Functionalized Chloroenamines in Aminocyclopropane Synthesis Part 11.[1] Bicyclo[3.1.0]hexane Derivatives Preferring a Chair Conformation

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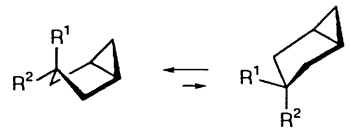
endo-endo-3,6-Diaminobicyclo[3.1.0]hexane species **6** prefer a chair conformation. This has been established by X-ray structure analysis of derivative **6c** and by ^{1}H and ^{13}C NMR spectroscopic analysis of compounds **6a** and **6b**. Intramolecular hydrogen bonding in **13**, the monoammonium salt of **6b**, can change the conformational situation.

A bicyclo[3.1.0]hexane skeleton generally prefers a boat conformation.[2] This was shown for the parent compound **1** by a combined analysis of electron diffraction and microwave spectroscopic data[3] and it was confirmed by several *ab initio*[4-8] and semiempirical calculations.[8,9] The real existence of a stable chair conformation **1C** of the parent bicyclic system, however, still remains an open question.

Only a few reports have appeared in the literature in which a chair conformation was given for a bicyclo[3.1.0]hexane species. The presence of a mixture of chair isomer **2C** (20.5%) and boat isomer **2B** (79.5%) was determined by the gas electron diffraction method in combination with molecular mechanics calculations in the case of *cis*-3-chlorobicyclo[3.1.0]hexane **2**.[10] A *trans* bicyclo[3.1.0]hexanol **5** should prefer a chair conformation in polar solvents at high dilution according to IR measurements of diastereomeric thujanols.[11]

(1α,3α,5α,6β)-3,6-Diaminobicyclo[3.1.0]hexanecarbonitriles **7c, d** prefer a boat conformation as shown by X-ray structure analysis of **7d**.[12] A chair conformation was predicted for the diastereomeric 1α,3β,5α,6β compounds **6c,d** as a result of the investigation of the dynamics of the N-heterocycle in the 6-position of **6c,d** and **7c,d**.[12]

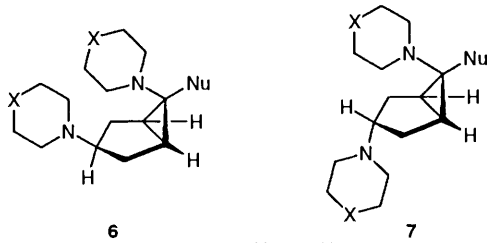
In this paper we confirm the presence of a chair conformation for compounds of type **6**. This is done by X-ray structure analysis of **6c** and by ^{1}H and ^{13}C NMR spectroscopy of further compounds **6a,b** in comparison with the data of the diastereomeric analogues **7a,b**. **6c,d** did not allow a ^{1}H NMR spectroscopic determination of the conformation owing to superposition of important signals even in the 400 MHz spectra.



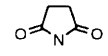
1–5B 1–5C

1 R^1 = H R^2 = H
2 R^1 = Cl R^2 = H
3 R^1 = H R^2 = Cl
4 R^1 = OH R^2 = H
5 R^1 = H R^2 = OH

Scheme 1



6 7

6, 7, 9	X	Nu
a	O	
b	O	H
c	O	CN
d	CH_2	CN

Scheme 2

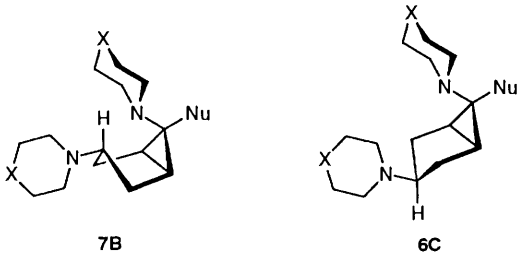
Results and Discussion

Preparation of further Pairs of Diastereomeric Diaminobicyclo[3.1.0]*hexanes* **6a**/**7a** *and* **6b**/**7b** *and Assignment of Configuration.*—Derivatives **6a,b** and **7a,b** could be obtained by the same procedures which were reported for the synthesis of **6c, d** and **7c,d**.[12] Thus 3-*endo*,6-*endo*-diamines **6a** and **6b** were available from chloroenamine **8** *via* bicyclohexanones **9a** and **9b** and subsequent reductive amination (yield of **6** in the reductive amination reaction: **6a**, 44%; **6b**, 51%).

The corresponding 3-*exo*,6-*endo*-diamines **7a** (41% yield) and **7b** (34%) were isolated from a chlorination–cyclopropanation sequence starting from enamine **11**.

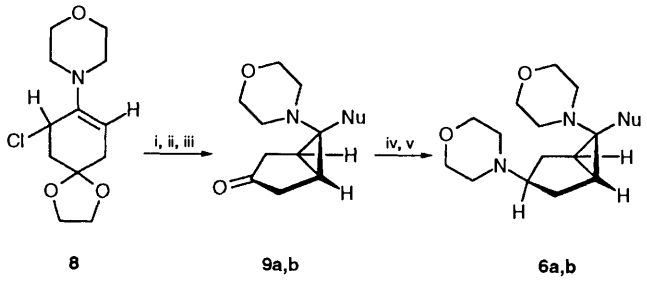
Monoammonium salts **13** and **14** were prepared from diastereomeric diamines **6b** and **7b** by titration with trifluoromethane sulfonic acid (0.1 mol dm^{-3} solution in isopropanol) in acetonitrile.

