Conformational Analysis of 4,5-Dihydro-1-phenyl-1*H*-2,4-benzodiazepines

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Received September 9, 1992 (Revised Manuscript Received July 9, 1993●)

Detailed conformational analysis of 1-phenyl-1*H*-4,5-dihydro-2,4-benzodiazepines using X-ray structures, nuclear Overhauser experiments, variable-temperature ^{1}H NMR, and MacroModel (MULTIC) reveals a rapid equilibrium between axial and equatorial comformations for the free base of **2**. The DCl salt of **2** and 1-methyl-1-phenyl analog **3**, however, prefer the axial conformation.

As part of an investigation of a new class of 1-phenyl-1*H*-4,5-dihydro-2,4-benzodiazepine antiarrhythmic agents exemplified by **1**,[3] a study of the conformational preferences of this system was initiated to help interpret and direct the SAR. Molecular models and conformational analyses of related benzo-fused heterocyclic systems **5–7** suggested that an equilibrium could be expected between two major conformations in which the 1-phenyl substituent occupies a pseudoaxial or pseudoequatorial orientation.[4–8] By employing X-ray crystallography, nuclear Overhauser experiments, variable-temperature ^{1}H NMR, and constrained grid searching on compounds **1–4**, a detailed conformational characterization of 1-phenyl-2,4-benzodiazepines was achieved.

X-ray Structures. Experimental evidence supporting the existence of a conformational equilibrium is seen in the X-ray diffraction structures for two forms of **1**.[9] Resolution of **1** by recrystallization from methanol with L-dibenzoyltartaric acid gives crystals in which the phenyl ring adopts the axial conformation (Figure 1). Tetrahydroisoquinoline **7** also crystallizes with axial phenyl.[8,10] On the other hand, the racemic free base of **1** crystallizes from methyl *tert*-butyl ether with phenyl in the equatorial position (Figure 2). The identification of two different solid-state conformations supports the original hypothesis that a conformational equilibrium is expected for the 1-phenyl-2,4-benzodiazepines based on the precedent reported for the related benzo heterocyclic systems but gives no indication of which, if either, is the preferred solution conformation. Examination of the X-ray structures does suggest, however, that the distances between several key hydrogen atoms are well within range to expect measurable NOE's.[11]

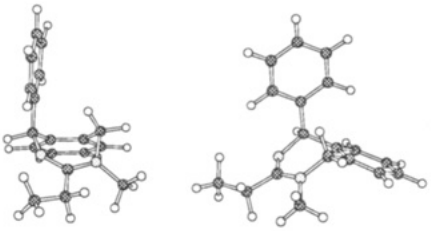
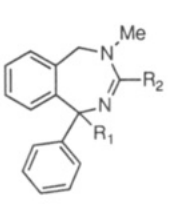
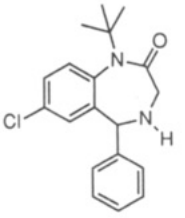


Figure 1. X-ray structure of **1ax**.



Compound	R1	R2
1	H	Et
2	H	Me
3	Me	Me
4	Me	Et



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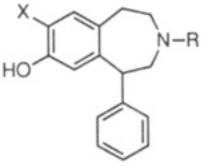
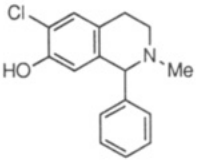


6a, X = HO, R = H
6b, X = Cl, R = Me



7

^{1}H NMR Experiments. The NOE spectra of **2** (free base) are consistent with an equilibrium mixture of

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● Abstract published in *Advance ACS Abstracts*, September 1, 1993.

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(3) Johnson, R. E.; Baizman, E. R.; Becker, C.; Bohnet, E., Bell, R. H.; Birsner, N. C.; Busacca, C. A.; Carabateas, P. M.; Gruett, M. D.; Hane, J. T.; Herrmann, J. L., Jr.; Josef, K. A.; Krafte, D. S.; Kullnig, R. K.; Michne, W. F.; Pareene, P. A.; Perni, R. B.; Salvador, U. J.; Sanner, M. A.; Schlegel, D. C.; Swestock, J.; Stankus, G. P.; Tatlock, J. H.; Volberg, W. A.; Weigelt, C. A.; Ezrin, A. M. *J. Med. Chem.*, in press.

