A Molecular Chameleon: Chair and Twist-Boat Conformations of a 5,9-Methanobenzo[8]annulene

Lee Fielding,* John K. Clark, and Ross McGuire

AKZO-Nobel Pharma Division, Organon Laboratories Ltd., Newhouse, Lanarkshire, Scotland, ML1 5SH

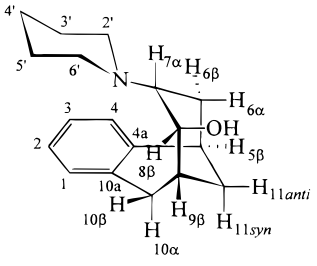
Received April 10, 1996[⊗]

A molecule that can change shape to suit its environment (a "molecular chameleon") is described. In solution there is an equilibrium between a compact chair conformation and an extended twist-boat conformation. Polar aprotic solvents favor the folded conformation (57% folded, 43% extended in DMSO-d_6 at 50 °C) and nonpolar solvents favor the extended conformation (100% extended in $CDCl_3$).

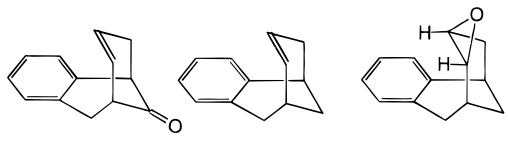
Introduction

The term molecular chameleon has sometimes been applied to molecules that undergo a solvent-induced conformation change.[1−4] Hydrogen bonding is frequently involved. Typically such molecules can fold to mask polar groups from nonpolar environments and consequently they adopt different conformations in polar and nonpolar solvents. Recently a "molecular umbrella" was described which can shield a hydrophilic group from a hydrophobic environment.[5] These observations are of interest to medicinal chemists and pharmacologists because they relate to the drug delivery problem—the difficulty of transporting hydrophilic drugs across lipophilic biological membranes.[6,7] It would be desirable to design drugs that could mask or disguise their hydrophilicity in order to cross a membrane.

A trans-axial arrangement of amine and hydroxyl groups destabilises the expected chair conformation of some cyclohexanes leading in some cases to a twisted boat conformation. This phenomena has been noted previously in decalins[8,9] and steroids.[10,11] We report here the results of an NMR and molecular mechanics study of the solvent dependent equilibrium between chair and twist-boat conformations of the nonfused cyclohexane ring in (5α,7*β*,8α,9α)-5,6,7,8,9,10-hexahydro-7-piperidino-5,9-methanobenzo[8]annulen-8-ol (**1**).



1



2 **3** **4**

Experimental Section

General Methods. Melting points are not corrected. Mass spectra were run in chemical ionization mode with methane reagent gas. Samples for infrared spectroscopy were prepared as KBr pellets. The eight-membered ring gains priority for nomenclature, but unfortunately this leads to an awkward numbering scheme for the interesting nonfused cyclohexane ring. The labels α and *β* refer to the plane of the eight-membered ring and the methine bridge is by definition α. The protons on C-11 are labeled *syn* and *anti* relative to the aromatic ring.

(5α,9α)-5,6,9,10-Tetrahydro-5,9-methanobenzo[8]-annulene (3). Hydrazine hydrate (75 mL) and potassium hydroxide (60 g) were added to a stirred solution of the ketone **2**[12] (80 g) in ethylene glycol (400 mL), and the mixture was stirred under reflux for 45 min. A partial take-off head was fitted, and the distillate was collected until no further product azeotroped over. The distillate was fully watered out and extracted twice with ether. The extract was washed, dried, and evaporated to give **3** (64 g) as a mobile liquid: GC-MS *m*/*z* MH^+ 171; ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 7.11 (m, 4H), 5.76 (m, 1H), 5.56 (m, 1H), 3.12 (s, 1H), 3.01 (dd, $J = 5.6, 16.6$ Hz, 1H), 2.64 (m, 3H), 2.0 (m, 3H). Anal. Found: C, 91.09: H, 8.54. $C_{13}H_{14}$ requires C, 91.71; H, 8.29%.

