Molecular structure of a macrocyclic bispidinone 15,18-diphenyl-4,7,10-trioxa-1,13-diazatricyclo[11.3.3.1^{15,18}]eicosan-20-one

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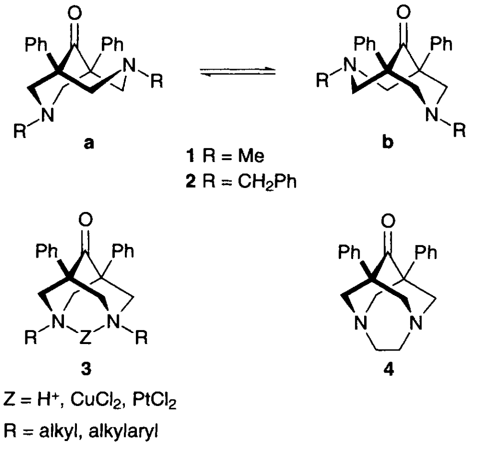
A crystal structure of the macrocyclic bispidinone 6 reveals a chair-boat conformation and a variable temperature ^{1}H NMR study demonstrates that in solution this configuration is in a degenerate equilibrium.

In the solid state *N,N*′-dialkyl derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-ones (bispidinones), such as **1** and **2**, adopt a chair-boat conformation which in solution rapidly equilibrates between the two degenerate forms **a** and **b**.[1] The bispidinone ring system is flexible and can be influenced by conformation directing properties. *N,N*′-Dialkylbispidinones rotate into the double chair configuration **3** upon protonation or the coordination of a transition metal between both terminal nitrogen atoms,[2] and the diazaadamantanone **4** accommodates the double chair conformation enclosed as a fragment of a seven-membered ring[3] (Scheme 1).

Changes between these conformational states can be attributed to varying repulsions between the lone pairs of electrons on the nitrogen atoms. In *N,N*′-dialkylbispidinones a pyramidal geometry at N is believed[4] to concentrate lone pair electron densities into a repulsive *endo–endo* interaction giving the chair-boat conformation. In coordination complexes **3** the electronic clash of N lone pair electrons is removed enabling a conformational change, and in the diazaadamantanone **4** a favourable *exo–exo* orientation of N lone pair electron densities is governed by the steric constraints imposed by the cyclic ring system.

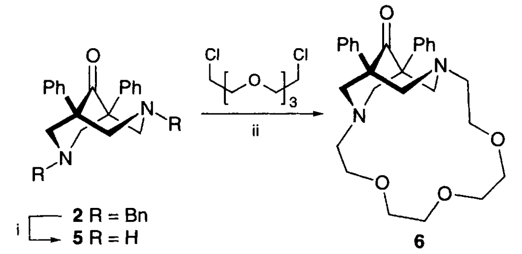
We have recently prepared novel macrocyclic bispidinone ionophores.[5] These contain the bispidinone frame as *N,N*′-dialkyl derivatives enclosed in cyclic systems that can range in size from 15 to 22 atoms. On the basis of the available data, the conformation of such adducts could not be clearly predicted. The bispidinone ring system could be thought to adopt a chair-boat conformation since it was a *N,N*′-dialkyl derivative or to adopt the double chair conformation as the result of its enclosure in a macrocyclic ring. We have now studied the molecular structure of the macrocyclic bispidinone **6** to elucidate the conformational properties of this class of compound.



Scheme 1 Conformational features of the bispidinone ring system

Synthesis of the macrocyclic bispidinone **6** was accomplished by the *N*-alkylation of the N-unsubstituted bispidinone **5**. This required the *in situ* generation of diiodo diethylene glycol from the homologous dichloride. Alkylation of **5** with the diiodide using sodium carbonate as a base in acetonitrile provided **6**. The bispidinone **5** could be prepared quantitatively after hydrogenolysis of the dibenzylbispidinone **2** with palladium–carbon in hot ethyl acetate. A Mannich condensation between dibenzyl ketone, formaldehyde and benzylamine acetate, in ethanol, was used to generate the dibenzylbispidinone **2** (Scheme 2).

The crystal structure of the macrocyclic bispidinone **6**† revealed molecules adopting the chair-boat conformation (Fig. 1). The geometry surrounding the nitrogen atoms was pyramidal in character, as indicated by the out-of-plane angle (q) of the *N*-alkyl bond from the chair C(12)–N(2)–C(14), q = 44.0° and boat C(3)–N(1)–C(15), q = 48.7° rings respectively. These values have been collated with those reported[4] for the dimethyl- and dibenzyl-bispidinones **1** and **2** (Table 1). The amount of pyramidal character at N found in the chair ring of the macrocyclic bispidinone **6** was significantly



