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1-AZA-5-HYDROXYMETHYL-3,7-DIOXABICYCLO[3.3.0]OCTANES: CHELATING PROPERTIES RELATED TO THEIR CONFORMATIONAL CHIRALITY

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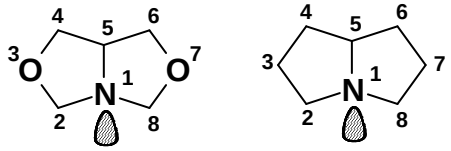
ABSTRACT. A structural approach is considered for some representative title compounds in order to explain their behaviour in gas phase (*ab initio* theoretical calculation) and in solution (dynamic NMR and IR methods). The results in terms of conformational analysis and chelate hydrogen bonds are discussed.

1. INTRODUCTION

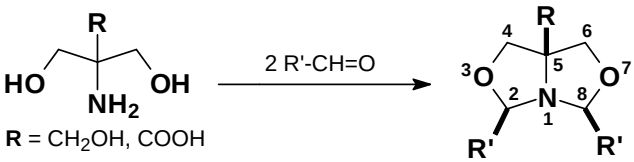
The 1-aza-3,7-dioxabicyclo[3.3.0]octane heterocyclic saturated system **A** (**Scheme 1**), as a synthetic easily available analogue of the core alkaloid pyrrolizidine, 1-azabicyclo[3.3.0]octane **B** is very well known along more than a half century[1] by the large use of its (poly)substituted derivatives.



A **B**

Scheme 1

Of particular interest, the C-5 (and optionally C-2, -8) substituted structures of type **A** are mentioned to be fertilisers, plasticisers, biocides, pesticides etc. mainly due to the simplicity of their synthesis: direct cyclocondensation between 2-substituted-2-amino-1,3-propanediols and a large variety of carbonyl compounds (**Scheme 2**).[2-9]



R = CH_2OH, COOH

1a: **R** = CH_2OH, **R'** = H
1b: **R** = COOH, **R'** = H
1c: **R** = CH_2OH, **R'** = Ph
1d: **R** = CH_2OH, **R'** = $CH_2C(Ph)_3$

Scheme 2

Nevertheless, the stereochemistry of this class of compounds remained obscure for more than 20 years after the synthesis of the parent compound of the series (Senkus, 1945)[1], *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane[!] **1a** (**Scheme 2**); thus, the structural knowledge in the field followed step by step the evolution of the NMR spectroscopy.[10-13]

Indeed, the basic stereochemical approach focused in considering, first, the magnitude of the geminal coupling patterns J_{gem} in the motif X-CH_2-Y- (X, Y = -N<, -NH-, -O-, -S-) including the 1,3-oxazolidine >N-CH_2-O- fragment in the title compounds (seen as *cis*-fused double 1,3-oxazolidine system, Crabb *et al.*[10-12]).

The first attempt to provide evidence for the general mobility of the 5-substituted-1-aza-3,7-dioxabicyclo[3.3.0]octane skeleton (suggested by inspection of Dreiding models and ^{1}H NMR spectra at variable temperature) was reported by Crabb in 1973.[11]

Later developments in the field by our group revealed more essential features:[14-16]

i) the absence of pyramidal inversion of the bridged nitrogen in both 4- or 5-substituted-1-aza-3,7-dioxabicyclo[3.3.0]octanes.

ii) the flipping of the basic molecular skeleton for some 5-hydroxymethyl derivatives in non polar solvents.

iii) the conformational and configurational chirality of these systems.

The structure in solid state of the 1-aza-3,7-dioxabicyclo[3.3.0]octane skeleton was scarcely analysed. To our knowledge, only two X-rays determined structures are known so far: by O'Connor[17] in 1973 {*r*-1-aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-carboxylic acid **1b** copper salt, **Scheme 2**} and more recently (2000) by Pavia[18] {*r*-1-aza-*c*-5-hydroxymethyl-*c*-2-*c*-8-diphenyl-3,7-dioxabicyclo[3.3.0]octane **1c** (**Scheme 2**)}.