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(9) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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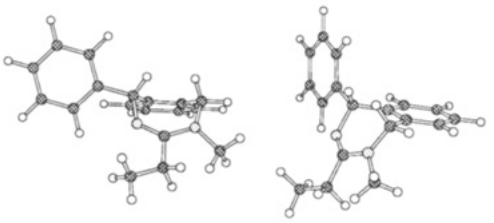


Figure 2. X-ray structure of **1eq**.

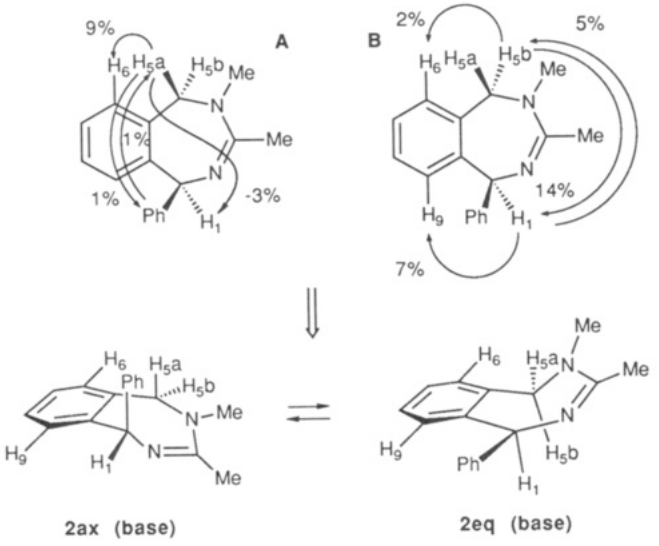


Figure 3. NOE for **2** (free base).

Table I. NOE Enhancements

		compd			
H irr	H enhan	**2** (base)	**3** (base)	**2** (DCl)	**3** (DCl)
1	5b	5			
	9	7	23	11	27
	o-Ph	4	4	2	4
5a	1	−3			
	5b	30	33	28	27
	6	9	−3	−6	−9
	o-Ph	1	14	4	8
5b	1	14			
	5a	27	39	31	32
	6	2	16	15	10
	Me4	1	2	4	1
o-Ph	1	10	2[a]	11	
	5a	1	1[a]	5	
	9	4	1[a]	2	

[a] Low power irradiation.

conformations **2ax** and **2eq**.[12] Irradiation of H5a in **2** (base) not only enhances *o*-Ph (1%) and vice versa but also affects H6 (9%) and shows a three-spin interaction with H1 (−3%) (Figure 3A and Table I). In addition, irradiation of H5b simultaneously enhances both H1 (14%) *and* H6 (2%) (Figure 4B). Finally, irradiation of H1 enhances *both* H9 (7%) and H5b (5%) (Figure 4B). The occurrence of NOEs across the top and bottom of the ring system strongly suggests that **2** (free base) is rapidly equilibrating between two major conformations **2ax** and **2eq**.

In fact, several features are strikingly different about the NOE spectra of **2** (free base) and **3** (free base) (Figure

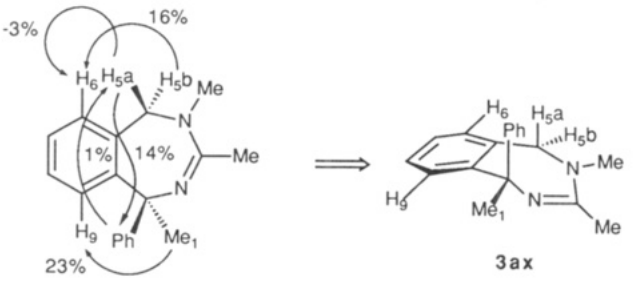


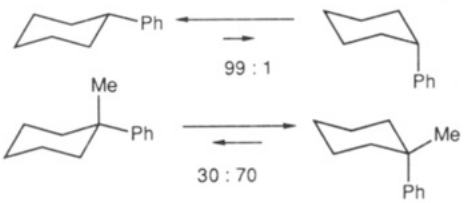
Figure 4. NOE for **3** (free base).

