Conformational NMR study of *N*-substituted-1,3,4,5-tetrahydro-1*H*-2-benzazepines

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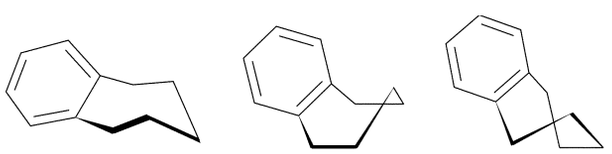
Received (in Cambridge) 6th September 2002, Accepted 17th October 2002
First published as an Advance Article on the web 22nd November 2002

The variable temperature (298–179 K) ^{1}H NMR spectra of *N*-substituted 2-benzazepines (compounds **2**–**7**) correspond to two puckered mirror-image (enantiomorphic) conformations, with a single chair-to-chair interconversion barrier for the benzazepine ring of *ca*. 11 kcal mol^{-1} in CD_2Cl_2 solution. A similar interconversion was detected for 1,3,4,5-tetrahydro-*N*-methylbenzazepine (compound **1**), of lower symmetry. The conformations of compounds **1**–**7** were assigned on the basis of the magnitude of ^{1}H-^{1}H vicinal coupling constants. The ^{1}H and ^{13}C NMR spectral assignments were determined by ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, and NOESY experiments.

Introduction

1,3,4,5-Tetrahydro-*N*-substituted 2-benzazepines continue to generate considerable interest because of their pharmacological properties.[1a–e] Synthetic approaches to benzazepines have been studied extensively.[2a–d]

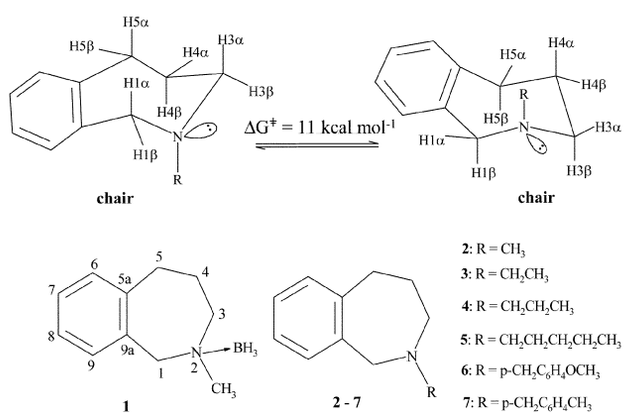
Theoretical studies of conformational phenomena have been reported for substituted 1,3,4,5-tetrahydro-2*H*-2-benzazepin-3-ones[3] and 1,3,4,5-tetrahydro-1*H*-2-benzazepine.[1a] Additionally, experimental NMR investigations of the conformations of the dihydrodibenz[b,f]azepines,[4a] *N*-acyltetrahydro-2*H*-1-benzazepines,[4b] 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-ones,[4c] and 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-ones [4d] have been published. The presence of a double bond within a seven-membered ring considerably alters the conformational situation: cycloheptane displays pseudorotation[5] within both the boat and the chair conformational families, while in cycloheptene the chair is relatively rigid without pseudorotation.[6] Previous investigations[7a–h] of various heterocyclic analogues of benzocycloheptene have demonstrated the frequent existence of three distinct seven-membered ring geometries: the chair (C), boat (B) and the twist–boat (TB) conformations (Scheme 1).



Scheme 1

In the above mentioned investigations, it was also established that conformational properties of heterocyclic analogues of benzocycloheptene depend on the position of the single heteroatom and also the polarity of substituents in the seven membered ring.

In spite of the extensive pharmacological and synthetic investigations of *N*-substituted tetrahydrobenzazepines with a nitrogen atom in the 2-position, their conformational behaviour has not yet been documented. In the present work, we report the temperature dependent ^{1}H and ^{13}C NMR spectra of *N*-substituted 1,3,4,5-tetrahydro-1*H*-2-benzazepines **1**–**7**. The barriers for conformational inversion were determined in CD_2Cl_2 solution. *N*-Substituted-2-benzazepines **2**–**7** display just two enantiomorphic chair conformations, which exchange through a ring inversion (Scheme 2) in the same manner



Scheme 2

as benzocycloheptene itself.[7i] The present work extends our investigation of benzo-heterocycloheptanes.[8]

Results and discussion

The assignment of proton spectra for compounds **1**–**7** (Scheme 2) is based on the ^{1}H–^{1}H COSY, NOE difference and NOESY experiments. The ^{1}H NMR spectral data of **1**–**7** are given in Table 1.

Assignment of the ^{1}H NMR spectra of 1–7

In the ^{1}H NMR spectra of **2**–**7** at 20 °C, singlet signals in the region 3.74–3.90 ppm can confidently be assigned to H-1 due to the deshielding effect of the electronegative nitrogen atom. In a similar manner, the multiplet signals in the region 2.94–3.13 ppm belong to H-3. The proton–proton connectivity, which was derived by selective irradiation or by COSY experiments, allowed the assignment of all of the aliphatic protons. At room

 DOI: 10.1039/b208633f

Table 1 The ^{1}H NMR chemical shifts (δ/ppm), multiplicity, and coupling constants (*J*/Hz) of seven-membered ring and *N*-substituent protons for compounds **1**–**7** in CD_2Cl_2 (position numbering is given in Scheme 3, below). Additional peaks are listed in the footnotes

