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ARTICLE *in* JOURNAL OF MOLECULAR STRUCTURE · NOVEMBER 2011

Impact Factor: 1.6 · DOI: 10.1016/j.molstruc.2011.08.047

Journal of Molecular Structure 1005 (2011) 178–185

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Theoretical and spectroscopic studies on the conformational equilibrium of 9-oxabispidines in solution

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ARTICLE INFO

Article history:
Received 19 July 2011
Received in revised form 24 August 2011
Accepted 24 August 2011
Available online 31 August 2011

Keywords:
9-Oxabispidine
Conformation
DFT calculation
Boat–chair equilibrium
Bispidine

ABSTRACT

The conformational behavior of *N*,*N*-dimethyl-9-oxabispidine and four 2-*endo*-substituted 9-oxabispidines (3,7-diaza-9-oxabicyclo[3.3.1]nonanes) in solution was investigated by theoretical and spectroscopic methods. The electronic energies of all conformers were calculated on the B3LYP/TZVP level of theory and solvent effects were taken into account by the continuum solvent model COSMO. Only two conformers, the double chair form **A1** (both N–R *exo*) and the boat–chair form **B2** (N_{chair}–R *exo*, N_{boat}–R *endo*), were of energetic relevance ($\Delta E \leqslant 18.2$ kJ mol^{-1}), with the former one strongly dominating (**A1**:**B2** $\geqslant$ 98:2 at room temperature), independent of the existence or nature of the 2-*endo*-substituent. Compared to the corresponding bispidines, the dominance of the double chair conformers **A1** was more pronounced in the 9-oxabispidines, presumably due to stronger N,O-repulsions in their boat–chair conformers **B2**. ^{1}H NMR studies on 21 2-*endo*-substituted 9-oxabispidines, using the ^3J coupling constants of the *exo*-methylene protons with the neighboring bridgehead protons as conformational probes, gave no evidence on a noticeable population of the boat–chair conformers **B** in solution, which is good agreement with the calculations. In addition, the experimentally determined proton shifts of two 2-*endo*-substituted 9-oxabispidines matched excellently with those calculated for their double chair conformers **A1**.

1. Introduction

The natural lupine alkaloid (−)-sparteine (**1**, Fig. 1) and the synthetic (+)-sparteine surrogate **2** [1,2], both possessing a chiral bispidine (3,7-diazabicyclo[3.3.1]nonane) skeleton as the central core, have found manifold applications in asymmetric synthesis [2,3]. These diamines are the ligands of choice for nearly all types of enantioselective deprotonations [2–4] and a steadily growing number of enantioselective catalytic transformations, such as the Pd(II)-catalyzed oxidative kinetic resolution of secondary alcohols [5]. We recently introduced the structurally closely related tri- and bicyclic 9-oxabispidines **3** and **4**, in which the methylene bridge of the bispidine system is replaced by an ether function [6–9]. Compared to **1** and **2**, these diamines are more easily available by total synthesis, thus permitting a convenient access to derivatives [6,7]. The tricycle **3**, for example, provided up to excellent 98% ee in enantioselective Cu(II)-catalyzed Henry reactions [7].

In addition to their use in asymmetric synthesis, bispidines also received great attention due to their conformational mobility in solution [10–18]. These diamines, in principle, can adopt the double chair conformation **A**, the boat–chair conformations **B** and **C** (unsubstituted resp. substituted ring in the boat form), and the double boat conformation **D** (Fig. 2). While the latter one, **D**, is normally strongly disfavored, the former ones, **A**–**C**, are often close in energy since the double chair conformation **A** is destabilized by a transannular N–N repulsion, which is avoided in the boat–chair conformations **B** and **C**. The relative populations of **A**, **B**, and **C** strongly depend on the substitution patterns of the respective bispidine derivatives, as known from several spectroscopic and theoretical investigations [10–18]. Galasso et al. [10], for example, calculated that the prototype, bispidine (**5**), occurs almost exclusively in the double chair conformation **5A**, presumably due to a stabilizing intramolecular hydrogen bridge, while the *N*,*N*-dimethyl derivative **6a** was predicted to exist as a quickly equilibrating mixture of the conformers **6aA** and **6aB** [10,11]. The latter result is in good agreement with the IR and photoelectron (PE) spectra measured, but in contrast to the NMR data, which indicate that the double chair conformation **6aA** is dominating in solution [10,12]. Bispidines with 2-*exo* substituents such as **7** often show a higher tendency to adopt the boat–chair conformation **C**, since this geometry permits an equatorial orientation of the 2-*exo* substituent [13]. In (−)-sparteine (**1**), which carries a 2-*exo*,3*N*-fused piperidine ring, the equilibrium is more or less fully shifted towards the boat–chair

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doi:10.1016/j.molstruc.2011.08.047

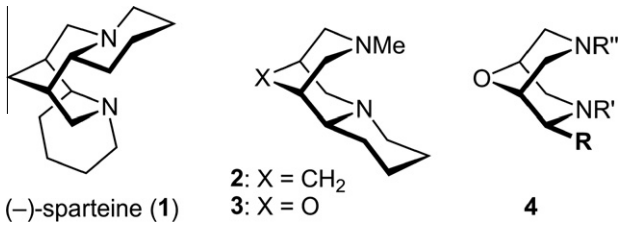


Fig. 1. Chiral bispidines and 9-oxabispidines.

conformation **1C** [14,15]. Functional groups at the bridging carbon atom also influence the conformational equilibrium. A lower steric demand as, for example, in the bispidone **8** can also favor boat–chair conformations of type **B** [16–18]. Furthermore, the 9-hydroxybispidine **9** was found to exist exclusively in the boat–chair form **9B** due to a stabilizing intramolecular hydrogen bridge [18].

