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Synthesis and Stereochemistry of Some 1,3-Oxazolidine Systems Based on TRIS (α,α,α-Trimethylolaminomethane) and Related Aminopolyols Skeleton. Part 1: (Di)spiro-1,3-oxazolidines

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Abstract—Synthesis of the title compounds is examined from the diastereoselectivity point of view; their stereochemical assignments are supported by high resolution NMR data, which are used to define their chirality and isomerisation aspects.

Introduction

TRIS® (α,α,α-trimethylolaminomethane or 1,1,1-tris-hydroxymethylaminomethane) is the trivial name of a very well known aminopolyol[1,2] belonging to the large class of β-aminoalcohols. A great number of heterocyclic saturated compounds based on its skeleton, mainly as five-membered (substituted-1,3-oxazolidines)[3–10] and fused five-membered structures (substituted-1-aza-3,7-dioxabicyclo[3.3.0]-octanes),[3–25] are mentioned in the literature. However, only minor attention has been paid to spiro-1,3-oxazolidines derived from TRIS (and of its analogous)[4,5,8–10,24] (Scheme 1).

Starting from the pioneering works of Bergmann,[3] Pierce[4,5] and Senkus,[10] the reaction of some simple cyclic ketones with β-aminoalcohols was explored either aiming at investigating the general reactivity of carbonyl compounds with amine nucleophiles or for applicative purposes only. Recently, azaoxaspiranes having an oxazolidine ring (Scheme 1) have been considered prodrugs acting as delivery systems because of their increased lipophilicity compared with that of the corresponding free β-amino-alcohol.[9] A preparative study[8] and patents called attention to the use of these compounds as pesticides.[21] It is emphasised that no structural assignment accompanied these papers (except for mass-spectra);[8] moreover, even the syntheses were the subject of some controversy.[8] Therefore, in this paper, our approach is primarily focused on preparative aspects.

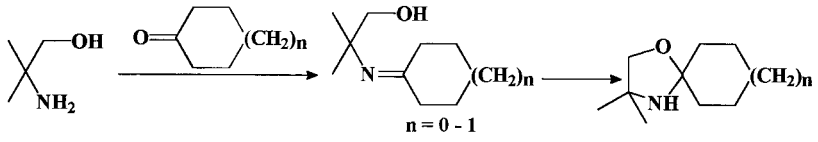
On the other hand, the stereochemistry of the title structures has been completely neglected so far. This includes the fundamental aspects of conformational analysis, diastereoisomerism, central and conformational chirality.

Thus, we also considered it of interest to enlarge the scope of the present study, in connection with related and recent work in the area.[26–32]

Results and Discussion

Synthesis

As depicted in Scheme 2, ten (di)spiro-1,3-oxazolidines



Scheme 1.

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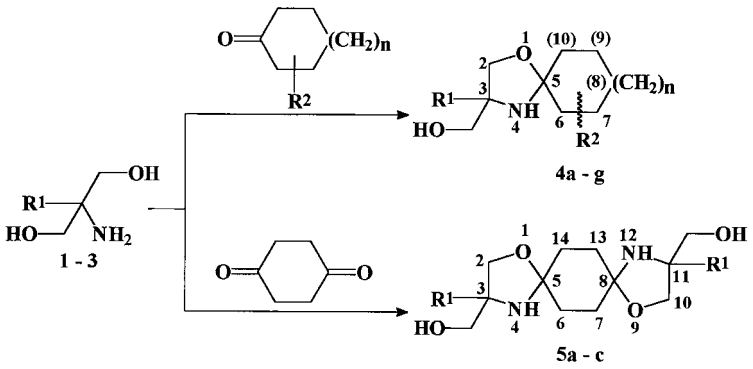


R^1	R^2	n	Aminopolyol	(Di)spiranes
$-CH_2OH$	H, Me, Et, ^{t}Bu	0 - 2	**1**	**4a – g, 5a**
Me	-	-	**2**	**5b**
Et	-	-	**3**	**5c**

Scheme 2.

have been prepared starting from TRIS **1** and its alkyl analogues **2** and **3** following the classical method of Pierce[4,5] and Senkus.[10] It is of note that our choice is, from a stereochemical point of view, supported by the different environment of the hydroxymethyl groups in the starting materials: homotopic (**1**) and enantiotopic (**2**,**3**). Monospiranes **4d**–**g** and all dispiranes **5** are new compounds. The representative results are depicted in Table 1.

Monospiranes. Variation of diastereoselectivity, shown by the synthesis of C-6-8 methylated monospiranes **4c**–**e** (Table 1, Scheme 3) could be explained by the preference of the bulky nucleophile (–OH group) for one of the diastereotopic faces of the imine double bond taking into account the stereocontrol promoted by the methyl group and Burgi–Dunitz trajectory requirements. All syntheses have been performed under thermodynamic control (e.g. up to 18 h in refluxing toluene). One can see the general preference for the second axial nucleophilic attack and the good '*3-alkylketone effect*' (compound **4d**) that gives a better diastereoselectivity as compared to **4c**. In the case of compound **4e**, the ΔG (=−6.53 kJ/mol) value for the C-2 equatorial methyl group in the starting 2-methylcyclohexanone (over 90% population of the 2-Me-equatorial conformer) would appear to be responsible for the complete diastereoselectivity found (Table 1). Anyhow, the explanation is based on also considering the closer position of the methyl group to the C=O double bond.[33–35]

The RHF/3-21G* molecular orbital calculations (with full geometry optimisation) support the above observations; Table 2 lists the relative differences between total energies of the possible conformers and diastereomers in the series **4c**–**e**.

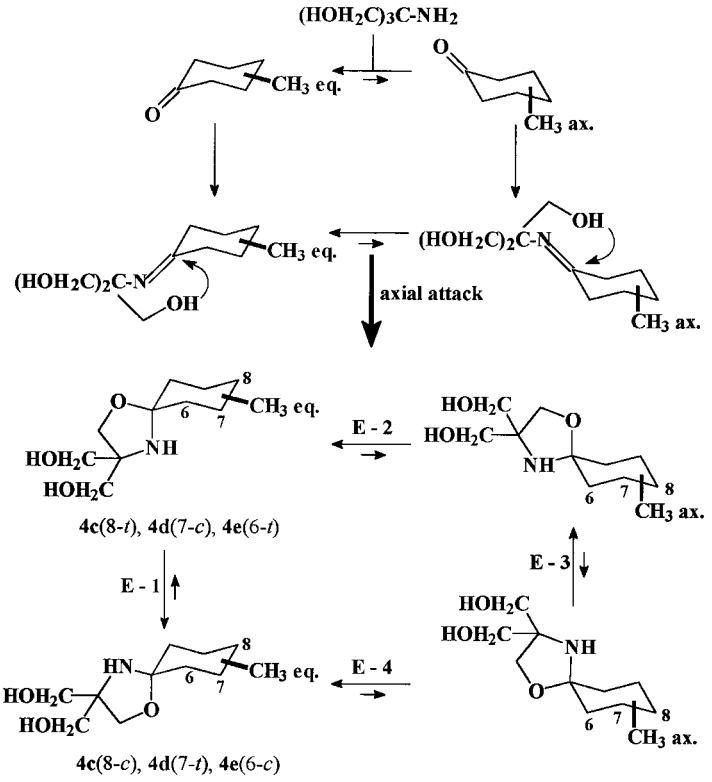
Thus, the calculations reveal that from the four (**E-1**–**4**) conformational or configurational equilibria only **E-1** and **E-2** (Scheme 3) are considerable and shifted to NH-eq.–Me-eq. diastereomers. The positive value ΔE=+1.84 kJ/mol for the compound **4e** (**E-2**, Scheme 3) suggests an axial position of the C-6 methyl group, in order to avoid

Table 1. Quantitative and qualitative results of the synthesis of (di)spiro-1,3-oxazolidines **4**,**5**

