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NUCLEAR MAGNETIC RESONANCE STUDIES OF INTRAMOLECULAR HYDROGEN BONDS IN MONOCATIONS OF SPARTEINE- AND α-ISOSPARTEINE-N-OXIDES

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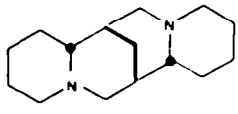
Abstract—The NMR spectra of perchlorate salts of sparteine- and α-isosparteine-N-oxides have been investigated in dimethylsulphoxide-d_6 solution. The results show a strong intramolecular hydrogen bond in the monocation of both N-oxides. This is in agreement with the anomalous high ratios of their first and second dissociation constants, and also with the conclusions from previous IR measurements. On this basis it is postulated that sparteine-$N_{(16)}$-oxide as well as α-isosparteine-N-oxide have a carbon-nitrogen skeleton in which all piperidine rings are present in the chair conformation.

INTRODUCTION

IN OUR previous investigations on the basicity of sparteine-type alkaloids[1] as well as on the structure of sparteine-N-oxide salts,[2] we showed that several compounds such as sparteine (I), α-isosparteine (II), sparteine-$N_{(16)}$-oxide (III) and α-isosparteine-N-oxide (IV) form monocations which are stabilized by intramolecular hydrogen bonds. All of these compounds possess a C—N skeleton built up of two quinolizidine rings fused in position 1,3. Assuming that the monoprotonated molecules I–IV are present in an all-chair configuration, it can be seen that the distance between $N_{(1)}$ and $N_{(16)}$ is not greater than 3 Å and that the nitrogen lone pairs of electrons are situated in a "*cis*" position to each other. Such an arrangement leads to an increase of the basicity of I–IV in comparison with an isolated quinolizidine system, and together with the very favourable conditions for intramolecular hydrogen bonding of the type: $N_{(1)}{}^+H \ldots N_{(16)}$ or $N_{(1)}{}^+H \ldots ON_{(16)}$ results in extremely high K_1/K_2 ratios.[1] In the course of IR spectroscopic studies it was found that particularly strong hydrogen bonds exist in the monoprotonated molecules of III and IV.[2]

I.



II.

III. $N_{(16)} \rightarrow O$

IV. $N_{(1)} \rightarrow O$ or $N_{(4)} \rightarrow O$

By means of X-ray analysis, it has been shown[3] that the hydrate of II has an all-chair configuration and it is most likely that this configuration is also retained by II

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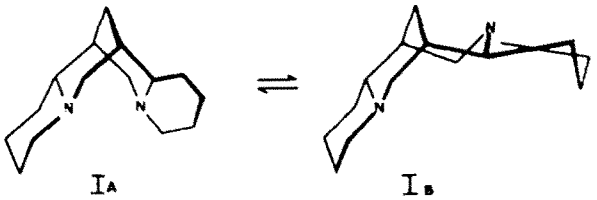
[1] M. Wiewiorowski and J. Skolik, *Bull. Acad. Polon. Sci. Ser. sci. chim.* **11**, 69 (1963).
[2] P. Baranowski, J. Skolik and M. Wiewiorowski, *Tetrahedron* **20**, 2383 (1964).
[3] M. Przybylska and W. H. Barnes, *Acta Cryst.* **6**, 377 (1953).

in solution. There is still some confusion, however, about the configuration of the isomeric compound I and its derivatives. In the molecule of I a transformation of



I_A I_B

ring C from a chair into a boat form, and *vice versa*, with the simultaneous inversion of $N_{(16)}$ can very easily be accomplished (IA ⇌ IB) and thus both configurations have been considered in the literature. The question as to which type of sparteine-skeleton configuration is present in a given situation is of intrinsic interest, since it has an important bearing on the mechanism of stereospecific chemical reactions of I and its derivatives, especially the N-oxide III.

Recently new data based on NMR spectra have been reported and they strongly support configuration IB for compounds possessing the sparteine skeleton.[4,5] However it has also been shown that the conclusions derived from NMR spectra of I in an apolar solvent cannot be generalized. There is also chemical and physicochemical evidence indicating that in a number of well known sparteine derivatives the skeleton has the IA configuration.[6]

With regard to these differing opinions, in the present paper we intend to discuss the results of NMR measurements on perchlorates of III and IV in dimethylsulphoxide-d_6 (DMSO-d_6) solution. These investigations were carried out as a continuation of our previous IR studies[3] and they shed some more light on the configuration of III and IV. For NMR measurements the perchlorate salts were chosen mainly because the perchlorate anion does not show a distinct tendency to form inter-ionic hydrogen bonds involving N^+H protons. Thus, information about the structure of protonated bases as obtained by this method would not be seriously disturbed. DMSO-d_6 was chosen as a solvent, following its successful use in NMR studies on intramolecular hydrogen bonds in monoanions of sterically hindered succinic acids. For comparison purposes the N^+H proton signal shifts of some model compounds such as perchlorate salts of several sparteine- and α-isosparteine derivatives, as well as of some substituted aliphatic diamines, were also recorded.