As yet nothing, however, is known about the conformational equilibrium of 9-oxabispidines of types **3** and **4** in solution and about the influence of 2-*endo* substituents or 2-*endo*,3*N*-fused rings on it. This prompted us to investigate the conformational behavior of a variety of 9-oxabispidines by spectroscopic methods and DFT calculations.

2. Experimental and computational details

The known 9-oxabispidines **3**, **10**, **11a–g**, **12a,c–f**, **13a,b**, **14a,b**, and **15** (Figs. 1 and 3) were synthesized as described in the literature [6–8], the new derivatives **11e**, **13c–e**, and **16** were prepared in analogy to these procedures (for details, see Supplementary material). All ^{1}H NMR spectra were acquired at 20 °C on a Bruker AV 400 instrument using the deuterated solvents $CDCl_3$ and CD_3OD as the internal references. The proton signals of 2-, 4-, 6-, and 8-H_{exo} were unambiguously identified by extensive 2D NMR experiments (COSY, HMQC, HSQC, and NOESY) and their ^3J coupling constants with the neighboring bridgehead protons 1-H or 5-H were extracted from the respective multiplets in the ^{1}H NMR spectra.

The various conformations of the 9-oxabispidines and bispidines were calculated using the GAUSSIAN 98 [19] and the TURBOMOLE 5.9 [20] program packages. The structures of the conformers were fully optimized on all levels of theory without symmetry restrictions, using standard settings for convergence criteria. All minimum energy structures were confirmed in their nature by frequency calculations. Calculations based on density functional theory (DFT) employing the BLYP and B3LYP exchange–correlation functional [21] were done with the TURBOMOLE program package. The BLYP functional was also employed in conjunction with the resolution of identity (RI) approximation of the Coulomb integrals [22], as

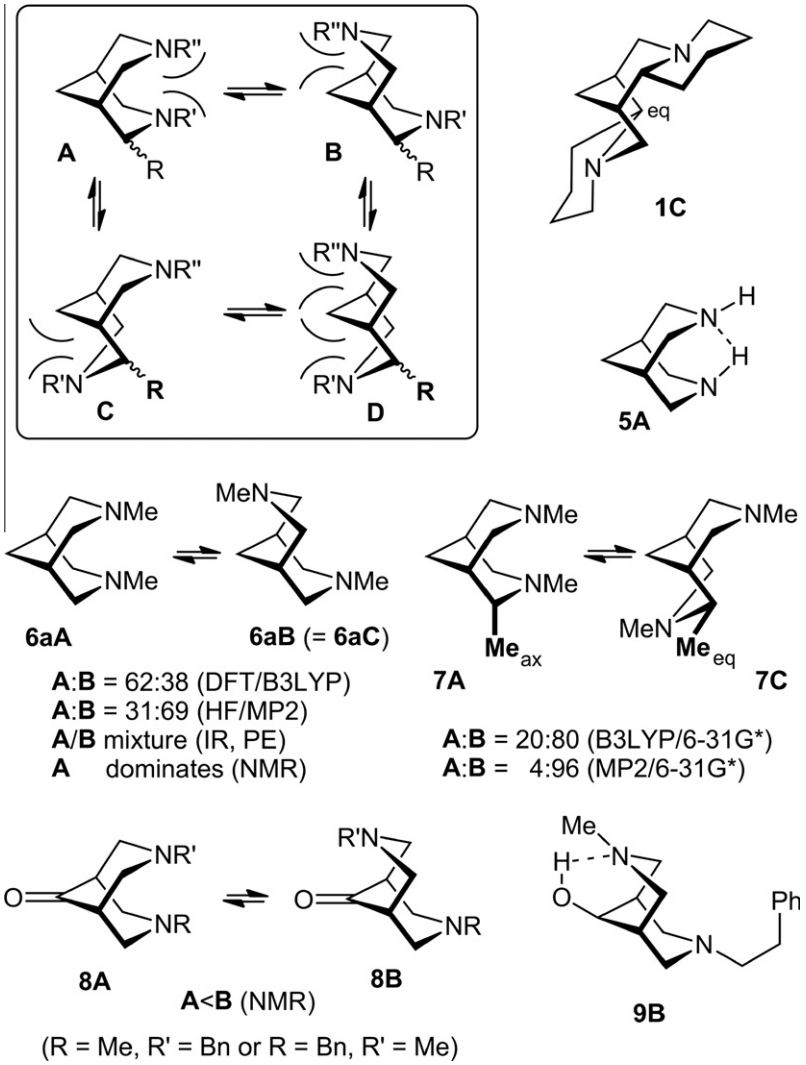


Fig. 2. Conformational behavior of selected bispidine derivatives at room temperature.