(5α,6α,7α,9α)-5,6,7,8,9,10-Hexahydro-6,7-epoxy-5,9-methanobenzo[8]annulene (4). 40% Peracetic acid (30 mL) was added to a stirred solution of the olefin **3** (18 g) in chloroform (150 mL) buffered with sodium acetate (6 g), maintaining the temperature at 0−5 °C. The reaction mixture was stirred vigorously at room temperature for 3 h. Water (0 °C) was then added followed by a solution of sodium metabisulfite. The chloroform layer was washed, dried, and evaporated to give the epoxide **4** (19.5 g) as a yellow oil. A sample was recrystallized from EtOH: mp 60−62 °C; GC-MS *m*/*z* MH^+ 187; ^{1}H NMR (200 MHz $CDCl_3$) *δ* 7.13 (m, 4H), 3.14

(1) Carrupt, P.-A.; Testa, B.; Bechalany, A.; El Tayar, N.; Descas, P.; Perrissoud, D. *J. Med. Chem.* **1991**, *34*, 1272.
(2) Gaillard, P.; Carrupt, P.-A.; Testa, B. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 737.
(3) El Tayer, N,; Mark, A. E.; Vallat, P.; Brunne, R. M.; Testa, B.; van Gunsteren, W. F. *J .Med. Chem.* **1993**, *36*, 3757.
(4) Leigh, D. A.; Moody, K.; Smart, J. P.; Watson, K. J.; Slawin, M. Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 306.
(5) Janout, V.; Lanier, M.; Regen, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1573.
(6) Van Bree, J. B. M. M.; De Boer, A. G.; Danhof, M; Breimer, D. D. *Pharm. Weekbl. [Sci].* **1992**, *14*, 338.
(7) Taylor, J. B.; Kennewell, P. D. *Modern Medicinal Chemistry*; Ellis Horwood: Chichester, 1993.
(8) Svoboda, M.; Tichy, M.; Fajkos, Sicher, J. *Tetrahedron Lett.* **1962**, 717.
(9) Girard, J. P.; Rossi, J. C.; Escale. R.; Vasickova, S.; Tichy, M. *Coll. Czech. Chem. Commun.* **1977**, *42*, 90.
(10) Fielding, L.; Grant, G. H. *J. Am. Chem. Soc.*, **1991**, *113*, 9785.
(11) Fielding, L.; Grant, G. H. *J. Am. Chem. Soc.*, **1993**, *115*, 1902.
(12) Gilbert, I. M.; Hewett, C. L.; Rae, D. R.; Redpath, J.; Savage, D. S.; Sleigh, T, *J. Chem. Soc., Perkin Trans. 1* **1995**, 133.

⊗ Abstract published in *Advance ACS Abstracts,* August 1, 1996.