In the present work, we attempt to a more comprehensive approach starting from one of the basic term of the series, *r*-1-aza-*c*-5-hydroxymethyl-(dynamic NMR and IR) and two related analogues.

2. RESULTS AND DISCUSSION

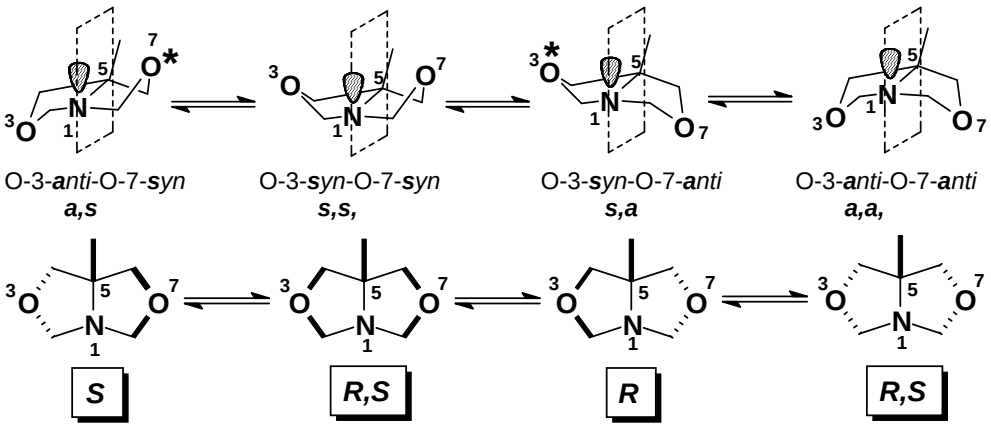
2.1. Conformational chirality

The *r*-1-aza-3,7-dioxabicyclo[3.3.0]-*c*-5-octane heterocyclic saturated system is intrinsic heterofacial. The crucial importance of this detail originates from our previous considerations about the conformational chirality exhibited by the skeleton itself (**Scheme 3**).[15]

Thus, one has to observe the four distinct conformers discriminated by the disposal of the oxygen atoms O-3, -7 with respect to the plane delimited by the lone-pair of the bridged nitrogen atom, N-1, C-5 and the ligand attached at C-5 (optionally H, not depicted). This plane is either an element of chirality or symmetry, depending on the sense of the puckering in the two oxazolidine rings, seen as *O*-envelope conformers:in enantiomeric conformers O-3-*anti*-O-7-*syn* and O-3-*syn*-O-7-*anti* (the *cis* ligands: the lone pair at N-1 and/or the ligand at C-5 are chosen as reference for the descriptors *syn* and *anti*), the sequence rule as N-1>C-5>H (or the ligand at C-5) indicates different configurations. If the *syn* successively labelled oxygen (*) is arbitrarily

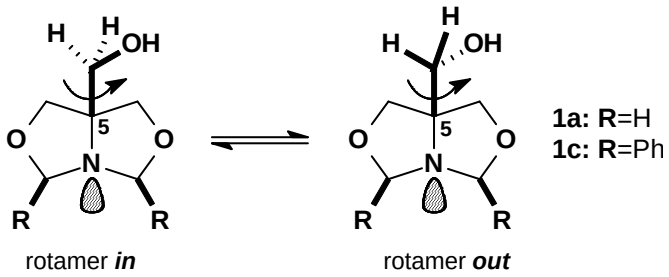
[!] The basic stereochemistry of the skeleton as *cis*-fused system is already very well documented;10-15, 17,18 according to I.U.P.A.C. nomenclature, the lone pair at N-1 is designed "*r*" as fiducial substituent.

given higher precedence than the *anti* one (that is, O-*syn* is always placed closer to the *cis* substituents), configuration *R* or *S* are easily to recognise. If so, the conformers O-3-*syn*-O-7-*syn* and O-3-*anti*-O-7-*anti*, are *mutatis-mutandis* diastereomeric *meso*-forms. If the substituent linked at C-5 is hydroxymethyl, besides the conformers described above, one has to also consider the corresponding possible rotamers generated by the (free?) rotation around the bond C-5-CH_2OH (**Scheme 4**).