Compound	T/°C	H-1	H-3	H-4	H-5
1[a]	+ 25°	4.32 (d, H1ax) 3.96 (dd, H1eq) J_{AB} = 14.5 ^3J(H1eq, H3eq) = 1.5	3.29 (ddd, H3ax) 3.17 (br dt, H3eq) J_{AB} = 14.2 ^3J(H3ax, H4ax) = 11.5 ^3J(H3eq, H4ax) = 3.4 ^3J(H3eq, H4eq) = 3.4	1.81 (ddd, H4ax) 1.90 (ddd, H4eq) J_{AB} = 14.4 ^3J(H4ax, H5ax) = 11.4 ^3J(H4eq, H5ax) = 3.5 ^3J(H4eq, H3eq) = 3.2 ^3J(H4ax, H3eq) = 3.4	2.98 (ddd, H5ax) 2.83 (ddd, H5eq) J_{AB} = 14.8 ^3J(H5ax, H4ax) = 11.4 ^3J(H5ax, H4eq) = 3.5 ^3J (H5eq, H4eq) =2.8 ^3J(H5eq, H4ax) = 6.2
	−80°	4.31 (d, H1ax) 3.91 (dd, H1eq) J_{AB} = 14.6	3.27 (ddd, H-3ax) 3.18 (br dt, H3eq) J_{AB} = 14.2 ^3J(H3ax, H4ax) = 10.5 ^3J(H3eq, H4ax) = 3.5 ^3J(H3eq, H4eq) = 3.5	1.80 (ddd, H4ax) 1.91 (ddd, H4eq) J_{AB} = 14.4	2.91 (ddd, H5ax) 2.78(ddd, H5eq) J_{AB} = 14.6 ^3J(H5ax, H4ax) = 10.5 ^3J(H5ax, H4eq) = 3.5 ^3J (H5eq, H4eq) =2.1 ^3J(H5eq, H4ax) = 5.1
2[b]	+ 25°	3.78 (s)	2.96–3.00 (m)	1.70–1.77 (m)	2.85–2.89 (m
	−80°	3.91 (d, H1ax) 3.56 (d, H1eq) J_{AB} = 14.1	2.80 (d, H3ax) 3.06 (d, H3eq) J_{AB} = 13.4	1.66 (br s, H4ax) 1.66 (br s, H4eq)	2.88 (br dd, H5ax) 2.72 (br d, H5eq) J_{AB} = 14.2 ^3J(H5ax, H4ax) = 11.4
3[c]	+ 25°	3.88 (s)	3.08–3.13 (m)	1.64–1.86 (m)	2.87–2.91 (m)
	−92°	4.07 (d, H1ax) 3.89 (d, H1eq) J_{AB} = 14.6	3.04 (d, H3ax) 3.34 (d, H3eq) J_{AB} = 13.5	1.81 (dd, H4ax) 1.66 (br d, H4eq) J_{AB} = 14.2 ^3J(H4ax, H5ax) = 11.5	3.07 (br dd, H5ax) 2.85 (br dd, H5eq) J_{AB} = 14.8 ^3J (H5eq, H4ax) = 6.1 ^3J(H5ax, H4ax) = 11.5
4[d]	+ 25°	3.74 (s)	2.94–2.98 (m)	1.56–1.63 (m)	2.76–2.80 (m)
	−88°	3.98 (d, H1ax) 3.70 (d, H1eq) J_{AB} = 14.4	2.91 (d, H3ax) 3.17 (d, H3eq) J_{AB} = 14.1	1.53 (dd, H4ax) 1.66 (d, H4eq) J_{AB} = 14.2 ^3J(H4ax, H5ax) = 11.7	2.93 (d, H5ax) 2.72 (dd, H5eq) J_{AB} = 14.1 ^3J(H5eq, H4ax) = 5.6
5[e]	+25°	3.90 (s)	3.09–3.13 (m)	1.68–1.76 (m)	2.87–2.91 (m)
	−88°	4.14 (d, H1ax) 3.88 (d, H1eq) J_{AB} = 14.4	3.04 (d, H3ax) 3.32 (dd, H3eq) J_{AB} = 14.1 ^3J(H3ax,H4ax) = 11.7	1.68 (dd, H4ax) 1.79 (dd, H4eq) J_{AB} = 14.2 ^3J(H4ax, H5ax) = 11.5	3.09 (dd, H5ax) 2.85 (dd, H5eq) J_{AB} = 13.8 ^3J(H5ax, H4eq) = 6.2 ^3J(H5eq, H4eq) = 4.5
6[f]	+ 25°	3.79 (s)	3.02–3.05 (m)	1.68–1.76 (m)	2.83–2.87 (m)
	−76°	3.90 (d, H1ax) 3.59 (d, H1eq) J_{AB} = 14.4	2.99 (dd, H1ax) 3.08 (d, H3eq) J_{AB} = 13.9 ^3J(H3ax, H4ax) = 12.1	1.57 (br d, H4ax) 1.68 (d, H4eq) J_{AB} = 14.6	2.93 (d, H5ax) 2.82 (dd, H5eq) J_{AB} = 14.6 ^3J(H5eq, H4ax) = 5.2
7[g]	+ 25°	3.81 (s)	3.01–3.05 (m)	1.65–1.72 (m)	2.83–2.87 (m)
	−93°	4.05 (d, H1ax) 3.72 (d, H1eq) J_{AB} = 14.6	2.96 (d, H3ax) 3.17 (d, H3eq) J_{AB} = 13.4	1.55 (br d, H4ax) 1.79 (q, H4eq) J_{AB} = 12.8	2.93 (d, H5ax) 2.76 (dd, H5eq) J_{AB} = 14.2 ^3J(H5eq, H4ax) = 4.8

[a] 2.27 (3H, s, CH_3). [b] 2.28 (3H, s, CH_3); 1.74–2.33 (3H, m, BH_3) 7.11–7.32 (4H, m, aromatic). [c] 2.43 (2H, q, *J* 7.1, H-2′), 1.08 (3H, t, *J* 7.1, H-3′); 7.07–7.17 (4H, m, aromatic). [d] 2.16 (2H, m, H-2′); 1.50 (2H, m, H-3′); 0.85 (3H, t, *J* 7.3, H-4′); 7.01–7.11 (4H m, aromatic). [e] 2.32–2.37 (2H, m, H-2′); 1.45–1.56 (2H, m, H-3′); 1.16–1.36 (4H, m, H-4′ + H-5′); 0.89 (3H, t, *J* 7.3, H-6′); 7.07–7.18 (4H, m, aromatic). [f] 3.45 (2H, s, H-2′); 7.18 (2H, d, *J* 8.7, H-4′/*ortho*, Ph); 6.84 (2H, d, *J* 8.7, H-5′/*ortho*, Ph); 3.78 (3H, s, OCH_3); 7.04–7.14 (3H, m, aromatic); 6.91 (1H, br d, *J* 6.9, aromatic); the signal at 6.90 ppm (*J* 6.9) belongs to H-9, which was assigned by the NOE difference experiment (see Scheme 4, below); at −76 °C, the H-2′ proton appears as AB type spectrum (see Fig. 5, below): δ_A 3.38 (1H, d, J_{AB} 12. 9); δ_B 3.32 (1H, d, J_{AB} 12. 9). [g] 3.45 (2H, s, H-2′); 7.15 (2H, d, *J* 7.6, H-4′/*ortho*, Ph); 7.08 (2H, d, *J* 7.6, H-5′/*ortho*, Ph); 7.01–7.12 (3H, m, aromatic); 6.90 (1H, d, *J* 6.9, aromatic); 2.29 (3H, s, CH_3); at −93 °C, the H-2′ proton give AB type spectrum: δ_A 3.47 (1H, d, J_{AB} 12. 8); δ_B 3.35 (1H, d, J_{AB} 12. 8).

temperature, the averaging of C-1 proton signals indicates the presence of two mirror images, puckered configurational isomers, which rapidly interconvert on the NMR time scale. This fast exchange renders equivalent the protons on either the α or β faces for positions 1, 3, 4 and 5 (see Scheme 2).