The presence of the bicyclo[3.1.0]hexyl system in **6**/**7** and **13**/**14** could be established from the ^{13}C NMR data (see Table 1). The unique *endo*-position of the morpholine at C(6) in **6a**/**7a**

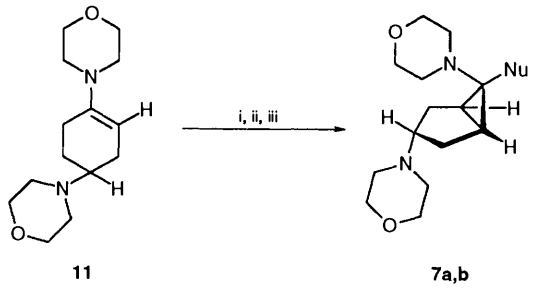


7B 6C

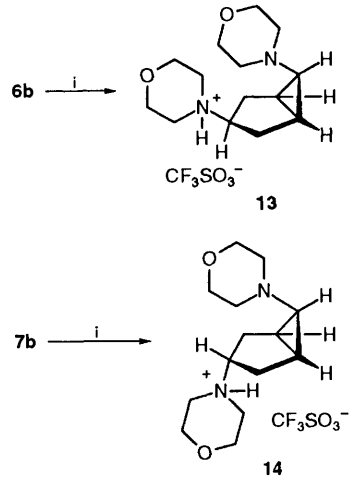
was indicated by the strong hindrance of the morpholine dynamics as shown by the ^{1}H NMR spectra. $\Delta G^{\ddagger}$ values of 72.4 kJ mol^{-1} (OCH_2)/72.8 kJ mol^{-1} (NCH_2) (for **6a**) and 77.4 kJ mol^{-1} (OCH_2)/77.5 kJ mol^{-1} (NCH_2) (for **7a**) for the topomerization of two methylene hydrogen atoms of the C(6)-morpholine clearly require to be in the *endo* position in both cases (for assignment of configuration by this method see ref. 13 and references cited therein). Again, the dynamics of the C(6)-morpholine are more hindered in **7a** than in **6a** (see ref. 12). The



Scheme 3 *Reagents:* i, succinimide, NaOH in acetonitrile/H_2O (10:1) for **9a**; $NaBH_4$ in acetonitrile for **9b**; ii, HCl/H_2O; iii, $NaOH/H_2O$; iv, morpholine (**10**) $(Pr^iO)_4Ti$; v, $NaBH_3CN$



Scheme 4 *Reagents:* i, *N*-chlorosuccinimide **12**; ii, succinimide, NaOH in acetonitrile/H_2O (10:1) for **7a**; $NaBH_4$ in acetonitrile for **7b**; iii, HCl/H_2O; iv, $NaOH/H_2O$



Scheme 5 *Reagent:* i, CF_3SO_3H

C(6) configuration of **6b**/**7b** was determined by $^3J_{Y.XX'}$ coupling in the ^1H NMR spectra (see ref. 14). The $^3J_{HH}$ values found for **6b**/**7b** (6.9 Hz), **13** (6.7 Hz, $CDCl_3$) and **14** (6.8 Hz, $CDCl_3$) are consistent with a 6-*endo*-morpholine configuration.

The localization of the proton on monoprotonation of the diamines **6b** and **7b** could be recognized by a change of $^1J_{CH}$ coupling of the involved N–C–H moiety in the ^{13}C NMR spectrum. In all cases protonation increased C(3)–H coupling by about 10 Hz with almost no change of C(6)–H coupling (Table 1) indicating the protonation of the C(3)-morpholine (see ref. 15). This is not unexpected since C(6) morpholine should be less basic owing to steric and electronic effects (*e.g.* cyclopropylamine: $pK_a = 9.10$;[16] isopropylamine: $pK_a = 10.67$[16]).

The C(3) configuration of bicyclohexyldiamines **6a**, **b** and **7a**, **b** could be determined by the chemical shift of the C(3) ^{13}C NMR signal in comparison with the analogous values of **6c**, **d** and **7c**, **d** and in combination with the X-ray structural analysis of compound **7d** (3α-isomer).[12]

A difference of about 8–10 ppm was found for the C(3) ^{13}C NMR signals within each pair of diastereomeric compounds **6a**/**7a** ($\Delta\delta$ 8.3), **6b**/**7b** ($\Delta\delta$ 9.5), **6c**/**7c** ($\Delta\delta$ 8.3)[12] and **6d**/**7d** ($\Delta\delta$ 8.4).[12] Thus, the C(3) signal of 3β-isomers **6** appeared uniformly at about 75 ppm; a highfield shifting of the C(3) signal to about 67 ppm was characteristic of 3α-isomers **7**. It is known that the protonation of an amino moiety is accompanied by almost no shift of the α-carbon ^{13}C NMR signals.[17] This is found for **7b**/**14** in $CDCl_3$ and CD_3CN (see Table 1). **6b**/**13** gave an analogous result only in $CDCl_3$; in CD_3CN, however, the protonation of **6b** generating **13** causes a highfield shifting of the C(3) signal by 7.8 ppm. ^1H NMR spectroscopy showed that a change of conformation is responsible for this phenomenon.