Scheme 3

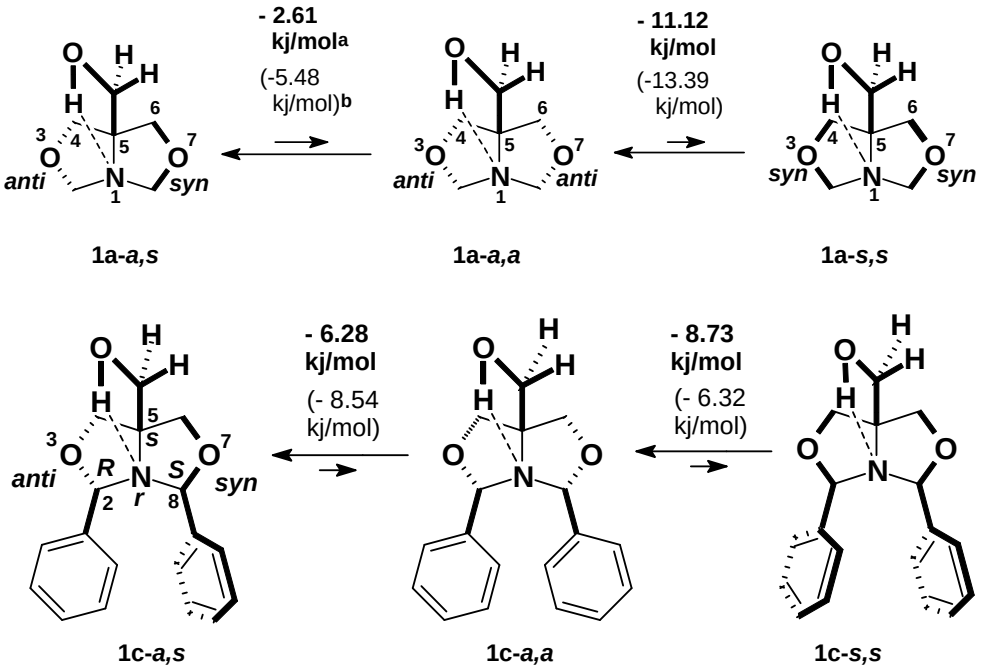
Depending on the orientation of the C-5-hydroxymethyl group, for the present discussion, only two rotamers were seen relevant to discriminate: rotamer ***in*** (in which intramolecular interactions are expected) and rotamer ***out*** (in which intermolecular interactions are expected).



Scheme 4

2.2. Evidence provided by *ab initio* RHF/6-31 G* molecular orbital calculation

The above anticipations were preliminarily checked by theoretical calculation (level RHF/6-31G* with optimisation of total energy). Thus, as shown in **Scheme 5**, the parent compound **1a** was involved in a double conformational equilibrium between three skeleton conformers as rotamers ***in***. The oxazolidine ring inversion took place about the C-O-C bonds since only O-3(7) envelope conformers were revealed. The same was valid if two phenyl groups were linked at positions C-2, -8 in an *all cis* spatial disposal with respect to ligands attached at N-1, C-2, -5, -8 (compound **1c**).



[a] total difference between the total energies (ΔΔE values) taking into account the orientation of the hydroxymethil group

[b] total difference between the total energies (ΔΔE values) by neglecting the orientation of the hydroxymethyl group

Scheme 5

The most stable conformer was the rotamer **1a-*a,s*** in which the oxygen in C-5-hydroxymethyl group was oriented as attempting to develop an intramolecular hydrogen bond with the *pseudo*-axial lone pair at N-1. Supplementary inspection of Dreiding model of **1a-*a,s*** indicated this interaction to be plausible: the calculated distances between the hydroxyl proton and the lone pair at N-1 *N*…*H*-O were found to range between 2.400-2.600 Å.

The incidence of an intramolecular hydrogen bond seemed to reduce the differences between the total energy of the most stable skeleton conformers (**1a, 1c[*]-*s,s* > 1a, 1c-*a,a* > 1a, 1c-*a,s***). Indeed, in **Scheme 5**, in round brackets, there are mentioned the same differences between the corresponding total energies (ΔΔE values) by neglecting the orientation of the C-5-hydroxymethyl group (previously described by us).[15] From the three possible skeleton diastereomeric conformers discriminated as ***a,a – a,s – s,s*** the later was disfavoured (and presumably even ruled out).