RESULTS AND DISCUSSION

Monoperchlorates of I and II in which intramolecular $N_{(1)}{}^+H \ldots N_{(16)}$ hydrogen bonds were observed in the course of p*Ka* measurements and IR spectroscopic studies (solid state and apolar solvent),[3] show N^+H proton signals at τ 3·45 and τ 3·70 respectively in DMSO-d_6 solution. Disalts I and II and also salts of monobasic α-oxoderivatives of I and II where hydrogen bonding is not expected, have N^+H proton signals in the region τ 0·00–3·00.* This indicates that the intramolecular hydrogen

* The exact τ-values of these signals are given in the experimental part (see page 1804).

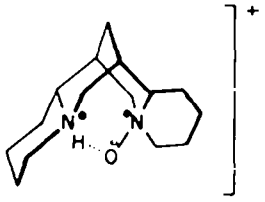
[4] F. Bohlmann, D. Schumann and Ch. Arndt, *Tetrahedron Letters* 2705 (1965).

[5] F. Bohlmann and D. Schumann, *Tetrahedron Letters* 2433 (1965).

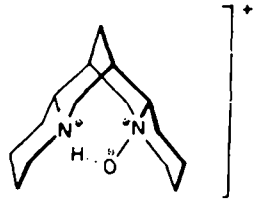
[6] M. Wiewiorowski, paper given at the *International IUPAC Symposium on the Chemistry of Natural Products*. Stockholm (1966).

[7] L. Eberson and S. Forsen, *J. Phys. Chem.* 64, 767 (1960).

bond in monosalts of I and II is disrupted in DMSO-d_6 solution. It is worthwhile mentioning that a similar situation is observed in the case of salts of N,N-dimethyl and N,N,N',N'-tetramethyl aliphatic diamines. In DMSO-d_6 solution the same shift order of τ 0·00–5·00 for di- and monosalts is observed, despite the fact that the latter exhibit intramolecular $N^+H \ldots N$ hydrogen bonds under other conditions.*



V



VI

In contrast to the salts discussed above, the N^+H proton signal shifts in monocations of sparteine-$N_{(16)}$-oxide (V) and α-isosparteine-N-oxide (VI), are extraordinarily large (in DMSO-d_6 $\tau = -8{\cdot}46$ and $-7{\cdot}66$ respectively). These values indicate that the N^+H proton in V and VI is involved in a very strong intramolecular hydrogen bond. This observation agrees with our previous conclusions drawn from IR measurements[8] and the high K_1/K_2 ratios.[1] Similar NMR measurements were carried out for V and VI using chloroform-d as a second solvent. Almost identical N^+H signal positions were obtained in both DMSO-d_6 and chloroform-d (see Table 1). This nearly complete resistance of V and VI to solvent effects again indicates that both structures are extremely stable.

TABLE 1. CHEMICAL SHIFTS IN PERCHLORATE SALTS OF SPARTEINE- AND α-ISOSPARTEINE-N-OXIDE (INTERNAL TMS STANDARD)

Compound	Solvent	Chemical shift of N^+H Signals (τ)	Distribution of CH protons (τ)			
			5·70–6·20	6·20–6·80	6·80–7·70	7·70–8·80
Sparteine-$N_{(16)}$-oxide ·H^+	DMSO-d_6	−8·46	1	5	4	16
Sparteine-$N_{(16)}$-oxide ·H^+	$CDCl_3$	−8·52	1	5	4	16
Sparteine-$N_{(16)}$-oxide 1·5·H^+	DMSO-d_6	−6·82 (and 0·46)	1	5	4	16
α-Isosparteine-N-oxide ·H^+	DMSO-d_6	−7·66	—	4	6	16
α-Isosparteine-N-oxide ·H^+	$CDCl_3$	−7·50	—	4	6	16
α-Isosparteine-N-oxide 2·H^+	DMSO-d_6	−5·08 (and 2·34)	—	4	6	16

Further protonation of V and VI results in two salts which can be obtained in crystalline form: the sparteine-$N_{(16)}$-oxide sesquiperchlorate and the α-isosparteine-N-oxide diperchlorate[8]. The NMR spectra of these salts in DMSO-d_6 solution show distinct N^+H and N^+OH signals in both cases. One of them is shifted very strongly downfield ($\tau = -6{\cdot}82$ and $-5{\cdot}08$ respectively) while the shift of the second proton signal is much smaller ($\tau = 0{\cdot}46$ and $2{\cdot}34$ respectively). In both cases these results suggest that a monocationic structure similar to V and VI is still present.