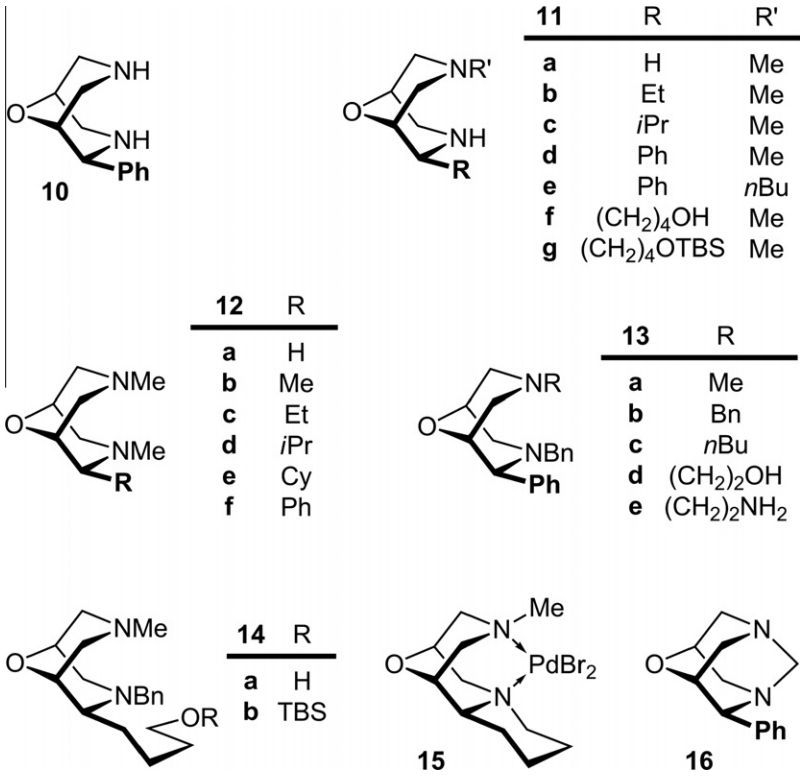


Fig. 3. Structures of the 9-oxabispidines investigated.

implemented in TURBOMOLE. In all cases a basis set of triple zeta quality (TZVP) was used [23], which contains three sizes of contracted functions and further p-functions to take polarization into account. Electrostatic contributions of the solvent environment were estimated by using the COSMO approach [24] with a dielectric constant of $\varepsilon = 15$. DFT calculations employing the B3LYP exchange–correlation functional were also performed with GAUSSIAN, using the standard 6-31G* basis set. ^{1}H NMR calculations were done on the B3LYP/TZVP COSMO ($\varepsilon = 15$) level of theory utilizing the gauge-including-atomic-orbital (GIAO) method [25] as implemented in TURBOMOLE. Relative chemical shifts were obtained by taking the absolute chemical shift of tetramethylsilane as the reference.

3. Results

3.1. DFT calculations on the conformational equilibrium

The conformational behavior of five 9-oxabispidines and five bispidines was studied in detail by DFT calculations. For each of the 2-*endo*-substituted and, thus, C_1-symmetric derivatives, 16 conformers had to be considered, originating from the chair/boat isomerism of the two morpholine or piperidine rings (conformers **A**–**D**, see Fig. 2) and the *endo*/*exo* disposition of the substituents at the nitrogen atoms (indices 1–4; 1: 3N–R and 7N–R *exo*; 2: 3N–R *exo*, 7N–R *endo*; 3: 3N–R *endo*, 7N–R *exo*; 4: 3N–R and 7N–R *endo*; for an illustration, see Fig. 4). In the case of the unsubstituted compounds, the number of conformers is reduced due to their C_{2v} symmetry.

A first method screening was done on 2-*endo*,*N*,*N*′-trimethyl-9-oxabispidine (**12b**) as the model compound. The electronic energies of the 16 conformers were calculated on different levels of theory (Table 1). Minimum structures were found for all conformers, except for **12bA4** and **12bD1**, in which the two N–Me groups would occupy the sterically more strongly hindered *endo*- and, respectively, *exo*-positions (Fig. 4). The gas phase calculations gave similar results, independent of the method used: The double chair conformation **12bA1** with the two N–Me groups in *exo*-position was the energetically most favored one, followed by the boat–chair conformation **12bB2** (3N–Me *endo*, 7N–Me *exo*, ΔE = 11.8–14.0 kJ mol^{-1}). The relative energies of the conformations **12bA2**, **12bA3**, and **12bB1**, in which one of the N–Me groups occupies the sterically more crowded position, ranged 14.2–17.5 kJ mol^{-1} higher than **12bA1**. All conformations **C** and **D** with the substituted piperidine ring in the boat form, thus forcing the 2-*endo*-substituent into an axial position, were energetically strongly disfavored.