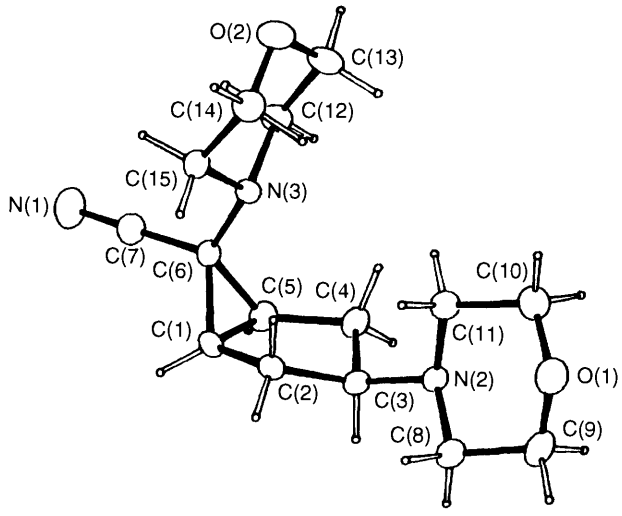


Fig. 1 ORTEP representation of **6c** with the atom-labelling scheme. Ellipsoids are scaled to enclose 30% of the electron density.

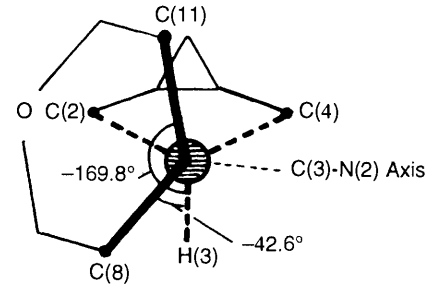


Fig. 2 Torsion of the C(3)–morpholine bond; dihedral angles H(3)–C(3)–N(2)–C(8) and H(3)–C(3)–N(2)–C(11)

X-Ray Structure Analysis of **6c**.—Suitable single crystals could be obtained for 3β,6β-diaminobicyclohexane-6-carbonitrile **6c** whose preparation is described in ref. 12. Using morpholine instead of piperidine as the amine component should not interfere with a direct comparison of the bicyclo[3.1.0]hexane structural data of both compounds **6c** and **7d** (for an X-ray plot of the 3α,6β-diaminobicyclohexanecarbonitrile **7d** see ref. 12).

The X-ray structure analysis of **6c** clearly demonstrated the presence of a chair conformation for the bicyclo[3.1.0]hexane skeleton. The value of 147.6° for the interplanar angle between C(1)C(2)C(4)C(5) and C(2)C(3)C(4) shows a clear buckle of the annulated five-membered ring (ring buckle $\alpha = -32.4°$).

Comparing the X-ray structural analyses of the two compounds **6c** and **7d** indicates that, in a bicyclo[3.1.0]hexane system, the conformation has no influence on the C–C distances of the cyclopropane system (see Table 2). This disproves an idea of Okazaki, Niwa and Kato[4] who based the preference for the boat conformation of a bicyclo[3.1.0]hexane skeleton on the

Table 1 ^{13}C NMR data of the aminobicyclo[3.1.0]hexane derivatives **6a**, **6b**, **7a**, **7b**, **9a**, **9b**, **13** and **14** δ (100.62 MHz), J in [] (Hz)

	Morpholine				Bicyclo[3.1.0]hexane			
	C(2, 6)		C(3, 5)		C(3)	C(2, 4)	C(1, 5)	C(6)
6a[a,b]	66.9	66.8	51.6	49.8	75.3 [132]	27.0	29.6 [170]	60.0
6b[a]	66.8	66.7	52.6	51.2	76.3 [135]	24.5	21.0 [168]	49.3 [163]
6b[c]	67.4	67.4	53.4	52.5	77.6	25.8	21.8	50.2
7a[a,d]	67.1	66.8	52.4	50.5	67.0 [139]	31.3	30.4 [172]	56.8
7b[a]	66.8	66.6	53.4	52.1	66.8 [139]	30.0	21.3 [167]	45.3 [162]
7b[c]	67.5	67.4	54.4	53.1	67.7 [139]	30.8	22.2 [166]	46.4 [161]
9a[a,e]	66.0		49.8		211.7	37.4	24.6 [175]	55.8
9b[a]	66.4		52.5		213.8	36.4	16.4 [173]	43.7 [167]
13[a]	66.4 [142]	64.1 [147]	52.9 [134]	50.7 [143]	73.1 [144]	24.2	20.9 [170]	48.6 [163]
13[c]	66.1 [143]	64.8 [146]	53.8 [137]	51.6 [143]	69.8 [150]	27.0	22.2 [172]	47.9 [169]
14[a]	67.1 [143]	63.6 [148]	53.7 [134]	51.9 [144]	68.7 [151]	28.4	20.8 [172]	44.8 [165]
14[c]	67.1 [141]	64.3 [143]	54.1 [133]	52.1 [145]	68.2 [154]	28.8	21.2 [171]	45.1 [169]

[a] $CDCl_3$. [b] Succinimide: 177.6, 27.8. [c] CD_3CN. [d] Succinimide: 177.7, 27.8. [e] Succinimide: 177.6, 27.8.

