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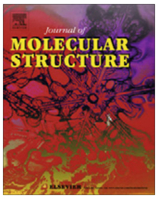

Effect of substituents and structural modification on conformational equilibrium in bis-quinolizidine system

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ABSTRACT

On the basis of literature interpretation of ^{13}C NMR and ^{1}H NMR spectra of bis-quinolizidine alkaloids, the values of free enthalpy ΔG of conformational equilibria of those compounds were calculated. The results were analysed together with the X-ray and DFT data to discuss the effects of different substituents attached to the sparteine system in various positions as well as the effects of structural modifications on conformational equilibria. The measure of the effect was expressed by $\Delta\Delta G$ value, defined as the difference in ΔG of the compound under consideration and its parent compound without a given substituent.

1. Introduction

The present paper is a continuation of the previous one, “Effect of hydroxy group on conformational equilibrium in bis-quinolizidine system”, [1a]. In the previous paper we presented an improved method for the determination of conformational equilibria in bis-quinolizidine alkaloids substituted by hydroxy groups.

In the present work the effect of other different substituents as well structural modifications of sparteine skeleton on conformational equilibria is discussed. The discussion is based not only on ^{13}C and ^{1}H NMR spectra but also on X-ray analyses and DFT calculations. The knowledge of spatial structure of bis-quinolizidine alkaloids is necessary for understanding of many biological phenomena (e.g. pharmacological activity, the taste etc.) involving this important group of natural products. Some sparteine derivatives have been used in folk medicine for the treatment of diabetes, eczema, as anti-inflammatory agents [2–5] as well as have been claimed to increase insulin secretion or decrease the level of glucose in the blood [6–8]. Recent investigation of the hypoglycaemic effect of some quinolizidine alkaloids has suggested that the compounds with more labile skeletons can be more effective [9]. Moreover, there is a relation between the state of conformational equilibrium of bis-quinolizidine compounds and the intensity of their bitter taste [10]. Sparteine (**1**), the main representative of bis-quinolizidine alkaloids, is a chiral diamine and has a widespread use as a chiral ligand in asymmetric synthesis [11,12] and selective polymerisation [13,14]. Alkylated (−)-sparteine is also used to prepare a series of compounds being as structure-directing agents in specifically crystallized large pore molecular sieves [15]. All these examples illustrate the significance of knowledge of bis-quinolizidine alkaloids stereochemistry, in particular their configuration and conformation. The most important group of quinolizidine alkaloids is sparteine (**1**) and its derivatives. The skeleton of sparteine (**1**) consists of two quinolizidine moieties: a *trans* and a *cis* one (Fig. 1). *Cis*-quinolizidine fragment is flexible owing to the possibility of nitrogen atom inversion which, in consequence, leads to a variety of structural changes which give rise to a set of possible conformations [16]. As follows from analysis of experimental [17,18] and theoretical [16] data, the most stable sparteine conformer of the lowest energy is **1A** (*trana–trans* with a boat ring C) whose energy differs from that of **1B** conformer (*trans cis* all-chair) (Fig. 1) by $\Delta E = 3.4$ kcal mol^{-1}, calculated by density functional theory (DFT) or $\Delta E = 4.5$ kcal mol^{-1} calculated by Hartree–Fock Second Order Moller–Plesset Perturbation (MF-MP) theory [16].

We have no X-ray data for sparteine as it is an oil at ambient temperature [19].

In the solid state the majority of sparteine derivatives adopt also almost exclusively the conformation with the boat ring C and *trans* junction of rings C/D. The exceptions are 13α-hydroxylupanine (**2**) [20a,21], 13β-hydroxylupanine (**3**) [21], 15-phenyl-14,15-didehydrosparteine (**4**) [22] which have the chair conformation of ring C and *cis* junction of rings C/D and

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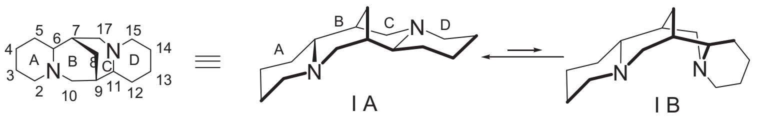
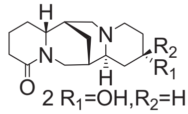


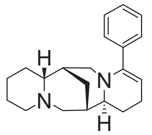
Fig. 1. Sparteine.

2-thionosparteine (**5**) which occurs as a 1:1 mixture of both conformers [23]. In solution, also some other bis-quinolizidine alkaloids adopt conformations with a great predominance of the chair conformation of ring C. Among them are aphylline (**6**) [24–26], aphyllidine (**7**) [27], 5,6-didehydromultiflorine (**8**) [28,18] and anagyrine (**9**) [29].