The implementation of solvent effects by using the continuum solvent model COSMO ($\varepsilon = 15$) led to an increase of the relative energies of the conformers **12bA2**, **12bA3** and **12bB1**, as compared to the gas phase calculations (ΔE = 19.5–20.7 kJ mol^{-1}). According to these results, only the boat–chair conformation **12bB2** possesses a noteworthy population besides the dominating double chair form **12bA1**.

The consideration of solvent effects seems to be crucial for an accurate description of the conformational behavior in solution, as obvious from the results obtained for *N*,*N*-dimethylbispidine (**6a**): According to our B3LYP/TZVP-COSMO calculations (Table 2), the energy difference between the two most stable conformers, the double chair **6aA1** and the boat–chair **6aB2**, is 7.3 kJ mol^{-1} in favor of **6aA1**, thus predicting a strong preference of **6aA1** in solution. This finding is in good agreement with earlier NMR spectroscopic investigations [10,12], whereas former gas phase calculations (see Introduction) gave rise to a close-to-equal contribution of **6aA1** and **6aB1** [10]. Moreover, the latter calculations predicted the conformer **6aB1**, in which the 7N–Me group occupies the sterically more hindered *exo* position, to be energetically favored over **6aB2** (7N–Me *endo*), which seems to be less likely.

The conformational behavior of five 9-oxabispidines, the bicyclic derivatives **12a**,**b**,**f**, (R = H, Me, Ph), the tricycle **3**, and the tetracycle **17**, and, for comparison, also of their 9-methylene counterparts, the

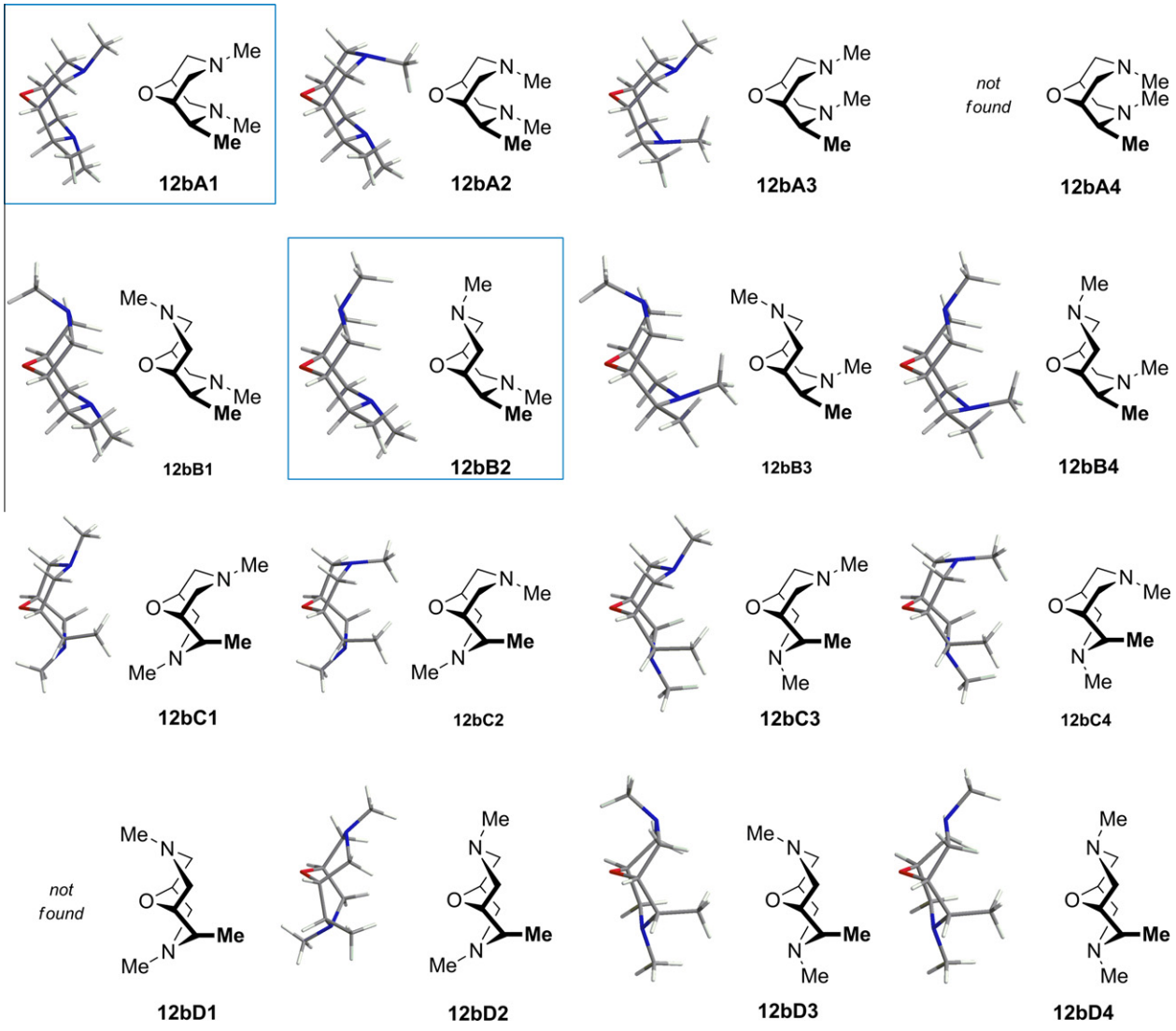


Fig. 4. Calculated minimum energy structures of the conformers of **12b**.