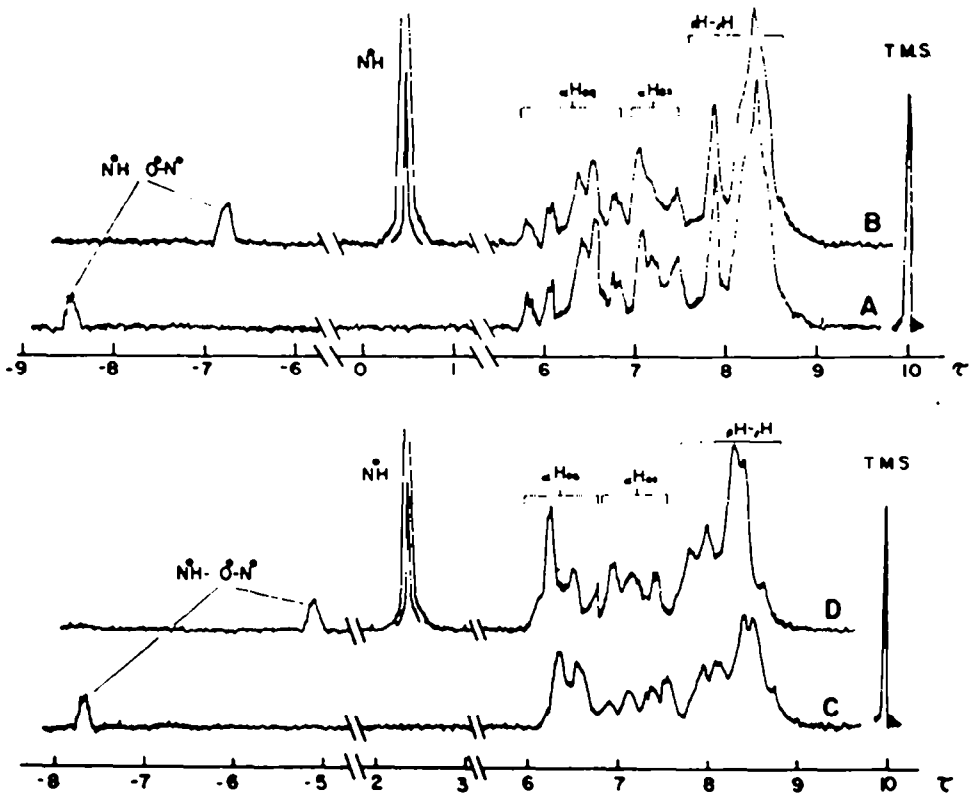


FIG. 1

The second proton (N^+OH) is exchanging rapidly between solute and solvent molecules and therefore the corresponding signal appears at a higher field (between τ 0·00 and 3·00; these limits are the same as those for the model salts mentioned earlier).

The conclusion derived from N^+H proton signal shifts is also supported by the observations made in the CH proton signal region. The NMR spectra of the mono- and sesquisalt of III are almost identical (Fig. 1, curves A and B) which indicates that in both cases the same skeleton configuration is present. A similar situation is found in the case of IV where the NMR spectra of mono- and disalt also coincide, as far as the CH region is concerned (Fig. 1, curves C and D). The existence of a stable disalt structure in DMSO-d_6 solution should give changes in the NMR spectra due to skeletal deformation caused by N^+H and N^+OH repulsion.

Recently published results of NMR measurements on *trans*- and *cis*-quinolizidine systems[4] as well as on protonated quinolizidine,[8] enable us to examine in more detail the CH signal region of V and VI. Assuming that VI consists of two *trans*-quinolizidine systems with all-chair conformation, the CH proton signal distribution in the NMR spectrum of VI should be similar to that reported for a protonated *trans*-quinolizidine molecule.† Indeed our measurements have shown a significant similarity

† For quinolizidine in tetrafluoroacetic acid the following CH signal distribution is reported[8]: CαHeq = 6·41 τ and 6·62 τ (2 protons), CαHax = 7·00 τ (broad peak, 3 protons), remaining protons (12) = 8·19 τ.

