
3a	H	H	3.46 (dd; J_{ax} 6.0; J_{ab} 14.3)	3.29 (dd; J_{bx} 6.8; J_{ab} 14.3)
3b	Br	H	3.33 (dd; J_{ax} 6.1; J_{ab} 14.4)	3.20 (dd; J_{bx} 6.4; J_{ab} 14.4)
3c	Cl	H	3.39 (dd; J_{ax} 6.1; J_{ab} 14.4)	3.25 (dd; J_{bx} 6.4; J_{ab} 14.4)
4a	H	H	4.04 (dd; J_{ax} 7.6; J_{ab} 12.2)	3.93 (dd; J_{bx} 4.0; J_{ab} 12.2)
4b	Br	H	4.02 (dd; J_{ax} 7.3; J_{ab} 12.2)	3.92 (dd; J_{bx} 4.0; J_{ab} 12.2)
4c	Cl	H	3.94 (dd; J_{ax} 7.4; J_{ab} 12.2)	3.84 (dd; J_{bx} 4.0; J_{ab} 12.2)
5a	H	H	3.39 (dd; J_{ax} 7.0; J_{ab} 14.1)	3.15 (dd; J_{bx} 5.8; J_{ab} 14.1)
5b	Br	H	3.27 (dd; J_{ax} 7.1; J_{ab} 14.2)	3.06 (dd; J_{bx} 5.4; J_{ab} 14.2)
5c	Cl	H	3.28 (dd; J_{ax} 7.0; J_{ab} 14.2)	3.08 (dd; J_{bx} 5.5; J_{ab} 14.2)
5d	F	H	3.27 (dd; J_{ax} 6.9; J_{ab} 14.2)	3.06 (dd; J_{bx} 5.6; J_{ab} 14.2)

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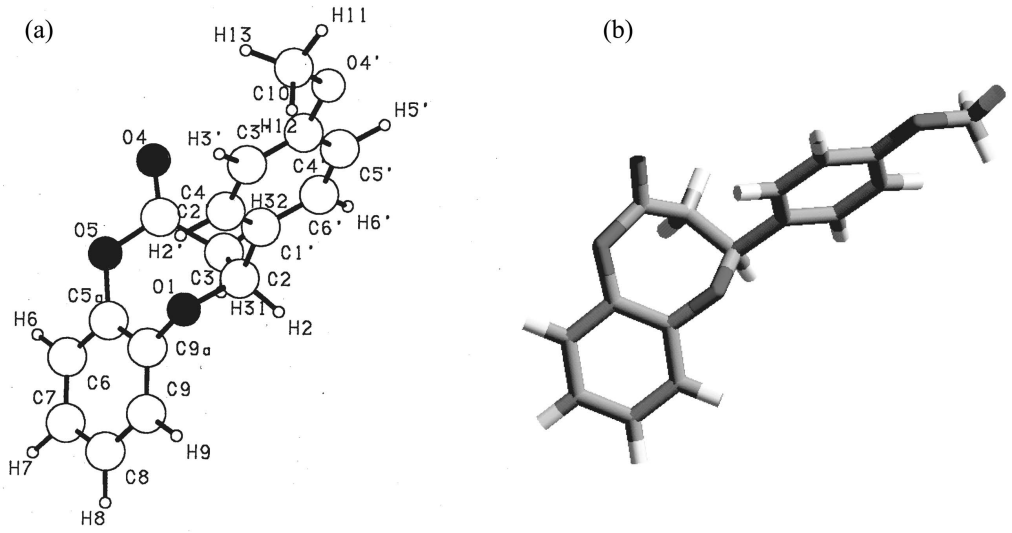

Fig. 1 (a) X-Ray crystal structure, showing the crystallographic numbering, and (b) computer-modelled "*gauche*" conformation of 4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzodioxepin-2-one **1e**.

