First ^{1}H NMR observation of chair–boat conformers in bispidinone system. Molecular structure of 3,7-diisopropyl-1,5-diphenyl-3,7-diazabicyclo-[3.3.1]nonane-9-one

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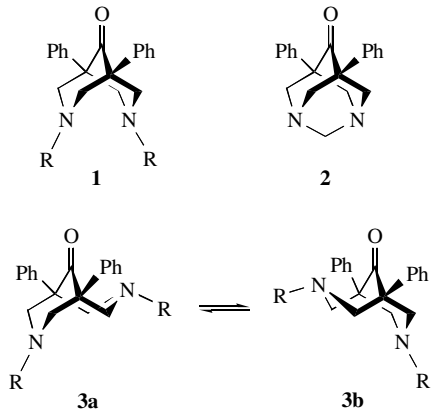
In the solid state bispidinone 4 exists in a CB conformation and in solution undergoes rapid degenerate interconversion CB ⇄ BC as revealed by variable temperature ^{1}H and ^{13}C NMR studies .

The conformational analysis of 3,7-diazabicyclo[3.3.1]nonanes (bispidines) is of considerable interest both from the theoretical viewpoint[1] and due to their biological activiy.[2] Recently, bispidines were recognised as perspective pre-organised ligands towards transition metals.[3,4] They are also of particular interest due to transformations of their chiral organolithium derivatives.[5] All complexes so far studied by X-ray diffraction show the bispidine's bicyclic backbone to exist in a double-chair (CC) conformation that resembles the adamantane structure and may cause specific complexation properties of these ligands.[3,6] The same solid state conformation is found in 1,5-diphenylbispidin-9-ones **1** (Scheme 1) (as well as for 5,7-diphenyl-1,3-diaza-adamantan-6-one **2**[7]) which have a carbonyl or nitroso function adjacent to the nitrogen atoms.[8,9] In contrast, in the solid state 3,7-dialkyl- and 3,7-ditosylsubstituted derivatives **3** present a chair–boat (CB) conformation.[4,9,10] Moreover, CB conformations exist in bispidine-based macrocyclic crown ethers.[11,12]



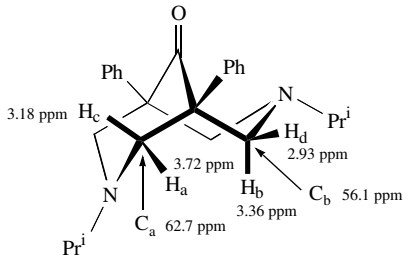
Scheme 1

Whereas the conformational effects in 1,5-diphenylbispidinones in the solid state have been extensively studied by X-ray diffraction techniques, there is little work devoted to their conformational behaviour in solution. In the mid 1970's, dipole moment investigations of 1,5-diphenyl derivatives led Scheiber and Nador to the assumption that in solution these compounds undergo a degenerate chair–boat ⇌ boat–chair (CB ⇌ BC) interconversion[13] (Scheme 1). Studying variable temperature ^{13}C NMR spectra of **3** (R = Me, CH_2Ph, Ts) revealed the same conclusion.[1,9,14] In the case where R = Me different values of the free activation energy $G^{\neq}$ (9.7 kcal mol^{-1} and 8.7 kcal mol^{-1} in refs. 14 and 1, respectively) were reported. The same parameter for R = CH_2Ph analogue is found to be 8.4 kcal mol^{-1} .[9]

As a consequence of the rapid equilibria **3a** ⇌ **3b** at room temperature the ^{1}H NMR spectra of the ring protons present an AB-system like quartet within the ranges 3.9–3.4 and 2.9–3.4 ppm. Recently, Black *et al.*[12] examined the dynamic proton NMR behaviour of macrocycle **3** [R + R = $CH_2(CH_2OCH_2)_3CH_2$] and reported that the high-field doublet assigned to the 'axial' protons of a bispidinone ring broadened on cooling and separated into a pair of doublets. The corresponding $G^{\neq}$ value is found to be 9.1 kcal mol^{-1} .