[*] it must however be observed the *configurational chirality* exhibited by **1c** at C-2, -8, possessing opposite configuration. Thus, **1c** is a *meso* form, N-1 and C-5 being *pseudo* chiral centers.

To conclude, the flexibility of the compounds **1a** and **1c** consisted globally in an enantiomeric inversion **1a, 1c-*a,s*** → **1a, 1c-*a,a*** → **1a, 1c-*s,a*** (one oxazolidine ring inversion, **Scheme 3**, **5**). The differences between the total energies of the chiral and the *meso* form conformation were too small (about 0.6 kcal/mol for **1a**) in order to anticipate the frozen arrangement ***a,s*** or ***a,a***.

In the end, we note that the X-rays previously determined structure for the compound **1b** by O'Connor (**Scheme 2**) was in agreement with our calculation, as **1b-*a,a*** frozen conformer.[17] Moreover, the calculated conformer **1c-*a,s*** was perfectly consistent with the X-rays determined structure by Pavia.[18]

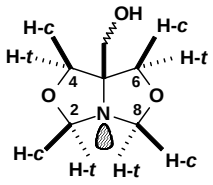
2.3. Conformational analysis based on dynamic NMR spectroscopy

In our recent paper,[15] we reported a satisfactory agreement between theoretical calculations and dynamic ^{1}H NMR data concerning the behaviour at low temperature (in non polar solvent, toluene-d_8) of the compounds **1a** and **1c**: the anticipated mobility of the bicyclic skeleton was evidenced by the general coalescence found for all the peaks assigned to the heterocyclic part of the molecule at about –40 ^{o}C for **1a** and –60 ^{o}C for **1c**. Unfortunately, they crystallised from the solvent below coalescence, preventing us to continue this investigation.

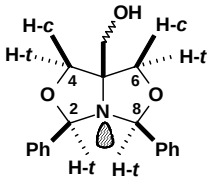
For the present discussion we assumed that the coalescence earlier found for the compounds **1a** and **1c** in toluene-d_8 depicted, in fact, the slow skeletal motion of their rotamers ***in***, or at least shifted conformational equilibria in which they were the dominant species (**Scheme 3-5**). Therefore, we extended our NMR analysis by using solvents possessing different chelating ability. The results are summarised in **Table 1**.