Table II. Selected ^{1}H NMR Data

	chemical shift (ppm)			
compound	H5a	H5b	H6	H9
2 base	4.01	4.67	7.2	6.75
2 DCl	4.86	3.67	7.3	7.48
3 base	4.21	3.12	7.04	7.61
3 DCl	4.66	3.55	7.23	7.72

4 and Table I). For example, irradiation of Me1 enhances only H9 (23%) and *o*-Ph (4%). Furthermore, irradiation of H5b enhances H6 (16%), and a three-spin negative enhancement (−3%) of H6 is observed upon saturation of H5a. No interaction is seen between Me1 and H5b, even though molecular models suggest close proximity of these groups in conformation **3eq**. These data suggest that **3** (free base) exists primarily in conformation **3ax**.

The shift in the position of the equilibrium favoring axial phenyl with 1-methyl substitution (**2ax** → **2eq** vs **3ax** → **3eq**) also occurs in phenylcyclohexanes. While 1-phenylcyclohexane favors the equatorial conformation, 1-methyl-1-phenylcyclohexane is more stable in the axial phenyl conformation.[13]



In contrast to the free base of **2**, the DCl salt of **2** more closely resembles **3** in its ^{1}H NMR and NOE spectra, suggesting a preference for the **2ax** conformation. For example, the chemical shifts of the H5a and H5b signals are reversed for **2** (base) and **2** (DCl) (Table II). The assignments for this AB system are primarily based on the NOE between *o*-Ph and the *upfield* doublet (4.01 ppm) in **2** (base) and the NOE between *o*-Ph and the *downfield* doublet (4.86 ppm) in **2** (DCl). NOEs are also observed between *o*-Ph and the downfield doublets in **3** (base) and **3** (DCl). Furthermore, irradiation of H1 in **2** (DCl) enhances *only* *o*-Ph (2%) and H9 (11%); H5b is unaffected (Figure 5). Irradiation of H5a not only enhances *o*-Ph (4%) and vice versa (5%) but also shows a three-spin negative enhancement of H6 (−6%). Irradiation of H5b does *not* affect H1 but enhances H6 (15%). In other words, transannular NOEs are only observed on the top side of **2** (DCl). Finally, the anisotropic effect of phenyl in the equatorial conformation puts H9 upfield of H6 in **2** (base). H9 is downfield of H6 in **2** (DCl), **3** (base), and **3** (DCl)

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Table III. ^{1}H NMR Data[a,b]

	compd			
position	2 (base)	3 (base)	2 (DCl)	3 (DCl)
1	6.15, s	1.76, s	5.88, s	2.22, s
3	2.02, s	2.05, s	2.56, s	2.72, s
4	3.00, s	2.87, s	3.21, s	3.17, s
5a	4.01, d, 14.3	4.21, d, 14.6	4.86, d, 15.0	4.66, d, 14.8
5b	4.67, d, 14.0	3.12, d, 14.3	3.67, d, 15.0	3.55, d, 14.8
6	|	7.04, dd, 1, 7.3	7.3, m	7.23, dd, 1.1, 7.4
7	7.14–7.21, m	7.25, dt, 1.4, 7.4	7.46, dt, 1.7, 7.2	7.46, dt, 1.3, 7.7
8	|	7.36, dt, 1.5, 7.6	7.52, dt, 1.2, 7.4	7.57, dt, 1.2, 7.5
9	6.75, d, 7	7.61, dd, 1, 8	7.48, bd, 7	7.72, dd, 1, 7.8
o-Ph	7.42, bd, 8	7.14, m	7.22, bd, 8	7.20, bd, 8.5
m-Ph	7.34, bt, 8	7.22, m	7.35, bt, 7.3	7.33, bt, 7.8
p-Ph	7.25, tt, 1, 8	7.15, tt, 1.3, 8.8	7.3, m	7.28, tt, 1.6, 7.3

[a] Solvent: CD_2Cl_2 at 30 °C. [b] Data reported as chemical shift downfield from internal TMS, multiplicity, *J* (Hz).