Compound	R^1	R^2	n	Yield (%) / mp (°C)	Diastereoselectivity (%) according to NMR spectra performed	
					DMSO-d_6	$CDCl_3$
4a	$-CH_2OH$	H	0	75 / 118–120	–	–
4b	$-CH_2OH$	H	1	86 / 118–119	–	–
4c[a]	$-CH_2OH$	8-Me	1	80 / 95–99	60*c*+40*t*	61*c*+39*t*
4d[a]	$-CH_2OH$	7-Me	1	50 / 83–86	85*t*+15*c*	82*t*+18*c*
4e[a]	$-CH_2OH$	6-Me	1	20 / 93–96	100*c*	90*c*+10*t*
4f	$-CH_2OH$	H	2	90 / 91–92	–	–
4g[a]	$-CH_2OH$	8-^{t}Bu	1	80 / 178–180	100*c*	75*c*+25*t*
5a[b]	$-CH_2OH$	–	–	81 / 216–217	100*t*	–
5b[b]	Me	–	–	75 / 144–145	100*u*-*t*	65*u*-*t*+35*l*-*t*
5c[b]	Et	–	–	75 / 134–135	100*u*-*t*	65*u*-*t*+35*l*-*t*

[a] Isolated as mixtures (and racemic, if chiral); the dominant diastereomer will be labelled as follows: **4c**(8-*c*), **4d**(7-*t*), **4f**(6-*c*) and **4g**(8-*c*); descriptors: *c* (*cis*) and *t* (*trans*) discriminate the diastereomer (**O-1** and $\mathbf{R^2}$ group as references); e.g. in **4c**(8-*c*) the O-1 and Me group (linked to C-8) are *cis* with respect to cyclohexane ring[38,39](see Scheme 3).

[b] Isolated as racemic mixtures (if chiral); the diastereomers are labelled as *u* (*unlike*, *meso* form) or *l* (*like*, racemic) with respect to the configurations at C-3 and C-11 (see further discussion and Schemes 2 and 4);[38,39]descriptors *t* (*trans*) or *c* (*cis*) refer to the disposal of O-1 and O-9 ligands with respect to cyclohexane ring.



Scheme 3.

two *gauche* interactions with the oxazolidine moiety, but combined COSY and NOE-difference experiments have proved its equatorial position (see Experimental and Stereochemistry sections).

To evaluate more properly the steric preference of the nucleophilic attack on a (substituted)cyclohexanone followed by a five-membered ring closure, compound **4g** was prepared. During the synthesis, ring inversion in the cyclohexane part is now ruled out (Scheme 3) and the diastereomeric ratio **4g**(8-*c*) vs **4g**(8-*t*) (the latter if formed) also indicates the conformational preference of an alkylamino group vs an alkoxy one when tied together in 1,3-oxazolidine ring. The synthesis was completely diastereoselective, as revealed by NMR spectra performed in DMSO-d_6, but in $CDCl_3$ we found a mixture of the two possible diastereomers (Table 1, compound **4g**); the corresponding A-value is about −2.72 kJ/mol (–NH– group in equatorial position). Thus, the result of the *counterpoise method*[33] demonstrates that the unsubstituted monospirane **4b** is also a rigid structure in the cyclohexane part, in DMSO-d_6, in agreement with RHF/3-21G* molecular orbital calculations (ΔE=−3.64 kJ/mol, –NH– group in equatorial position). In turn, in $CDCl_3$, compound **4b** should be a flipping spirane and NMR spectra are consistent with a single averaged structure. More evidence regarding this solvent dependent behaviour[36,37] will be discussed later. One can finally conclude that the synthesis of compounds **4** (Table 1 and 2) and their stereochemistry in the alicycle part are closely related.

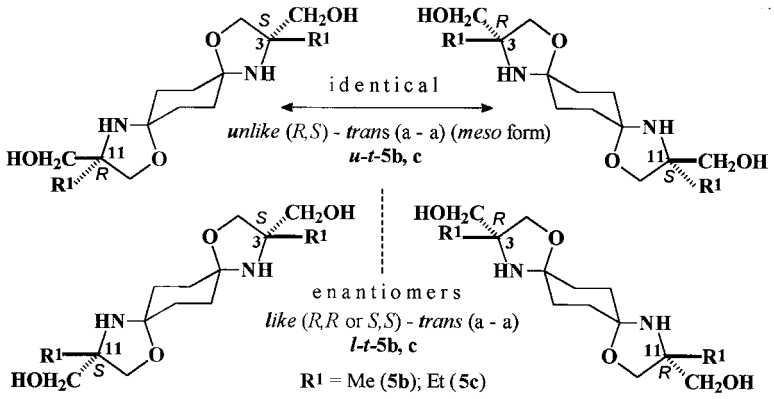
Table 2. Results of the RHF/3-21G* molecular orbital calculations for the *cis–trans* diastereomers **4c–e** (major diastereomer in **bold**) (see Scheme 3)

Equilibrium	ΔE (kJ/mol) (position of methyl group)[a]		
E-1	−3.52 (C-8)	−3.77 (C-7)	−4.44 (C-6)
	Ratio[b]	Ratio[b]	Ratio[b]
	4c(8-*c*):4c(8-*t*)	**4d(7-*t*):4d(7-*c*)**	**4e(6-*c*):4e(6-*t*)**
DMSO-d_6	1.5:1	5.7:1	only **4e(6-*c*)** found[b]
$CDCl_3$	1.7:1	4.6:1	9:1
E-2	−3.52 (C-8)	−4.23 (C-7)	+1.84(C-6)
E-3	−3.77 (C-8)	−7.45 (C-7)	−4.52 (C-6)
E-4	−10.80 (C-8)	−15.44 (C-7)	−7.11 (C-6)

[a] Negative values indicate the equilibria shifted as depicted in Scheme 3.
[b] Diastereoselective ratios calculated based on ^{1}H NMR and (or) QC NMR spectra (see Table 1).

Dispiranes. The synthesis of the dispiranes **5** afforded diastereomerically pure compounds only, as shown by the NMR spectra performed in DMSO-d_6 with increased sensitivity (300, 400 and 600 MHz) (Table 1). Therefore, the present discussion is, for the moment, restricted to these preliminary results. Thus, the parent compound **5a** exhibited a *trans*-(***t***) diequatorial configuration of the 1,4-cyclohexane unit. Then, unexpected complete diastereoselectivity occurred in the synthesis of **5b**,**c** isolated as *unlike* (***u***)-*trans* (***t***) diastereomers[38,39] (*meso* forms, Scheme 4).

Since in the starting materials **2** and **3**, the two hydroxymethyl groups are enantiotopic, they have different prochirality and any structure built from two identical units (aminodiols **2**+**2** or **3**+**3**) would yield a pair of diastereomers [***u*** (*unlike*) and ***l*** (*like*)]. To explain these results, we believe that such long distance stereocontrol is the consequence of the existence of a discrete intermediate in which steric requirements should be crucial from both ends of the molecule. The conformational preference of the



Scheme 4.

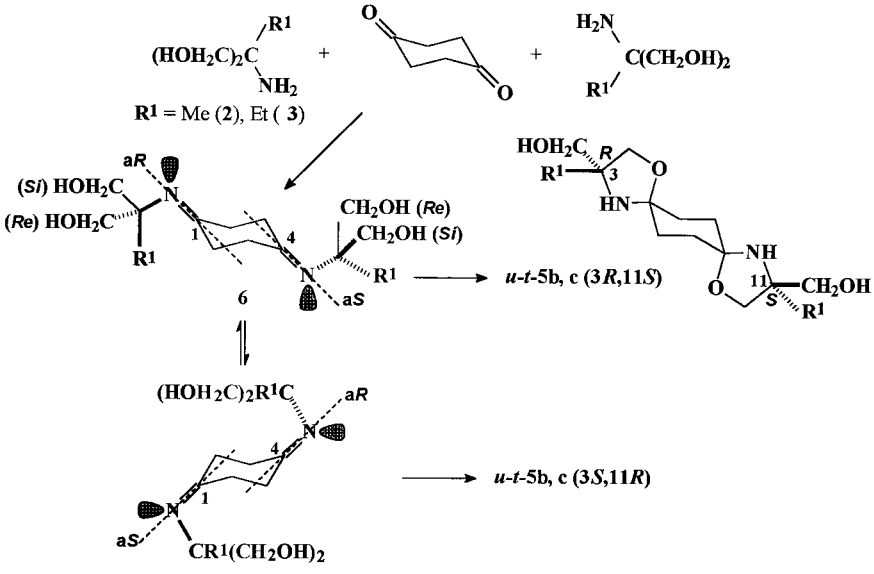
1,4-cyclohexandione (as a twist-boat conformer) is, in our opinion, not relevant in this case, but a double imine intermediate **6** is (Scheme 5, see also Scheme 3).