S0022-3263(96)00667-6 CCC: $12.00 © 1996 American Chemical Society

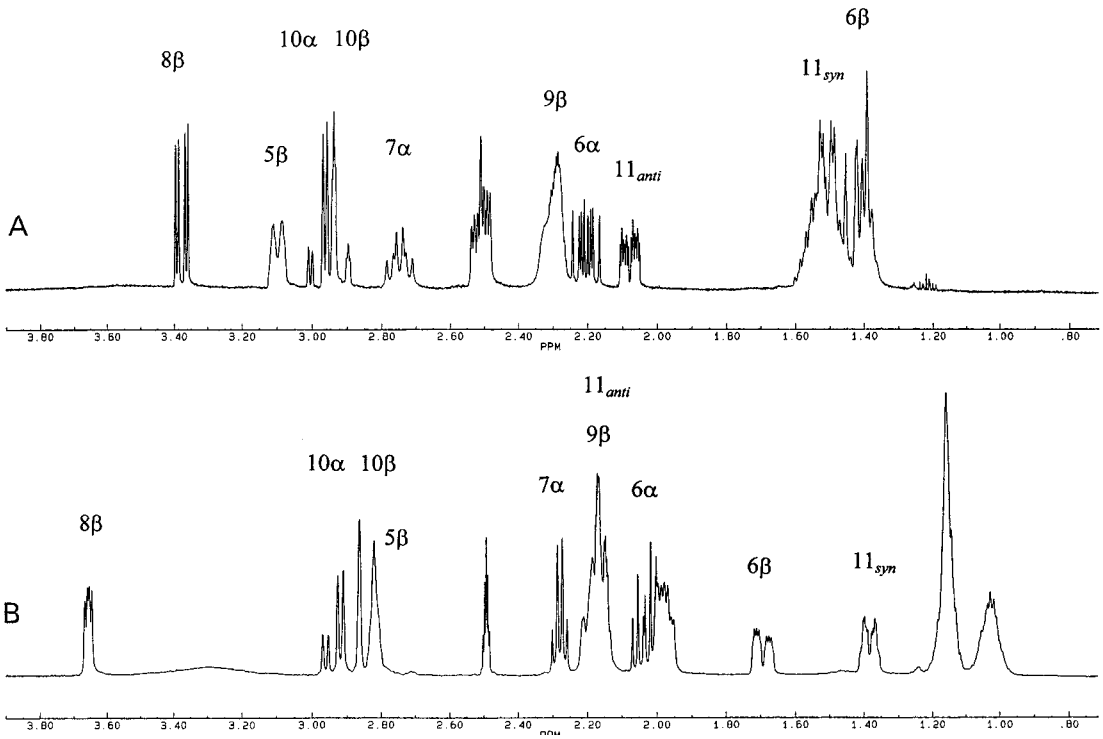


Figure 1. The aliphatic region of the 400 MHz ^{1}H NMR spectra of **1** in (A) $CDCl_3$ at 20 °C; and (B) DMSO-d_6 solution at 50 °C.

(dd, J = 6.1, 17.2 Hz, 1H), 3.06 (s, 1H), 2.7 (m, 3H), 2.63 (s, 1H), 2.16 (dd, J = 6.0, 15.1 Hz, 1H), 1.93 (m, 2H), 1.55 (m, 1H). Anal. Found: C, 84.06; H, 7.90. $C_{13}H_{14}O$ requires C, 83.82; H, 7.58%.

(5α,7α,8α,9α)-5,6,7,8,9,10-Hexahydro-7-piperidino-5,9-methanobenzo[8]annulen-8-ol (1). The preceding epoxide **4** (35 g) was dissolved in a mixture of methoxyethanol (150 mL), piperidine (50 mL), and water (5 mL), and the mixture was heated under reflux for 6 h. The cooled solution was fully watered out and extracted with dichloromethane. The extract was washed, dried, and evaporated to give the crude product as an orange oil (45 g) which was converted to the hydrochloride salt (in dichloromethane) and subsequently crystallized from ethanol/ether. An aliquot of the salt (11 g) was converted to the free base (9.6 g) and further purified by chromatography on silica gel (200 g) eluting with dichloromethane/EtOH/NH_4-OH 400/10/1−200/10/1. The recovered material (7.9 g) was reconverted to the hydrochloride salt and crystallized twice from ethanol/ether to give pure **1**.HCl (8.1 g): mp 200−210 °C dec; IR (KBr) 3285, 2750−2450, 1622, 1492 cm^{-1}. Anal. Found: C, 70.24; H, 8.60; N, 4.45; Cl, 11.88. $C_{18}H_{26}ClNO$ requires C, 70.22; H, 8.51; N, 4.55; Cl, 11.52%. This material was reconverted to the free base for the NMR experiments.

NMR. NMR data were acquired from 5 mg (^{1}H) or 40 mg (^{13}C) of **1** dissolved in 0.7 mL of the appropriate solvent on Bruker AMX 400 and DRX 400 spectrometers. $CDCl_3$ data were acquired at 20 °C and DMSO-d_6 at 50 °C. Assignment of the ^{1}H spectra were straightforward from COSY spectra and a consideration of vicinal couplings to distinguish between the geminal pairs of protons. The assignments were later validated by GOESY experiments.[13] The ^{13}C assignments followed from HETCOR and HMBC experiments. ^{1}H Chemical shifts and spin−spin couplings were obtained by simulating the experimental data with the spectral simulation program PANIC[14] and are accurate to ±0.001 ppm or ±0.2 Hz, except where they are given to 0.01 ppm or are indicated to be approximate. ^{1}H Chemical shifts are referenced to internal TMS. ^{13}C Chemical shifts are referenced to the solvent signal at 77.0 ppm for $CDCl_3$ and 39.6 ppm for DMSO-d_6.