Table 2 Selected bond distances, torsional angles and interplanar angles of 1α,3β,5α,6β-3,6-dimorpholinobicyclo[3.1.0]hexane-6-carbonitrile **6c** compared with the corresponding data for the analogous 3α-compound **7d** (from ref. 12)[a]

	6c	**7d**
Bond lengths (Å)		
C(1)–C(5)	1.488(3)	1.481(2)
C(1)–C(6)	1.503(3)	1.508(2)
C(5)–C(6)	1.502(3)	1.509(2)
C(6)–N(3)	1.425(2)	1.412(1)
C(3)–N(1)	1.455(3)	1.466(1)
Torsional angles (°)		
$H(1)–C(1)–C(2)–H(2)_M$	−110.59	−80.6
$H(1)–C(1)–C(2)–H(2)_N$	11.16	37.9
$H(2)_M–C(2)–C(3)–H(3)$	159.21	−27.6
$H(2)_N–C(2)–C(3)–H(3)$	38.90	−147.6
Interplanar angles (°)		
C(1)C(5)C(6)–C(1)C(2)C(4)C(5)	112.5	67.8
C(1)C(2)C(4)C(5)–C(2)C(3)C(4)	147.6	21.6

[a] The terms $H(2)_M$, $H(4)_M$ and $H(2)_N$, $H(4)_N$ were used in Table 2 instead of $H(2)_A$, $H(4)_A$ and $H(2)_B$, $H(4)_B$ for better comparison with the other spectroscopic data, respectively. The latter designation is found in the deposited data. $H(2)_M/H(4)_M$ are in the *endo* position and $H(2)_N/H(4)_N$ are in the *exo* position of the bicyclo[3.1.0]hexane system.

interaction of the HOMO of the C(2)–H(2eq)/C(4)–H(4eq) bonds with the C(1)–C(5) antibonding cyclopropane orbital. A distinctly longer C(1)–C(5) bond would be expected for **7d** with respect to **6c** if this were correct. Unexpectedly, different C(3) configurations of **6c** and **7d** did not affect the distance between the two amino groups [N(2)–N(3) distance: **6c**, 4.28 Å; **7d**, 4.34 Å].

The steric repulsion of the two *syn* morpholine moieties in the diamine **6c** is clearly decreased by adopting a chair conformation **6cC** with an equatorial orientation of the large substituent in C(3) position. This should be the main reason for the chair conformation of compounds of type **6**. Unfavourable interaction of the two nitrogen lone pairs is additionally minimized by an almost perpendicular arrangement of the two morpholine rings. The torsion of the C(3)–morpholine bond can be expressed by the dihedral angles H(3)–C(3)–N(2)–C(8) and H(3)–C(3)–N(2)–C(11) (see Fig. 2).

Assignment of Conformation of the Diastereomeric Diamines **6** *and* **7** *and their Monoprotonated Species* **13**/**14** *by* ^1H *NMR Spectroscopy.*—The diastereomeric diamines **6a**/**7a** and **6b**/**7b** and their monoprotonated species **13**/**14** gave well separated ^1H NMR signals for all hydrogen atoms of the bicyclic system. The coupling constants of the corresponding hydrogen atoms were ascertained from the spectra. This allowed the determination of conformation of compounds **6**, **7**, **13** and **14**. In the case of **6a**/**6b** the correctness of the experimentally obtained data was checked by simulation of the ^1H NMR spectra by the LAOKOON III program[18] (Table 3).

The coupling between *endo* hydrogen atoms $H(2)_M/H(4)_{M'}$ and the bridgehead hydrogen atoms $H(1)_X/H(5)_{X'}$ served as the simplest indicator for the conformation of the bicyclic system: A 'zero coupling' between these hydrogen atoms, characteristic of a boat conformation of a bicyclo[3.1.0]-hexane system,[19] could be observed for diamines **7a**,**b**. In contrast, the $H(2)_M/H(4)_{M'}$ ^1H NMR signal of the analogous diastereomers **6a**,**b** gave a clear splitting by the vicinal $H(1)_X/H(5)_{X'}$ atoms (Tables 3 and 4) indicating a chair conformation.

Knowledge of the C(3) configuration (X-ray structure analyses of **6c** and **7d**, ^{13}C NMR data) also allowed assignment of conformation of compounds **6**, **7**, **13** and **14** *via* the magnitude of the coupling of $H(3)_A$ with $H(2)_M/H(4)_{M'}$ and $H(2)_N/H(4)_{N'}$. Independently of the solvent, **6a**,**b**, **7a**,**b** and **14** showed relatively large coupling constants $J_{3,2M}/J_{3,4M'}$ and $J_{3,2N}/J_{3,4N'}$ indicating an axial C(3)–H bond in each case (chair conformation of **6** and boat conformation of **7** and **14**). The $J_{3,2M}/J_{3,4M'}$ coupling of monoammonium salt **13** was differing markedly in chloroform and in acetonitrile. An axial C(3)–H moiety (= chair conformation of **13**) is present only in chloroform ($J_{3,2M}/J_{3,4M'}$ = 8.8 Hz). In acetonitrile, however, a coupling constant $J_{3,2M}/J_{3,4M'}$ = 2.6 Hz was found. Such a small coupling requires an equatorial C(3)–H moiety and consequently the existence of a boat conformation due to the known C(3)-β-configuration of **13** [*e.g.* analogous coupling for **2** with its equatorial C(3)–H unit: 1.8 Hz].[19]

In accordance with this, **13** gave a small, but clear $J_{1,2M}/J_{5,4M'}$ coupling in $CDCl_3$ (chair conformation) and no $J_{1,2M}/J_{5,4M'}$ coupling in acetonitrile (boat conformation) (Fig. 3 and Table 4).