Its suggested *anti* configuration has, as a positive consequence, the same steric compression against methylene protons linked to C-2, -3, -5, -6 in cyclohexane moiety. Moreover, **6** is itself a *meso* form, having two opposite sense chirality axes (a*R*, a*S*). Even if a chair–chair homomeric inversion of **6** is considered, the *u-t*-spirodiastereomers (*meso* forms) **5b**,**c** are formed. If the chirality axes are identical, e.g. **6** (a*R*,a*R*) or **6** (a*S*,a*S*) (not depicted), the double imine derivative **6** is an *l*-diastereomer, yielding the racemic mixtures, ***l-t*-5b**,**c**. Another stereochemical requirement (revealed by manipulation of Dreiding models) is a double axial attack on the >C=N bonds; this again involves opposite prochirality of the $-CH_2OH$ nucleophiles at both ends of the molecule: $(-CH_2OH)_{Si}$ at C-1 and $(-CH_2OH)_{Re}$ at C-4. Thus, the R^1 group, the less bulky substituent, is placed near the equatorial cyclohexanyl protons to afford ***t*-5b**,**c** spirodiastereomer (*meso* form).

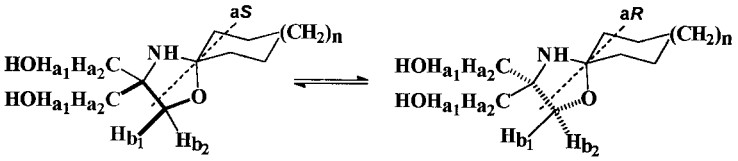
Stereochemistry

Monospiranes. In this section, attention is focused on the influence of the two types of chirality encountered in this series: *central* and *axial*. Thus, only the last one is expected to reveal the conformational behaviour of the oxazolidine ring; concerning the alicycle ring, it is obviously rigid (compounds **4c**–**e**, **4g**) or unpredictable, at least from our data (compounds **4a**,**f**). If an axis is the single stereogenic element (Scheme 6), monospiranes without any chiral centre should be a pair of conformational enantiomers, **a*R*** and **a*S***.

The envelope–envelope ring inversion of the oxazolidine fragment, as proposed in Scheme 6 (flexibility around C-2), is supported only by careful inspection of Dreiding models (flexibility around N-4 can be also considered). Hereafter, all evidence regarding the stereochemistry of monospiranes will be discussed based on NMR data (Tables 3 and 4, Scheme 2 and 6).



Scheme 5.



Scheme 6.

Monospiranes with no chiral center—the enantiomeric inversion: As a general remark, the conformational behaviour of the oxazolidine ring, depicted in Scheme 6, is confirmed (compounds **4a**–**c**,**f**,**g**). Thus, the C-2 geminal heterocyclic protons ($H_{b1,b2}$) diastereotopic in a rigid structure, have been found enantiotopic (isochronous) because the structure is flipping. The same is valid, *mutatis–mutandis*, for the C-3 geminal hydroxymethyl groups. However, the substitution test reveals, for each hydroxymethyl group, the same geminal anisochronism (protons $H_{a1,a2}$ are diastereotopic in each **a*R*** or **a*S*** environment). If the entire molecule is rigid (**a*R*** or **a*S***) (Scheme 6), two distinct AX $-CH_2OH$ systems should be observed and two different $-CH_2OH$ signals since the substitution test would yield **4** (2 respectively) diastereomers. If flipping (**a*R*–a*S***), protons having different prochirality but belonging to different hydroxymethyl groups become enantiotopic and a single AX system is obtained (Fig. 1, compound **4b**).

Next, data listed in Table 3 illustrate that the diastereotopicity $\Delta\delta = H_{a1} - H_{a2}$ maintains the same range (0.06–0.08 ppm) that depends neither on the shape of the alicycle fragment, nor on its alkyl substitution at C-8. The

Table 3. Relevant chemical shifts δ (ppm) and coupling constants J (Hz) in ^{1}H NMR spectra of the monospiranes **4** (major diastereomer is labelled in **bold**)

Compound and solvent	%	R^2	n	δ H_{a1}	δ H_{a2}	$\Delta\delta$ $H_{a1,\,a2}$	J_{gem} $H_{a1,a2}$	δ H_{b1}	δ H_{b2}	J_{gem} $H_{b1,b2}$
4a		H	0							
DMSO-d_6	–			3.34(s)[a]	3.34(s)	0.00	0.00	3.51(s)	3.51(s)	–
$CDCl_3$	–			3.65(d)[b]	3.59(d)	0.06	10.9	3.62(s)	3.62(s)	–
4b		H	1							–
DMSO-d_6	–			3.62(d)	3.58(d)	0.04	10.9	3.85(s)	3.85(s)	–
$CDCl_3$	–			3.61(d)	3.53(d)	0.08	10.8	3.68(s)	3.68(s)	–
4c		8-Me	1							
DMSO-d_6				Unresolved multiplet						
(8-*c*)	60			in the 3.30–3.28ppm		–	–	3.55(s)	3.55(s)	–
(8-*t*)	40			region		–	–	3.57(s)	3.57(s)	–
$CDCl_3$										
(8-*c*)	61			3.62(d)	3.54(d)	0.08	11.0	3.67(s)	3.67(s)	–
(8-*t*)	39			3.59(d)	3.52(d)	0.07	11.2	3.69(s)	3.69(s)	–
4d		7-Me	1							
DMSO-d_6										
(7-*t*)+(7-*c*)	–			3.32(s)	3.29(d)	0.03	11.1	3.56(d)	3.54(d)	8.6
$CDCl_3$										
(7-*t*)	82			3.60(d)	3.52(d)	0.08	10.8	3.64(s)	3.63(s)	–
				3.59(d)	3.52(d)	0.07	10.8			
(7-*c*)	18			3.60(d)	3.53(d)	0.07	10.9	3.68(s)	3.68(s)	–
				3.59(d)	3.53(d)	0.06	10.9			
4e		6-Me	1							
DMSO-d_6										
(6-*c*)	100			3.42(d)	3.35(d)	0.07	11.7	3.58(d)	3.54(d)	8.4
$CDCl_3$										
(6-*c*)	90			3.58(d)	3.53(d)	0.05	10.8	3.64(d)	3.61(d)	6.9
(6-*t*)	10			3.58(d)	3.51(d)	0.07	10.8	3.64(d)	3.61(d)	6.9
4f		H	2							
DMSO-d_6				3.33(d)	3.29(d)	0.04	10.8	3.53(s)	3.53(s)	–
$CDCl_3$				3.59(s)	3.53(d)	0.06	10.8	3.64(s)	3.64(s)	
4g		8-^{t}Bu	1							
DMSO-d_6										
(8-*c*)	100			3.31(s)	3.31(s)	0.00	0.00	3.35(s)	3.35(s)	–
$CDCl_3$										
(8-*c*)	75			3.68(d)	3.57(d)	0.11	11.3	3.72(s)	3.72(s)	–
(8-*t*)	25			3.61(d)	3.53(d)	0.08	11.0	3.70(s)	3.70(s)	–

[a] Singlet.
[b] Doublet.