Low temperature ^{1}H NMR spectra of 1–7. In compound **1**, which contains the $N(CH_3)BH_3$ fragment, at low temperature the protons on the α and β faces are non-equivalent. The proton spectrum of **1** (Fig. 1) at −19 °C displays broadened lines for the H1ax, H3ax and H4eq protons. The increasing line broadening for the H2, H3 and H4 (but not for H1ax) protons of the seven-membered ring of compound **1** as the temperature is lowered from −19 °C to −88 °C is probably explained by the increasing viscosity of the solution. In contrast to the low temperature ^{1}H NMR spectra of **1**, the room temperature ^{1}H NMR spectrum of **1** shows sharp lines for the protons of the seven membered ring. These features can be explained as follows: at low temperatures only one conformer is present in appreciable concentration; as the temperature increases, a second minor conformer is in equilibrium with the first and the rate of conformational exchange is comparable to the frequency separation of the isochronous sites; at higher temperatures, the conformational equilibrium is fast on the NMR timescale, and the averaged spectrum has narrow lines.

At low temperature, the protons on the α and β faces of the benzazepines **2**–**7** are also non-equivalent (see Scheme 2). The ^{1}H–^{1}H COSY experiment revealed the vicinal and geminal couplings of the protons in positions 3–5, and the geminal couplings were identified in the ^{1}H–^{13}C COSY spectrum, yielding a sequence of three methylene groups. The most deshielded methylene protons at position 1 were assigned C-1 in the seven membered ring. The axial protons in positions 3 and 5 were identified by two large couplings (*ca.* 10–15 Hz), one gem-

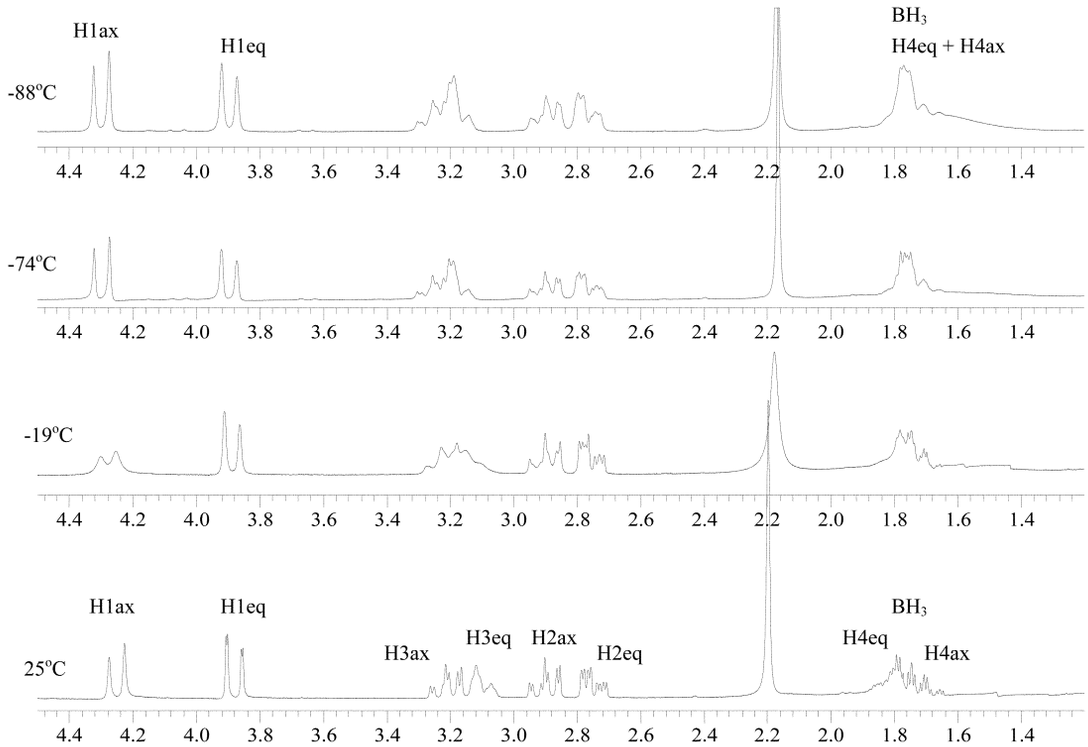


Fig. 1 Portion of ^{1}H NMR temperature dependence spectra of **1** in CD_2Cl_2.

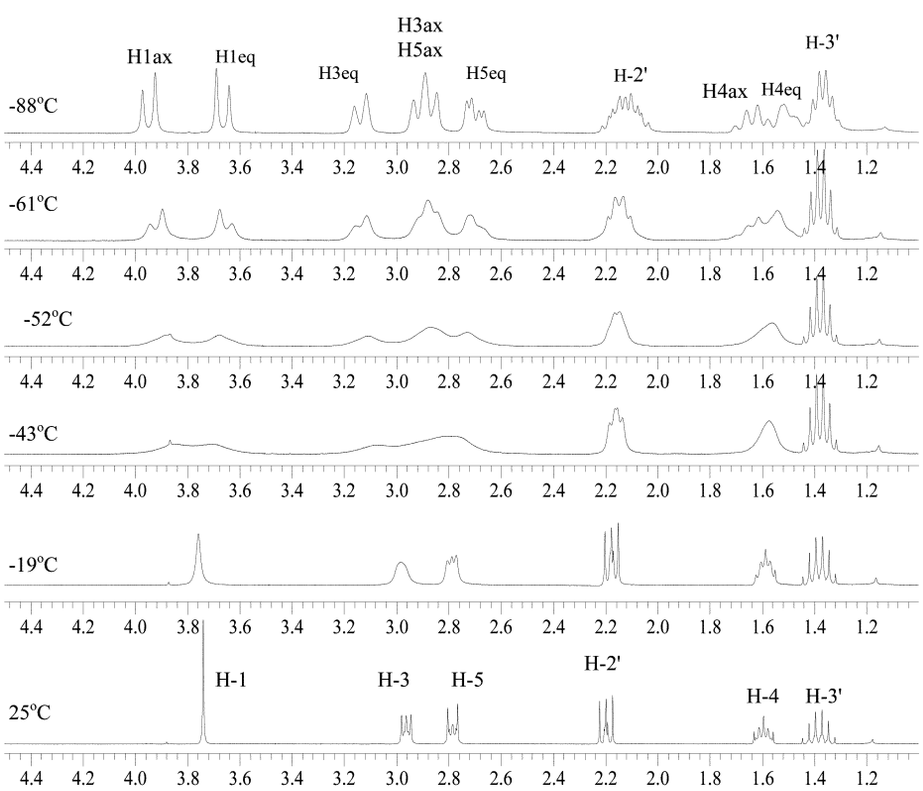


Fig. 2 Portion of ^{1}H NMR temperature dependence spectra of **4** in CD_2Cl_2.

