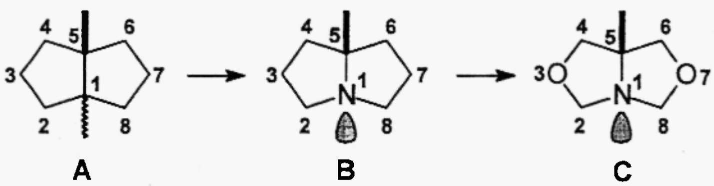
FIRST EXAMPLES OF THE CONFORMATION CHIRALITY OF HETEROBICYCLO[3.3.0]OCTANES : 3,7-DIOXA-*r*-1-AZABICYCLO[3.3.0]OCT-*c*-5-YL-METHOXYPYRAZINES

Camelia Berghian,[a,b] Mircea Darabantu,[a,b] Pedro Lameiras,[b] Nelly Plé[b] and Alain Turck[b]
[a]"Babes-Bolyai" University, Department of Organic Chemistry, 11 Aranyi Jànos str., RO-400028 Cluj-Napoca, Romania
[b]Université de Rouen, Institut de Recherche en Chimie Organique Fine (I. R. C. O. F.), BP-08, F- 76131 Mont Saint-Aignan Cedex, France
*e-mail : darab@chemubbcluj.ro; darabantu@cluj.astral.ro; Fax : 00 40 264 59 08 18; Tel. 00 40 264 59 38 33

Abstract: The first two examples of the conformation chirality of *cis*-heterobicyclo[3.3.0]octanes as *c*-5-substituted-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octanes are discussed and supported by ^{1}H DNMR spectroscopy and X-Ray crystallographic data.

Introduction

The bicyclo[3.3.0]octane **A** (**Scheme 1**) has a well documented stereochemistry as *cis*- or *trans*-fused cyclopentane skeleton (1).



Scheme-1

By replacing one of the bridged carbons with a heteroatom, *e.g.* N, the core alkaloid pyrolizidine **B**, 1-azabicyclo[3.3.0]oc-tane is obtained whose earlier reported conformation analysis revealed only the flipping of the pyrolidine rings in a large domain of temperature (2). One of the dioxa analogues of **B**, 3,7-dioxa-1-azabicyclo[3.3.0]octane **C** is synthetically much easier available (3) and made the object of a lot of structural investigation (2) because of its extensive applications (4). Both **B** and **C** are *cis* stable fused systems: no pyramidal inversion involving the bridged nitrogen occurs (5,6).

Our previous findings in the domain of 3,7-dioxa-1-azabicyclo[3.3.0]octanes **C** synthesis and stereochemistry established as essential approach its oriented conformation mobility (5,7,8). They were based on the *ab initio* RHF/6-21G* and 6-31*G data (gas phase as well as solvation models) and were evidenced by DNMR and X-Ray crystallographic data (5,8). However, "clean" DNMR spectra of **C** (considered by us as fused double 1,3-oxazolidine system) are not known to agree with a frozen conformation in solution.

Thus, the aim of the present communication is to be the first to reveal the nature of frozen conformation of compounds of type **C** issued from DNMR in solution against the solid state (X-Ray Crystallographic data). No such approach was reported so far.

Results and Discussions

1. Conformation consideration

The 3,7-dioxa-1-azabicyclo[3.3.0]octane skeleton is heterofacial since all its (hetero)atoms are prostereogenic centres (**Scheme 2**) (9). Therefore, it is crucial to observe that, besides the molecule itself, only the achiral substitution of the hydrogen at C-5 keeps the validity of the below considerations†: a four component equilibrium whose terms are discriminated by the sense of puckering in the two oxazolidine rings as *syn*/*anti* O-3/O-7 envelope conformers, is generated. This oriented flexibility, apparently restrictive as rotation about the C-