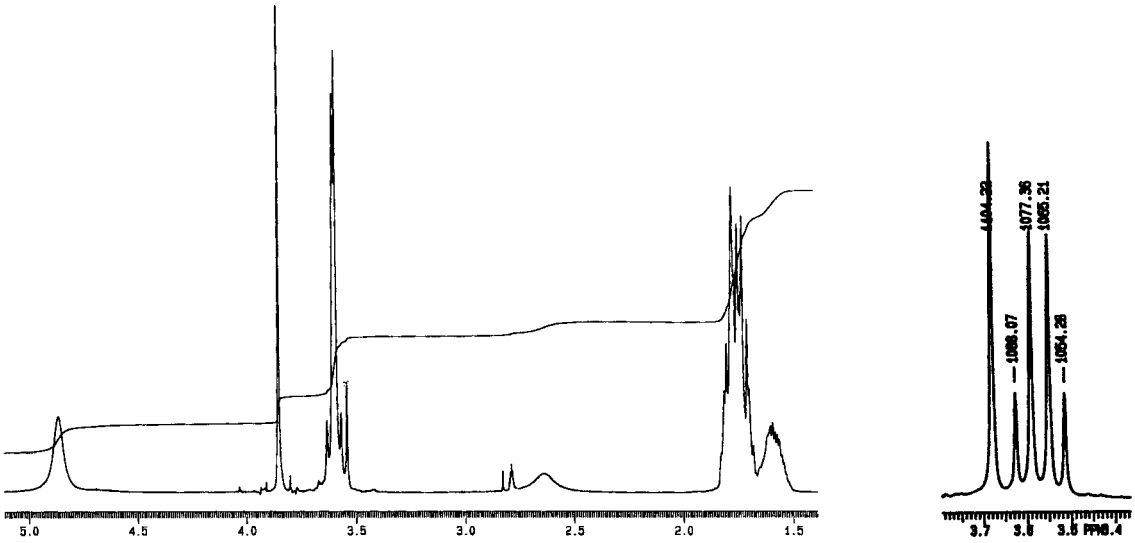


Figure 1. ^{1}H NMR spectrum of monospirane **4b** (solvent DMSO-d_6, from downfield to upfield): –O*H*, $H_{b1,b2}$, $H_{a1,a2}$, –N*H*–, cyclohexyl; detail: ^{1}H NMR spectrum in $CDCl_3$: $H_{b1,b2}$, $H_{a1,a2}$.

diastereotopicity due only to axial chirality is better exhibited in $CDCl_3$ than in DMSO-d_6.

Monospiranes possessing one chiral center in the alicycle part—the diastereomeric inversion: In the case of monospiranes **4d**,**e**, the same ring inversion is now diastereomeric (two stereogenic elements in each *cis* and *trans* diastereomer, Scheme 7).

Table 4. Relevant chemical shifts δ (ppm) in ^{13}C NMR spectra of the monospiranes **4** (major diastereomer labelled in **bold**)

Compound	–CH_2OH	C-2	C-3	C-5	–CH_3
4a					
DMSO-d_6	63.2	68.3	66.4	104.4	–
$CDCl_3$	65.5	69.3	77.3	–	–
4b					
DMSO-d_6	63.5	67.8	66.2	94.8	–
$CDCl_3$	65.3	68.9	66.3	96.1	–
4c					
DMSO-d_6					
(8-*c*)	63.5	67.9	65.9	94.2	21.9
(8-*t*)	63.4	67.7	66.6	95.3	21.6
$CDCl_3$					
(8-*c*)	65.3	68.8	65.9	95.6	21.9
(8-*t*)	64.6	68.9	66.7	96.6	21.5
4d					
DMSO-d_6					
(7-*t*)	63.5	68	65.8	94.8	22.3
(7-c)	66.7	68	67.6	95.7	22.3
$CDCl_3$					
(7-*t*)	65.3	69.1	65.9	96.2	22.4
(7-c)	64.63 and 64.57	68.7	66.8	97	22.4
4e					
DMSO-d_6					
(6-*c*)	63.0 and 63.5	68.7	65.6	96.5	14.8
$CDCl_3$					
(6-*c*)	65.1 and 65.3	69.5	65.7	97.9	14.6
(6-*t*)	64.9 and 65.7	69.5	65.7	97.2	14.9
4f					
DMSO-d_6	63.2	67.5	66.4	98.2	–
$CDCl_3$	65	68.8	66.3	100.2	–
4g					
DMSO-d_6					
(8-c)	63.5	68	65.9	94.2	–

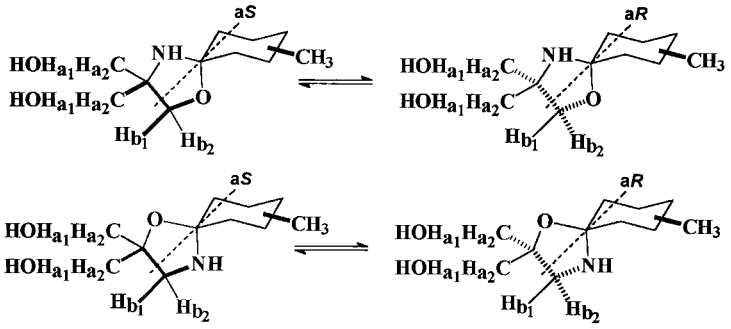
Therefore, we would have expected to detect four ^{1}H AX systems ($H_{a1,a2}$) and four ^{13}C distinct signals for –*C*H_2OH units; unfortunately, complete discrimination of peaks has been impossible because of overlapping (Tables 3 and 4). The same is true for the diastereotopic C-2 methylene. Finally, we point out two remarks:

- in the case of compound **4e**, the flipping oxazolidine fragment should be hindered by the steric hindrance promoted by the C-6 methyl group because NMR calculations are consistent with its equatorial position (see Experimental).
- spectra performed in $CDCl_3$ allowed a better separation but not enough for the COSY experiments. Consequently, only intensity of peaks and magnitude of *J*-values (Table 3) support assignments of signals to each diastereomer.

To conclude, in the monospirane series **4**, data from Tables 3 and 4 reveal about the same diastereotopicity if just one or both stereogenic elements are present in the molecule (single stereogenic axis or together with a stereogenic center).

Dispiranes. As their synthesis, conformational analysis of dispiranes is supported by the NMR evidence restricted to DMSO-d_6 used as solvent. Preliminary observation is that ***t*-5a** has no chiral centre; meanwhile ***t*-5b**, **c** possess two chiral centers, C-3, -11 [***t*** (*trans*) indicates the *trans* disposal of the two –NH– groups in cyclohexane ring]. The ^{1}H NMR spectrum of dispirane ***t*-5a** is quite similar to **4b** (Fig. 2, Scheme 8).

Since the eight cyclohexanyl protons present an overlapped AX system (hence, a rigid alicyclic conformation and a *trans* configuration regarding the substituents linked to C-5 and C-8), based also on the stereochemical assignments



Scheme 7.

for monospirane **4b**, one has now to consider two chirality axes and the conformational equilibria depicted in Scheme 8. From all four stereoisomers, only three **I, II** (identical with **IV**) and **III** are distinct structures: conformational enantiomers **I**–**III** and conformational diastereomers **I**–**II** and **II**–**III**. The already discussed ^{1}H NMR spectrum, exhibiting a single averaged structure, is consistent with these equilibria.

Very difficult structural problems are raised by the dispiranes ***t*-5b**,**c** in order to clarify their stereochemistry (configuration *l* or *u* at C-3 and C-11) according to the

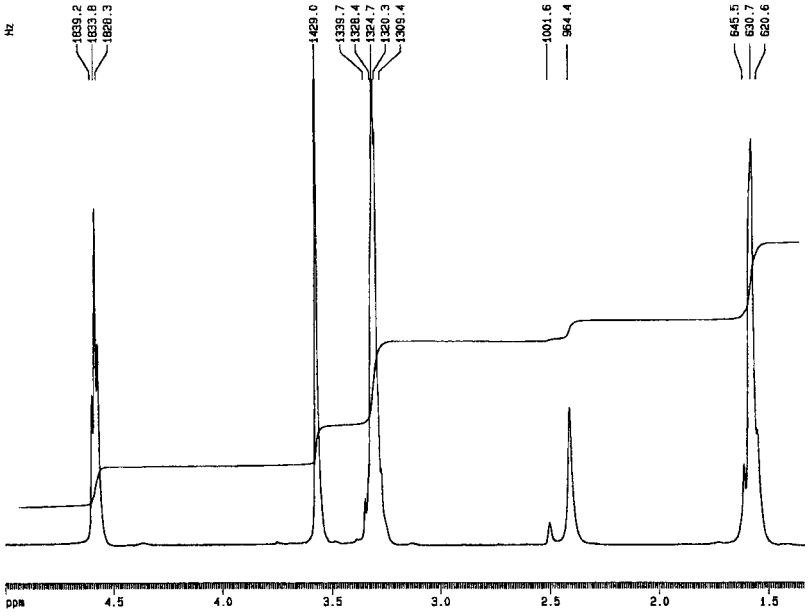
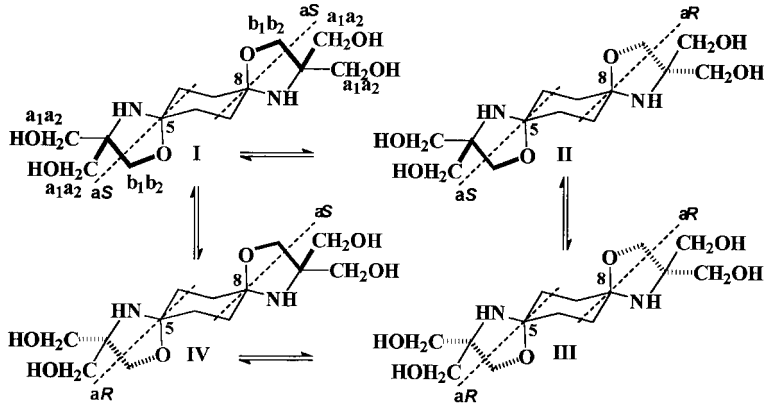