Scheme 2 *Reagents and conditions*: i, H_2-Pd/C, EtOAc; ii, NaI, Na_2CO_3, MeCN

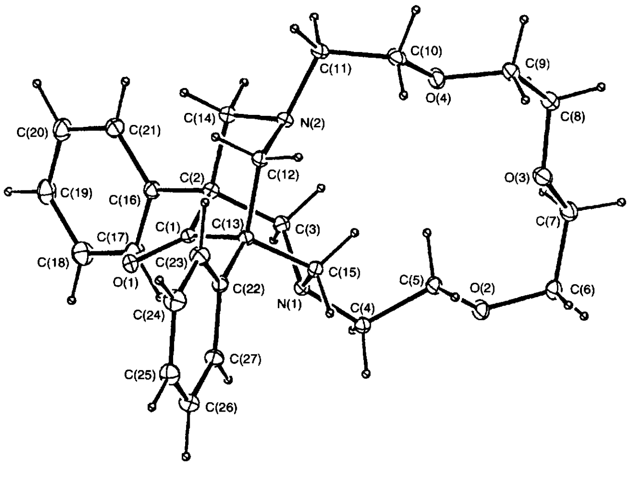
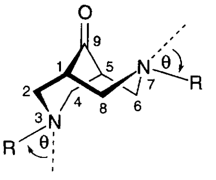


Fig. 1 ORTEP drawing of the macrocyclic bispidinone **6**

Table 1 The out-of-plane angle (θ) of the N–R bond for the chair C(2)–N(3)–C(4) and boat C(6)–N(7)–C(8) rings,[a] the average out-of-plane angle (θ), and the barrier for the degenerate chair-boat intraconversion ($\Delta G^\ddagger$) in the bispidinone rings of **1**, **2** and **6**



Bispidinone	R	θ(chair)°	θ(boat)°	θ(average)°	$\Delta G^\ddagger$/kJmol^{-1}
1	Me	50.6	54.5	52.5	40.6
2	CH_2Ph	49.1	47.7	48.4	35.0
6	$CH_2(CH_2OCH_2)_3CH_2$	44.0	48.7	46.4	38.1

[a] For the macrocycle **6**, atom labels C(12)–N(2)–C(14) and C(3)–N(1)–C(15) correspond to the generic atom lables C(2)–N(3)–C(4) and C(6)–N(7)–C(8) used for the chair and boat rings of 3,7-diazabicyclo[3.3.1]nonan-9-ones respectively.

lower than the values reported for the bispidinones **1** and **2**. This loss can be attributed to ring strain generated by the macrocyclic structure. Comparatively an increase in pyramidal character at N in the boat ring of **6** would be consistent with the development of ring strain within the macrocyclic structure. The magnitude of pyramidal character at N found in the boat ring of the macrocycle **6** is only slightly greater than the value recorded for the dibenzylbispidinone **2** but distinctly less than the amount reported for the dimethylbispidinone **1**. This divergence might result from varying steric congestion between *N*-alkyl groups and the boat rings of bispidinones, the limit being reflected in the dimethyl compound **1**. The dihedral angles N(1)–C(15)–C(13), y = 110.5° and N(2)–C(12)–N(13), y = 109.2° were found in the macrocycle **6**. This indicated that the apex of the boat C(3)–N(1)–C(15) and chair C(12]–N(2)–C(14) rings of the bispidinone frame in **6** are compressed to a greater extent than the apex of rings found[6] in the non-macrocyclic bispidinones **1** and **2**.

At room temperature ^1H NMR spectroscopy can identify the protons of the 1,5-disubstituted bispidinone ring system as an AB quartet. This pattern derives from geminal coupling between the isolated axial and equatorial protons. In **6**[‡] the doublet assigned to the rapidly equilibrating axial protons of the bispidinone ring broadened on cooling and separated into an identifiable pair of doublets (dv = 213 Hz) corresponding to the axial protons of the immobile chair and boat rings. The coalescence temperature was −73 °C and this corresponds to $\Delta G^\ddagger$ 38.1 kJ mol^{-1} for the degenerate **a–b** interconversion. A correlation between $\Delta G^\ddagger$ and the degree of pyramidal character at N in bispidinones was originally proposed[4] after a study of *N,N′*-dialkyl- and *N,N′*-diacyl-bispidinones. A comparison of these values reported[4] for the bispidinones **1** and **2** with those found for the macrocycle **6** show that such a relationship is unlikely (Table 1).

These results indicate that macrocyclic bispidinones such as **6** can adopt a distorted version of the chair-boat conformation commonly found in other *N,N′*-dialkylbispidinones.

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Footnotes

[†] *Crystal data* for **6** $C_{27}H_{34}N_2O_4{\cdot}0.5(C_2H_5OH)$, M = 473.60, monoclinic, space group $P2_1/c$, a = 12.5900 (7), b = 9.2145 (2), c = 24.8426 (13) Å, β 118.009 (2)°, Z = 4. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No 1. Any Request to the CCDC for this material should quote the full literature citation and the reference number 182/191.

[‡] The ^1H NMR spectrum of **6** was recorded at 400 MHz in CD_2Cl_2. For comparison the bispidinone **1** was also examined in this solvent. $\Delta G^\ddagger$ for **1** in CD_2Cl_2 did not change from the value reported[4] in CD_2Cl_2–CS_2.

References

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