Table 1

^{1}H NMR data (δ, ppm) for the compounds **1a, c**



1a

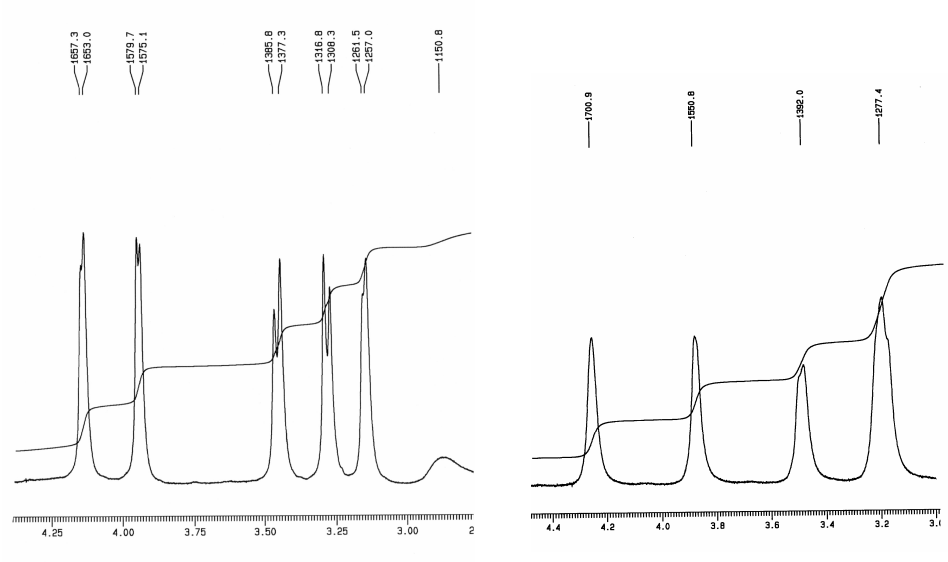


1c

Nr.	Solvent	T_i (K) ↓ T_f(K)	H-2(8)-*c*[a]	H-2(8)-*t*[a]	H-4(6)-*c*	H-4(6)-*t*
1a	Toluene-d_8	298	3.94	4.14	3.28	3.45
		233	3.93	4.35	3.21	3.53
	$CDCl_3$	298	4.40	4.45	3.73	3.77
	DMSO-d_6	298	4.26	4.39	3.66	3.71
	MeOD-d_4	328	4.408	4.431	3.764	3.805
		180	4.397	4.431	3.788	3.788
1c	Toluene-d_8	298	-	5.32	3.77	3.52
		213	-	5.24	3.93	3.58
	DMSO-d_6	298	-	5.58	3.93	3.82
	MeOD-d_4	328	-	5.565	4.071	3.895
		180	-	5.510	3.954	3.877

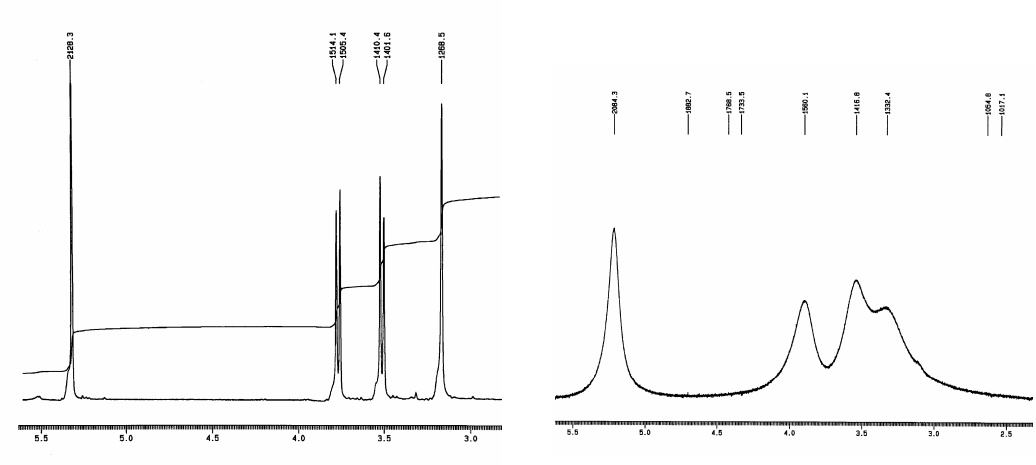
[a] the location of heterocyclic protons as ***c*** (*cis*) or ***t*** (*trans*) with respect to the lone pair of N-1 and the C-5-hydroxymethyl group us by means of NOE-diff Experiments[15] was previously reported by us.

The ^{1}H NMR spectra at variable temperature are presented in **Figures 1-3**. For comparison, the spectra previously recorded in toluene-d_8 are also shown.[15] They support the below discussion.



a **b**

Figure 1. *^{1}H NMR spectra of the compound **1a** in toluene-d_8 (400 MHz); **a)** 273 K (from downfield to upfield, see assignments in **Table 1**): H-2(8)-t, H-2(8)-c, H-4(6)-t, H-4(6)-c, 5-CH_2O, OH; detail **b)** coalescence at 233 K*



a **b**

Figure 2. *^{1}H NMR spectra of the compound **1c** in toluene-d_8 (400 MHz); detail **a)** 273 K (from downfield to upfield, see assignments in **Table 1**): H-2(8)-t, H-4(6)-c, H-4(6)-t, 5-CH_2O; detail **b)** coalescence at 213 K.*