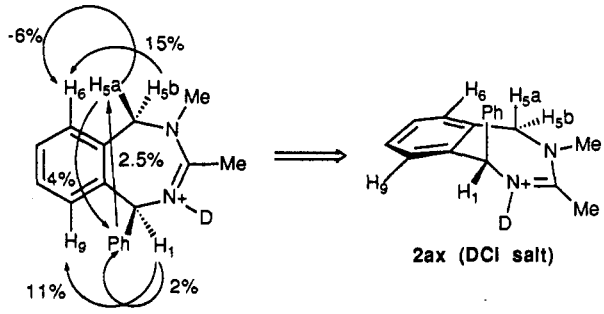
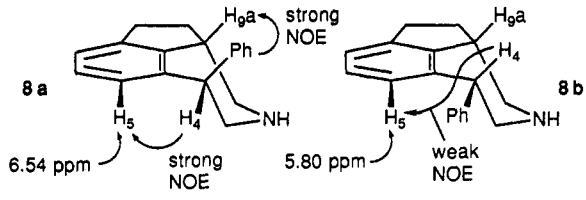


Figure 5. NOE for **2** (DCl salt).

(Table II). All of these observations suggest a preference for the axial conformation in **2** (DCl).

Our results closely parallel the NMR data and analysis of the conformationally restricted compounds **8a** and **8b**.[14] The axial conformation is assigned to isomer **8a** because of the strong NOEs for H4 → H5 and *o*-Ph → H9a and the downfield shift of H5. Equatorial isomer **8b** exhibits a weak H4 → H5 NOE and an upfield shift for H5.



Finally, the NOE data collected for **3** (DCl) are also consistent with conformation **3ax** (Table I and Figure 6). Important features are the three-spin negative enhancement of H6 by H5a (−9%), strong enhancement of H6 by H5b (10%), and strong Me1 → H9 enhancement (27%). Conspicuous by its absence is an interaction between Me1 and H5b. Again, NOEs are observed only across the top of the ring system. Structural and conformational assignments based on the *lack* of expected NOEs are riskly under the best of circumstances, but variable-temperature ^{1}H NMR experiments support the conclusion that only **2**

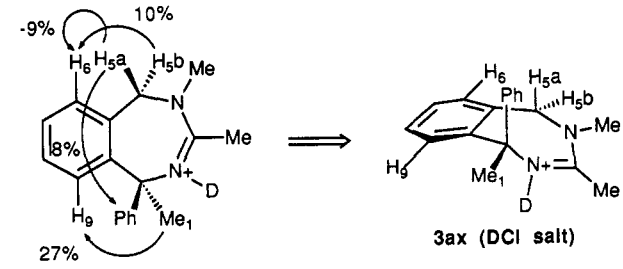


Figure 6. NOE for **3** (DCl).

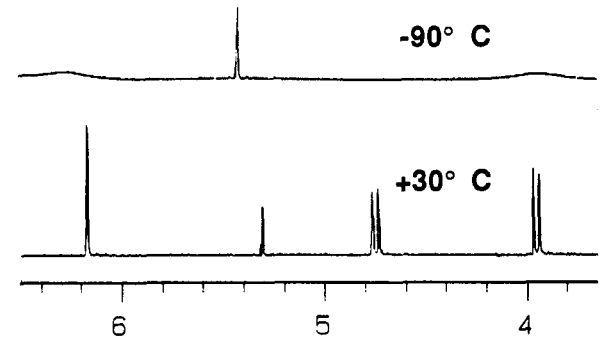


Figure 7. VT NMR for **2** (base).