Modeling. Both chair and twist-boat forms of the molecule were constructed using the Chem-X[15] system of programs and assigned Gasteiger[16] partial charges. Energy minimization about the C-7−N bond followed by molecular mechanics optimization using the Chem-X force field gave the minimum energy structures in each case. Surface areas were calculated by the Connolly method[17] using a probe radius of 1.2 Å and surface point density of 10 points/Å. The calculated vicinal couplings are from two computer programs, CAGPLUS[18] and GANDOUR.[19]

Results and Discussion

The ^{1}H NMR spectrum of **1** is remarkably solvent dependent. Representative spectra of $CDCl_3$ and DMSO-d_6 solutions are shown in Figure 1 and spectral parameters are given in Table 1.

At 400 MHz in $CDCl_3$ the signal from H-8β is a double doublet due to vicinal couplings to H-7α and H-9β. The signals from H-6α and H-7α are well resolved multiplets and it can be seen that some large splittings contribute to the overall line shapes. Full assignment of these lines (Table 1) reveals large vicinal couplings between H-6α, H-6β, H-7α, and H-8β and their neighbors that are consistent with quasi-axial positions for H-7α and H-8β, and a boatlike conformation of the nonfused cyclohexane ring. The unassigned peaks in Figure 1A at 2.5, 2.3, and 1.5 ppm are due to the piperidine moiety and are unremarkable.

As the solvent was changed to DMSO-d_6 (in a titration, data not shown), the spectrum smoothly and gradually changed its appearance to that shown in Figure 1B. The most striking aspect of the DMSO-d_6 data is not so much the obvious chemical shift changes but the changes in line shapes, especially of H-5β, H-6α, H-7α, and H-8β. These changes reflect reduced vicinal couplings in the

(13) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037.
(14) *Bruker Report*. Technical Report Vol. 3, Bruker: Karlsruhe, Germany, 1979; p 23.
(15) Chemical Design Ltd., Oxford, England.
(16) Gasteiger, J.; Marsili, M. *Tetrahedron* **1980**, *36*, 3219.
(17) Connolly, M. L. *Science* **1983**, *221*, 709 (QCPE 429).
(18) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
(19) Colucci, W. J.; Jungk, S. J.; Gandour, R. D. *Magn. Reson. Chem.* **1985**, *23*, 335.

Table 1. Chemical Shifts and Coupling Constants from the 400 MHz ^{1}H NMR Spectra of 1 in DMSO-d_6 at 50 °C and $CDCl_3$ at 20 °C

	chemical shifts (ppm)			couplings (Hz)	
	DMSO-d_6	$CDCl_3$		DMSO-d_6	$CDCl_3$
5β	2.82	3.097	6α6β	−14.3	−13.4
6α	2.035	2.204	10α10β	−16.9	−16.6
6β	1.693	1.424	11_{anti} 11_{syn}	−13.6	−13.1
7α	2.278	2.747			
8β	3.656	3.376	9β8β	3.1	3.8
9β	2.15	2.29	8β7α	5.5	11.2
10α	2.934	2.977	7α6α	6.0	7.6
10β	2.847	2.925	7α6β	5.7	11.2
11_{anti}	2.15	2.078	6α5β	6.2	10.2
11_{syn}	1.383	1.509	6β5β	2.6	∼1
			5$\beta$$11_{anti}$		2.1
			5$\beta$$11_{syn}$	∼3	∼1
			9$\beta$$11_{anti}$		5.5
			9$\beta$$11_{syn}$	3.8	3.7
			9β10α	6.6	4.9
			9β10β	∼1	1.6