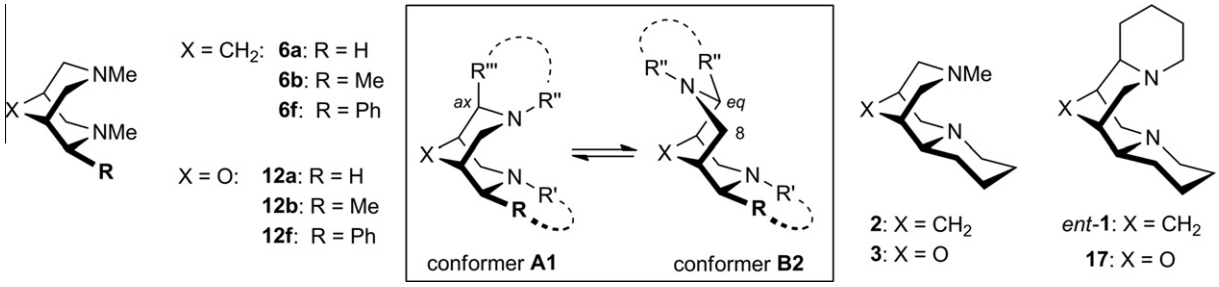
Table 1
Relative electronic energies (kJ mol^{-1}) of all 16 conformers of the 9-oxabispidine **12b** on different levels of theory.

Conformer (position of 3N–Me,7N–Me)	B3LYP/6-31G*	B3LYP/TZVP	BLYP/TZVP	BLYP/TZVP – RI	BLYP/TZVP – RI – COSMO[a]	B3LYP/TZVP – COSMO[a]
A1 (exo,exo)	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
A2 (endo,exo)	**14.2**	**14.8**	**14.5**	**15.0**	19.5	19.6
A3 (exo,endo)	**14.8**	**15.8**	**15.4**	**16.0**	20.7	20.8
A4 (endo,endo)	_[b]	_[b]	_[b]	_[b]	_[b]	_[b]
B1 (exo,exo)	**16.5**	**17.5**	**17.3**	**16.8**	19.8	20.7
B2 (endo,exo)	**14.1**	**13.6**	**13.5**	**12.9**	**12.2**	**12.8**
B3 (exo,endo)	48.0	49.0	47.9	47.6	49.4	51.0
B4 (endo,endo)	45.6	45.2	44.1	43.7	41.9	43.2
C1 (exo,exo)	18.9	20.2	19.6	19.3	25.0	26.1
C2 (endo,exo)	55.4	55.3	53.7	53.6	56.5	58.6
C3 (exo,endo)	23.5	24.1	24.0	23.8	26.5	26.8
C4 (endo,endo)	59.9	59.5	58.2	58.0	57.9	59.5
D1 (exo,exo)	_[b]	_[b]	_[b]	_[b]	_[b]	_[b]
D2 (endo,exo)	49.9	49.2	47.6	47.0	45.7	47.7
D3 (exo,endo)	71.7	72.7	70.6	69.7	68.9	71.8
D4 (endo,endo)	68.2	67.9	65.8	64.9	61.5	64.1

[a] $\varepsilon = 15$.
[b] No minimum energy structure found.

bispidines **6a**,**b**,**f**, **2**, and *ent*-**1**, was therefore investigated using the B3LYP/TZVP-COSMO formalism (Table 2). The same trends were observed in the two substance classes: In good agreement with our previous model studies, only the double chair conformers **A1** and the boat–chair forms **B2** were of energetic relevance ($\Delta E \leqslant 18.2$ kJ mol^{-1}; for details, see Supplementary material), with

Table 2
Relative electronic energies [B3LYP/TZVP-COSMO ($\varepsilon = 15$)] (kJ mol^{-1}) of the conformers **A1** and **B2** of different 9-oxabispidines and bispidines and their calculated equilibrium distributions at room temperature



9-Oxabispidines				Bispidines			
Compd.	**A1**	**B2**	**A1:B2**[a]	Compd.	**A1**	**B2**	**A1:B2**[a]
12a	0.0	11.5	98:2[b]	**6a**	0.0	7.3	91:9[b]
12b	0.0	12.8	>99:1	**6b**	0.0	8.0	96:4
12f	0.0	15.7	>99:1	**6f**	0.0	11.5	99:1
3	0.0	11.1	99:1	**2**	0.0	6.1	92:8
17	7.1	0.0	5:95	*ent*-**1**	18.2	0.0	>1:99

[a] Calculated from $\Delta E_{\mathbf{A1,B2}}$ using the Boltzmann equation; the population of all other conformers is less than 0.2% (for details, see Supplementary material).
[b] Higher population of **B2** since this conformer is degenerated for reasons of symmetry.

