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Conformational Analysis of 2,3-Dihydro-2,2-dimethyl-1,4-benzoxazepines and their 1,5-Isomers†

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Summary. Conformational analysis of 2,3-dihydro-2,2-dimethyl-1,4-benzoxazepines (**1**, **3**, **5**, and **7**) and their 1,5-isomers (**2**, **4**, and **6**) was performed by temperature dependent NMR measurements. The effect of substituents on the ring inversion was studied. The results obtained were corroborated by AMI calculations.

Keywords. Ring inversion; Stereochemistry; Dihydro-1,4-benzoxazepines; Dihydro-1,5-benzoxazepines.

Konformationsanalyse von 2,3-Dihydro-2,2-dimethyl-1,4-benzoxazepinen und ihren 1,5-Isomeren

Zusammenfassung. Die Konformation von 2,3-Dihydro-2,2-dimethyl-1,4-benzoxazepinen (**1**, **3**, **5** und **7**) und ihren 1,5-Isomeren (**2**, **4** und **6**) wurde mittels temperaturabhängiger NMR-Spektroskopie untersucht. Der Einfluß von Substituenten auf die Ringinversion wird diskutiert. Die erhaltenen Resultate werden durch AMI-Rechnungen bestätigt.

Introduction

Conformational analysis of 1,4- and 1,5-benzoxazepines has hitherto received little attention. So far, only the conformational analysis of 2-aryl-2,3-dihydro-1,4-benzoxazepines [1] and 2,3-dihydro-2-mehtyl-1,5-benzoxazepines [2] has been described in the literature. In our previous papers [3, 4] syntheses of 2,3-dihydro-2,2-dimethyl-1,4-benzoxazepines and their 1,5-isomers have been published.

Owing to structural relationships of these benzoxazepines to benzodiazepines of important biological activity, a detailed investigation of their conformational behaviour seemed to be expedient. As far as the related 1,5-benzodiazepinones are

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concerned, a cycloheptane-type chair conformation has been proposed for the seven-membered heterocyclic ring by *Aversa et al.* [5]. However, according to *Duddeck et al.* [6] the possibility of a chair conformation of the benzocondensed seven-membered ring should be excluded since a further planar moiety, an amide group, is attached to the benzene ring. In the solid state, the dihedral angle of the =C–N–C(=O)–C unit amounts to 4.2° as determined by X-ray diffraction. The seven-membered heterocyclic ring was, therefore, considered to adopt a boat conformation. Comparative studies have revealed that replacement of the nitrogen atom by oxygen is almost without influence on the conformation, *i.e.* the related benzodiazepines and benzoxazepines adopt similar boat conformation [2]. In the course of dynamic NMR studies of 2,3-dihydro-2-methyl-1,5-benzoxapines [2], the energy barrier of the ring inversion (*ca.* 12 kcal/mol) of the N-substituted derivatives could be determined only in few cases. Energy barriers of other compounds investigated were so low that no coalescence or considerable line brodening was observed even at −70°C [2].

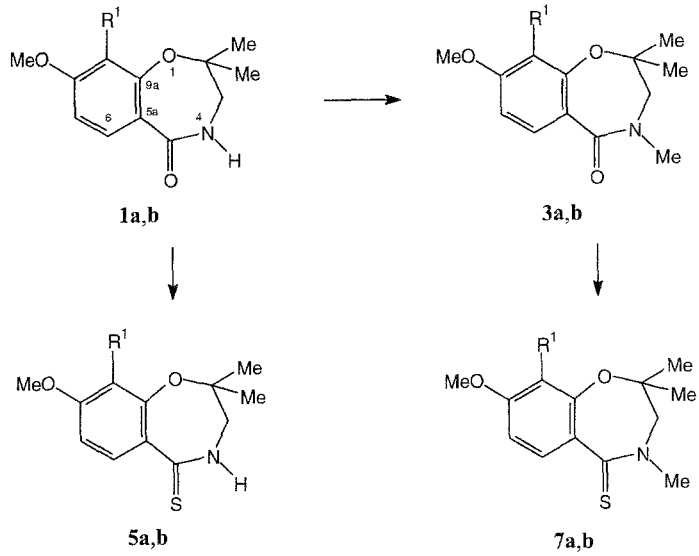
Results and Discussion

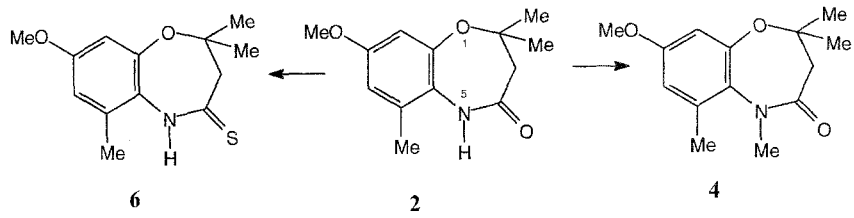
Conformational analysis of 2,3-dihydro-2,2-dimethyl-1,4-benzoxazepines (**1**, **3**, **5**, and **7**) and their 1,5-isomers (**2**, **4**, and **6**) (Scheme 1) has been performed by temperature-dependent NMR measurements.