Figure 2. ^{1}H NMR spectrum of dispirane **5a** (solvent DMSO-d_6, from downfield to upfield): –O*H* (4.58 ppm, t, J=5.4 Hz), $H_{b1,b2}$ (3.57 ppm, s), $H_{a1,a2}$ (3.33 and 3.29 ppm, dd, J=11.1 Hz), –N*H*– (2.41 ppm, br.s), cyclohexyl (1.59 and 1.56 ppm, dd, J=12.4 Hz).



Scheme 8.

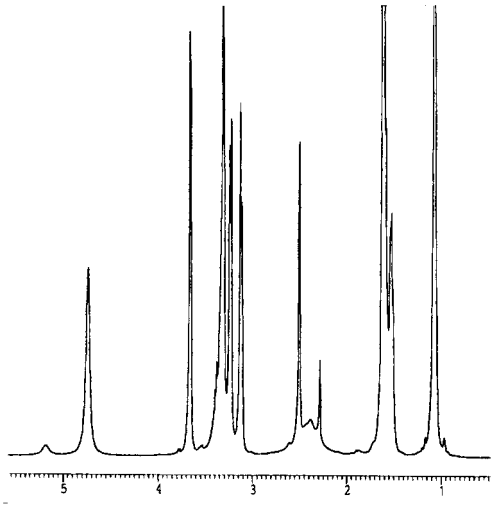


Figure 3. ^{1}H NMR spectrum of dispirane **5b** (600 MHz, solvent DMSO-d_6 from downfield to upfield): –O*H*, $H_{b1,b2}$, $H_{a1,a2}$, –N*H*–, cyclohexyl, –CH_3.

reaction model proposed (Scheme 4 and 5). A serious drawback of our study has been the fact that they have shown good solubility only in DMSO-d_6. Increased sensitivity of ^{1}H NMR detection (300, 400, 600 MHz instruments) did not separate the peaks, in the cyclohexane part, crucial for definite assignments. Thus, just a single type of stereoisomer has been detected in the spectrum of each compound [e.g. one singlet for methyl groups in ***t*-5b**, one (overlapped) doublet of doublets for methyl groups in ***t*-5c** etc.] (see Fig. 3, Scheme 9 and further Table 6).

To discriminate, by means of NMR, the two possible *l*- or *u*-diastereomers (Scheme 9, just a single enantiomer is depicted) one must observe that in ***u*-*t*-5b**,**c** diastereomers, cyclohexanyl protons labelled with the same letter are enantiotopic whereas, in ***l*-*t*-5b**,**c** they are homotopic. Unfortunately, no ^{1}H AA′XX′ system (4 signals, 32 peaks, *u*-form) and no (two) distinct ^{1}H AX systems (4 signals, 8 peaks, *l*-form) were revealed (Fig. 3, compound **5b**). Obviously, no useful data have been provided by the ^{13}C NMR spectra because in each of the *u*- or *l*-environment only two types of distinct methylene carbons can be exhibited (see nuclei labelled as X and Y, Scheme 9 and Table 6). That is, we have assigned a *u*-configuration for both ***t*-5b**,**c** compounds according to the chemistry depicted in Scheme 5.

The ring–ring tautomerism

The failure of any attempt to complete structural assignments for dispiranes has required a re-examination of the NMR investigation. That is, by using NMR solvents other than DMSO-d_6, the unexpected role of 'mobile' protons has been surprisingly put in evidence. In DMSO-d_6, the hydroxyl protons have been found as clear triplets (in fact overlapped doublets of doublets) (Figs. 2 and 3), triplets near coalescence, or broad singlets but located in about the same region (4.65–4.70 ppm). One can assume their fixed location in hydroxymethyl group, chelate developed with the solvent or a rapid change with the solvent. δ-Values of amine protons (broad singlet) ranged about 2.5 ppm.

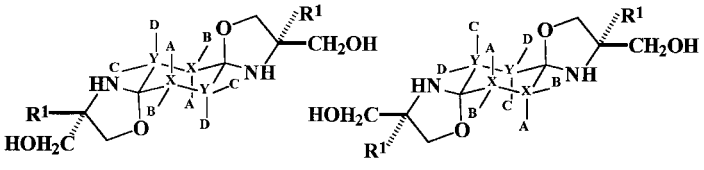
In $CDCl_3$, the NMR spectra have a completely different appearance. Thus, all 'mobile' protons have been found as a unique broad singlet, shifted upfield (in the region 2–3 ppm), suggesting an intramolecular rapid change of their environment. This hypothesis has been also supported by the very poor solubility of all spiranes in $CDCl_3$ (5–10 times less than in DMSO-d_6) and allowed us to consider the effect of intramolecular hydrogen bonds.

On the other hand, the results listed in Table 1 indicate different compositions of diastereomers, depending on the NMR solvent used. Then, it is pertinent to rule out that these differences should be the result of a different sensitivity of detection ($CDCl_3$ vs DMSO-d_6). We believe that, as soon as intramolecular hydrogen bonds are effective ($CDCl_3$), an isomerisation occurs and hereafter we will call it *ring–ring tautomerism*. It is favoured by the intramolecular hydrogen bonds that increase –OH group nucleophilicity as well as non-ionic transition states (S_N2-like mechanism). The equilibria seem to be fast because spectra re-recorded after several days indicated the same ratio between 'tautomers'.

Two types of tautomerism should be taken into account.

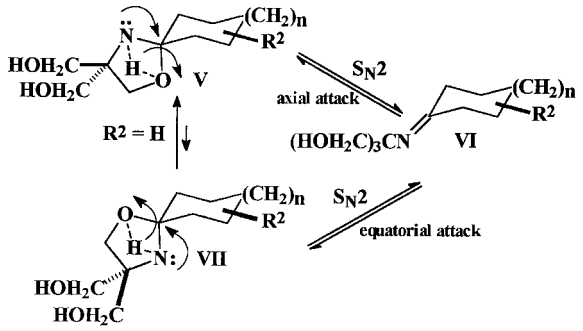
- *Homomeric ring–ring tautomerism (compounds **4a**, **b**, **f**):* as illustrated in Scheme 10 (R^2=H), in this type of tautomerism the two tautomers could not be revealed by NMR because of the rapid conformational equilibrium between conformers **V**–**VII**. A typical example is monospirane **4b** (Fig. 1). In this trivial case, the two tautomers are, in fact, conformational diastereomers.
- *Diastereomeric ring–ring tautomerism (compounds **4c**, **d**, **e**, **g**):* in this case, the two tautomers are distinct as *cis*, *trans* diastereomers (O-1 and R^2 as reference). The most relevant example is monospirane **4g** (R^2=^{t}Bu, Fig. 4).

The ratio *cis*:*trans* (about 3:1, in $CDCl_3$) allows us to estimate best the incidence of equatorial attack vs. axial attack on the diastereotopic faces of the hypothetical imine intermediate **VI** (Scheme 10), that is now an authentic ananchomeric structure.



***u*-*t*-5b** (**R1** = Me), **-5c** (**R1** = Et) ***l*-*t*-5b** (**R1** = Me), **-5c** (**R1** = Et)

Scheme 9.



Scheme 10.