A few years ago, a new shape of bis-quinolizidine skeleton has been found in the crystal structure of N-ethylsparteinium bis(trifluoromethanesulphonate) (**10**) [15] as well as in the structures of sparteine, 2-phenylsparteine and 2-methylsparteine N-16-oxides (**11–13**) [30], which can be characterised as chair–chair–boat–chair form with *cis*-fusion of C/D rings (*trans–cis* CCBC).

Protonation of sparteine causes changes in conformation and configuration. The sparteine cation in sparteine perchlorate (**14**) adopts an all-chair *cisoidal* conformation with *trans–cis* configuration of two quinolizidine parts of the molecule, rings A/B and C/D, respectively [31,32]. Protonation of sparteine takes place at the N1 atom, while in the cations of its 2-substituted derivatives the N16 atom is protonated [33–37].


2 R_1=OH,R_2=H
3 R_1=H,R_2=OH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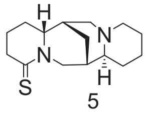
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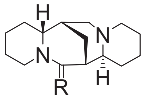
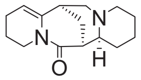

6 R=O
71 R=S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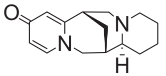
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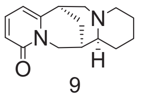
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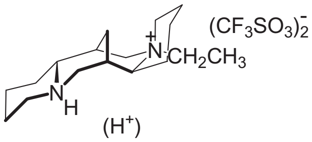
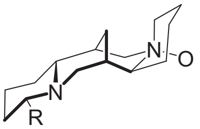
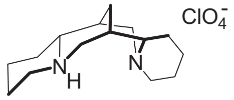

(H^+)
10


11 R=H
12 R=C_6H_5
13 R=CH_3


(H^+)
14

The X-ray structures of these series of compounds [38] are consistent with the results of theoretical study (DFT and MP2 [16]). DFT method predicts a strong preference (7.3 kcal mol^{-1}) for all-chair conformation with protonation at N1 with a hydrogen bond N$^+$(1)–H···N(16) and 11.2 kcal mol^{-1} for sparteine derivatives protonated at N16 with a hydrogen bond N$^+$(1)···H–N(16). The di-protonated salts have the same structural preferences as the parent free bases, with ring C in the boat form [39–42,16]. In solution, bis-quinolizidine alkaloids occur in conformational equilibrium [18,1a].

The present paper deals mostly with the structures of sparteine derivatives in solution. The fact that these compounds occur in conformational equilibria deserves more attention as it is important from the point of view of their biological activity. In the present paper, we do not discuss the conformation of hydroxy derivatives of bis-quinolizidine as well as their ethers and esters [1a]. We have added to the present paper only one recent example which was not included in our previous publication [1a]. The bis-quinolizidine compounds which cannot change the ring C conformation are also excluded. This group of compounds includes 15-oxosparteine, 17-oxosparteine and their derivatives [43–52] as well as their thiono analogues which have ring C in a sofa conformation [53–57].

The conformation of ring C cannot be changed also in the epi-N(16)-oxides of sparteine and its derivatives [58], in their salts [59–63] as well as in epi-N(16) methiodide and epi-N(16)-methioperchlorate of sparteine [64].

Another group of compounds whose conformation is not discussed in the present paper are quinolizidine–piperidine alkaloids. Some of them can also occur in conformational equilibrium involving ring C [65,66]. The numerous applications of sparteine and its derivatives are related to their conformational dynamics.

2. Results and discussion

We have proposed a method for quantitative determination of conformational equilibrium in bis-quinolizidine alkaloids [18,28] based on C12 and C14 chemical shifts as well as on the H7–H17β coupling constant. Knowing the chemical shifts of a given atom in the conformational mixture and chemical shifts of the same atoms in the pure conformers, i.e. δ_1 and δ_2, the fraction of the particular conformer in the conformational equilibrium can be calculated. Instead of the pure conformers the appropriate model compounds can be applied. Our original models were sparteine (**1**) (ca. 100% of the boat conformer) and 5,6-didehydromultiflirine (**8**) (ca. 100% of the chair conformer). The criteria of choice of the model compounds were the highest and lowest chemical shift value of C12 and C14 atoms as well as the highest and lowest value of $J_{7-17\beta}$ coupling constants of all compounds with the sparteine skeleton known at that time to us [18]. The latter criterion could be used for the calculation of the fraction of conformers also in some quinolizidine–piperidine alkaloids [65,66] and some bispidine derivatives [67]. Many new