^{1}H and ^{13}C chemical shifts of the newly synthesized compounds **3–7** are summarized in Table 1 and 2. If necessary, assignment of the ^{13}C chemical shifts has been corroborated by semiselective 1D INEPT [7] measurements optimized for long-range couplings ($J(C, H) = 7$ or 3 Hz, Table 3). Polarization transfer induced from the selected proton reveals the carbon atoms at two or three bond distances from the appropriate proton. In the case of the 1,4-benzoxazepines **1**, **3**, **5**, and **7**, the 6-H signal shows a considerable paramagnetic shift ($\delta = 7.48 - 7.95$ ppm) as a consequence of the anisotropic effect of the *peri* positioned carbonyl group.

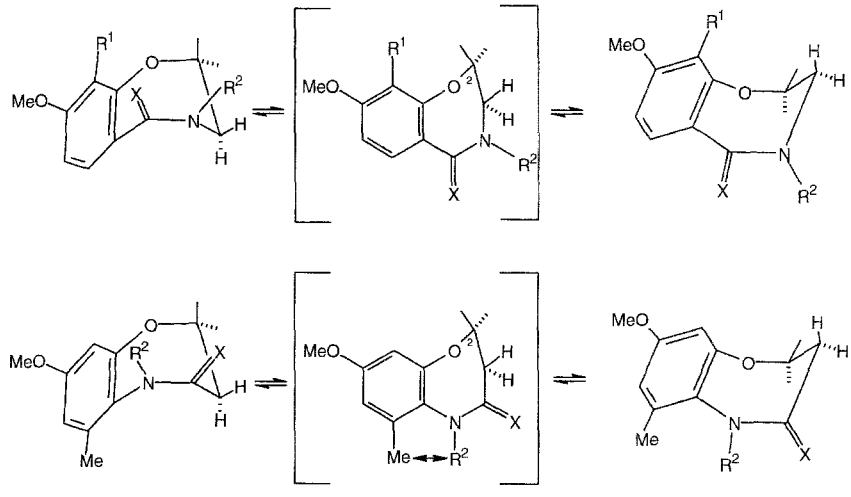
Chemical shift values of atoms C-5a, C-6, C-8, and C-9a of the condensed aromatic ring are characteristically different for the two structural isomers. As a consequence of the fact that in the 1,5-isomers the amide moiety is connected *via* its nitrogen atom to the condensed aromatic ring, whereas in the 1,4-isomers the connectivity is established *via* the carbon atom C-5a suffers a paramagnetic shift due to the different substituent effects [8]. C-6, C-8, and C-9a, however, show a diamagnetic shift in the 1,5-isomers. The measured ^{13}C chemical shifts are in accordance with those found previously for 1,4- [1] and 1,5-benzoxazepines [2].

Taking into account the flexibility of the condensed seven-membered heterocyclic ring and the expected low coalescence temperature, our investigations have been performed in a 1:1 v/v mixture of methanol-d_4/chloroform-d_1. At room temperature, the geminal Me_2-2 and 3-H_2 protons gave pairwise identical, *i.e.* averaged chemical shift values which reveal the fast interchange of the boat conformers of the seven-membered ring (Scheme 2). We suppose that the boat/boat interconversion takes place *via* a transition state where all but the C-2 atoms in the ring are nearly in one plane. Decrease of temperature results in the coalescence of the above mentioned signals and the separation of the *quasi-* axial and *quasi-*equatorial ones. The free enthalpy of activation ($\Delta G^{\#}$) of the ring inversion (see