inal and one axial–axial. Similarly, the axial proton in position 4 was indicated by three large couplings. The NOE's to the axial protons in positions 3 and 5 identified the axial proton in position 1. The ^{1}H chemical shifts and coupling constants are given in Table 1. Compounds **2**–**7** gave the same dynamic ^{1}H NMR spectral changes at low temperatures. Temperature dependent ^{1}H NMR spectra (aliphatic region) for compounds **4** and **7** as representative examples are given in Figs. 2 and 3 respectively.

Conformations of the seven-membered rings in 1–7

As mentioned above, benzocycloheptene, the basic carbon framework of this study, was shown by ^{1}H NMR spectroscopy [7i] to exist solely in the chair form (C).

The absence of ^{1}H and ^{13}C NMR spectral changes for **1**–**7** in CD_2Cl_2 solution upon lowering the temperature to −93 °C confirms the existence of two enantiomorphic chair (C*) conformations of these molecules. The same chair to chair

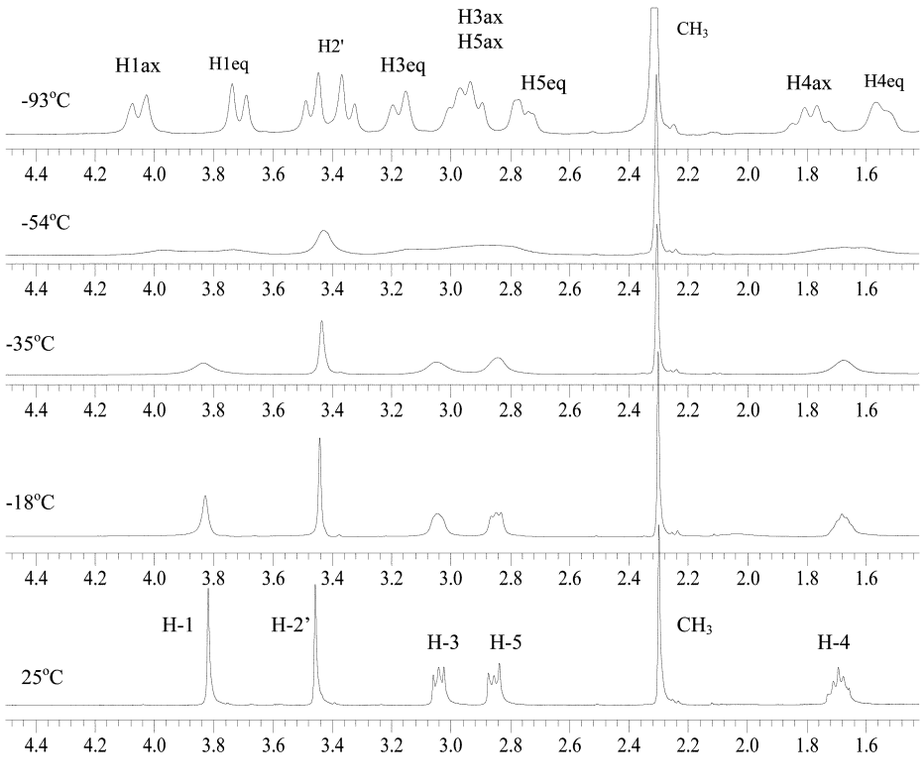


Fig. 3 Portion of ^{1}H NMR temperature dependence spectra of **7** in CD_2Cl_2.

(C ⇆ C*) (see Scheme 2) conformational inversion was observed for the hetero- analogue of 2,3,4,5-tetrahydro-2-benzoxapines.[7c]

Compound **1**, containing the $N(CH_3)BH_3$ structural unit, at ambient temperature shows relatively rigid chair conformations with axial (CH_3) and equatorial (BH_3) preferences of these in both groups in contrast to **2**–**7**. The axial (CH_3) and equatorial (BH_3) preferences in **1** are proved by NOESY and also by the magnitude of ^{11}B NMR chemical shifts as explained below. It has been shown on the basis of the magnitude of the ^{11}B NMR chemical shifts that six-membered heterocycles containing the same structural unit $N(CH_3)BH_3$ demonstrate chair conformations with equatorial preference to the BH_3 group.[9a–c] It is established that ^{11}B NMR chemical shifts in the range from −7 to −9 ppm are characteristic for compounds containing a BH_3 group with equatorial position. The axial preference of the BH_3 group shows higher chemical shifts in the range from −12 to −20 ppm. The ^{11}B NMR spectrum of **1** shows a broad signal at −7.3 ppm which is comparable to the value of ^{11}B NMR chemical shift (*ca.* −8.0 ppm) of an equatorial BH_3 group.

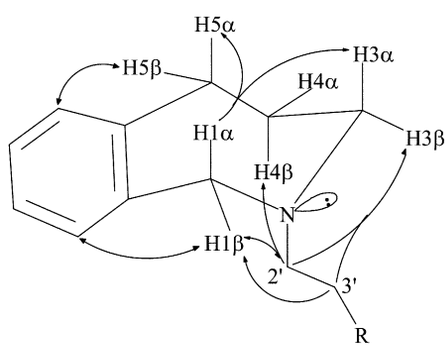
In addition, the NOESY spectrum of **1** indicates the diaxial arrangement of CH_3 and H-4β.

Large values of vicinal coupling constants (see Table 1) in the range of 11–12 Hz for all compounds ($^3J_{H4ax,H5ax}$ and $^3J_{H4ax,H3ax}$) confirm the chair conformation for **2**–**7** at low temperature.

The NOESY spectra of **2**–**7** displayed the cross-peaks expected for the 1,3-diaxial position in chair conformations (Scheme 3), a representative NOESY spectum of **4** is given in Figure 4 (−80 °C). As in **1**, the substituent at the nitrogen of all compounds, **2**–**7**, prefers the axial position as demonstrated by the NOE's between H-α protons and protons in the substituent (H-2′) and the axial protons in position H-4β. Interestingly, the NOE was observed between protons H-3′ and H-1β, H-3′ and H-3β, indicating spatial proximity of the two protons H-1β and H-3β to the alkyl chain.