Intramolecular N–H–N hydrogen bonding should be the reason for the boat conformation of **13**. It is well known that acetonitrile is more suited for intramolecular N···H···N hydrogen bonding in monoprotonated diamines.[20] In chloroform, however, the C(3)-morpholine N–H unit interacts with the anion rather than with the C(6)-morpholine moiety due to a tight ion pair. X-Ray structural evidence for the competing interaction of an ammonium N–H moiety with the anion or with a second intramolecular amino function has been reported in the literature.[21,22]

N–H–N hydrogen bonding in **13B** in acetonitrile was also indicated by the downfield shifting of the $H(6)_Y$ signal from 1.79 ppm in $CDCl_3$ to 1.95 ppm in CD_3CN. The diastereomeric monoammonium salt **14** gave no shifting of the $H(6)_Y$ signal upon using different solvents (see Table 4).

Conformational investigations of the monoammonium salt **13** pointed out that determination of C(3) configuration in compounds of type **6**, **7**, **13** and **14** *via* the chemical shift of the C(3) ^{13}C NMR signal must be applied carefully. The δ_C value of the C(3) atom of **6**, **7**, **13** and **14** is influenced by the

Table 3 ^{1}H NMR data of the dimorpholinobicyclo[3.1.0]hexylpyrrolidinedione diastereomers **6a** and **7a** δ (400 MHz, $CDCl_3$, J in Hz)[a,b]

	Bicyclohexane[c]								
	$H(1)_X$ $H(5)_{X'}$	$H(2)_M$ $H(4)_{M'}$	$H(2)_N$ $H(4)_{N'}$	$H(3)_A$	$J_{1,2M}$ $J_{5,4M'}$	$J_{1,2N}$ $J_{5,4N'}$	$J_{2M,3}$ $J_{4M',3}$	$J_{2N,3}$ $J_{4N',3}$	$J_{1,5}$
6a	1.72	1.55	2.08	3.20	1.5	6.5	10.3	7.9	8.5
7a	1.82	2.14	1.96	3.04	0	4.0	8.5	8.0	8.0
	6-C-Morpholine[d]							3-C-Morpholine[d,e]	
	$H(2)_A$ $H(6)_A$	$H(2)_B$ $H(6)_B$	$H(3)_X$ $H(5)_X$	$H(3)_Y$ $H(5)_Y$	$J_{2A,2B}$ $J_{6A,6B}$	$J_{2B,3Y}$ $J_{6B,5Y}$	$J_{3X,3Y}$ $J_{5X,5Y}$	$H(2)_{A,A'}$ $H(6)_{A,A'}$	$H(3)_{X,X'}$ $H(5)_{X,X'}$
6a	3.76	3.54	2.76	2.44	10.9	11.7	12.0	3.70	2.50
7a	3.75	3.50	2.82	2.43	11.4	11.4	12.1	3.72	2.45

[a] Coupling constants J were determined by decoupling experiments and optimized by simulation of the ^{1}H NMR spectra by the LAOKOON-III program;[18] the coupling between $H(1)_X$ and $H(5)_{X'}$ (XX' coupling of the AMM'NN'XX' system) is essential for a correct simulation of the spectra. [b] Succinimide (4 H, two broad, unsplit signals): **6a**: 2.61, 2.74; **7a**: 2.61, 2.73. [c] Numbers of atoms correspond to the usual counting in a bicyclo[3.1.0]hexane system; $H(2)_M$ and $H(4)_{M'}$ are in the *endo* position and $H(2)_N$ and $H(4)_{N'}$ are in the *exo* position of the bicyclic skeleton. [d] Numbers of atoms correspond to the usual numbering in a morpholine system. [e] AA'XX' system.

Table 4 ^{1}H NMR chemical shifts of $H(3)_A$ and $H(2)_M/H(4)_{M'}$ and selected coupling constants $^3J_{HH}$ of the 3,6-diaminobicyclo[3.1.0]hexane diastereomers **6**/**7** and their monoammonium salts **13**/**14**, δ, J in Hz

Compound	Solvent	$H(3)_A$	$^3J_{AM}$ $^3J_{AM'}$	$^3J_{AN}$ $^3J_{AN'}$	$H(2)_M$ $H(4)_{M'}$	$^3J_{MX}$ $^3J_{M'X'}$	$H(6)_Y$
6b	$CDCl_3$	3.12	10.5	8.1	1.78	1.4	1.60
6b	CD_3CN	3.04	10.6	7.8	1.62	1.6	1.31
7b	$CDCl_3$	2.94	7.7	7.7	1.88	0	1.57
7b	CD_3CN	2.90	7.7	7.7	1.84	0	1.51
13	$CDCl_3$	3.80	8.9	8.1	1.75	1.8	1.79
13	CD_3CN	3.60	2.6	8.6	2.06	0	1.94
14	$CDCl_3$	3.69	8.0	8.3	2.06	0	1.66
14	CD_3CN	3.83	8.0	8.3	2.18	0	1.64