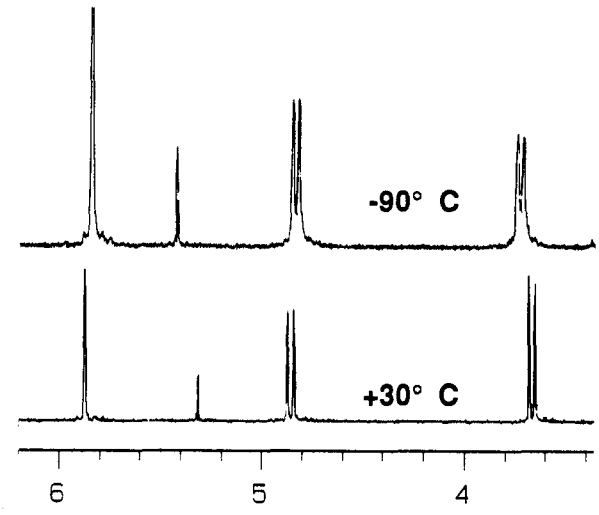


Figure 8. VT NMR for **2** (DCl).

(free base) exhibits two detectable conformations, whereas the **2** (DCl), **3** (free base), and **3** (DCl) heavily favor the axial conformation. ^{1}H NMR spectra were recorded for compounds **2** (free base), **2** (DCl), and **3** (free base) at +30, −10, −50, and −90 °C. Whereas **2** (free base) reaches coalescence at about −90 °C (Figure 7), little line broadening is seen for **2** (DCl) (Figure 8) and **3** (free base).

Constrained Grid Search. Conformations of **1** and **4** were also studied using the MULTIC option of MacroModel.[15,16] MULTIC allows for a systematic search of conformational space by employing a torsion angle tree-searching algorithm. The user defines a set of rotatable bonds, an increment of rotation, and a ring-closure bond. The program generates starting structures corresponding to all possible combinations of torsion angles, and, if present, satisfying the constraint of ring closure. Each of

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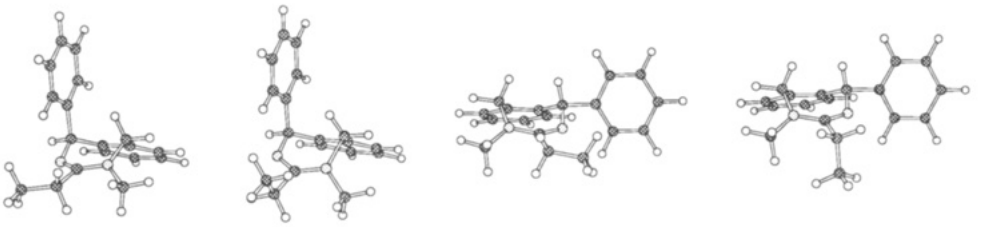


Figure 9. MacroModel Conformations of **1**.

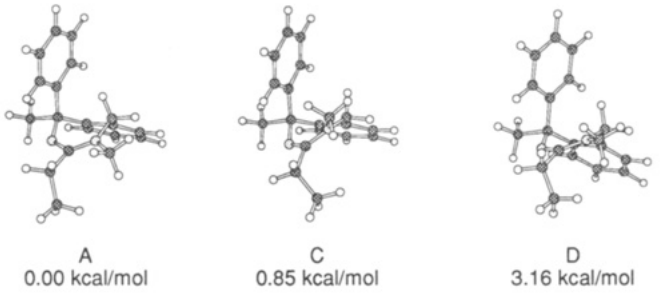
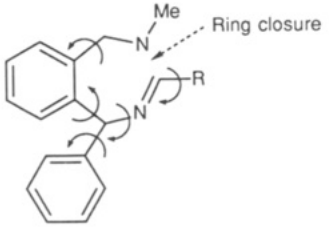


Figure 10. MacroModel Conformations of **4**.

these structures is minimized (MM2), and unique, low-energy structures are saved as relevant conformations.[17] For both **1** and **4**, an increment of 20° for five torsion angles and ring closure between C3 and N4 constrained to a distance of 1–2 Å are chosen.