We have previously described the possible criteria for determining the conformations of 1,5-diphenylbispidinones in solution.[15] Chemical shifts of carbonyl carbons as well as carbons at *ipso*-position in phenyl rings for CC conformation **1** appear to lie at higher fields as compared to those of type **3**. Thus, compounds **3** [R = Me, allyl, CH_2Ph, CH(Ph)Me, CH_2CH_2CN, CH_2CO_2Et] have carbonyl carbon chemical shifts at 210–212 ppm and those of *ipso*-carbons at 142–144 ppm while for **1** (R = Ac) and **2** these values are 204–205 and 134–135 ppm, respectively. On this basis, we also suggest the conformational type **3** for several new bispidinones (R = Et, Pr^i, CH_2CH_2OMe, 2-furylmethyl, $CH_2CH_2CH_2OEt$). Here we report that our rationale is unambiguously confirmed by dynamic ^{1}H and ^{13}C NMR spectroscopic studies and crystal structure investigation in the case of *N*,*N*′-diisopropylsubstituted diphenylbispidinone **4**.†

In the ^{13}C NMR spectra of **4** below –74 °C, the peak that at room temperature corresponds to the resonances of four methylene carbons splits into a pair of broadened signals of equal intensity (labelled C_a and C_b, see below), which are separated by 6.6 ppm at –100 °C. The signal related to the carbons of the isopropyl methyl groups also splits into two peaks at 17.56 and 17.04 ppm, while that related to the methine carbons is broadened. At the same time, the Ph–C–C(O)–C–P h moiety demonstrates sharp resonance signals within the whole temperature range studied. All these facts are in complete accordance with an assumption of a degenerate CB ⇌ BC



Scheme 2

† The sealed evacuated degassed sample of 0.17 M concentration in absolute CD_2Cl_2 was used. All measurements were performed on a Varian VXR-400 spectrometer. The temperature calibrations were carried out by conventional techniques (with a standard methanol sample). **4**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C) δ: 7.43–7.23 (m, 10H, Ph), 3.57 (d, 4H, CH_2, ^2J 10.4 Hz), 3.21 (d, 4H, CH_2, ^2J 10.4 Hz), 3.06 (sept, 2H, CH, ^3J 6.4 Hz), 1.08 (d, 6H, Me, ^3J 6.4 Hz). ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C) δ: 212.14 [C(9)], 144.76 (C_{ipso}), 128.15 (C_{meta}), 127.30 (C_{ortho}), 126.72 (C_{para}), 60.92 (CH_2), 55.01 [C(1) and C(5)], 54.67 (CH), 18.53 (Me).

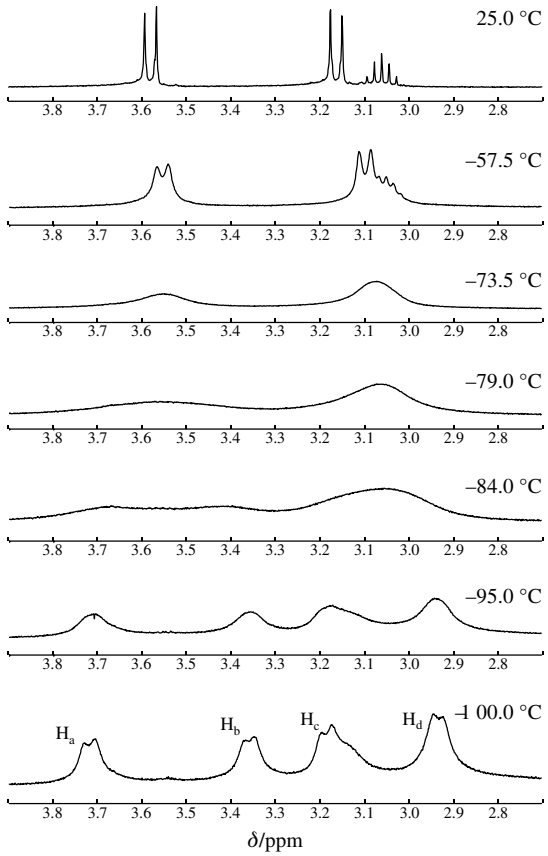


Figure 1 VT ^{1}H NMR spectra of **4** (aliphatic region).

interconversion taking place. Slowing of this process at low temperatures makes it possible to observe individual signals of chair and boat conformations.

Equally dramatic changes are observed in the ^{1}H NMR spectrum when the temperature is lowered. At –100 °C the methyl and methine groups of the isopropyl substituents give two pairs of broadened signals at 1.13 and 0.99 ppm, and at 3.13 and 2.93 ppm, respectively, whilst four skeleton protons H_a, H_b, H_c and H_d are represented by four signals corresponding to two AB systems (Figure 1).

Table 1 Coalescence temperatures (CT), ν values and calculated $G^{\neq}$ for **4**.