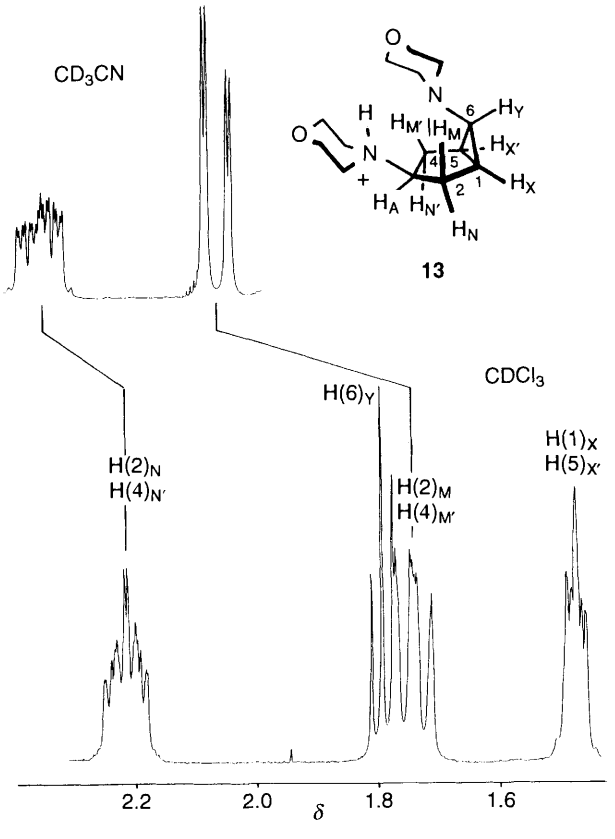
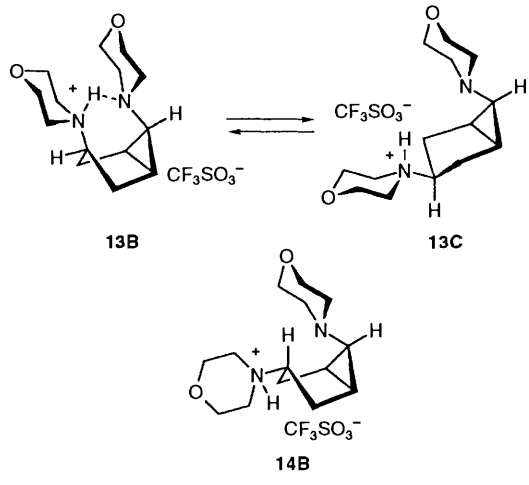


Fig. 3 ^{1}H NMR signals of the bicyclo[3.1.0]hexyl system of the monoammonium salt **13** in chloroform; $H(2)_M/H(4)_{M'}$ $H(2)_N/H(4)_{N'}$ signals in acetonitrile



Scheme 6

conformation rather than by the 3α or 3β structure of these bicyclo[3.1.0]hexane compounds. In a boat conformation, the C(3) atom is located above the cyclopropane ring and is influenced by its anisotropic effect (for ^{1}H NMR highfield shifting by a cyclopropane system see ref. 23).

Conclusion

A heterocyclic amino function in the 3-position of a 6-*endo*-aminobicyclo[3.1.0]hexane skeleton prefers an equatorial position. The presence of this anchoring group leads to a chair conformation for 3β-diastereomers **6** and to a boat conform-

ation of 3α-diastereomers **7**. In the case of 3β-monoammonium salt **13**, intramolecular hydrogen bonding can surpass the effect of the anchoring group. **13** represents the first bicyclo-[3.1.0]hexane species for which a solvent dependent preference for a boat or a chair conformation could be clearly established.

Experimental

^1H and ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer, Me_4Si was used as internal standard. *J*-Values are in Hz. IR spectra were measured with a Perkin-Elmer 397 Infrared Spectrophotometer. Microanalyses were performed with a Perkin-Elmer 2400 Elemental Analyzer. Melting points were taken using a Mettler FP 61 apparatus and are uncorrected. A Büchi B-680 Chromatography System was used for the MPLC separations, B-685 column, ϕ: 26 mm, length: 460 mm; Büchi UV–VIS Filter Photometer as detector, 254 nm.

1-{(1α,5α,6α)-6-*Morpholino*-3-*oxobicyclo*[3.1.0]*hex*-6-*yl*}pyr*rolidine*-2,5-*dione* **9a**.—A mixture of sodium hydroxide (0.40 g, 10 mmol) and succinimide (0.99 g, 10 mmol) was added to a solution of chloroenamine **8**[12] in acetonitrile (60 cm^3) and water (6 cm^3). The mixture was stirred for 2 h at 60 °C. Then the solvent was removed *in vacuo* and the residue was dissolved in chloroform (40 cm^3). Cleavage of the ketal function was achieved by addition of aqueous hydrochloric acid (6 mol dm^{-3}, 4 cm^3) and stirring for 2 h at room temperature. Addition of sodium hydroxide (2.5 mol dm^{-3}, 40 cm^3) and extraction with chloroform (3 × 25 cm^3) gave crude **9a** which was washed with methanol (2 × 25 cm^3) and purified by recrystallization from acetonitrile (60 cm^3). Yield 1.38 g (49%), m.p. 229 °C (decomp.) (Found: C, 60.1; H, 6.5; N, 10.0. $C_{14}H_{18}N_2O_4$ requires C, 60.42; H, 6.52; N, 10.07%); ν_{max}(KBr)/cm^{-1} 1745 and 1710 (C=O); δ_H($CDCl_3$) 1.97 (2 H, $H_{X1X1'}$), 2.38 (2 H, $H_{NN'}$), 2.63 (2 H, $H_{MM'}$) (MM'NN'XX'-system, carbocycle), 2.73 (4 H, br s, succinimide), 2.44 (2 H, H_Y), 2.75 (2 H, H_{X2}), 3.42 (2 H, H_B) and 3.66 (2 H, H_A) (ABXY-system, morpholine).