Thermodynamic parameters for the ring inversion in compounds 2–7

The free energy of activation at the coalescence temperature (T_c) ($\Delta G^{\ddagger}$/kcal mol^{-1}) for the conformational exchanges in compounds **2**–**7** were determined by using the Eyring equation.[12]



Scheme 3 Arrows show the NOE's between the protons of the seven membered ring, which were deduced by NOESY spectra at low temperature (−80 °C, CD_2Cl_2).

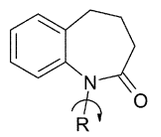
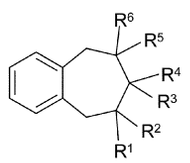
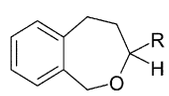
$$\Delta G^{\ddagger} = 4.575 \times 10^{-3} T_c(9.97 + \log(T_c/(\Delta\nu^2 + 6J_{AB}^2)^{1/2})$$

The rate of inversion at the coalescence temperature was calculated from the expression $k_{coalescence} = \pi(\Delta\nu^2 + 6J_{AB}^2)^{1/2}/(2^{1/2})$,[12] where $\Delta\nu = \nu_A - \nu_B$ (in Hz) is the difference in chemical shift between the centers of the two doublets arising from the methylene protons, and J_{AB} is the coupling constant of geminal protons. The rate constants (k/s^{-1}) of inversion of benzazepine rings at the corresponding coalescence temperature (T_c) are given in Table 3.

The $\Delta G^{\ddagger}$ values for compounds **2**–**7** have an average value of 10.8 kcal mol^{-1}. The differences between compounds are within the experimental error of *ca.* 0.5 kcal mol^{-1}, indicating that the substituents at the nitrogen atom do not have a significant effect on $\Delta G^{\ddagger}$. Furthermore, the $\Delta G^{\ddagger}$ values for AB patterns in the ring and protons on substituents at the nitrogen are the same, indicating that nitrogen inversion is fast on the NMR timescale.

The values of the free energy of activation for **2**–**7** are comparable to the values found for derivatives of benzocycloheptenes, 1,3,4,5-tetrahydro-2*H*-benzazepin-2-ones and 1,3,4,5-tetrahydro-1*H*-benzoxapines which are given in Table 2.

Table 2 Barriers ($\Delta G^{\ddagger}$/kcal mol^{-1}) to conformational inversion in derivatives of benzocycloheptene and in their hetero- analogs

Compound	Substituents	$\Delta G^{\ddagger}$/kcal mol^{-1}	Reference
	Bu	13.6	4*c*
	CH_2Ph	13.5	4*c*
	Et	13.2	4*c*
	^{i}Pr	16.4	4*c*
	$R^1 = R^2 = R^5 = R^6 = D$, $R^3 = R^4$	13.6	11
	$R^1 = R^2 = R^5 = R^6 = H$, $R^3 = R^4$	11.8	15
	$R^3 = R^4 = R^5 = R^6 = H$, $R^1 = R^2 = CH_3$	11.4	15
	R = H	9.4	7*c*
	$R = OCH_3$	8.8	7*c*

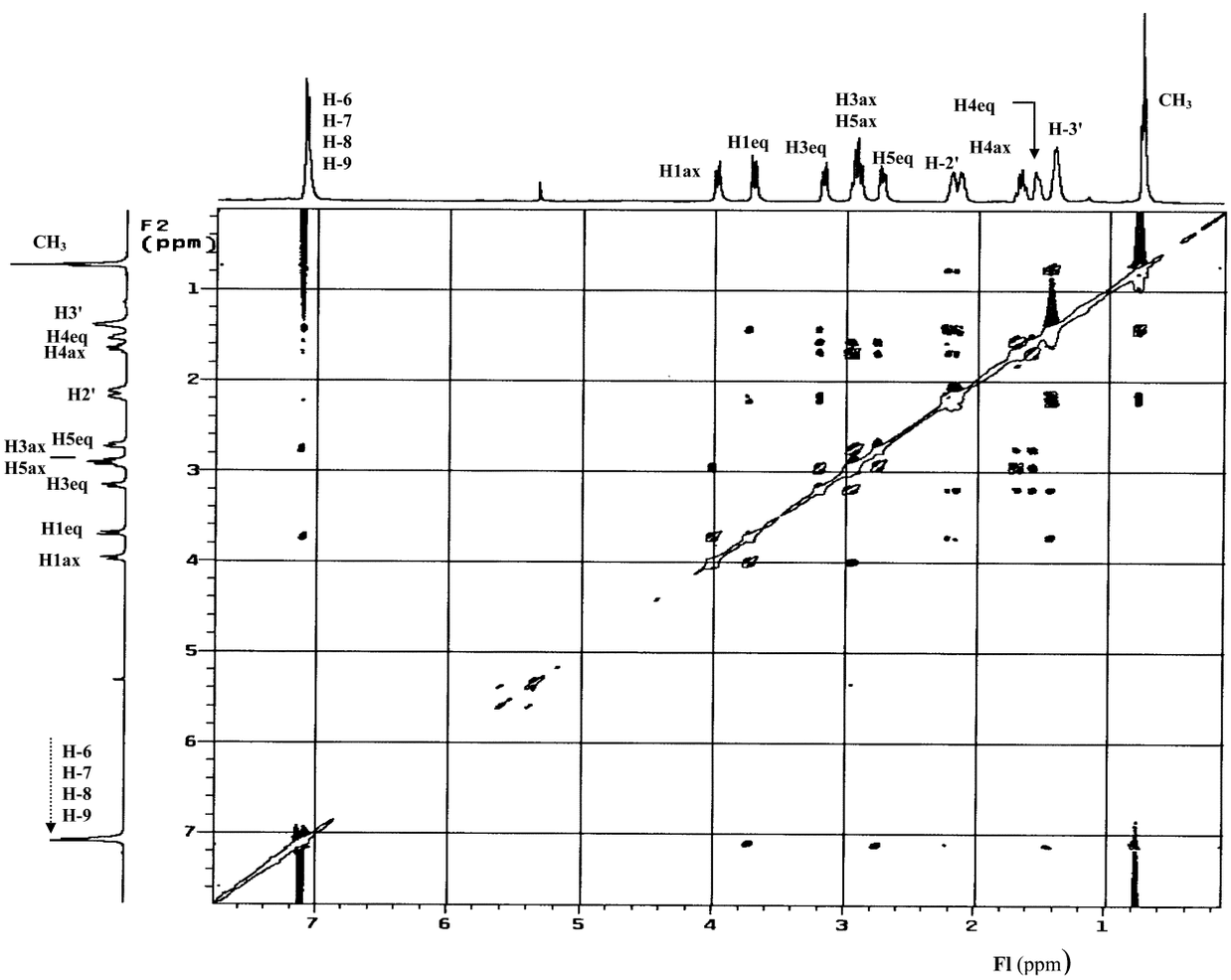


Fig. 4 NOESY spectrum of **4** in CD_2Cl_2 at −80 °C.