Ring–ring tautomerism in the case of dispiranes. Obviously, the most complex isomerisation has been exhibited by the dispiranes **5**. Unfortunately, the parent compound ***t*-5a** was quite insoluble in both $CDCl_3$ and C_6D_6 thus preventing us from recording NMR spectra. Consequently, no information was available about the possible changing of the *cis*:*trans* diastereoisomerism in the alicycle fragment (*trans*-1,4-di-eq.–NH– against *cis*-1,4-ax.–eq.–NH–). In turn, compounds ***u-t*-5b,c** provided evidence for modification of spectra (Table 5 and 6, Scheme 11).

Although the complete description of all terms **VIII–X** involved in the above equilibria is quite impossible, the number of typical coupling patterns can be estimated. In the case of compound **5b** (R^1=Me), the hyperfine structure of ^{1}H NMR spectrum allows significant assignments (Fig. 5a–d).

The C-2, -10 methylenes $H_{b1,b2}$ (four doublets of doublets, typical value[36,37] J_{gem}=8.7 Hz) are placed in the region (**A**, **B**) and best separated to allow estimation of the diastereomeric composition. In the region (C) there are 4 pairs of geminal protons $H_{a1,a2}$ (typical value[36,37] J_{gem}=10.4–10.5 Hz) that is consistent with four environments (in **IX**, two distinct AX systems $H_{a1,a2}$ are expected instead of four because of flipping of the molecule as a homomeric inversion). In the zone (D) one can identify four types of methyl groups and the most intense peak belongs to **VIII** (***u-t*-5b**), then to **X** (***l-t*-5b**) and the smallest two ones, but having the same intensity, are reasonably assigned to diastereomers **IX** (***l*-** and ***u-c*-5b**) since they are located on different flipping structures (homomeric inversion).

Similar results have been derived from the spectra of dispirane **5c** (Table 6) but intermediates of type **IX** have been detected only in small traces that makes their assignments hazardous.

Extension of these phenomena has been observed by choosing another pair of solvents: D_2O and C_6D_6 (Fig. 6, compound **5b**).

As expected, in D_2O just one diastereomer is present, whereas in C_6D_6 both ***u-t*-** and ***l-t*-5b** are detected in a

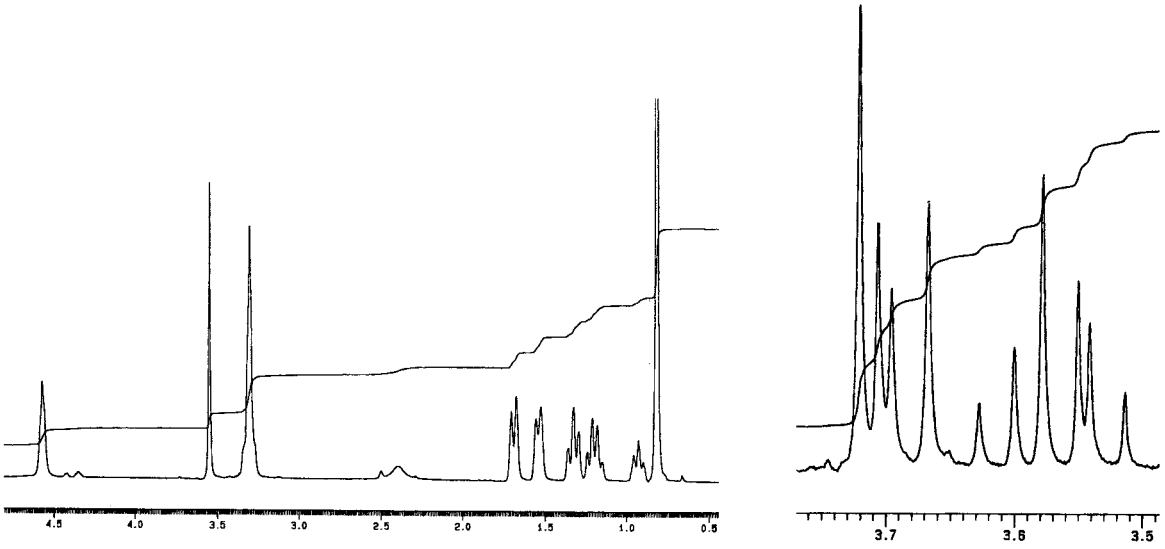


Figure 4. ^{1}H NMR spectrum of monospirane **4g** (solvent DMSO-d_6, from downfield to upfield): –O*H*, $H_{b1,b2}$, $H_{a1,a2}$, –N*H*–, cyclohexyl, ^{t}Bu; detail: ^{1}H NMR spectrum in $CDCl_3$: $H_{b1,b2}$, $H_{a1,a2}$ (coupling patterns as shown).

Table 5. Possible tautomers formed by isomerisation of dispiranes **5b**, **c** (see also Scheme 11)

Starting tautomer (DMSO-d_6)	Mixture of tautomers observed ($CDCl_3$)			
	Disposal of –NH–groups	Configuration at C-3 and C-11	Symbol	Conformation
***u-t*-5b,c VIII**	*trans* (*t*)	*like* (*R*+*R* or *S*+*S*)	***l-t*-5b,c**	Rigid **X**
	cis (*c*)	*like* (*R*+*R* or *S*+*S*)	***l-c*-5b,c**	Flipping **IX**
	cis (*c*)	*unlike* (*R*+*S*)	***u-c*-5b,c**	Flipping **IX**

Table 6. Relevant NMR data (δ, ppm and J, Hz) of the tautomers **VIII–X** derived from dispiranes **5b,c**

Stereoisomer (solvent)	δ-Values (ppm, ^{1}H and ^{13}C) for the relevant positions							
	%	C-2, -10	$-CH_2OH$	C-3, -11	C-5, -8	$-CH_2-$	$-CH_3$	Cyclohexyl
***u-t*-5b** (DMSO-d_6)								
^{1}H NMR	100	3.66, 3.31 (d, 7.8)[a]	3.23, 3.12 (d, 10.0)	–	–	–	1.07 (s)[b]	1.61–1.52 (m)[c]
^{13}C NMR		71.5	66.5	62.1	94.4	–	23.6	34.9, 34.4
***u-t*-5b** ($CDCl_3$)								
^{1}H NMR	57	3.76, 3.54 (d, 8.7)	3.39, 3.30 (d, 10.5)	–	–	–	1.24 (s)	2.00–1.60 (m)
^{13}C NMR		72.6	66.7	62.4	94.6	–	23.75	35.0, 34.8
***l-t*-5b** ($CDCl_3$)								
^{1}H NMR	35	3.77, 3.56 (d, 8.5)	3.38, 3.29 (d, 10.4)	–	–	–	1.25 (s)	2.00–1.60 (m)
^{13}C NMR		72.6	66.7	62.7	95.0	–	23.6	35.44, 35.37
***l-,u-c*-5b** ($CDCl_3$)								
^{1}H NMR	8	3.87, 3.65, 3.56, 3.54 (d, 8.7)	3.41, 3.40, 3.39, 3.38 (d, 10.5)	–	–	–	1.29, 1.24 (s)	2.00–1.60 (m)
^{13}C NMR		72.8, 77.3	66.7	62.7	95.00, 94.97	–	23.83	36.78, 36.84, 38.16
***u-t*-5b** (C_6D_6)								
^{1}H NMR	55	3.60, 3.27 (d, 8.5)	3.22, 3.11 (d, 10.4)	–	–	–	0.89 (s)	2.00–1.40 (m)
***l-t*-5b** (C_6D_6)								
^{1}H NMR	45	3.61, 3.24 (d, 8.4)	3.26, 3.13 (d, 10.2)	–	–	–	0.85 (s)	2.00–1.40 (m)
***u-t*-5b** (D_2O)								
^{1}H NMR	100	3.82, 3.56 (d, 8.5)	3.45, 3.38 (d, 10.4)	–	–	–	1.18 (s)	1.80–1.60 (m)
***u-t*-5c** (DMSO-d_6)								
^{1}H NMR	100	3.61, 3.37 (d, 8.3)	3.24, 3.20 (d, 9.5)	–	–	1.46, 1.41 (dd, 7.4, 7.0)[d]	0.81 (t, 7.4)[e]	1.60–1.54 (m)
^{13}C NMR		70.5	64.0	64.9	94.2	28.2	8.5	34.7, 34.4
***u-t*-5c** ($CDCl_3$)								
^{1}H NMR	65	3.66, 3.61 (d, 8.8)	3.38, 3.37 (d, 10.5)	–	–	1.54, 1.47 (dd, 7.5, 7.5)	0.89 (t, 7.5)	2.00–1.40 (m)
^{13}C NMR		70.7	64.4	65.6	94.3	29.16	8.5	34.7, 34.6
***l-t*-5c** ($CDCl_3$)								
^{1}H NMR	35	3.64, 3.63 (d, 8.8)	3.39, 3.34 (d, 10.5)	–	–	1.55, 1.48 (dd, 7.5, 7.5)	0.90 (t, 7.5)	2.00–1.40 (m)
^{13}C NMR		70.7	64.5	65.9	94.7	29.21	8.8	35.24, 35.20

[a] Doublet.
[b] Singlet.
[c] Multiplet.
[d] Doublet of doublets.
[e] Triplet (overlapped doublet of doublets).