(1α,5α,6β)-6-*Morpholinobicyclo*[3.1.0]*hexan*-3-*one* **9b**.—A mixture of chloroenamine **8**[12] (6.23 g, 25 mmol) and sodium borohydride (9.08 g, 250 mmol) in acetonitrile (300 cm^3) was stirred at 60 °C for 5 d. The solid was removed by centrifugation and the solvent of the clear solution was evaporated *in vacuo*. The ketal was cleaved by addition of aqueous hydrochloric acid (4 mol dm^{-3}, 30 cm^3) and stirring at room temperature for 1 h. Addition of aq. sodium hydroxide (5 mol dm^{-3}, 30 cm^3) and extraction with dichloromethane (6 × 20 cm^3) gave crude **9b** which was purified by distillation in a Kugelrohr apparatus (b.p. 150 °C/0.001 Torr). In the case of uncomplete solvolysis the solvolytic procedure was repeated. Yield 1.89 g (44%), m.p. 50 °C (Found: C, 66.2; H, 8.6; N, 7.9. $C_{10}H_{15}NO_2$ requires C, 66.27; H, 8.34; N, 7.73%); ν_{max}(KBr)/cm^{-1} 1730 (C=O); δ_H($CDCl_3$) 1.54 (2 H, $H_{XX'}$), 1.89 (1 H, H_Y, J_{XY} 6.4), 2.15 (2 H, $H_{NN'}$), 2.50 (2 H, $H_{MM'}$) (MM'NN'XX'Y-system, carbocycle), 2.47 (4 H), 3.59 (4 H) (broad unsplit signals, morpholine).

(1α,3β,5α)-3,6-*Diaminobicyclo*[3.1.0]*hexane Derivatives* **6a**, **b**.—*General procedure*. A mixture of bicyclohexanone **9** (2.0 mmol, **9a**: 0.56 g, **9b**: 0.36 g), morpholine **10** (0.17 g, 2.0 mmol) and titanium tetraisopropoxide (1.14 g, 4.0 mmol) was stirred for 1 h at room temperature. Sodium cyanoborohydride (0.13 g, 2.0 mmol) and ethanol (20 cm^3) were added and stirring was continued for 24 h. Water (20 cm^3) was added, the solid was removed by suction, and the remaining solution was concentrated to a volume of 20 cm^3. Excess sodium borohydride was destroyed by addition of aq. hydrochloric acid (12.5 mol dm^{-3}, 4 cm^3) and stirring for 1 h at room temperature. Basification with aq. sodium hydroxide (2.5 mol dm^{-3}, 30 cm^3), extraction with dichloromethane (4 × 20 cm^3) and evaporation of the solvent gave crude diamines **6a**, **b**. **6a** was recrystallized from methanol (30 cm^3) at −18 °C; **6b** was distilled in a Kugelrohr apparatus (b.p. 100 °C/0.0001 Torr) and was crystallized from diethyl ether (30 cm^3) at −18 °C.

1-{(1α,3β,5α,6α)-3,6-*Dimorpholinobicyclo*[3.1.0]*hex*-6-*yl*}-*pyrrolidine*-2,5-*dione* **6a**. Yield 0.31 g (44%), m.p. 191 °C (Found: C, 61.6; H, 7.7; N, 12.0. $C_{18}H_{27}N_3O_4$ requires C, 61.87; H, 7.79; N, 12.03%); ν_{max}(KBr)/cm^{-1} 1705 (C=O).

4,4'-{(1α,3β,5α,6β)-*Bicyclo*[3.1.0]*hexane*-3,6-*diyl*}*dimorpholine* **6b**. Yield 0.26 g (51%), m.p. 106 °C (Found: C, 66.0; H, 9.4; N, 11.2. $C_{14}H_{24}N_2O_2$ requires C, 66.63; H, 9.59; N, 11.10%); δ_H($CDCl_3$) 1.25 (2 H, $H_{X1X1'}$), 1.31 (2 H, $H_{MM'}$), 1.60 (1 H, H_Y, $J_{X,Y}$ 6.9), 1.78 (2 H, $H_{NN'}$), 3.12 (1 H, H_{A1}) (AMM'NN'XX'Y system, carbocycle), 2.43 (8 H, H_{X2}, H_{X3}) and 3.63 (8 H, H_{A2}, H_{A3}) (AA'XX' systems, morpholines).