An examination of the data collected in Table 2 (with the assumption of $\Delta S^{\ddagger} = 0$) provokes the following general comments. They clearly show that ring inversion is dependent on the nature of the heteroatom in the seven-membered ring, its position, and on the polarity of substituents on the seven-membered ring backbone. The measured value of the free energy of activation for **2**–**7** is higher by *ca.* 2.0 kcal mol^{-1} as compared to 2-benzoxapines[7*d*] and is lower by *ca.* 2.3 kcal mol^{-1} to 1-benzazepin-2-ones.[4*c*] The increased flexibility for chair to chair ring inversion of 2-benzoxapines can be explained by the possible effect of conjugation between the ring oxygen and aromatic ring and also by the anomeric effect. The higher barrier to conformational inversion of 1-benzazepin-2-ones can explained on the basis of partial double bond character of the N–CO bond.[13]

^{13}C NMR spectral assignments of 1–7 and conformation

The ^{13}C NMR spectra of **1**–**7** did not show any changes on lowering the temperature to −93 °C in CD_2Cl_2 solution (Table 4) indicating the presence of two mirror-image conformers, which displayed the same chemical shifts.

The carbon chemical shift assignments of **1**–**7** were based on the one-bond and multiple-bond correlations with protons,

Table 3 Coalescence temperatures (T_c/°C), methylene shift positions (δ/ppm), geminal coupling constant (J/Hz), rate constant of inversion (k_c/s^{-1}) and free energies of activation ($\Delta G^{\ddagger}$/kcal mol^{-1}) for the conformational inversion of *N*-substituted-2-benzazepines **2**–**7** in CD_2Cl_2

Compound	Proton	δ_A	δ_B	$\Delta\nu$/Hz	$^2J_{AB}$/Hz	T_c/°C	k_c/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
2	H-1	3.91	3.56	105	14.1	−46	245.4	10.8
	H-3	3.06	2.80	78	13.4	−46	187.9	10.8
3	H-1	4.01	3.89	36	14.6	−47	113.2	11.1
	H-3	3.34	3.04	90	13.5	−45	213.8	10.8
	H-5	3.07	2.86	63	14.8	−48	172.1	10.8
4	H-1	3.95	3.67	84	14.4	−43	203.2	11.0
	H-3	3.13	2.88	75	14.1	−42	184.1	11.1
	H-5	2.87	2.70	51	14.1	−41	137.4	11.3
5	H-1	4.13	3.87	78	14.5	−46	177.6	10.8
	H-3	3.32	3.04	84	14.1	−46	202.5	10.8
	H-5	3.09	2.85	72	13.5	−45	176.7	10.9
6	H-1	3.90	3.59	93	14.4	−64	221.8	9.9
	H-3	3.08	2.99	27	13.9	−65	96.9	10.3
	H-4	1.68	1.57	33	14.6	−53	108.2	10.9
	H-5	2.93	2.82	33	14.6	−64	134.7	10.3
	H-2′	3.38	3.32	18	12.9	−66	80.7	10.6
7	H-1	4.05	3.72	99	14.6	−53	234.7	10.4
	H-3	3.17	2.96	63	13.4	−53	158.4	10.6
	H-4	1.79	1.55	72	12.8	−53	174.3	10.5
	H-5	2.93	2.76	51	14.1	−53	137.4	10.7
	H-2′	3.47	3.35	36	12.8	−54	106.0	10.8

[a] $\Delta G^{\ddagger} = 4.575 \times 10^{-3} T_c(9.97 + \log(T_c/(\Delta\nu^2 + 6J_{AB}^2)^{1/2}$. [b] $k_{coalescence} = \pi(\Delta\nu^2 + 6J_{AB}^2)^{1/2}/(2^{1/2})$.

Table 4 ^{13}C NMR spectral data of *N*-substituted-2-benzazepines **1**–**7** in CD_2Cl_2. Additional peaks in the footnotes

Comp	T/°C	C-1	C-3	C-4	C-5	C-5a	C-6	C-7[i]	C-8[i]	C-9	C-9a
1[a]	25°	65.9°	65.4°	23.7	34.2	142.3	129.0	126.7	128.9	131.5	132.9
	−68°	65.5	65.4	23.4	34.2	142.4	128.9	126.6	128.8	131.5	132.5
2[b]	25°	62.5	61.7	26.2	36.2	143.6	129.1	126.3	127.6	130.1	139.9
	−80°	61.0	60.3	24.5	35.1	142.9	128.3	126.8	128.3	129.4	138.4
3[c]	25°	59.0	58.3	25.1	35.9	142.9	126.1	127.5	128.9	129.9	139.2
	−80°	59.4	59.0	25.0	36.2	142.9	128.7	125.8	127.1	129.7	139.3
4[d]	−30°	59.0	58.7	24.3	36.0	142.9	128.7	125.8	127.1	129.8	139.3
5[e]	25°	59.0	58.5	26.6	35.8	142.7	128.7	127.3	127.4	129.8	139.2
6[g]	25°	59.0	58.3	24.9	36.0	143.0	128.8	125.9	127.4	130.1	138.6
7[h]	25°	59.2	58.7	25.2	36.1	143.1	128.7	125.8	127.1	129.9	139.4
	−93°	58.3	57.5	23.6	35.6	142.8	125.4	126.9	128.4	129.8	138.5

[a] 45.2 (CH_3) at 25 °C; 44.2 (CH_3) at −68 °C. [b] 43.6 (CH_3) at 25 °C; 42.1 (CH_3) at −68 °C. [c] 12.4 (CH_3), 47.6 (CH_2N) at 25 °C. [d] 55.3 (C-2′), 20.6 (C-3′), 11.9 (C-4′) at 25 °C; 54.6 (C-2′), 20.5 (C-3′), 11.9 (C-4′) at −30 °C. [e] 53.0 (C-2′), 29.4 (C-3′), 24.5 (C-4′), 22.4 (C-5′), 13.9 (C-6′) at 25 °C. [g] 55.4 (C-2′), 55.2 (OCH_3), 158.7 (C-6′), 134.8 (C-3′), 130.6 (2/C-4′, Ph), 113.6 (2/C-5′, Ph) at 25 °C. [h] 57.5 (C-2′), 21.1 (CH_3), 136.1 (C-6′), 136.4 (C-3′), 128.8 (2/C-4′, Ph), 128.9 (2/C-5′, Ph) at 25 °C; 55.8 (C-2′), 20.9 (CH_3), 135.3 (C-6′), 136.3 (C-3′), 128.8 (2/C-4′, Ph), 128.6 (2/C-5′, Ph) at −93 °C. [i] Chemical shifts assignments for C-7 and C-8 could be reserved.

seen in the HETCOR, HETCOR-LR and HMBC spectra and are listed in Table 4.