Scheme 1



Scheme 2

Table 4) has been determined by means of the coalescence temperatures (t_c) and from the $\Delta\delta$ values (Hz) measured at low temperature, the latter values being characteristic for the state without exchange [9]. Similar $\Delta G^{\#}$ values obtained for compounds **1a** and **2** indicate that the positions of the nitrogen and carbonyl group in the amide moiety are almost without influence on the conformation of the seven-membered ring. This is true for thioamides **5a** and **6** as well. Comparison of the pairs of compounds **1**, **3** and **5a**, **7a**, respectively, shows that the NH→NMe transformation enhances the free enthalpy which is a consequence of the higher delocalization in a tertiary amide. As expected, the presence of a methyl group at position 9 is without influence on the energy since there is no steric interaction between the methyl group and the nonbonding electron pair of the oxygen atom. The amide→thioamide conversion results in an enhancement of the $\Delta G^{\#}$ values both in the case of 1,4- and 1,5-benzoxazepines. The delocalization propensity of the thioamide is higher than that of the amide group, resulting in a more rigid heterocyclic ring. As a consequence, the barrier of the ring inversion is enhanced.

The NH→NMe conversion of 2,3-dihydro-7-methoxy-2,2,6-trimethyl-1,5-benzoazepin-4(5H)-one (**2**) results in a strong steric interaction. In the ^{1}H NMR spectrum of compound **4** measured at room temperature, the signals of the geminal methyl groups and those of 3-H_2 protons are separated which means that the ring inversion is hindered even at this temperature. Therefore, this compound was heated in *DMSO*-d_6 to determine the energy barrier. The secondary amide→ tertiary amide conversion results in an enhancement of $\Delta G^{\#}$ of *ca.* 15 kcal/mol compared to the value obtained for compound **2**. This may be a consequence of the steric interaction of the methyl groups in position 6 and the nitrogen atom in the transition state, corroborating at the same time the supposed mechanism of the ring inversion (cf. Scheme 2).

Molecular modelling

The stereochemistry of compounds **1–7** in the ground state was calculated and optimized by AM1 semiempirical methods of the SPARTAN program package [10]. Inspection of the ring inversion on a *Dreiding* stereomodel indicated that the sign of the dihedral angle between the aromatic ring and the plane of the amide moiety changes during the inversion. The motion of the 7 membered ring passes through an arrangement of the atoms where all ring atoms except C(2) are coplanar. Considering the strong ring strain and the steric repulsion between the amide group and C(6)-H or C(6)-Me in this arrangement, we presumed it to be similar to the transition state of the ring inversion. Holding the 6 atoms mentioned above coplanar, an AM1 geometry optimization was performed for the rest of the molecule. The structures obtained by this calculation together with the ground state are shown in Fig. 1.

Performing a complete normal mode analysis resulted in more than one imaginary frequency in a range as low as 460–60 cm^{-1}. This means that, although this hypothetic structure is not a real transition state, it is not too far from the saddle point on the hyper surface.

ΔH differences derived from heat of formation values calculated for the ground states and the hypothetic transition states are in accordance with the $\Delta G^{\#}$ values

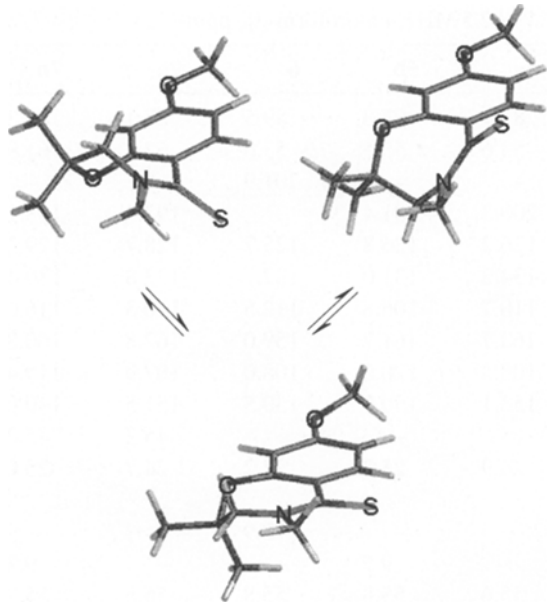


Fig. 1. Geometries of the ground state and the hypothetic transition state of compound **7a** as obtained by AM1 calculations

(cf. Table 4) determined by NMR measurements (the differences did not exceed 1.9 kcal/mol, except for compound **2** and **6**). These results corroborate our expectations concerning the geometry of the hypothetic transition state of the ring inversion and reveal that the contribution of the entropy term is within the range of the experimental error. The highest ΔH value was obtained for compound **4**. Considerable differences (7.4 kcal/mol) between the ΔH values determined by AM1 calculations and $\Delta G^{\#}$ values obtained from NMR measurements were found only for compounds **2** and **6**. In these cases, the AM1 calculation provided