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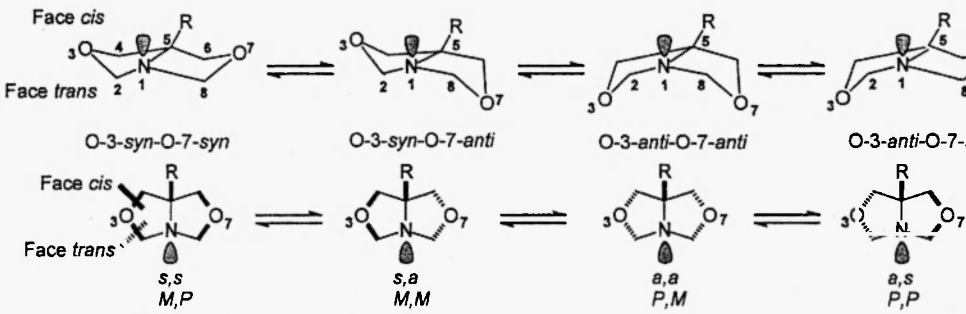
†(homomorphic)substitution(s) of all other hydrogen atom(s) at C-2 (and /or C-8) generates intrinsic configuration (poly)chirality; the same is valid for the substitution at C-4 (and / or C-6) as well as all combinations of these substitutions. We previously analysed this stereochemistry (5).

O-C bonds only, *in a single oxazolidine ring inversion*, is issued from our previous calculation and fully supported by X-Ray crystallographic data (5,6,8,10). The lone pair of the bridged nitrogen, as fiducial substituent (9), and the ligand at C-5, including H-5, are hereafter chosen to be the references for the descriptors *syn* and *anti* and for the diastereotopic faces of the molecule: *cis* and *trans* (**Scheme 2**). Furthermore, by applying the helicity rule to the two torsion angles of the bonds O-3-C-2-N-1-C-5 and O-7-C-8-N-1-C-5 (seen as two elements of chirality), the below steric relationships are easy to observe (11):



R = H, Me, Et, CH_2OR'; R' = H, Me, Et, Bzl, etc.

Scheme-2

- The O-3-*syn*-O-7-*anti* (*s,a* or *M,M*) and O-3-*anti*-O-7-*syn* (*a,s* or *P,P*) are enantiomeric conformers.
- The O-3-*syn*-O-7-*syn* (*s,s* or *M,P*) and O-3-*anti*-O-7-*anti* (*a,a* or *P,M*) are diastereomeric *meso* form conformers.

Our earlier calculation also predicted that the occurrence of the (*s,s*) *meso* form can be reasonably *a priori* ruled out, being *ca.* 11.0 $kJmol^{-1}$ less stable than the (*a,a*) *meso* form and *ca.* 13.5 $kJmol^{-1}$ less stable than the enantioforms (*a,s* = *s,a*). It follows that only the equilibriums (*s,a*) ← (*a,a*) → (*a,s*) are noteworthy but the magnitude of the corresponding ΔE (*ca.* -2.5 $kJmol^{-1}$, -0.6 $kcalmol^{-1}$, even smaller in polar solvents) precludes the discrimination of the frozen conformation to be (*a,s*) (5,8).

Extension of the above considerations consisted in tying together at C-5 position (*e.g.* **linkage***) two dioxaazabicyclooctane units. The stereoisomerism is now exacerbated given that ten conformations are possible (**Scheme 3**): three pairs of enantioforms (racemates **I-II**, **III-IV**, **V-VI**) and four *meso* forms (**VII**, **VIII**, **IX**, **X**). Extrapolation of the concepts from **Scheme 2** should consider again each of equilibriums as *just one oxazolidine ring inversion around C-O-C bonds*. Consequently, the pair of enantioforms **I-II** originates directly from no *meso* form but twice from two different pairs of enantioforms **III-IV** and **V-VI** respectively. Since the individual (*s,s*) stereochemistry is energetically disfavored, the equilibriums in **Scheme 3** could be simplified: only two pairs of enantioforms, **I-II** and **V-VI**, and two *meso* forms **IX-X** are hereafter under investigation.

A serious complication in this class arises from the observation that current NMR methods cannot discriminate the racemate **I-II** (C_2-symmetry) from its corresponding *meso* form **IX** (C_s-symmetry) as we recently pointed out (8).

2. Synthesis

We prepared the 3,7-dioxa-1-azabicyclo[3.3.0]octanes substituted at C-5 position **2a** and **2b** able to illustrate the above considerations. In this purpose, since we earlier concluded that the ligand at C-5 should be a polar group (**Scheme 2**) as well as the NMR solvent‡, a chloro π-deficient system such as chloropyrazines, appeared suitable to be the good **linkage** (**Scheme 4**). The structures **2a**, **2b** were obtained by enlarging our already published methodology (8) inspired from Broadbent's pioneering work (4b).