the former one dominating for the bi- and tricyclic diamines. Compared to the unsubstituted prototypes **12a** and **6a**, the influence of a 2-*endo* alkyl substituent as in **12b** and **6b** or of a 2-*endo*,3*N*-fused piperidine ring as in **3** and **2** on the relative energies of the minor conformers **B2** is more or less negligible; a noticeable destabilization was only observed for the 2-*endo*-phenyl substituted derivatives **12f** and **6f**, probably caused by a stronger steric interaction of the phenyl group with the axial proton 8-H$_{exo}$ in the boat–chair form **B2**. In contrast to the bi- and tricyclic derivatives, the boat–chair conformation **B2** was strongly preferred in the tetracycles **17** and *ent*-**1**. This exception is caused by the additional 6-*exo*,7*N*-fused piperidine ring, which can occupy an energetically favorable equatorial position in the boat form. The latter result is in accordance with former experimental observations and calculations done on (−)-sparteine (**1**) [14], the enantiomer of *ent*-**1**.

The most distinctive difference between the 9-oxabispidines and the bispidines is given by the relative energies of the boat–chair conformers **B2**, which are significantly less stable within the 9-oxabispidines ($\Delta\Delta E$ = 4.2–11.1 kJ mol^{-1}). This effect is clearly seen from the populations of the two conformers **A1** and **B2** at room temperature (contribution of all other conformers <0.2%), which were calculated from the relative energies using the Boltzmann equation. While noticeable amounts of **B2** (1–9%) occur for the bispidines **6a**, **6b**, and **2** in the equilibrium, the corresponding 9-oxabispidines **12a**, **12b**, and **3** exist more or less exclusively in the double chair form **A1** ($\geqslant$98%). Consequently, the dominance of the conformer **B2** over **A1** in the tetracycle **17** is also less pronounced than in its methylene-analog *ent*-**1** (**17**: **A1**:**B2** = 5:95, ΔE = 7.1 kJ mol^{-1} vs. *ent*-**1**: **A1**:**B2** < 1:99, ΔE = 18.1 kJ mol^{-1}). From these findings it can be concluded that the transannular 1,4-repulsions in the boat–chair conformers **B2** must be significantly stronger in the 9-oxabispidines than in the corresponding bispidines; thus, the destabilizing interactions between the lone pairs of the nitrogen and the oxygen atoms exceed those between the nitrogen lone pair and the methylene bridge.

3.2. Spectroscopic investigations on the double chair – boat–chair equilibrium in solution

The ^{1}H and ^{13}C NMR spectra of all known bispidines that are predicted to exist as mixtures of double chair and boat–chair conformers show a single set of signals, indicating that conformational changes occur rapidly with respect to the NMR time scale. Although a direct observation of the conformers is not possible by ^{1}H NMR, the ^3J coupling constants of the *exo*-methylene protons 2-, 4-, 6-, and 8-H$_{exo}$ with the neighboring bridgehead protons can be used to gather information about the dominating species (Fig. 5) [16]. With the dihedral angles between these protons being roughly 60° in the double chair conformation **A**, all these ^3J coupling constants must be small, typically ranging between 2.0 and 4.5 Hz. For example, 4.2 Hz were measured in *N*,*N*-dimethylbispidine (**6a**) and 2.3 Hz in *N*-Methylbispidine [12]. By contrast, large ^3J coupling constants, as found in **9** (^3J = 10.6 Hz) [18], will result if one of the two rings adopts a boat conformation as in **B** or **C** since the respective protons in the boat ring are aligned synperiplanar.

We therefore used the ^3J coupling constants as the probes to determine the preferred conformation of 9-oxabispidines in solution. A set of 21 9-oxabispidines was investigated, including the secondary diamine **10**, seven 7*N*-monoalkylated and twelve 3*N*,7*N*-dialkylated derivatives (**11a**–**g**, **12a**,**c**–**f**, **13a**–**e**, and **14a**,**b**, see Fig. 3), and the tricycle **3** (see Fig. 1). In all cases, the ^3J coupling constants determined ranged between 2.3 and 4.5 Hz (Table 3), thus providing clear evidence of a dominance of the double chair conformer **A** in solution, independent of the existence and the nature of an 2-*endo* substituent and the substitution pattern at the nitrogen atoms. The NMR solvents used, $CDCl_3$ (less polar, non-protic) and CD_3OD (more polar, protic), had also no effect on the conformational behavior, as obvious from the similar ^3J coupling constants found for **11d** in $CDCl_3$ and CD_3OD.

The, in part, relatively large ^3J coupling constants of up to 4.5 Hz are probably a consequence of slightly flattened chair geometries, caused by the N–N repulsion in the double chair conformations **A**. Comparable ^3J coupling constants of 3.9–4.4 Hz, for example, were measured for the 9-oxabispidines **12a**, **13b**, and **3** and the pallada complex **15** [6], which possesses a heteroadamantane framework. In good agreement with this, nearly identical N–N distances of 3.00–3.02 Å, which are slightly shorter than the sum of the van der Waals radii of the nitrogen atoms (3.10 Å), were calculated for the double chair conformations **A1** of **12a**, **3**, and **15** and found in the X-ray structure of **13b** (Fig. 6, left) [26]. Smaller ^3J coupling constants (2.3–3.0 Hz) were only detected in the 9-oxabispidines **10** and **11** with secondary amino functions. The N–N repulsion in these