Table 1. ^{1}H chemical shifts of compounds **3–7** (250 MHz, chloroform-d_1, ppm)

	3a	**3b**	**4**[a]	**5a**	**5b**	**6**	**7a**	**7b**
3-H_2	3.31	3.28	2.14 2.45	3.17	3.18	2.91	3.49	3.48
6-H	7.59	7.48	–	7.93	7.81	–	7.95	7.83
7-H	6.77	6.76	6.71	6.72	6.76	6.61	6.72	6.68
9-H	6.49	–	6.45	6.43	–	6.47	6.40	–
NH	–	–	–	9.65	–	7.53	–	–
MeN	3.25	3.25	3.02	–	–	–	3.70	3.70
Me_2-2	1.41	1.41	1.17 1.44	1.36	1.41	1.51	1.40	1.39
Me-6	–	–	2.24	–	–	2.31	–	–
Me-9	–	2.11	–	–	2.11	–	–	2.09
MeO-8	3.84	3.88	3.74	3.70	3.89	3.80	3.81	3.85

[a] Dimethylsulfoxide-d_6

Table 2. ^{13}C chemical shifts of compounds **3–7** (62.5 MHz, chloroform-d_1, ppm)

	3a	**3b**	**4**[a]	**5a**	**5b**	**6**	**7a**	**7b**
C-2	85.7	86.0	85.9	87.7	87.8	89.5	87.1	87.3
C-3	57.7	57.5	44.4	53.6	53.5	53.6	62.1	61.9
C-4	–	–	170.4	–	–	201.9	–	–
C-5	169.3	169.9	–	200.3	201.4	–	197.4	198.1
C-5a	121.5	119.6	130.4	126.2	126.8	125.7	128.7	129.2
C-6	131.4	127.9	134.3	134.2	131.0	132.7	133.8	130.4
C-7	110.0	105.7	112.5	110.7	106.8	112.5	110.3	116.0
C-8	162.9	160.8	157.5	163.7	161.7	159.0	162.8	160.8
C-9	108.0	122.3	107.4	108.3	120.0	108.0	107.9	119.4
C-9a	154.6	152.2	149.3	153.1	150.3	150.5	151.5	149.0
MeN	36.6	36.5	35.5	–	–	–	45.2	45.2
Me_2-2	24.7	25.0	26.0	24.9	25.2	27.2	24.7	25.0
			27.0					
Me-6	–	–	18.7	–	–	17.9	–	–
Me-9	–	9.2	–	–	9.5	–	–	9.3
MeO-8	55.4	55.6	55.4	55.6	55.8	55.8	55.5	55.7

[a] Dimethylsulfoxide-d_6

Table 3. Long-range ^1H-^{13}C correlations of compounds **3–6** determined by semiselective 1D INEPT measurements (J(C, H) = 7Hz)

	Proton	Carbon
3b[a]	Me-9	C-9; C-9a
4	9-H	C-5a; C-7; C-8; C-9a
5a	9-H	C-5a; C-7; C-8; C-9a
	MeO-8	C-8
6	9-H	C-5a; C-7; C-8; C-9

[a] Optimized for J (H, C) = 3 Hz

Table 4. Comparison of coalescence temperature and thermodynamic parameters ($\Delta G^{\#}$, kcal/mol) of the ring inversion of benzoxazepines **1–7** with the calculated heat of formation of the hypothetic transition state

	1a	**1b**	**2**	**3a**	**3b**	**4**[b]	**5a**[c]	**6**[f]	**7a**	**7b**
t_c (°C)	−92	−93	−92	−49	−48	186	−88	−77	−19	−20
$\Delta G^{\#}$	8.6	8.6	8.6	10.8	10.7	23.5	9.1	9.3	12.2	12.1
H[d]	−85.6	−91.3	−94.9	−79.7	−85.3	−86.4	−28.9	−36.9	−22.4	−27.9
H*[e]	−77.8	−82.8	−78.9	−70.8	−75.3	−63.2	−18.8	−20.2	−10.1	−14.7
ΔH	7.8	8.5	16.0	8.9	10.0	23.2	10.1	16.7	12.3	13.2