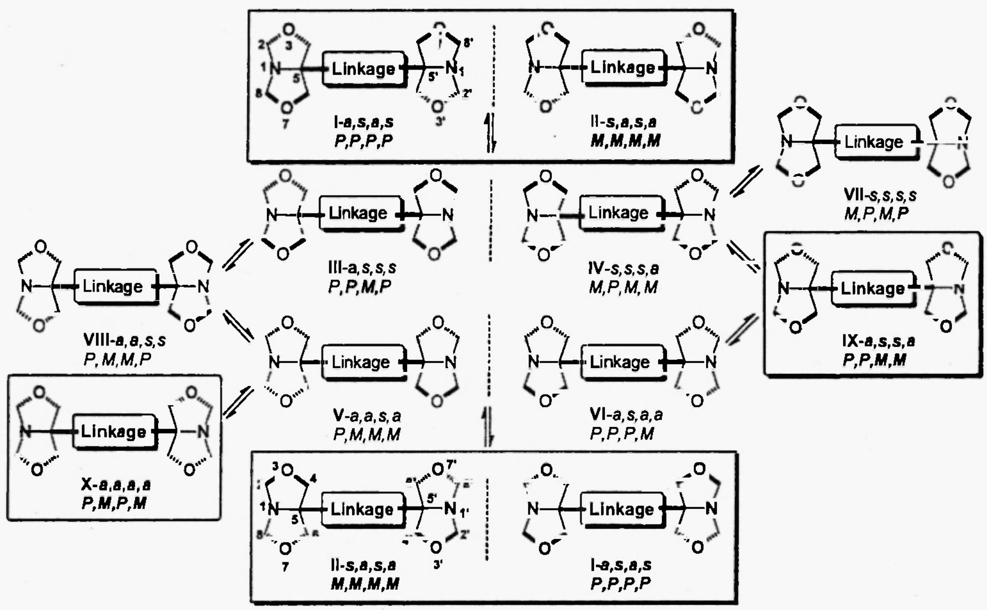
*Obviously, the **linkage** should be highly symmetric i.e. C_{nh}, C_{nv} group etc.

‡Indeed, if the C-5 substituent is hydroxymethyl, alkyl or alkoxy, only in the case of 5-hydroxymethyl derivatives a general coalescence is observed in the range 213-193 K (5) in [D_8]toluene; in [D_4]MeOD, only the compound **1** revealed a single "internal clock" (260 K) (9) suitable for the use of Eyring equation ($\Delta G^{\neq}$ = 53.25 $kJmol^{-1}$); it was assigned prudently as type (*a,a*) *meso* form (R' = H, **Scheme 2**) (8).

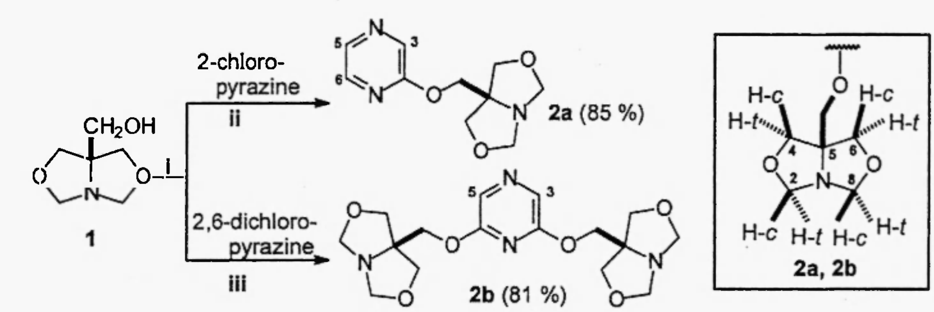
3. Structural investigations

The ^{1}H DNMR experiments of the compounds **2a**, **2b** were run in [D_8]-THF on 400 MHz time scale (ΔT=343-183 K).