Spectrum	Nuclei	CT/°C	ν (–100 °C)/ Hz	$G^{\neq}$/ kcal mol^{-1}
^{13}C	C_a and C_b	–74.5±1.5	659	8.6±0.1
^{1}H	H_a and H_b	–83.5±1.0	145	8.7±0.1

By means of selective homo- and heteronuclear double resonance experiments, protons H_a and H_c were found to be part of one spin system that also includes C_a, while the signals of H_b, H_d and C_b correspond to another.

The obtained data allow us to assume tentatively that H_a, H_c and C_a belong to a chair ring while H_b, H_d and C_b are assigned to a boat ring. Indeed, the literature data prove that the low-field signals in the ^{13}C NMR spectra of the natural sparteinic alkaloids correspond to the rings of the boat conformation.[16] It was also established that in the ^{1}H NMR spectrum of sparteine, which exists in a CB conformation, the signal of the equatorial proton of the ring in the chair conformation is downfield shifted as compared to that in the boat conformation.[17] The nitrogen lone pair in quinuclidines and related systems is also known to have a shielding effect on the adjacent axial proton.[17] Thus, the signals in the ^{13}C and ^{1}H NMR spectra of **4** at –100 °C should be preferably assigned as shown on Scheme 2.

The consecutive changes in the ^{1}H NMR spectrum upon cooling or heating present an additional argument for the given assignment (see Figure 1). It is clearly seen that the signals H_a–H_b and H_c–H_d collapse in pairs. It is the very same picture that should be expected for the simultaneous inversion of both of the six-membered rings of **3** (see Scheme 1) in which the axial chair-ring protons exchange with the equatorial protons of the boat-ring and *vice versa*. From this point of view, it becomes apparent that the AB-system observed in the room-temperature ^{1}H NMR spectra of 1,5-diphenylbispidinones is derived from the superposition of four signals, and it is incorrect to assign any of observable doublets to the 'axial' or 'equatorial' protons.[4,12]

The free activation energy of interconversion of **4** was calculated by the CT method on the basis of the measured coalescence temperatures of the signals of the skeleton carbons and hydrogens. The derived $G^{\neq}$ values are in close agreement (Table 1).

X-Ray analysis of compound **4** confirmed the CB conformation in the solid state (Figure 2).‡ The asymmetric unit contains