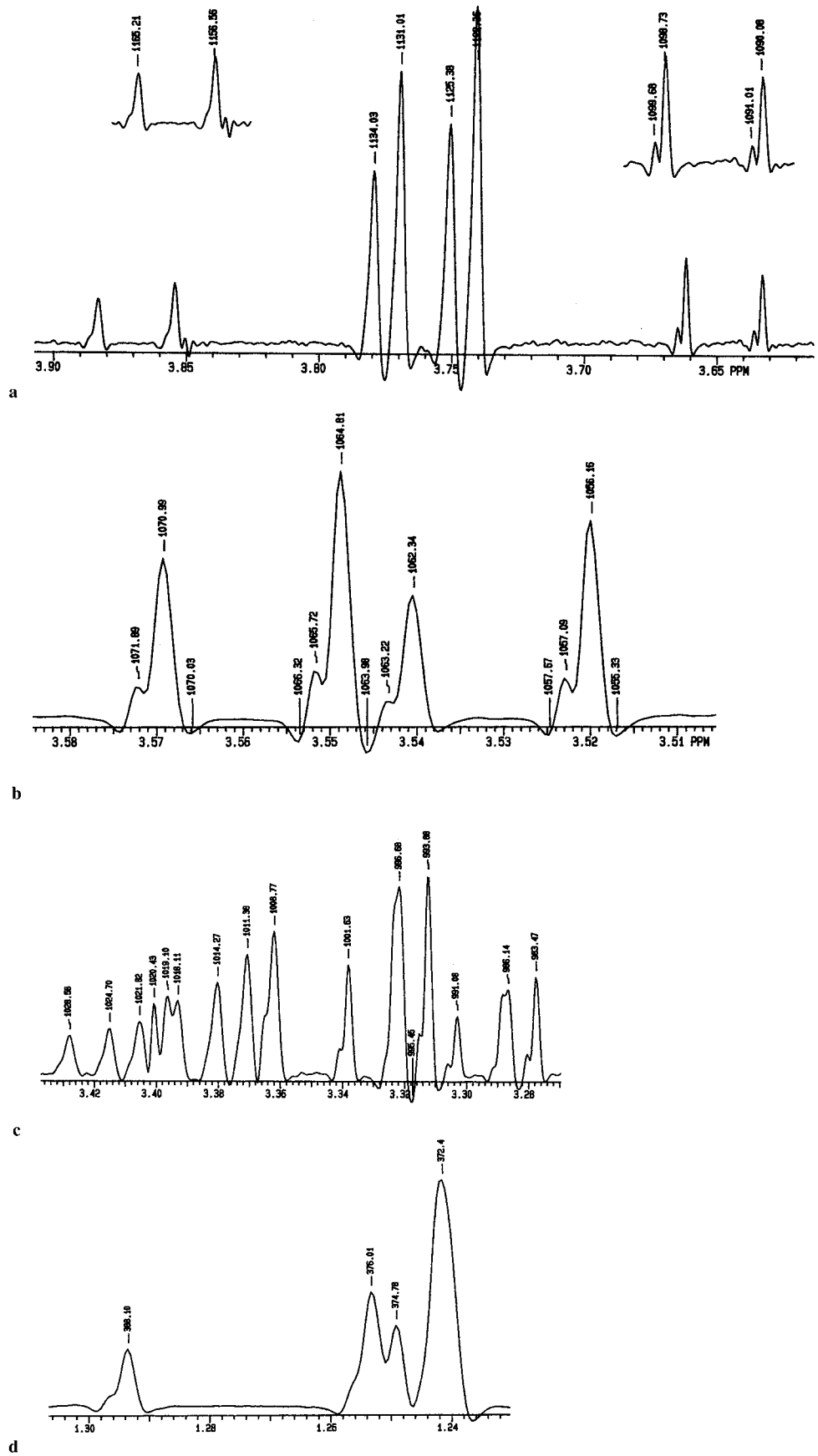
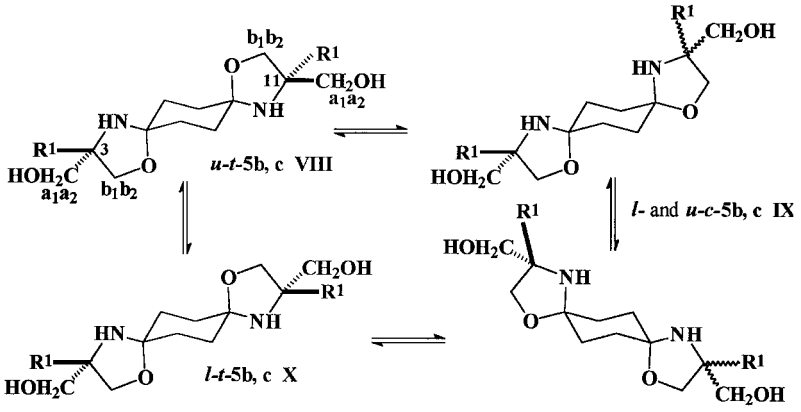


Figure 5. ^{1}H NMR of the dispirane **5b** (solvent $CDCl_3$, from downfield to upfield): (a) H_{b1}(**IX**), H_{b1}(**X**), H_{b1}(**VIII**), H_{b2}(**IX**); (b): H_{b1}(**IX**), H_{b2}(**X**), H_{b2}(**IX**), H_{b2}(**VIII**); (c) $H_{a1,a2}$(**VIII**–**X**); and (d) $-CH_3$(**IX**), $-CH_3$(**X**), $-CH_3$(**IX**), $-CH_3$(**VIII**).



Scheme 11.

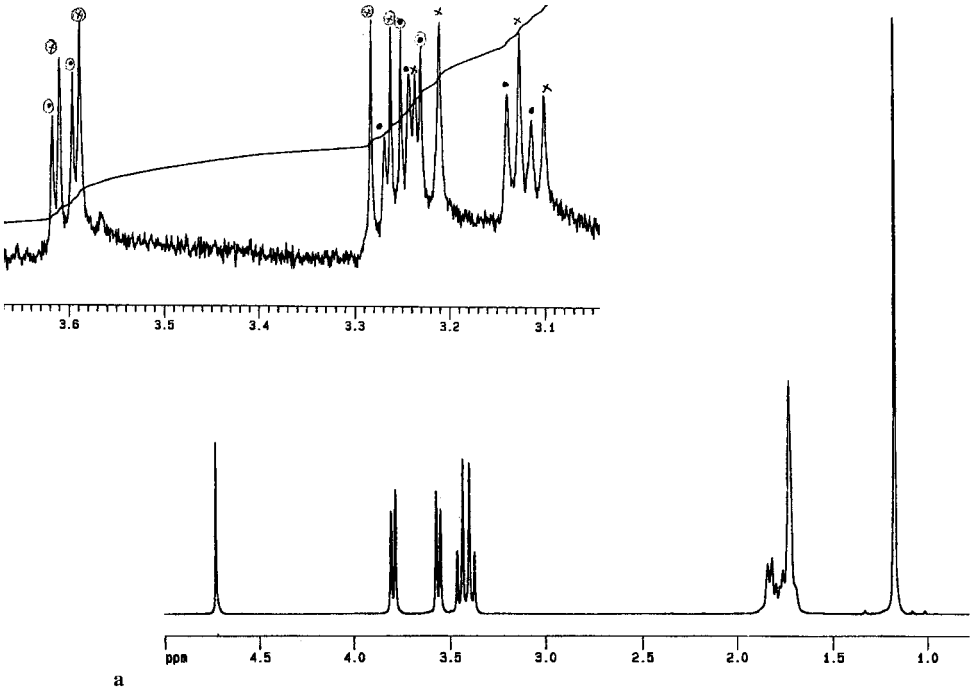


Figure 6. ^{1}H NMR spectrum of dispirane **5b** (solvent D_2O, from downfield to upfield): –O*H* and –N*H*–, $H_{b1,b2}$, $H_{a1,a2}$, cyclohexyl, –CH_3); detail ^{1}H NMR spectrum in C_6D_6: H_{b1}(**X**), H_{b1}(**VIII**), H_{b2}(**VIII**), H_{a1}(**X**), H_{b2}(**X**), H_{a1}(**X**), H_{a2}(**X**), H_{a2}(**VIII**).

different ratio than in $CDCl_3$. Moreover, the tautomers ***l-c-*** and ***u-c-*****5b**,**c** are not detectable in C_6D_6.