Table 2. Data from the 100 MHz ^{13}C NMR Spectra of 1 in $CDCl_3$ at 20 °C and DMSO-d_6 at 50 °C

	$CDCl_3$	DMSO-d_6
1	130.0	128.3
2	125.9	124.4[a]
3	125.9	125.3[a]
4	128.9	128.0
4a	145.1	143.0
5	32.0	32.2
6	26.3	28.0
7	63.7	63.7
8	70.0	70.1
9	34.7	34.2
10	36.8	33.7
10a	134.6	136.7
11	24.5	25.4
2′,6′	49.6	51.0
3′,5′	26.6	25.7
4′	24.7	24.3

[a] These assignments may be reversed.

upper region of the nonfused cyclohexane ring. The data in mixed solvents demonstrates that there is an equilibrium between chair and twist-boat conformations which are in fast exchange on the NMR time scale, and hence the changes in the ^{1}H NMR spectra are charting a shift in the equilibrium from the twist-boat conformation in $CDCl_3$ toward the chair conformation in DMSO-d_6. The magnitude of the vicinal couplings suggest that the equilibrium is pushed some way toward its extreme in $CDCl_3$ (i.e. mostly the twist-boat conformation), but both conformers contribute to the spectrum in DMSO-d_6. Another feature of the DMSO-d_6 data is that *all* of the piperidine signals are shifted upfield with respect to the $CDCl_3$ data (the average upfield shift over all ten protons is 0.33 ppm). This is a consequence of the piperidine ring entering the shielded region above the benzene ring.

The ^{1}H NMR spectra of **1** in C_6D_6 and DMF-d_6 are very similar to those in $CDCl_3$ and DMSO-d_6 respectively, suggesting that the phenomenon is general for nonpolar and polar aprotic solvents.

The ^{13}C NMR of **1** was not very solvent dependent (see Table 2) and changes in chemical shifts due to the conformation change are not readily discerned from the small shifts (±1−2 ppm) that are simply due to the change of medium and chemical shift reference. Probably the only ^{13}C shifts that unambigously report on the conformation change are those that are observed for the fused aromatic carbons C-4a and C-10a which move 2.1 ppm upfield and 2.1 ppm downfield, respectively, as the solvent is changed from $CDCl_3$ to DMSO-d_6, and that

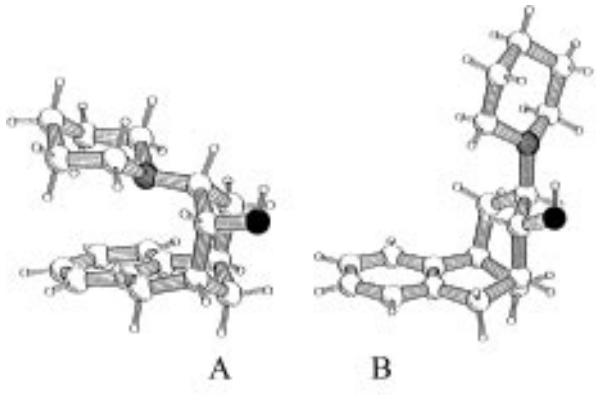


Figure 2. Molecular mechanics-derived geometries of (A) the chair conformation of **1**, and (B) the twist-boat conformation of **1**. Carbon atoms are unshaded, nitrogen atoms are cross hatched, and oxygens are solid.

observed from C-10 (3.1 ppm downfield shift). Although these shifts are subtle, they are interesting because they occur in the rigid region of the molecule and hence β and γ effects in the ^{13}C spectrum complement the directly observed ^{1}H shifts in the flexible region of **1**.