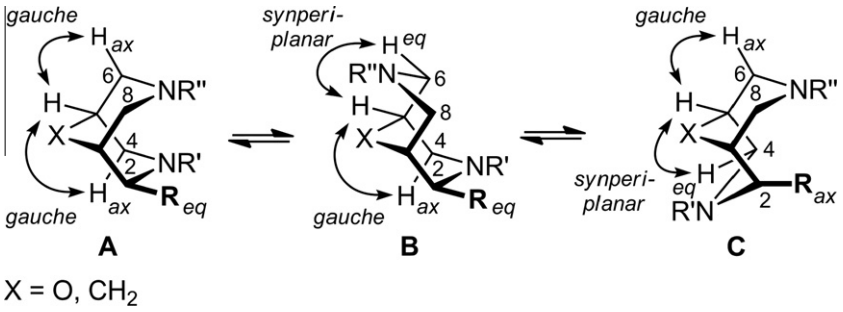


Fig. 5. Axial vs. equatorial orientation of the *exo*-methylene protons in the conformers **A**–**C**.

Table 3
^3J coupling constants (Hz) of the *exo*-methylene protons 2-, 4-, 6-, and 8-H_{exo}.[a]

Compound	Solvent	^3J(2-H_{exo}/1-H)	^3J(8-H_{exo}/1-H)	^3J(4-H_{exo}/5-H)	^3J(6-H_{exo}/5-H)
10	$CDCl_3$	2.3	2.9	3.7	2.9
11a	CD_3OD	3.7	3.8	3.7	3.8
11b	CD_3OD		3.6	3.9	3.1
11c	CD_3OD	3.4	3.7	4.0	3.6
11d	CD_3OD		3.6		3.6
	$CDCl_3$		3.8	3.9	3.4
11e	$CDCl_3$	2.4	3.7	3.8	3.1
11f	$CDCl_3$		3.5		3.0
11g	$CDCl_3$		3.5		3.0
12a	CD_3OD	4.2	4.2	4.2	4.2
12c	CD_3OD			4.2	4.0
12d	CD_3OD			4.3	4.0
12e	CD_3OD			4.3	
12f	$CDCl_3$	4.0	3.8	4.5	3.9
13a	$CDCl_3$		3.7		4.0
13b	$CDCl_3$		3.5	4.2	3.9
13c	$CDCl_3$	4.1	3.6	4.2	4.0
13d	$CDCl_3$	3.9		4.4	3.5
13e	$CDCl_3$	4.0	3.5	4.3	3.7
14a	$CDCl_3$		4.3	4.2	3.6
14b	$CDCl_3$		4.4	4.2	4.5
3[b]	$CDCl_3$		4.3	4.4	4.2
15[b]	$CDCl_3$		4.2	3.9	4.0
16[b,c]	$CDCl_3$	<2	<2	<2	<2

[a] ^{1}H NMR spectra were measured at 400 MHz in $CDCl_3$ or CD_3OD; missing ^3J coupling constants could not be determined due to signal overlap or higher order multiplicities.
[b] Numbering as in the bicyclic 9-oxabispidines.
[c] Broadened signals with just partially resolved ^3J couplings.

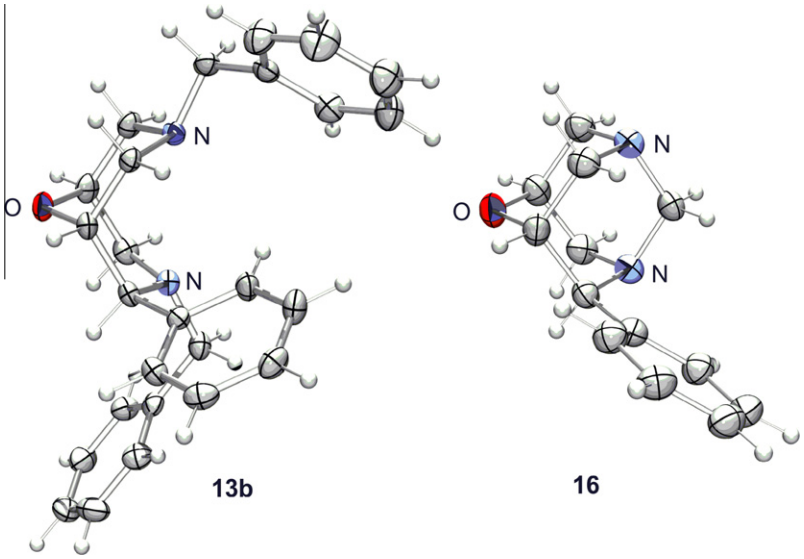


Fig. 6. X-ray structures of **13b** and **16** [26]. Thermal ellipsoids are set at the 50% probability level. N–N distances: **13b**: 3.00 Å; **16**: 2.50 Å.