[a] Measured in an 1:1 v/v mixture of methanol-d_4/chloroform-d_1 (250 MHz); [b] measured in dimethylsulfoxide-d_6 (100 MHz); [c] measured in an 10:1 v/v mixture of acetone-d_6/chloroform-d_1 (250 MHz); [d] heat of the formation of the ground state; [e] heat of the formation of the hypothetic transition state; [f] imine-thiol tautomer: $H = -38.0, H^* = -26.8$, $\Delta H = 11.2$

considerably higher values. It is presumed that – as a result of the higher tautomerization propensity of thioamide **6** in comparison with the appropriate amide **2** – the ring inversion takes place *via* a thiol-imine tautomer where the steric interaction of the methyl group at position 6 and the N-5 atom is reduced. In the case of compound **6**, an AM1 calculation provided $\Delta H = 11.2$ kcal/mol; the difference between $\Delta G^{\#}$ and this value decreased to 1.9. All these findings confirm that the hypothetic transition state may be close to the real transition state and give a valuable starting point for following studies of these conformational motions.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-250 and Jeol FX-100 spectrometers. Chemical shifts are given on the δ scale and referenced to internal *TMS*.

Compounds **1a**, **1b**, **2**, **5a**, **5b**, and **6** were prepared as described previously [3, 4].

Molecular modelling

All calculations were run on an Indigo-2 Silicon Graphics workstation using the SPARTAN [10] software package. The ground state conformers of the compounds were generated using standard bond lengths and angles and preoptimized using molecular mechanics (Sybyl force field). The geometry optimizatons were carried out by standard AM1 semiempirical calculations.

The structure of the hypothetic transition state geometry was generated by the following method: The dihedral angles (O(1)-C(9a)-C(5a)-N(5), C(9a)-C(5a)-N(5)-C(4), C(5a)-N(5)-C(4)-C(3)) of the ground state structure were constrained to 0 degree (at sigma = 100), and a Sybyl force field geometry optimization was run with this constraint option. This resulted in an arrangement wherein the 6 atoms of the 7 membered ring were in a common plane except for C(3). Holding the 6 atoms coplanar with the freeze option, an AM1 geometry optimization was performed for the rest of the molecule.

General procedure for the synthesis of compounds **3a**, **3b**, *and* **4**

Methyl iodide (0.5 ml) dissolved in anhydrous dimethylformamide (20.0 ml) was added to a stirred mixture of the appropriate benzoxazepine (**1a**, **1b**, or **2**; 1.0 g), anhydrous dimethylformamide (20.0 ml), and NaH (0.5 g) at °C. The mixture was stirred at room temperature for 16 h, diluted with water and extracted with chloroform. The chloroform solution was washed with brine, dried over $CaCl_2$, and the solvent was evaporated under reduced pressure to afford the N-methyl derivatives **3a**, **3b**, and **4**.

2,3-Dihydro-8-methoxy-2,2,4-trimethyl-1,4-bennzoxazepin-5(4H)-one (**3a**)

White crystals from methanol; yield: 65%; m.p.: 91–92 °C; calcd. for $C_{13}H_{17}NO_3$: C 66.36, H 7.28; found: C 66.51, H 7.31%.

2,3-Dihydro-8-methoxy-2,2,4,9-tetramethyl-1,4-benzoxazepin-5(4H)-one (**3b**)

White crystals from methanol; yield: 71%; m.p.: 108–109°C; calcd. for $C_{14}H_{19}NO_3$; C 67.44, H 7.68; found: C 67.25, H 7.71%.

2,3-Dihydro-8-methoxy-2,2,5,6-tetramethyl-1,5-benzoxazepin-4(5H)-one (**4**)

Colourless oil; yield: 75%; calcd. for $C_{14}H_{19}NO_3$: C 67.44, H 7.68; found: C 67.58, H 7.79%.

General procedure for the preparation of compounds **7a** *and* **7b**

A mixture of compound **3a** or **3b** (2.0 mmol), *Lawesson's* reagent (2 mmol), and anhydrous toluene (10 ml) was refluxed for 3h. The solvent was evaporated under reduced pressure, and the residue was crystallized from methanol to afford compounds **7a** or **7b**.

2,3-Dihydro-8-methoxy-2,2,4-trimethyl-1,4-benzoxazepin-5(4H)-thione (**7a**)

Yellow crystals from methanol; yield: 45%; m.p.: 141–142°C; calcd. for $C_{13}H_{17}NO_2S$: C 62.13, H 6.82, S 12.73; found: C 62.27, H 6.74, S 12.50%.

2,3-Dihydro-8-methoxy-2,2,4,9-tetramethyl-1,4-benzoxazepin-5(4H)-thione (**7b**)

Yellow crystals from methanol; yield: 33% m.p.: 197–198°C; calcd. for $C_{14}H_{19}NO_2S$: C 63.38, H 7.22, S 12.06; found: C 63.51, H 7.18, S 12.11%.

Acknowledgements

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