We will start the discussion with the compound **2a** (**Figure 1**). At room temperature (and above) a single mediated (?) species we detected. In the alicyclic zone of the spectrum, the two expected methylenic AB systems were displayed: aminalic (N-1-CH_2-O-3/ N-1-CH_2-O-7, $\Delta\delta/^{2}J$=1.43) and aliphatic (C-5-CH_2-O-3/C-5-CH_2-O-7, $\Delta\delta/^{2}J$=1.32). NOESY-Experiments established the *cis* oriented protons, *vs.* the fiducial substituent, to be more deshielded than the *trans* oriented ones (**Scheme 4**). We assigned this spectral shape to describe, in fact, the below conformation interconversion:



Scheme 3



i: 1.05 eq. KH / THF / 40 °C / THF / 1.5 hrs.; ii: 1.05 eq. 2-chloropyrazine / THF / from 60 °C to r.t. / 24 hrs.; iii: 0.48 eq. 2,6-dichloropyrazine / THF / from 60 °C to r.t. / 24 hrs.

Scheme 4

$$\mathbf{2a}\ (a,s) \rightleftharpoons \mathbf{2a}\ (a.a) \rightleftharpoons \mathbf{2a}\ (s,a) \quad \text{(Eq. 1)}$$

In Eq. 1, one can recognize two diastereomeric equilibriums and, globally, an enantiomeric inversion (predicted in **Scheme 2**) in which the homofacial protons H-2 *vs.* H-8, and H-4 *vs.* H-6 (**Scheme 4**) were enantiotopic. Below the room temperature, the coalescence was simultaneously reached (273-263 K) in both the regions of the bicycle, aminalic and aliphatic. Hence, we found two "internal clocks" as two A_2 systems. At 253 K the separation of the signals was again almost complete as two new AB systems: aminalic ($\Delta\delta/^{2}J$=1.21) and aliphatic ($\Delta\delta/^2J$=1.00). We ascertained this spectral appearance to the frozen **2a** of type (*a,a*) (*meso* form, C_s symmetry, **Scheme 2**). At 253 K, two pairs of parameters $\Delta\delta(c\text{-}t)$ and ^2J were available to estimate the free enthalpy of activation $\Delta G^{\neq}$ for the diastereomeric inversions (Eq. 1) seen each as a first-order reaction: ***inversion of a single oxazolidine ring*** [Eyring equations 2, 3 (12)]:

$k_c = 2.22\ (\Delta v^2 + 6J^2)^{0.5}$ (sec^{-1}) (Eq. 2)

$\Delta G^{\neq} = 19.14\ T_c\ (10.32 + \log T_c/k_c)$ (Jmol^{-1}) (Eq. 3)

We first approximated T_c (coalescence temperature) as 268 K and, for the aminalic methylenes, with $\Delta v(c\text{-}t)$=6.8 Hz and ^2J=5.6 Hz , we found k_c=34.0 sec^{-1}. For the aliphatic methylenes, with $\Delta v(c\text{-}t)$=9.0 Hz and ^2J=9.0 Hz, we established k_c=52.9 sec^{-1}. To estimate the $\Delta G^{\neq}$, the real k_c should be twice the observed value since **2a** is a double oxazolidine system: 68.0 and 105.7 sec^{-1} respectively. These values provided much closed $\Delta G^{\neq}$ as 56.0 kJmol^{-1} and 55.0 kJmol^{-1} quite similar with that previously find for **1** [**Scheme 4**, 53.25kJmol^{-1}, (8)].

We note, however, the following remarks:

a) We had to use $\Delta\delta$ and J values not well below coalescence (253 *vs.* 268 K) because, just below 253 K (**Figure 1**), another slow process occurred (see discussion later on).

b) We had to consider each of the above equilibriums (Eq. 1) as equally populated; hence the k_c value was the same for the forward and reverse process. Supporting reason is that, as already mentioned, the calculated ΔE values (*a,s vs. a,a*) in this class (**Scheme 1**) are very small [*e.g.* -0.87 kJmol^{-1} for **1** in DMSO and around -2.5 kJmol^{-1} in gas phase (8)].