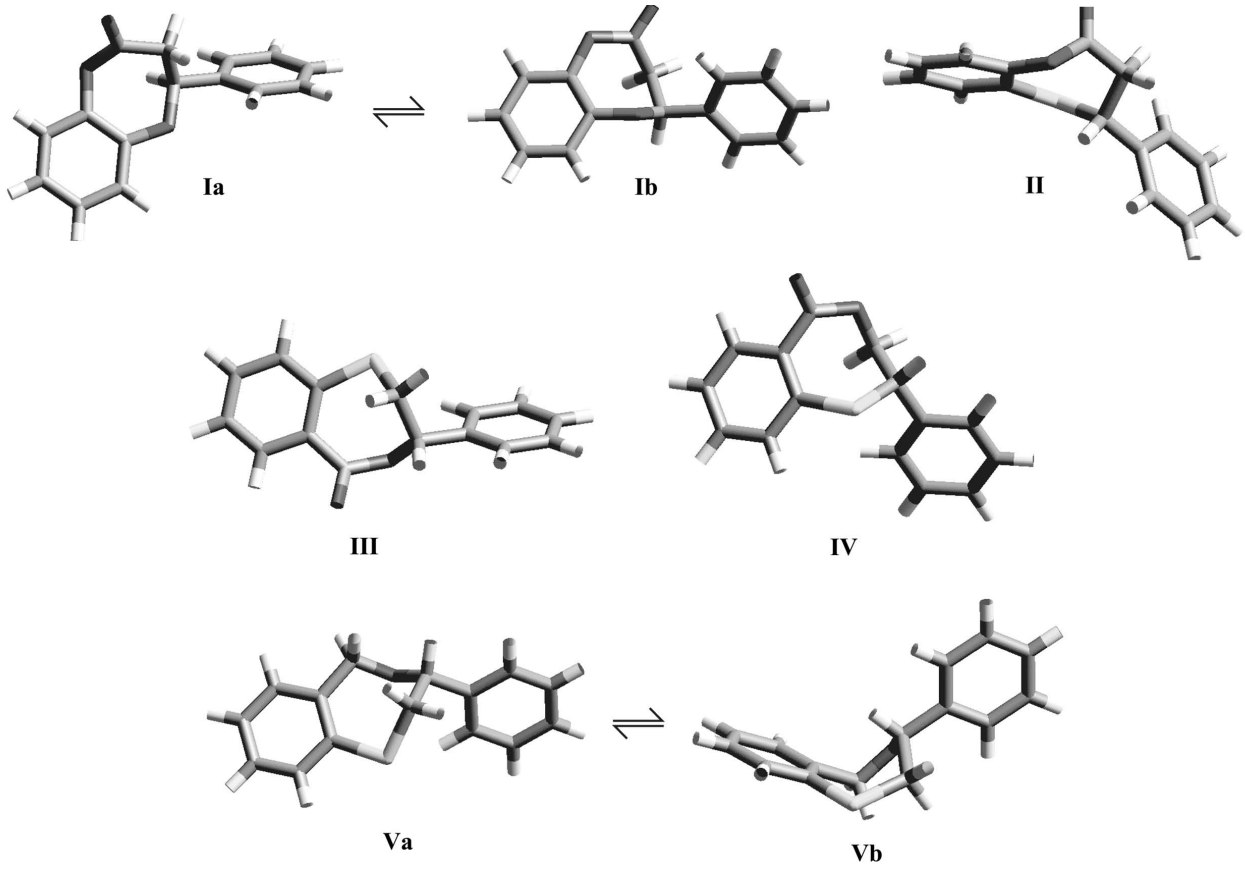

Fig. 2 Computer-modelled, energy-minimised structures for the benzodioxepine and benzoxathiepine derivatives; - **1a** (Ia and Ib); **2a** (II); **3a** (III); **4a** (IV); and **5a** (Va and Vb).

and the observed vicinal coupling constants (J_{ax} and J_{bx}) may well be weighted averages of the values for the contributing conformers. In fact, the *ca* 1 Hz difference between J_{ax} and J_{bx} could be attributed to the contribution of conformer **Ia**. Computer modelling of the 4'-methoxy analogue **1e** itself afforded three low-energy conformers, the *least* stable of which (Fig. 1b) exhibits *gauche* dihedral geometry consistent with the X-ray crystal structure.