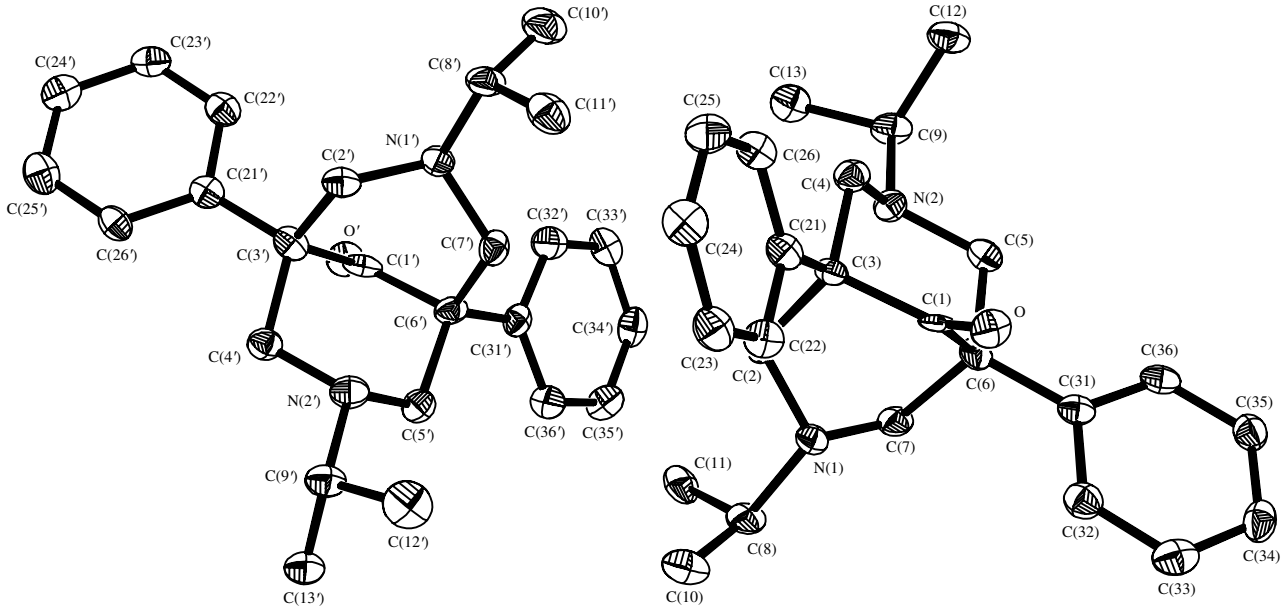


Figure 2 Molecular structure of **4**. Selected bond lengths (Å): O–C(1) 1.212(5), N(1)-C (7) 1.457(6), N(1)-C (2) 1.465(6), N(1)-C(8) 1.487(6), N(2)–C(5) 1.460(6), N(2)-C (4) 1.463(6), N(2)-C (9) 1.485(6), O′-C(1′) 1.220(5), N(1′)–C(2′) 1.453(6), N(1′)-C (7′) 1.469(6), N(1′)-C(8 ′) 1.493(6), N(2′)-C (5′) 1.454(6), N(2′)-C (4′) 1.455(6), N(2′)-C (9′) 1.485(6); selected bond angles (°): C(7)–N(1)-C(2) 110.1(4), C(7)–N(1)–C(8) 112.9(4), C(2)–N(1)–C(8) 113.9(4), C(5)–N(2)-C(4) 111.6(4), C(5)-N(2)–C(9) 112.3(4), C(4)-N(2)-C (9) 115.1(4), C(2′)–N(1′)-C (7′) 110.4(4), C(2′)-N(1′)–C(8′) 113.5(4), C(7′)–N(1′)-C(8′) 114.4(4), C(5′)–N(2′)-C (4′) 111.8(4), C(5′)–N(2')-C(9′) 114.6(4), C(4′)–N(2′)-C(9′) 112.6(4).

two independent molecules with very close geometrical parameters for a bispidinone skeleton. However, the conformations of N-CH Me_2 groups are not the same. The differences between relative C-C– N–C angles range within 8.1–1 1.4°. Both nitrogen atoms are pyramidal [C-N-C angles are within 110.1(4)–115.4(4)°]. It is of interest that N–C(isopropyl) bonds [1.485(6)–1.493(6) Å] are systematically longer than N-C(sk eleton) bonds [1.453(6)–1 .469(6) Å].

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‡ The single crystal of **4** of approximate dimensions 0.2×0.2×0.1 mm was mounted in inert oil on the top of glass fibre and transferred to a cold nitrogen stream on a Siemens SMART CCD diffractometer. *Crystal data*: $C_{25}H_{32}N_2O$, M = 376.53, monoclinic, a = 11.9515(2), b = 18.0538(4), c = 19.9549(1) Å, β = 91.678(1)° (refined from all collected reflections during data reduction[18]), V = 4226.18(12) Å^3, space group $P2_1/c$, Z = 8, D_c = 1.184 g cm^{-3}, $F(000)$ = 1632, μ(MoK) = 0.072 mm^{-1}. Total of 25403 reflections (7445 unique, R_{int} = 0.1965) were measured using graphite monochromated MoK radiation (λ = 0.71073 Å at 100.0(2) K. Data were collected in the range $1.53 < \theta < 25.00$ ($-15 \le h \le 15$, $-2\,3 \le k \le 13$, $-2\,3 \le l \le 25$); ω scan mode with a step of 0.3° (40 s per step) was used. The Siemens SAINT software was applied for data reduction.[18] Absorption correction was not performed since it did not lead to any improvement of the data.[19] 7078 reflections with $I > -3\sigma(I)$ were used in further calculations. The structure was solved by direct methods[20] and refined by full matrix least-squares on F^2 (ref. 21) with anisotropic thermal parameters for all non-hydrogen atoms. All H atoms were found from difference Fourier syntheses and refined in an isotropic approximation [H(2B), H(26) and H(22′) with fixed U_{iso} = 0.03 Å^2]. The weighting scheme was $w^{-1} = \sigma^2(F^2) + 9.1459P$, where $P = (2F_c^2 + F_o^2)/3$. The final residuals were: R_1 = 0.0892, wR_2 = 0.01473 for 3936 reflections with $I > 2\sigma(I)$ and 0.1955, 0.2227 for all data and 759 parameters. GOOF = 1.143, maximum shift/e.s.d. = 0.000, maximum ρ = 0.335 e Å^{-3}. Atomic coordinates, bond lenghts, bond angles and thermal parameters have been deposited at Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 1999. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/46.

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