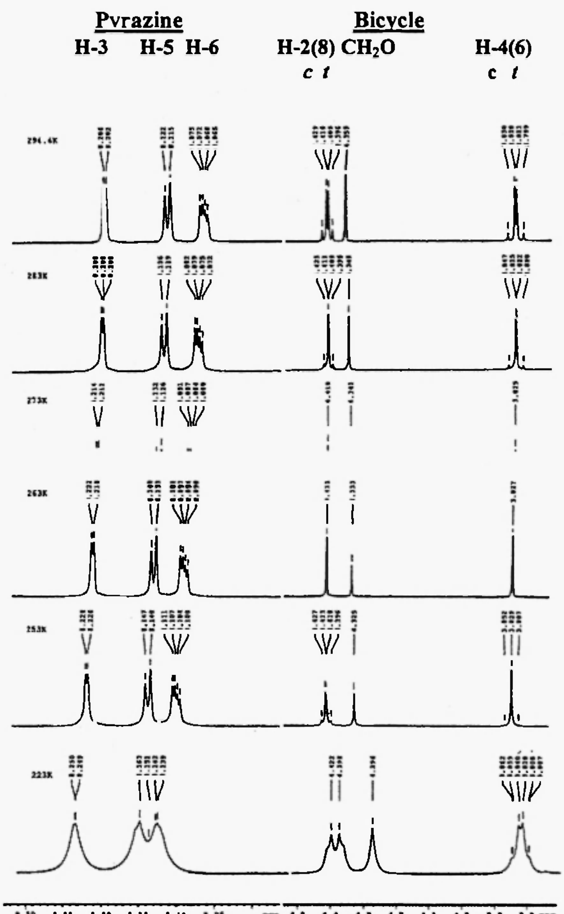
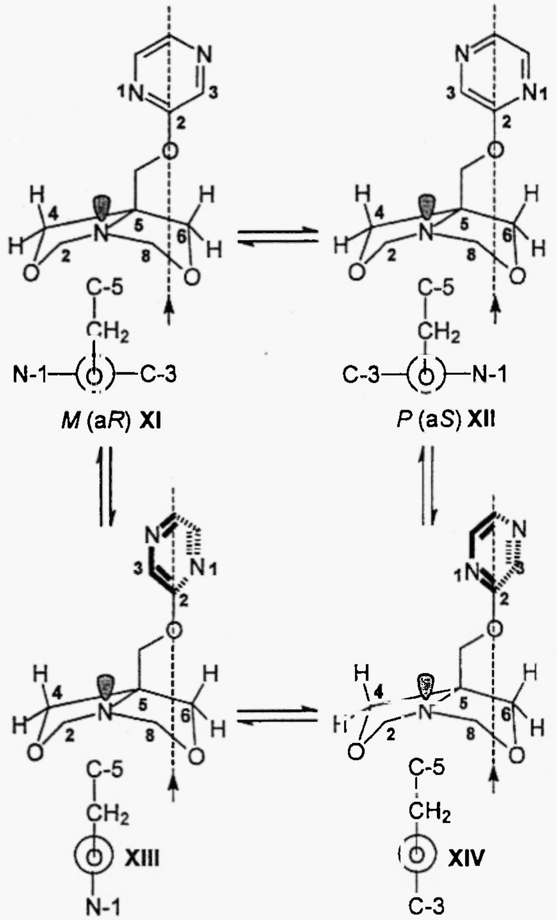


Figure 1: ^{1}H DNMR of the compound **2a** (400 MHz, [D_8]-THF)

Below 253 K, besides the subsequent broadening of all the signals in the spectrum of **2a** (**Figure 1**, 223 K), the unexpected multiplicity of the peaks of the methylenes C-4(6) was also exhibited. One might give explanation for this behavior by the slow rotation of the pyrazine ring about the C-2(pyrazine)-O bond (**Scheme 5**). Indeed, we previously demonstrated that the 5-substituted-dioxaazabicyclo[3.3.0]octanes exist as exclusive *out* rotamers with respect to the orientation of the C-5-substituent *vs.* bicycle (8). Thus, this new slow motion could now generate four rotamers: **XI-XII** with orthogonal orientation against bicycle and **XIII-XIV** with bisectional orientation (**Scheme 5**). The last ones are C_s symmetric but diastereomeric: two different environments are obtained providing the corresponding two sets of δ values. In **XI-XII** the bond C-2(pyrazine)-O is an axis of chirality: **XI-XII** are enantiomers. Hence, the anisochrony of the homofacial positions of the bicycle 2 *vs.* 8 and 4 *vs.* 6 is created. As shown in **Figure 1**, some diastereotopicity was observed only at the position 4 and 6 as six peaks (from theoretically eight) to suggest two partially overlapped AB systems. Anyhow, the diastereotopicity as $\Delta\delta$ values (ppm) H-4-*c vs.* H-6-*c* and H-4-*t vs.* H-6-*t*, assigned arbitrarily, was poor: 0.01 ppm.