Conclusion

Mono- and dispirooxazolidines derived from TRIS or some of its analogues are available in satisfactory yields and distereoselectivity; their stereochemical behaviour is versatile but suitable to NMR monitoring and dependent on the solvent used. Chirality is better explained by a stereogenic axis than a stereogenic center. Isomerisations may occur and they are promoted by the intramolecular mobility (hydrogen bonds included) of amine and hydroxyl protons. We have defined this phenomenon as ring–ring tautomerism.

Experimental

Melting points (Boetius) are not corrected. All reagents were purchased from Aldrich®. ^{1}H NMR and ^{13}C NMR were performed on VARIAN-Gemini 300 and Brucker AM 400 spectrometers for all compounds. For dispiranes **5b**,**c**, spectra were also recorded on a Brucker AM 600 instrument. QC NMR spectra were performed on VARIAN-Gemini 300 operating at 75 MHz for ^{13}C, by using 80–100 mg/sample in standard tubes and a delay time $D1=10$. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. Samples were prepared by using commercially available DMSO-d_6 and measured after complete dissolution in standard tubes (about 30 mg for ^{1}H and 60–70 mg for ^{13}C NMR spectra). For spectra recorded in $CDCl_3$ 5–10 mg/sample in standard tubes were used. Hyperfine structure of ^{1}H NMR was obtained

on diluted samples only by using RESOLV macro on VARIAN-Gemini 300, after 128 transients (special attention was paid to neglect negative peaks). All reactions were monitored by TLC on MERCK silica gel, by using benzene: methanol 3:1 v/v as eluent (visualisation in I_2 bath). The RHF/3-21G* molecular orbital calculations were performed by using Spartan 5.0 package of programs; Spartan version 5.0, Wavefunction Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA.

Preparation of mono- and dispiranes (typical procedure)

TRIS as 0.30–0.50 M suspension in toluene (50 mL) [for aminodiols **2**, **3** in benzene (50 mL)] and cyclic ketone (molar ratio ketone/TRIS=1.5–3.5: 1; for synthesis of dispiranes stoichiometric ratio) were stirred under reflux in a Dean–Stark trap until TLC monitoring showed no more evolution of the reaction (18–21 h). In the case of monospiranes **4** the crude reaction mixture was neutralised with solid Na_2CO_3 and filtered hot. The organic solution was evaporated in vacuo and the residue was crystallised from an appropriate solvent. Dispiranes **5** were preliminary isolated as crude products by filtering the reaction mixture at room temperature then recrystallised from an appropriate solvent. Monospiranes **4d–g** and all dispiranes **5** have not been previously reported. Compounds **4a–c** were prepared according to literature.[8]

Yields (%), mp (°C, solvent), elemental analysis and NMR data (if not collected in Table 3, 4 and 6) are listed below.

4-Aza-3,3-bishydroxymethyl-*t*-7-methyl-*r*-1-oxaspiro[4.5]-decane and 4-aza-3,3-bishydroxymethyl-*c*-7-methyl-*r*-1-oxaspiro[4.5]decane, 4d. 50; 83–86 (*n*-heptane); white crystalline powder. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.50%, H, 10.05%, N, 6.60%; found: C, 61.37%, H, 9.83%, N, 6.50%.

4-Aza-3,3-bishydroxymethyl-*c*-6-methyl-*r*-1-oxaspiro[4.5]-decane and 4-aza-3,3-bishydroxymethyl-*t*-6-methyl-*r*-1-oxaspiro[4.5]decane, 4e. 20; 93–96 (Et_2O+*n*-heptane); white crystalline powder. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.15%, H, 9.59%, N, 6.45%; found: C, 61.37%, H, 9.83%, N, 6.50%. δ_H (400 MHz; DMSO-d_6). Assignment of equatorial position of C-6 methyl group: NOE on doublet at 0.85 ppm (Me group, d, J=5.7 Hz) showed the enhancement of multiplet located in 1.56–1.49 ppm region, assigned to H_{6a}, $H_{7a,7e}$; COSY experiment showed that H_{10e} 1.75 ppm (ddd, J=4.5, 4.6 and 13.0 Hz) is coupled with H_{10a}, $H_{9a,e}$ which were located in a different region than above, 1.45–1.36 ppm.

4-Aza-3,3-bishydroxymethyl-1-oxaspiro[4.6]undecane, 4f. 90; 91–92 (Et_2O); white crystalline powder. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.50%, H, 9.88%, N, 6.77%; found: C, 61.36%, H, 9.83%, N, 6.50%.

4-Aza-3,3-bishydroxymethyl-*c*-8-tertbutyl-*r*-1-oxaspiro-[4.5]decane and 4-aza-3,3-bishydroxymethyl-*t*-8-*tert*-butyl-*r*-1-oxaspiro[4.5]decane, 4g. 80; 178–180 (Et_2O); white crystalline powder. Anal. Calcd. for $C_{14}H_{27}NO_3$: C, 65.60%, H, 10.40%, N, 5.50%; found: C, 65.33%, H, 10.57%, N, 5.44%.

***trans*-4,12-Diaza-3,11-di(bishydroxymethyl)-1,9-dioxa-dispiro[4.2.4.2]tetradecane, 5a.** 81; 216–217 (DMF); white crystalline powder. Anal. Calcd for: $C_{14}H_{26}N_2O_6$; found: C 53.00%, H 8.15%, N 8.75%; found: C 52.81%, H 8.23%, N 8.80%. δ_C (100 MHz; DMSO-d_6) 94.2 (2C, C-5, -8), 67.9 (2C, C-3, -11), 66.1 (2C, C-2, -10), 34.5 (4C, C-6, -7, -13, -14), 63.4 (4C, 4×-*C*H_2OH).

(3*R,11*S**)-*trans*-4,12-Diaza-3,11-bishydroxymethyl-3,11-dimethyl-1,9-dioxadispiro[4.2.4.2]tetradecane, *u*-*t*-5b; (3*R**, 11*R**)-*trans*-4,12-diaza-3,11-bishydroxymethyl-3,11-dimethyl-1,9-dioxadispiro[4.2.4.2]tetradecane, *l*-*t*-5b; (3*R**,11*S**)-*cis*-4,12-diaza-3,11-bishydroxymethyl-3,11-dimethyl-1,9-dioxadispiro[4.2.4.2]tetradecane, *u*-*c*-5b; (3*R**,11*R**)-*cis*-4,12-diaza-3,11-bishydroxymethyl-3,11-dimethyl-1,9-dioxadispiro[4.2.4.2]tetradecane, *l*-*c*-5b.** 75; 144–145 (Acetone); white crystalline powder. Anal. Calcd for $C_{14}H_{26}N_2O_4$: C, 58.50%, H, 9.25%, N, 10.00%; found: C, 58.72%, H, 9.15%, N, 9.78%.

(3*R,11*S**)-*trans*-4,12-diaza-3,11-diethyl-3,11-bishydroxy-methyl-1,9-dioxadispiro[4.2.4.2]tetradecane *u*-*t*-5c; (3*R**, 11*R**)-*trans*-4,12-diaza-3,11-diethyl-3,11-bishydroxymethyl-1,9-dioxadispiro[4.2.4.2]tetradecane, *l*-*t*-5c.** 75; 134–135 (Acetone); grey crystalline powder. Anal. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.00%, H, 9.71%, N, 9.10%; found: C, 61.12%, H, 9.61%, N, 8.91%.

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