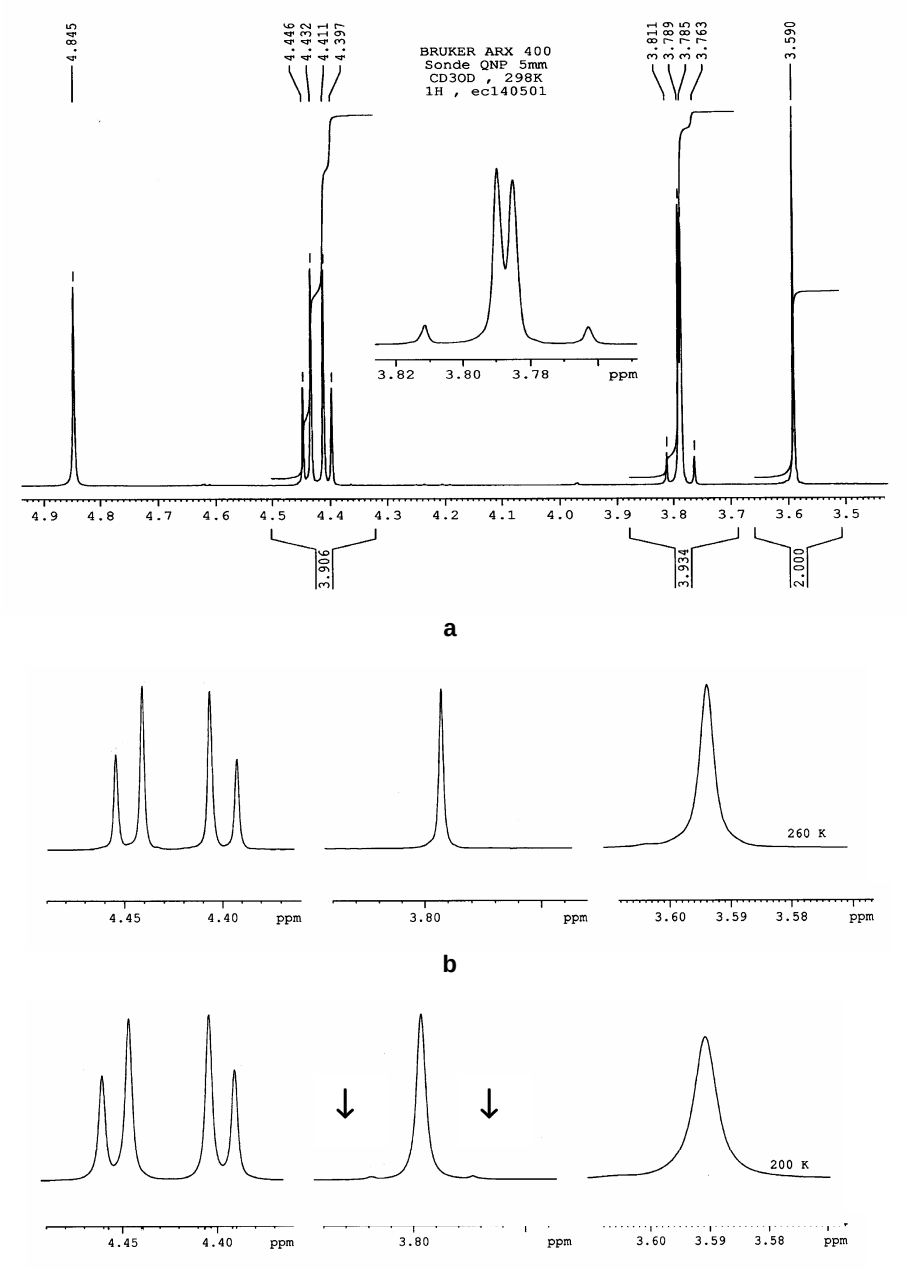


Figure 3. *^{1}H NMR spectra of the compound **1a** in MeOD-d_4 (400 MHz); detail **a)** 328 K (from downfield to upfield, see **Table 1**): H-2(8)-t, H-2(8)-c, H-4(6)-t, H-4(6)-c, 5-CH_2O; detail **b)** coalescence at 260 K; detail **c)** new splitting at 200 K .*

A priori, single DMSO-d_6 allowed us to assign **1a** and **1c** as rather flipping rotamers ***out*** because the hydroxyl proton was clearly displayed as a partially overlapped doublet of doublets (a triplet) with a typical ^3J value as 5.0-5.5 Hz in a domain not larger than 0.25 ppm (4.89 – 5.16 ppm).