One-bond heterocorrelation HETCOR spectra of **1**–**7** provide easy carbon assignments of C-1, C-3, C-4, C-5 on the seven-membered moiety on the basis of previously established proton assignments.

The assignments of C-5a and C-9a on the fused benzene ring were supported by HMBC cross peaks. Unequivocal chemical shift assignments for two for C-6 and C-9 were made on the basis of correlations in HMBC spectra with the H-1 and H-5 protons.

As a representative example of the HMBC spectra of **1**–**7**, we have shown the contour plot maps of **2** (Fig. 5).

All the aromatic protons were overlapped in the spectra of **1**–**7**, therefore C-6 and C-9 were assigned on the basis of the long-range couplings to H-5 and H-9 correspondingly, and C-7 and C-8 were assigned on the basis of prediction of chemical shifts using the equation $\delta = 128.5 + \Sigma S$ (S means "substituent" which here refers to the $^5CH_2$–CH_2 and $^1CH_2N$ groups from the seven-membered ring).

As mentioned above, the methyl group in **1** prefers the axial position, as compared to related compounds, as demonstrated by the ^{11}B and ^{13}C NMR chemical shifts.[9a–c] It is known that the magnitude of ^{13}C NMR chemical shifts for compounds containing the same $N(CH_3)BH_3$ structural fragment as in **1** is 45.2 ppm. The ^{13}C NMR spectrum of **1** displayed a chemical shift for the CH_3 group at 44.2 ppm, which is comparable to the magnitude of chemical shift (45.2 ppm) of a methyl group with an axial preference.

A comparison of the ^{13}C NMR chemical shifts in **1** and **2** (Scheme 4) illustrated the effect of the BH_3 substituent: the equatorial BH_3 group induced a downfield shift on C-1 by +3.4 ppm and on C-2 by +3.7 ppm and upfield shifts on C-3 by −2.5 ppm and on C-5 by −2.2 ppm, respectively.

To conclude, compounds **2**–**7** illustrate two puckered mirror-image (enantiomorphic) conformers of the benzazepine ring, with chair-to-chair interconversion barriers of 11 kcal mol^{-1} in CD_2Cl_2 solution. The low temperature chair conformations of **2**–**7** revealed that the alkyl substituents on the nitrogen prefer axial positions.

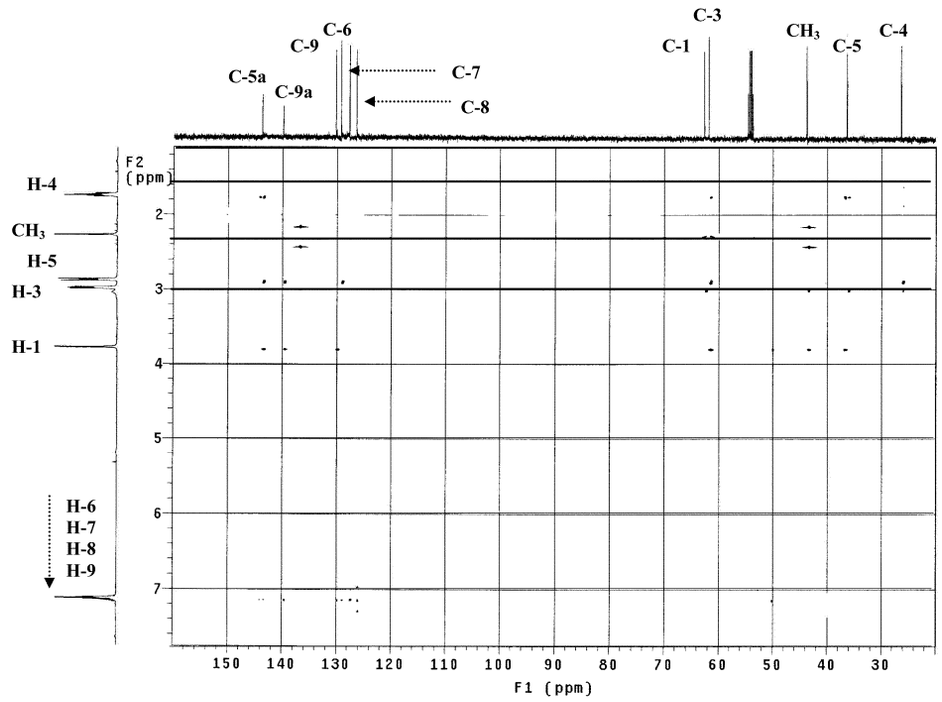
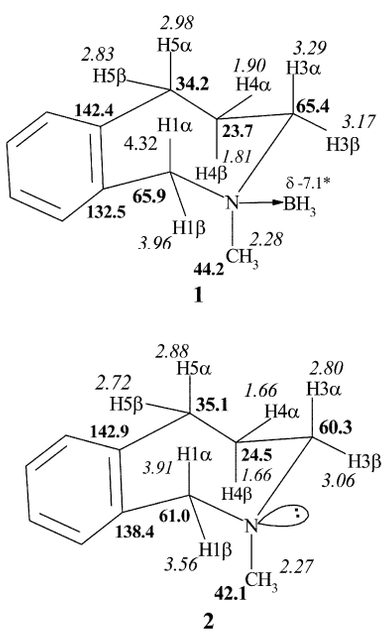


Fig. 5 HMBC spectrum of **2** in CD_2Cl_2 at 25 °C.



Scheme 4 Chemical shifts in compounds **1** and **2** (^{1}H NMR in italics; ^{13}C NMR in bold; ^{11}B NMR: asterisk).