If the above hypothesis is correct, the compound **2b** should not exhibit this behavior because of the two bulky bicyclic fragments linked in "meta" positions of the pyrazine ring. Undeniably, the ^{1}H DNMR spectra evidenced only the coalescence at about 263 K, two "internal clocks", issued from the slow motion of the bicyclic skeletons (**Figure 2**). Above 263 K, we assigned the structure of **2b** to mediate the selected conformation equilibriums depicted in **Scheme 3**: they involved only the conformations of type **I, II, V, VI, IX, X**. Below coalescence, as disclosed by the number of the coupling patterns, a structure C_{2v} symmetric, consistent with the type **X** (**Scheme 3**) was supported. The k_c and $\Delta G^{\neq}$ values were calculated by means of the same relationships (Eq. 2, 3) for each bicycle. A major simplification we had to apply: each bicycle of **2b** was considered independently involved in conformation equilibriums analogous to those described by the Eq. 1. Along with decreasing the temperature, a convergence of the k_c values in the two regions, aminalic (136.6 sec^{-1}) and aliphatic (155.6 sec^{-1}), was observed . Almost identical was the barrier of the oxazolidine ring inversion as $\Delta G^{\neq}$ values, in good agreement with those of **1** and **2a**: 53.4 and 53.1 $kJmol^{-1}$.

Attempting at growing appropriate crystals of **2a** failed. In turn, to our surprise, the stereochemistry in solid state of **2b**



Scheme 5

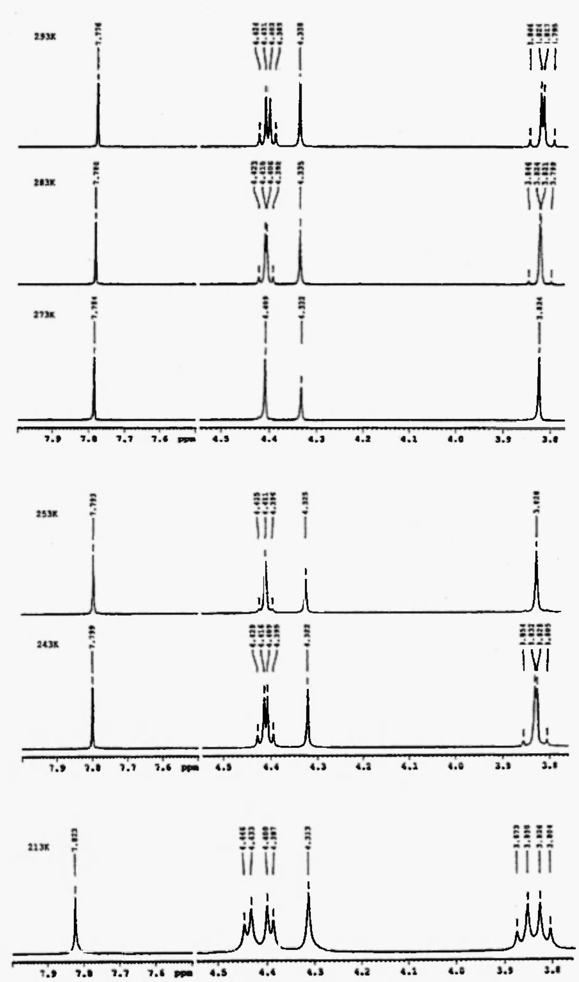


Figure 2: [1]H DNMR of the compound **2b** (400 MHz, [D_8]-THF)

revealed the chiral conformations of type **II** and **IX** (**Scheme 3**). Thus, the X-Ray crystallographic analysis (**Figure 3**) established this compound to be a non-stoichiometric solvate of dichloromethane (used to develop crystals): one molecule of solvent was captured in the channels of the network with an occupation factor of 0.96. This chelating aptitude appeared mandatory to the stereochemistry of the elementary cell as enantioform against *meso* form (type **II** *vs.* **IX**, **Scheme 3**). In fact, two crystalline diastereomeric forms were detected: in **Figure 3**, the enantioform of type **II** of **2b** is shown as major structure, 87 %; the *meso* form of type **IX** of **2b** had minor occurrence, 13 % (not depicted). We note that the changing of the stereochemistry from enantioform **II** of **2b** to *meso* form **IX** caused important distortions, mainly of the C-O bonds, in both dioxaazabicyclo[3.3.0]octane units. The molecule of