(1α,3α,5α)-3,6-*Diaminobicyclo*[3.1.0]*hexane Derivatives* **7a**, **b**.—A solution of *N*-chlorosuccinimide **12** (1.34 g; 10 mmol) in dichloromethane (100 cm^3) was added dropwise over 1 h at −25 °C to a solution of enamine **11**[12] (2.52 g, 10 mmol) in dichloromethane (60 cm^3). The mixture was stirred for 1 h at 25 °C, then the cooling bath was removed and stirring was continued for 2 h. After removal of the solvent the crude chloroenamine was extracted with pentane (2 × 100 cm^3) at 35 °C. Crude chloroenamine was obtained by evaporation of pentane; its reaction with succinimide or sodium borohydride and work-up was done in an analogous fashion to that described for the synthesis of **6a** and **6b**. **7b** was purified by MPLC (silica gel, diethyl ether as solvent) instead of distillation.

1-{(1α,3α,5α,6α)-3,6-*Dimorpholinobicyclo*[3.1.0]*hexan*-6-*yl*}-*pyrrolidine*-2,5-*dione* **7a**. Yield 1.44 g (41%), m.p. 226 °C (decomp.) (Found: C, 61.6; H, 7.6; N, 12.0. $C_{18}H_{27}N_3O_4$ requires C, 61.87; H, 7.79; N, 12.03%); ν_{max}(KBr)/cm^{-1} 1705 (C=O).

4,4'-{(1α,3α,5α,6β)-*Bicyclo*[3.1.0]*hexane*-3,6-*diyl*}*dimorpholine* **7b**. Yield 0.86 g (34%), m.p. 62 °C, b.p. 120 °C/0.005 Torr (Found: C, 66.5; H, 9.5; N, 11.0. $C_{14}H_{24}N_2O_2$ requires C, 66.63; H, 9.59; N, 11.10%); δ_H($CDCl_3$) 1.37 (2 H, $H_{X1X1'}$), 1.57 (1 H, H_Y, $J_{X,Y}$ 6.9), 1.83 (2 H, $H_{NN'}$), 1.88 (2 H, $H_{MM'}$), 2.94 (1 H, H_{A1}) (AMM'NN'XX'Y system, carbocycle), 2.43, 2.48 (8 H, broad unsplit, $H_{X2X2'X3X3'}$), 3.67 (4 H, broad unsplit, $H_{A2A'2}$), 3.71 (4 H, AA' part of an AA'XX' system, $H_{A3A'3}$) (morpholines).

Monohydrotrifluoromethanesulfonates of the Diamines **6b** *and* **7b**.—*General procedure*. A solution of diamine (0.5 mmol; **6b**/**7b**: 126.2 mg) in acetonitrile (20 cm^3) was exactly titrated with trifluoromethanesulfonic acid (0.1 mol dm^{-3} in propan-2-ol) with a titration apparatus. The reaction mixture was stirred at room temperature for 30 min. Removal of the solvent *in vacuo*, trituration of the residue with diethyl ether (3 × 20 cm^3) and drying of the residue *in vacuo* gave pure ammonium salts in quantitative yield.

4-{(1α,3β,5α,6β)-6-*Morpholinobicyclo*[3.1.0]*hexan*-3-*yl*}*morpholinium trifluoromethanesulfonate* **13**. M.p. 168 °C (Found: C, 44.7; H, 6.2; N, 6.9. $C_{15}H_{25}F_3N_2O_5S$ requires C, 44.77; H, 6.26; N, 6.96%).

4-{(1α,3α,5α,6β)-6-*Morpholinobicyclo*[3.1.0]*hexan*-3-*yl*}*morpholinium trifluoromethanesulfonate* **14**. M.p. 185 °C (Found: C, 44.7; H, 6.2; N, 7.1. $C_{15}H_{25}F_3N_2O_5S$ requires C, 44.77; H, 6.26; N, 6.96%).

X-Ray Structure Analysis of **6c**.—Single crystals were obtained from an ethereal solution of **6c**.[12]

Crystal data. $C_{15}H_{23}N_3O_2$, M = 277.4. Monoclinic, a = 8.272(3), b = 12.397(4), c = 14.829(4) Å; β = 90.42(4)°, V =

1520.7(8) Å^3; space group $P2_1/c$, $Z = 4$, $D_x = 1.211$ g cm^{-3}. Colourless crystal. Crystal dimensions 0.6 × 0.3 × 0.7 mm, μ(Mo-Kα) = 0.76 cm^{-1}.

Data collection and processing. Enraf–Nonius CAD4 diffractometer, $\omega/2\theta$ mode with ω scan width = 0.85 + 0.35 tanθ, ω scan speed 1.66–4.0 deg min^{-1}, graphite-monochromated Mo-Kα radiation; 2604 reflections measured ($2.0 < \theta < 24.0°$), 2501 unique [merging $R = 0.045$], giving 1710 with $I < 2.2\sigma(I)$.

Structure analysis and refinement. The structure was solved by direct methods. Refinement was performed by a full-matrix-least-squares program. Hydrogen atoms were localized in a ΔF map and refined with isotropic temperature factors. Refinement converged at $R = 0.0429$ and $R_w = 0.0384$, weighting scheme: $w = 4F_o^2/[\sigma(I)^2 + (PF_o^2)^2]$ ($P = 0.015$). The largest shift/error ratio at this stage was < 0.06. The residual electron density was < 0.13.[24,*]

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* Tables of atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme see 'Instructions for Authors (1993),' *J. Chem. Soc., Perkin Trans. 2*, 1993, issue 1.

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