Experimental

The ^{1}H and ^{13}C NMR spectra were acquired on a Varian GEMINI spectrometer operating at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C, equipped with a 5 mm probe. The ^{1}H and ^{13}C chemical shifts are referenced to TMS as internal standard. All two-dimensional experiments were acquired using standard Varian software. The phase-sensitive NOESY spectrum was acquired at −80 °C on a Varian INOVA 500 MHz spectrometer. ^{11}B NMR spectra of **1** were acquired on a VXR-300 spectrometer operating at 96.2 MHz. $BF_3.O(C_2H_5)_2$ was used as the external standard. The temperature was calibrated using methanol and ethylene glycol standards for low and high temperatures respectively. The temperature was accurate to ±0.5 °C. Compounds **1**–**7** were synthesized by known procedures.[14]

References

1 (*a*) G. L. Grunewald, V. H. Dahanukar, P. Ching and K. R. Criscione, *J. Med. Chem.*, 1996, **39**, 3539; (*b*) E. J. Trybulski, R. I. Fryer, E. Reeder, A. Walser and J. Blount, *J. Med. Chem.*, 1983, **26**, 1596; (*c*) E. J. Trybulski, L. Benjamin, S. Vitone, A. Walser and R. I. Fryer, *J. Med. Chem.*, 1983, **26**, 367; (*d*) R. W. Fuller, B. B. Molloy and S. K. Hemrick, *Biochem. Pharmacol.*, 1979, **28**, 528; (*e*) W. H. Miller, F. E. Ali, W. E. Bondinell, J. F. Callahan, R. R. Calvo, D. S. Eggleston, R. C. Haltiwanger, W. F. Huffman, S-M. Hwang, D. R. Jakas, R. M. Keenan, P. F. Koster, T. W. Ku, C. Kwon, K. A. Newlander, A. J. Nichols, M. F. Parker, J. M. Samanen, L. S. Southall, D. T. Takata, I. N. Uzinskas, R. E. Valocik, J. A. Vasko-Moser, A. S. Wong, T. O. Yellin and C. C. K. Yuan, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2481.

2 (*a*) A. R. Katritzky and A. J. Boulton, in *Advances in Heterocyclic Chemistry*, Academic Press, New York, 1974, vol. 17, p. 49; (*b*) R. Gámez-Montaño, M. I. Chávez, G. Roussi and R. Cruz-Almanza, *Tetrahedron Lett.*, 2001, **42**, 9; (*c*) A. I. Meyers and R. H. Hutchings, *Tetrahedron*, 1993, **49**, 1807; (*d*) Y. Ishihara, T. Tanaka, S. Miwatashi, A. Fujishima and G. Goto, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2993.

3 R. M. Keenan, J. F. Callahan, J. M. Samanen, W. E. Bondinell, R. R. Calvo, L. Chen, C. DeBrosse, D. S. Eggleston, R. C. Haltiwanger, S. M. Hwang, D. R. Jakas, T. W. Ku, W. H. Miller, K. A. Newlander, A. Nichols, M. F. Parker, L. S. Southhall, I. Uzinskas, J. A. Vasko-Moser, J. W. Venslavsky, A. S. Wong and W. F. Huffman, *J. Med. Chem.*, 1999, **42**, 545.

4 (*a*) C. R. Ellefson, L. Swenton, R. H. Bible, Jr. and P. M. Green, *Tetrahedron*, 1976, **32**, 1084; (*b*) A. Hassner and B. Amit, *Tetrahedron Lett.*, 1977, 3023; (*c*) G. P. Johnson and B. A. Marples, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3399; (*d*) D. Duval, P. Hennig, J. P. Bouchet, J. Vian, J. L. Peglion, J. P. Volland, N. Platzer and J. Guilhem, *Magn. Reson. Chem.*, 1997, **35**, 175.

5 R. Knorr, C. Ganter and J. D. Roberts, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 556.

6 E. A. Noe and J. D. Roberts, *J. Am. Chem. Soc.*, 1971, **93**, 7261.

7 (*a*) S. Désilets and M. St-Jacques, *Tetrahedron*, 1988, **44**, 7027; (*b*) F. Sauriol-Lord and M. St-Jacques, *Can. J. Chem.*, 1979, **57**, 3221; (*c*) S. Désilets and M. St-Jacques, *J. Am. Chem. Soc.*, 1987, **109**, 1641; (*d*) R. St-Amour and M. St-Jacques, *Can. J. Chem.*, 1983, **61**, 109; (*e*) A. Blanchette, F. Sauriol-Lord and M. St-Jacques, *J. Am. Chem. Soc.*, 1978, **100**, 4058; (*f*) R. St-Amour, M. T. P. Viet and M. St-Jacques, *Can. J. Chem.*, 1984, **62**, 2830; (*g*) A. Lachapelle and M. St-Jacques, *Can. J. Chem.*, 1987, **65**, 2575; (*h*) H. Hart and J. L. Corbin, *J. Am. Chem. Soc.*, 1965, **87**, 3135; (*i*) M. St-Jacques and C. Vaziri, *Org. Magn. Reson.*, 1972, **4**, 77.

8 A. R. Katritzky, N. G. Akhmedov, I. Ghiviriga and P. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1816.

9 (*a*) A. Flores-Parra, N. Farfán, A. I. Hernández-Bautista, L. Fernandez-Sánchez and R. Contreras, *Tetrahedron*, 1991, **47**, 6903; (*b*) A. Flores-Parra, G. Cadenas-Pliego, L. M. R. Martínez-Aguilera, M. L. García-Nares and R. Contreras, *Chem. Ber.*, 1993, **126**, 863; (*c*) M. Güizado-Rodríguez, A. Flores-Parra, S. A. Sánchez-Ruiz, R. Tapia-Benavides, R. Contreras and V. I. Bakhmutov, *Inorg. Chem.*, 2001, **40**, 3243.
10 C. Piccinni-Leopardi, O. Fabre and J. Reisse, *Org. Magn. Reson.*, 1976, **8**, 233.
11 S. Kabuβ, H. Friebolin and H. Schmid, *Tetrahedron Lett.*, 1965, 469.
12 A. Mannschreck, G. Rissmann, F. Vögtle and D. Wild, *Chem. Ber.*, 1967, **100**, 335.
13 W. E. Stewart and T. H. Siddall, *Chem. Rev.*, 1970, **70**, 517.
14 A. R. Katritzky, R. Maimait, R. G. Akhmedova and Y-J. Xu, *Synthesis*, 2002, **5**, 601.
15 E. Grunwald and E. Price, *J. Am. Chem. Soc.*, 1965, **87**, 3139.