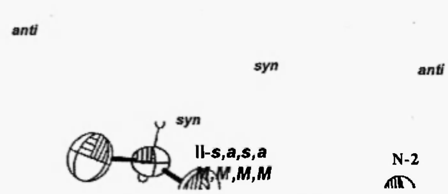


Figure 3: The X-Ray crystalographically determined structure of the compound **2b**

dichloromethane was also distorted. Consequently, the alternative architecture **IX** was less stable and with lower chelating aptitude. Indeed, the inclusion of dichloromethane was crucial: the network was stable only in the presence of the solvent.

Conclusions

In summary, the 5-substituted-3,7-dioxa-1-azabicyclo[3.3.0]octanes with a pyrazinyl fragment provide two useful examples of clean exploring the conformation analysis of the dioxaazabicyclooctane by means of DNMR. The essential features to consider are the conformation chirality of the bicycle skeleton seen as a *cis* fused double **1**,3-oxazolidine system and its flexibility around the C-O-C bonds only. The energetic barrier of the single ring inversion can be estimated by classic methods to range between 53-56 $kJmol^{-1}$ (12.7-13.4 $kcalmol^{-1}$).

Experimental

General

The melting point is uncorrected; it was carried out on ELECTROTHERMAL® instrument. Current NMR spectra were recorded on Brucker® AM 300 instrument operating at 300 and 75 MHz for ^1H and ^{13}C nuclei respectively. The ^1H DNMR spectra were run on Brucker® AM 400 instrument operating at 400 MHz for ^1H nuclei with each step 10 K decreasing the temperature. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); IR spectra were performed on a Perkin-Elmer® 16 PC FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Mass spectrum (MS) was recorded on an ATI-Unicam Automass® apparatus, fitted (or not) with a GC-mass coupling (high-resolution J&W column, 30 m, 0.25 mm ID, flow rate: 1.2 mL min^{-1}).

2-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxypyrazine (2a) (85 %) yellowish crystalline powder, m.p.=128-129 °C (pentane); [Found: C, 53.50; H, 6.09; N, 18.55. $C_{10}H_{13}N_3O_3$ requires: C, 53.81; H, 5.87; N, 18.82%]; R_f (75% ligroine/acetone) 0.40; ν_{max} (film NaCl) 2868 (m), 1524 (s), 1465 (m), 1413 (s), 1361 (m), 1289 (s), 1134 (m), 1032 (s), 1002 (s), 915 (s), 832 (m), 692 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$, 293 K) *heteroaromatic*: 8.19 (1 H, d, J=1.5 Hz, H-3), 8.09 (1H, d, J=3.0 Hz, H-5), 8.01 (1 H, dd, J=1.5, 1.5 Hz, H-6), *alicyclic*: 4.47 (2 H, d, J=5.7 Hz, H-2, -8-*c*), 4.41 (2 H, d, J=5.7 Hz, H-2, -8-*t*), 4.33 (2 H, s, 5-OCH_2), 3.83 (4 H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 160.1 (IC, C-2), 140.9 (1 C, C-6), 137.5 (1 C, C-3), 136.1 (1 C, C-5); *alicyclic*: 88.6 (2 C, C-2, -8), 74.4 (2 C, C-4, -6), 71.9 (1 C, C-5), 69.0 (1 C, 5-O-CH_2). MS (EI, 70eV); m/z (rel. int. %): 223 (6) [M^+], 178 (14), 163 (13), 114 (100), 98 (17), 86 (9), 68 (26), 58 (11), 42 (18), 41 (59).

The synthesis of the compound **2b** was described elsewhere (8); the X-Ray data (bond lengths, bond angles) including the NBO analysis of the compound **2b** we previously reported (8). CCDC 199978 data of **2b** can be obtained free of charge at www.ccdc.cam.ac.uk/cont/retrieving.html or from the Cambridge Data Centre, 12 union Road, Cambridge CB2 1EZ.UK; Fax: (internat) +44-1223/336-033 E-mail: deposit@ccdc.cam.ac.uk.

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