1,5-*Benzoxathiepin*-2-ones **2a–d**: As expected, replacement of oxygen by the less electronegative sulfur results in a significant upfield shift (*ca* 1 ppm) of the 4-methine proton in the 1,5-benzoxathiepin-2-ones **2a–d** from *ca* δ5.7 to 4.7 ppm. It is also expected that the consequent elongation of the carbon–heteroatom bond would have conformational implications, including a change in the dihedral geometry, presumably reflected in the somewhat different vicinal coupling constants (J_{ax} = 7.1±0.1 Hz; J_{bx} = 9.55±0.15 Hz). The consistent difference (*ca* 2.5 Hz) between J_{ax} and J_{bx} in the compounds examined suggests that, in solution ($CDCl_3$), the methine proton (4-H_x) is *gauche* to one of

the methylene protons (3-H_a) and *anti* to the other (3-H_b) – a stereochemical arrangement which is clearly evident in the X-ray crystal structure of the *p*-chlorophenyl analogue **2c** (Fig. 3). Computer modelling of the parent compound **2a** affords a low-energy conformer **II** (Fig. 2), which exhibits similar dihedral geometry (ϕ = 56.9 and 178.3°) about the $C_2 - C_3$ bond as the crystal structure of the *p*-chlorophenyl analogue.

4,1-Benzoxathiepin-5-one derivatives **3a–c** and **4a–c**: In the 3-phenyl-2,3-dihydro-4,1-benzoxathiepin-5-ones **3a–c** the vicinal coupling constants are comparable in magnitude (J_{ax} = 6.05±0.05 Hz; J_{bx} = 5.6±0.2 Hz), implying that the methine proton (2-H_x) is gauche to *both* diastereotopic methylene protons (3-H_a and 3-H_b). Computer modelling affords conformer **III** (Fig. 2), in which the 2-methine proton is, in fact, *gauche* to *both* 3-methylene protons (ϕ = 80.0 and –37.0°) and the phenyl substituent is equatorially disposed.

In the isomeric 2-phenyl substituted analogues **4a–c**, however, the vicinal coupling constants differ significantly (J_{ax} = 7.4±0.2 Hz; J_{bx} = 4.0 Hz), implying significantly different torsion angles between the methine (3-H_x) proton and each of the methylene protons (2-H_a and 2-H_b), respectively. Computer modelling of the parent system **4a** affords a low-energy conformer **IV** (Fig. 2), which exhibits dihedral geometry consistent with the observed coupling constants, *i.e.* the 2-methine proton is *gauche* to one of the vicinal methylene protons and *anti* to the other (ϕ = 65.3 and –178.3°).

4,1-Benzoxathiepine derivatives **5a–c**: In this series, the vicinal coupling constants differ by *ca* 1.5 Hz (J_{ax} = 7.0±0.1 Hz; J_{bx} = 5.6±0.2 Hz)] – a situation comparable to that observed with the 1,5-benzodioxepin-2-ones **1a–g**, suggesting that, in each case, the methine proton (3-H_x) is *gauche* to *both* methylene protons (2-H_a and 2-H_b). Computer modelling again suggests the existence, *in vacuo*, of two low-energy conformers, **Va** and **Vb**. The former exhibits the expected *gauche* dihedral geometry (ϕ = 40.8 and –76.2°), while the latter [in which the 3-methine proton is *anti* to one of the 2-methylene protons (ϕ = 162.9 and –80.7°)] also, presumably, contributes to the conformational equilibrium in solution.