The chair and twist-boat conformations of **1** were modeled with Chem-X and the minimum energy structures are illustrated in Figure 2. In the twist-boat conformation the piperidine ring occupies an equatorial position of the nonfused cyclohexane ring in a relatively unconstrained part of the molecule. The O−N distance is 2.82 Å, which would permit a stabilizing hydrogen bond. C−C−C bond angles around C-10 and the bridgehead carbons C-9 and C-5 are close to tetrahedral angles (109.9 ± 0.8°) impling no strain in the 5,9-methanobenzocyclooctane moiety. The chair conformation is characterized by a trans-diaxial orientation of the piperidine and hydroxyl groups. The O−N distance increases to 3.65 Å as the hydrogen bond is relaxed, and the piperidine ring is parallel to and directly superimposed over the benzene ring. In this conformation at CPK radii there is a small gap between the piperidine and benzene rings. At van der Waals radii this space is fully occupied and is clearly a solvent excluded space. The solvent accessible surface area was found to decrease from 242 Å^2 in the twist-boat conformation to 218 Å^2 in the chair conformation. The slightly opened bond angles between C-10a−C-10−C-9 (114.3°) and C-10−C-9−C-8 (114.2°) probably reflects some strain due to van der Waals contacts between the rings, but this strain cannot be great because the C-4a−C-5−C-6 angle is normal (110.9°). The twist-boat conformer is calculated to be 4.0 kcal mol^{-1} higher energy in than the chair conformer. Gas phase molecular mechanics calculations do not adequately reflect the subtle influences of solvent environment and hydrogen bonding which play a major role in the equilibrium.

It is of interest to quantify the actual proportions of the two conformers in solution. For two species in fast exchange any measured vicinal coupling ($^3J_{obs}$) is the weighted sum of its components; i.e. in this case the couplings in the chair and twist-boat molecules. Hence if the couplings in each rotamer ($^3J_{chair}$ and $^3J_{boat}$) are known, each vicinal coupling within the fused ring is potentially a measure of the equilibrium. In this case the sets of reference couplings, $^3J_{chair}$ and $^3J_{boat}$ are unknown, but they might be estimated from the calculated geometries and a well parameterized Karplus equation. Table 3 lists, for both geometries, all torsion

Table 3. Calculated and Observed Vicinal Couplings in 1

	chair		$^3J_{obsd}$		twist-boat	
	torsion angle	$^3J_{calcd}$ (1)/(2)[a]	DMSO-d_6	$CDCl_3$	$^3J_{calcd}$ (1)/(2)[a]	torsion angle
9β8β	−60.2	3.3/3.7	3.1	3.8	4.0/4.5	-129.4
8β7α	67.7	2.6/0.3	5.5	11.2	9.8/10.5	173.1
7α6α	52.0	3.7/5.6	6.0	7.6	7.8/8.1	−32.1
7α6β	−65.6	2.7/2.4	5.7	11.2	9.0/10.1	−149.8
6α5β	−62.4	2.7/2.2	6.2	10.2	7.7/6.8	−30.4
6β5β	54.3	3.8/4.6	2.6	~1	1.0/1.6	86.8
5β11$_{anti}$	61.2	2.8/3.9		2.1	1.8/2.8	69.6
5β11$_{syn}$	−59.0	3.1/2.6	~3	~1	4.4/3.7	−50.4
9β11$_{anti}$	−56.6	3.5/2.9		5.5	4.6/3.8	−49.5
9β11$_{syn}$	63.6	2.5/3.4	3.8	3.7	1.7/2.6	70.7
9β10β	79.9	1.1/1.9	~1	1.6	2.3/3.4	64.8
9β10α	−37.6	6.6/5.3	6.6	4.9	3.8/3.0	−54.2

[a] Two values of the calculated coupling are given. (1) is derived from CAGPLUS[18], (2) comes from GANDOUR[19] using a substituent constant 2.0 for all akyl groups.

angles within the nonfused cyclohexane ring, values of ^3J calculated with two different Karplus curves, and the observed vicinal couplings from both solutions. It can be seen that four of the couplings (8β7α, 7α6α, 7α6β, and 6α5β) are sensitive to the conformation change whereas the remainder are either not involved, or the couplings expected are not sensitive to the change in torsion angle (i.e. 9β8β and 6β5β). Inspection of the columns five and six ($^3J_{obs}$ in $CDCl_3$, and $^3J_{calc}$ for the twist-boat conformer) reveals that the calculated couplings by the two methods are in good agreement with each other and are in very good agreement with the observed couplings. The average deviation ($^3J_{calc} - {}^3J_{obs}$) over all 12 dihedrals is −0.4 Hz, so it is clear that there is no strong bias in the $^3J_{obs}$ values in the direction expected from participation of the chair conformation, and therefore it is reasonable to conclude that the $CDCl_3$ solution corresponds to near 100% of the twist-boat conformer.