Obviously, DMSO-d_6 had to be ruled out for experiments at low temperatures. Hence, compound **1a** was tested by variable temperature NMR experiments in MeOD-d_4; it was expected that in this solvent, **1a** be also strongly chelated, involving this time, besides all heteroatoms, the rotamer ***out***. Indeed, careful inspection of spectra revealed the coalescence of the aliphatic methylenes C-4(6) (AB system $\Delta\delta$ / ^2J=1.16, doublet of doublets ^2J =9.0 Hz, **Figure 3a**) into a singlet at 260 K (A_2 system, **Figure 3b**) and kept as such up to 220 K. Indeed, in the end of our analysis, the metylenes C-4(6) exhibited a partially overlapped doublet of doublets (another AB system $\Delta\delta$ / ^2J=1.02, ^2J=9.0 Hz, **Figure 3c**). No modification was detected in the aminalic part (O-3-C-2-N-1-C-8-O-7) of the molecule.

Completely different than in toluene-d_8, the similarity between **1a** and **1c** disappeared if MeOD-d_4 was used (**Table 1**): no coalescence was observed for **1c**, but an important decrease of geminal anisochrony in the aliphatic zone C-4-C-5-C-6 (from about 0.18 ppm to 0.08 ppm) due, presumably, to a slight shielding of protons H-4(6)-*c* promoted, by the slower rotation of the two *cis*-phenyl ring. Although this evolution was similar to **1a**, it might be assigned that the diphenyl derivative **1c** was a much more flipping structure in MeOD-d_4 than in toluene-d_8 and more flipping than **1a** in both solvents.[19]

In turn, the 5-hydroxymethyl derivative **1a** revealed higher flexibility in non-polar solvents (T_c=233 K as rotamers ***in***) than in chelating ones (MeOD-d_4, T_c=260 K as rotamers ***out***). On the other hand, the coalescence found for **1a** in MeOD-d_4 in the aliphatic zone (**Figure 3a-c**) was normal since in any alternative conformation the protons H-4(6)-*c* and H-4(6)-*t* were diastereotopic (**Scheme 3, 5**). So, the last splitting of the unique signal at coalescence could be assigned: avoiding extrapolation of our results, we believe that the conformational evolution of **1a** was towards a symmetrical frozen structure of type **1a-*a,a*** (*meso* form, **Scheme 5**).

2.4. Evidence provided by the IR spectroscopy

The behaviour of the 5-hydroxymethyl group was also examined by IR spectroscopy. Thus, the selected 5-hydroxymethyl derivatives **1a**, **1c** and **1d** were analysed in chloroform, which best allowed the variations of concentration. The choice for the above structures was evidently motivated by the absence at C-2(8) of any other chelating fragment, in order to avoid unpredictable intermolecular interactions, other than already investigated. The results are collected in **Table 2**.

As expected, the two typical bands in the region of interest (up to 3400 cm^{-1}) were displayed: a strong absorption (large band) assigned to $\nu_{assoc.}$ and a very weak band at higher frequency for $\nu_{non\text{-}assoc}$. Dilution step by step was carried out until (reasonably) equal absorbencies were displayed.

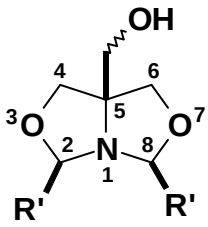
Our conclusions are resumed as follows:

The *cis*-diphenyl derivative **1c** was the less sensitive to the variations of concentration and the comparison with **1a** and **1d** regarding $\Delta\nu$=f(ΔC) values inferred us about its preferred association: it is very likely that the intermolecular hydrogen bonds were mainly realised between C-5-CH_2O-*H*…*N* groups belonging each to a different unit (as rotamers ***out***). That is, at higher concentration, **1c** was less associated than **1a** and **1d** since its bridged nitrogen was more “protected" by the

two-phenyl groups from both steric and electronic points of view. In the case of compound **1d**, the intercalation of a methylene group between C-2, -8 and the bulky triphenylmethane environments avoided this steric hindrance.