In summary, ^{1}H NMR vicinal coupling constants constitute a sensitive probe for exploring the dihedral geometry and, hence, the puckering of the seven-membered ring in the title compounds. A combination of these results with X-ray crystallographic and molecular modelling data provides useful insights into the conformational preferences of these compounds.

Experimental

The synthesis and spectroscopic (^{1}H- and ^{13}C NMR, HRMS) analysis of compounds **1a–g**, **2a–d**, **3a–c**, **4a–c** and **5a–d** have been reported previously.[4,5]

The X-ray data were collected with graphite-monochromated Mo-K_a radiation, λ = 0.71069 cm^{-1}, θ range 2 to 30°, on a CAD4 diffractometer (University of Natal, Pietermaritzburg). Structures were solved by direct methods, hydrogen atoms were included in calculated positions and refinement was by full-matrix least-squares methods using SHELX-76.[7] Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 297921 (for **1e**) and CCDC 297922 (for **1e**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK, fax: + 44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

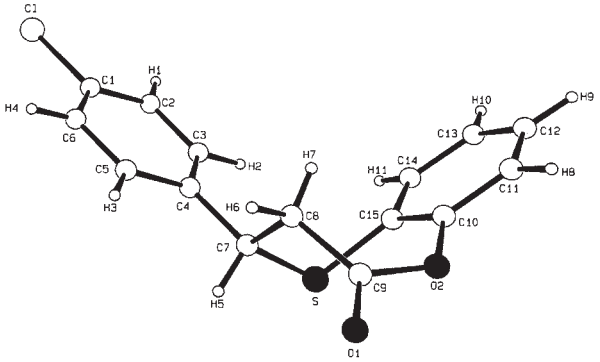

Fig. 3 X-Ray crystal structure of 4-(4-chlorophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one **2c**., showing the crystallographic numbering.

X-Ray data for 4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzodioxepin-2-one **1e**: $C_{16}H_{14}O_4$, formula weight: 270.28. Space group $P2_1$, no. 4 (non-standard setting); *a* = 5.3700 (18), *b* = 9.1922 (11), *c* = 13.8950 (28) Å, α = 101.164 (13); β = 90.00; γ = 90.00°, *V* = 672.91 (28) Å^3, Z = 2, F(000) = 284.00, D_c = 1.334 g cm^{-3}, μ = 0.57 cm^{-1}. 4045 reflections collected, 3147 unique with $I > \sigma(I)$; refinement converged at R_1, wR_2 = 0.0812 (unit weights).

X-Ray data for 4-(4-chlorophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one **2c**. $C_{15}H_{11}ClO_2S$, formula weight: 290.77. Monoclinic, space group C2/c; *a* = 21.663(4), *b* = 4.693(2), *c* = 26.602(4) Å, α = 90.00; β = 103.09(2); γ = 90.00°, *V* = 2634 Å^3, Z = 8, F(000) = 1200, D_c = 1.463 g cm^{-3}, μ = 3.85 cm^{-1}, 3045 reflections collected, 1824 unique with $I > 3\sigma(I)$; refinement converged at R_1 = 0.0402, wR_2 = 0.0425{w = 1/[σ^2(F) + 0.0006F^2]}.

Computer modelling

The parent structures **1a–5a** were modelled using the Accelrys software platform Cerius^2 on a Silicon Graphics O^2 computer, and Molecular Mechanics minimisation of conformational energies was achieved using the Universal force-field. Conformational space was explored using a combination of Molecular Dynamics and Simulated Annealing routines.

This material is based on work supported by the National Research Foundation. We also thank Professor John Field and Ms Niyum Ramesar (University of Natal, Petermaritzburg) for collecting the X-ray diffraction data, the Deutscher Akademischer Austauschdienst (DAAD) for a bursary (A.C.G.) and Rhodes University for generous financial support.

Received 2 November 2005; accepted 23 February 2006
Paper 05/3616

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