Using the calculated values (mean of two methods) of $^3J_{chair}$ and the values from $CDCl_3$ solution for $^3J_{boat}$ it is now possible to use $^3J_{obs}$ to determine the equilibrium in DMSO-d_6 solution. Using the four torsions that are sensitive to the conformation change, the result is 43% twist-boat, and 57% chair (±4%). The excellent internal agreement between these four measures is an important validation of the arguments used to estimate $^3J_{boat}$ and $^3J_{chair}$.

Finally some limited variable temperature ^{1}H NMR experiments were carried out to explore any possible dynamic effects in solutions of **1**. Over the temperature range −18 °C to +57 °C, the $CDCl_3$ solution spectra did not change significantly other than for some broadening of the signals from piperidine protons. Notably there was no measurable change in any of the diagnostic vicinal couplings. These observations reinforce the notion that the twist-boat form is the only significant conformation in the nonpolar solvent. Dynamic effects were observed from DMSO-d_6 solutions over the range +21 °C to +97 °C. There was no significant change to the signals from protons attached to C-10 and only minor changes to those attached to C-11 (as expected for protons in the rigid lower part of the system). However the signals from H-7α and H-8β were temperature dependent. H-8β shifted upfield and the vicinal coupling to H-7α increased as the temperature was raised (Figure 3). Similar behavior was seen in the signal from H-7α which moved downfield and exhibited larger couplings as the temperature was raised. These observations indicate that in the polar solvent the equilibrium between chair and twist-boat conformations shifts to favor the twist-boat form at higher temperatures and the folded chair form at lower temperatures.

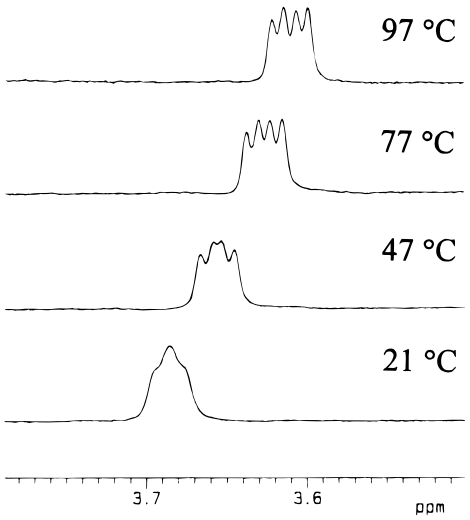


Figure 3. Dynamic behavior of **1** in DMSO-d_6. The ^{1}H NMR signal of H-8β is shown as a function of temperature. The vicinal couplings (Hz) to H-7α and H-9β are the following: 21 °C, 3.4/3.4; 47 °C, 5.0/3.3; 77 °C 5.8/3.1; and 97 °C 6.6/3.0.

Conclusion

Previous studies of trans amino-ols in cyclohexane derivatives have shown that the position of the equilibrium between chair and twist-boat conformations is determined by a fine balance between steric effects, hydrogen bonding, and solvation, with the former two effects being of most importance.[11] In this example it would appear that van der Waals interactions between the benzene and piperidine rings may be an additional factor. The extended twist-boat conformation (with a hydrogen bond) is favored in nonpolar aprotic solvents, while in polar solvents the molecule folds into the more compact chair conformation, masking some of its hydrophobic surfaces.

Acknowledgment. We would like to thank Philip Dennison (Strathclyde University) and Leon Orbons (N. V. Organon, Oss, The Netherlands) for help acquiring NMR data, and Kees Haasnoot (N. V. Organon, Oss) and Duncan Rae (Organon Laboratories) for helpful discussions that substantially improved this document.

JO960667X