Table 2

Relevant absorbtions (as ν, cm^{-1}) in IR spectra of the compounds **1a**, **1c** and **1d**



1a: **R'** = H
1c: **R'** = Ph
1d: **R'** = CH_2CPh_3

No.	C ($mol\ l^{-1}$)	ν OH assoc. (cm^{-1})	ν OH non assoc. (cm^{-1})	Δν non assoc. *vs.* assoc. (cm^{-1})	$\Delta\nu_{assoc.} = f(\Delta C)$ (cm^{-1})
1a	0.5000	3457	3628	171	81
	0.1000	3462	3627	165	
	0.0500	3469	3628	159	
	0.0250	3483	3628	145	
	0.0125	3521	3628	107	
	0.0062	**3538**	**3628**	**90**	
1c	0.5020	3523	3627	104	24
	0.2510	3533	3627	94	
	0.1250	3540	3627	87	
	0.0625	3542	3627	85	
	0.0064	3547	3627	80	
	0.0012	**3547**	**3627**	**80**	
1d	0.2500	3465	3637	172	89
	0.1250	3485	3635	150	
	0.0625	3495	3635	140	
	0.0312	3516	3637	121	
	0.0031	**3553**	**3636**	**83**	

Following dilution, there was an obvious convergence towards the absorption around 3545 cm^{-1} which could be assigned as the intramolecular hydrogen bond developed, in all three cases, by the rotamers ***in*** (a five membered chelate). The small differences observed should be the consequence of the expected variable basicity of the bridged nitrogen in a particular environment. The influence of the substituents linked at C-2, -8 consisted, this time, in their specific electronic effect.

In the end, considering as characteristic for the present cases the magnitude of the medium final value $\Delta\nu_{non\text{-}assoc.\ vs.\ assoc.}$ (**Table 2**) about 85 cm^{-1}, it should be mentioned its similarity with 1,3-alkanediols of type $RR'C(CH_2OH)_2$ (78-89 cm^{-1});[20] it was greater than in cycloalkane-1,2- or 1,3-diols (33-61 cm^{-1}).[21,22]

3. CONCLUSION

The structural investigation for some 1-aza-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octanes consisted in three points of view whose coherence was ensured by considering: the conformational chirality of the basic skeleton and its flexibility

around the C-O-C bonds. The last one depends on the chelating aptitude of the solvent and orientation (rotamers ***in - out***) of a hydroxymethyl group linked at C-5. The energetic barrier of the ring inversion was influenced by the polarity of the solvent. Two fused 1,3-oxazolidine *O*-envelope conformers was a useful stereochemical approach for the azadioxabicyclooctane system since good to excellent agreements were found between theoretical calculation and experimental data.

4. EXPERIMENTAL

Current NMR spectra were recorded on Brucker® AM300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively.

Dynamic NMR spectra were performed on Brucker® ARX400 instrument operating at 400 and 100 MHz for ^{1}H and ^{13}C nuclei respectively with each step 10 K decreasing temperature. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All NMR spectra were measured in anhydrous commercially available deuterated solvents. All chemical shifts (δ values) were given throughout in ppm; all coupling patterns (*J* values) were given throughout in Hz. Locking, shimming and acquisition were made without spinning.

IR spectra were performed on a Perkin-Elmer® 16 PC FT-IR spectrometer. Only relevant absorptions were listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong].

Molecular orbital calculation: the conformational space of the systems have been investigated by using the "Conformer Distribution" facility (MMFF force field) from Spartan'o2® [Spartan'o2, Wavefunction, Inc. Irvine, CA]. The set of conformers thus generated has been subjected, within the same package, to full geometry optimization at the RHF/6-31G* *ab initio* level. The default convergence criteria (Energy = 0.000001 hartrees, rms gradient = 0.000450 hartrees/bohr) have been imposed throughout all the *ab initio* computations.

The synthesis of the compounds **1a**, **1c** and **1d** was previously reported by us[15] according to Senkus[1,8] and Crabb.[11]

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