Table 4
Experimental and calculated ^{1}H NMR shifts (ppm) of the methylene protons of **12f** and **3**.[a]

	2-H_{exo}	4-H_{exo}	4-H_{endo}	6-H_{exo}	6-H_{endo}	8-H_{exo}	8-H_{endo}
12f:							
$\delta_{exp.}$	3.46	2.70	3.14	2.45	3.03	2.01	2.72
$\delta_{calcd,conf.A1}$	3.44	2.66	2.93	2.41	2.79	1.89	2.61
$\delta_{calcd,conf.B2}$	3.33	2.45	**2.54**	**2.93**	**2.13**	2.20	**2.27**
3:[b]							
$\delta_{exp.}$	2.27	2.56	2.82	2.40	2.92	2.25	2.92
$\delta_{calcd,conf.A1}$	2.20	2.58	2.63	2.36	2.68	2.19	2.80
$\delta_{calcd,conf.B2}$	2.06	2.36	**2.22**	**2.89**	**2.00**	**2.66**	**2.15**

[a] Experimental ^{1}H NMR shifts were measured at 400 MHz in $CDCl_3$; calculated shifts (for a full listing, see Supplementary material) were referenced to the computed shift of TMS.
[b] Numbering as in the bicyclic 9-oxabispidines.

derivatives and, thus, the distortion of the chair geometries is presumably lowered because of intramolecular N–H–N hydrogen bonding. The impact of the N–N distance on the size of the ^3J coupling constants is also obvious from the *N*,*N*-methylene bridged 9-oxabispidine **16**: the ^{1}H NMR signals of the *exo*-protons were slightly broadened adumbrating small ^3J couplings of <2 Hz. This is in good agreement with the relatively short N–N distance of 2.50 Å found in the X-ray structure of **16** (Fig. 6, right) [26].

Nevertheless, a noteworthy population of the boat–chair conformers **B** (the alternative boat–chair conformations **C** are not of relevance according to calculations above) cannot be fully excluded since a fast equilibrium with respect to the NMR time scale would also cause larger ^3J coupling constants. Another possibility to rule out a significant population of **B** is given by the ^{1}H NMR chemical shifts of the *exo*- and *endo*-methylene protons, which strongly depend on the conformation. We thus calculated the proton shifts of the optimized double chair and boat–chair conformers **A1** and **B2** of the bicyclic 9-oxabispidine **12f** and the tricycle **3** (Table 4), giving particularly large differences in the chemical shifts for 6-H_{endo} and 6-H_{exo} ($\Delta\delta$ = 0.52–0.68 ppm). The experimentally measured proton shifts are in excellent agreement with those calculated for the double chair conformers **A1** ($\Delta\delta \leqslant 0.24$ ppm), but poorly match with the calculated shifts for the boat–chair conformers **B2** ($\Delta\delta$ = 0.45–0.92 ppm for 4-H_{endo}, 6-H_{exo}, 6-H_{endo}, and 8-H_{endo}). More importantly, any upfield shifts for 4-, 6-, and 8-H_{endo} or downfield shifts for 6- and 8-H_{exo}, as expected from the calculations if the boat–chair conformations **B2** would significantly contribute to the conformational equilibrium in solution, were not detected, again making a significant population of **B2** very unlikely.

4. Conclusion

The double chair form **A** is the dominating conformer of unsubstituted and 2-*endo*-substituted 9-oxabispidines in solution, as proven by spectroscopic and theoretical investigations. DFT-calculations on the B3LP/TZVP level of theory under consideration of solvent effects by the continuum solvent model COSMO revealed that only two conformers, the double chair form **A1** (both N–R *exo*) and the boat–chair form **B2** (N_{chair}–R *exo*, N_{boat}–R *endo*), were of energetic relevance ($\Delta E \leqslant 18.2$ kJ mol^{-1}). The former ones, **A1**, are strongly dominating in the 9-oxabispidines **12a**,**b**,**f**, and **3** (**A1**:**B2** $\geqslant$ 98:2 at room temperature), independent of the existence or nature of a 2-*endo*-substituent R (R = H, Me, Ph) or a 2-*endo*,3*N*-fused piperidine ring. The tetracycle **17**, by contrast, was calculated to primarily exist in the boat–chair conformation **B2**, which permits an energetically favorable equatorial orientation of the additional 6-*exo*,7*N*-fused piperidine ring. The same trends were found for the corresponding bispidines **6a**,**b**,**f**, **2**, and *ent*-**1**, but the preference for the conformer **A1** was less pronounced. Therefore, the destabilizing N,O-repulsions in the boat–chair forms **B2** of the 9-oxabispidines must be stronger than the N,CH_2-interactions in the boat–chair forms of the corresponding bispidines. The calculations are in excellent agreement with ^{1}H NMR spectroscopic investigations done on a set of 21 9-oxabispidines, in which the ^3J coupling constants of the *exo*-methylene protons with the neighboring bridgehead protons were used as conformational probes. In all cases, small the ^3J coupling constants of 2.3–4.5 Hz were detected, as expected if the morpholine rings adopt chair-like geometries, thus clearly pointing to a strong dominance of the double chair conformers **A** in solution. This is also supported by the excellent correlation of the experimentally measured ^{1}H NMR shifts of **12f** and **3** with those calculated for their double chair conformers **A1**.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft. Dedicated to Prof. Dr. hc Bringmann on the occasion of his 60th birthday.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2011.08.047.

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