Four low-energy conformations are identified for **1**, the lowest with phenyl axial and a second conformation at only 0.7 kcal/mol higher energy with phenyl equatorial (Figure 9). The difference between axial conformations 9A and 9B seems to arise primarily from the orientation of the ethyl group. The two lowest energy conformations are in very good agreement with the X-ray structures of **1** discussed earlier (all heavy atom RMSD = 0.18 Å for **1ax** and Figure 9A; all heavy atom RMSD = 0.28 Å for **1eq** and Figure 10C). This method also predicts the three lowest energy conformations with axial phenyl for the 1-methyl analog **4** (Figure 10). The orientation of ethyl and degree of pucker in the diazepine ring account for the differences between these conformations.

Conclusions. NMR, X-ray, and computational experiments with compounds **1**–**4** provide a detailed conformational analysis of the 1-phenyl-1*H*-4,5-dihydro-2,4-benzodiazepine system. Whereas the free base exists in rapid equilibrium between the axial and equatorial conformations, the salt heavily favors the axial conformation. This remains an interesting but unexplained phenomenon. Furthermore, 1-methyl analogs **3** and **4** also favor the axial phenyl conformation. The characterization of this ring system will influence the direction and interpretation of structure–activity relationships for a new class of antiarrhythmic agents.[3]

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Experimental Section

All ^{1}H NMR spectra were run on a Varian VXR500S spectrometer at 500 MHz in CD_2Cl_2.

X-ray Diffraction Analysis.[9] A SIEMENS R3m/V diffractometer was used for data collection. All calculations were done with SIEMENS' SHELXTL PLUS (Release 4.21/V).

1ax. Colorless prisms were obtained by recrystallization of the D-dibenzoyltartrate salt from methanol. Crystal data: triclinic, space group $P\bar{1}$ (No. 1), a = 7.466(15) Å, b = 10.532(2) Å, c = 11.225(2) Å; α = 104.444(11)°, β = 93.631(11)°, γ = 98.437(11); V = 840.9(3) Å^3; Z = 1; d_{calc} = 1.285 g/cm^3; μ = 0.758 mm^{-1}. Formula: $C_{18}H_{20}N_2{\cdot}C_{18}H_{24}O_8{\cdot}0.85CH_3OH$ = 650.8. Reflections were measured in the ω-scan mode, using a graphite monochrometer Mo Kα doublet (λ = 1.541 78 Å, scan range ω = 1.20°) radiation source. The structure was solved by direct methods and refined with full-matrix least-squares methods. A total of 2509 reflections were observed with $F > 3.0\sigma(F)$. The number of parameters refined was 452. The final R factors were R = 3.93% and R_w = 5.67%.

1eq. Colorless prism were obtained by recrystallization of the racemic free base from methyl *tert*-butyl ether. Crystal data: monoclinic, space group $P2_1/c$ (No. 14); a = 8.4347(1) Å, b = 19.666(4) Å, c = 9.218(2) Å, β = 106.257(1)°; V = 1467.9(4) Å^3; Z = 4; d_{calc} = 1.196 g/cm^3; μ = 0.066 mm^{-1}. Formula: $C_{18}H_{20}N_2$ = 264.37. Reflections were measured in the ω-scan mode, using a graphite monochrometer Mo Kα doublet (λ = 0.7169 Å, scan range ω = 1.20°) radiation source. The structure was solved by direct methods and refined with full-matrix least-squares methods. A total of 1966 reflections were observed with $F > 4.0\sigma(F)$. The number of parameters refined was 205. The final R factors were R = 4.64% and R_w = 7.59%.

Acknowledgment. The contribution of Dr. Richard Moore (formerly of Eastman Kodak) for assistance with NMR spectra is gratefully acknowledged.

Supplementary Material Available: ^{1}H NMR spectra for **2** (free base), **2** (DCl), **3** (free base), and **3** (CDl) (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.