[8] H. P. Hamlow, S. Okuda and N. Nakagawa, *Tetrahedron Letters* 2553 (1964).

between the two. In the NMR spectrum of VI (Fig. 1, curve C) there are two signals between 6·20 τ and 6·80 τ roughly corresponding to four protons. By analogy with the assignment for protonated quinolizidine, they can be regarded as equatorially oriented $C_\alpha H$. On the same grounds, the four peaks between 6·80 and 7·70 τ, approximately equivalent to six protons, can be reckoned as the axially situated $C_\alpha H$. The remaining three large peaks between 7·70 and 8·80 τ which correspond to sixteen protons are due to the $C_\beta H$ and $C_\gamma H$. The ratio of C_αHeq (4) to C_αHax (6) is in agreement with the configuration given in formula VI.

Applying the same CH proton distribution limits to the NMR spectrum of V (Fig. 1, curve A), it can be seen that in the C_αHeq region (6·20–6·80 τ) three peaks occur which correspond to roughly five protons, while in the C_αHax region (6·80–7·70 τ) there are two signals approximately equivalent to four protons. In the $C_\beta H$–$C_\gamma H$ region (7·70–8·80 τ) two large peaks are found corresponding to sixteen protons. Moreover in the spectrum of V, a doublet with peaks at 5·85 τ and 6·05 τ is observed which correspond to roughly one proton. This downfield signal is closely connected with a *cis*-quinolizidine system with chair-chair conformation and can be assigned either as the methine proton at $C_{(11)}$ or the axially oriented proton at $C_{(17)}$.* The discussed $C_\alpha H$ signal distribution is in agreement with the configuration shown by formula V.

The conclusions drawn from the previously discussed N^+H signal shifts also throw some light on the configuration of V and VI. As can be seen from molecular models of these compounds, an intramolecular hydrogen bond as represented in formulae V and VI can be formed only when the carbon-nitrogen skeleton has the all-chair configuration. As far as the skeleton of the free bases I and II is concerned, there is no doubt that in II the all-chair configuration is present in the solid state[3] and in solution. The second stereoisomer has a skeleton in which configuration IA remains in an equilibrium with IB. In apolar solvents at room temperature this equilibrium is shifted towards IB.[4]

If under the conditions in which $N_{(16)}$ oxidation takes place, sparteine is present in configuration IB, then one would expect the same IB skeleton for the product III. There is much less steric hindrance to the addition of an oxygen atom to $N_{(16)}$ in a IB skeleton than in a skeleton with IA configuration. The same argument could be used for the N oxidation of II. Unfortunately, there is not much evidence for the configuration of the free bases of III and IV. There are only some data which show that both compounds have an intrinsic tendency to form intramolecular hydrogen bonds.[9] The free bases III and IV are very hygroscopic and it was not possible to obtain them in the unhydrated form. It was suggested[9] that in both compounds a water molecule is bonded ionically, leading to a cation which is stabilized by an intramolecular hydrogen bond $[(N^+H \ldots ON)^+OH^-]$. From these investigations and our own observations we assume that during the N oxidation of I and II under acidic conditions two main competing factors appear which determine the configuration of the products. One of

* It was found[4] that the signal shifted farthest downfield in the spectrum of β-isosparteine, which has a skeleton consisting of two *cis*-quinolizidine rings with chair-chair conformation, is due to the methine protons at $C_{(6)}$ and $C_{(11)}$.

In the case of *cis*-phenyl(4)-quinolizidine, the signal shifted farthest downfield is assigned[4] to the axially oriented proton at $C_{(6)}$. This position is equivalent to $C_{(17)}$H-ax in V.

[9] M. Wiewiorowski and P. Baranowski, *Bull. Acad. Polon. Sci., Ser. sci. chim.* **10**, 537 (1962).

these factors is the repulsion between both basic centers $N_{(1)}$ and $N_{(16)}$ and the steric requirements favouring the formation of a IB skeleton. The other factor is the tendency to form intramolecular hydrogen bonds in the protonated state, which stabilizes the structure IA. The data reported in this paper show that the determining factor is the second one.

It seems that the addition of an oxygen atom takes place after the formation of the all-chair configuration, since there is no possibility for N-inversion during protonation if the lone pair of electrons of $N_{(16)}$ is involved in a covalent N—O bond. For this reason the all-chair configuration is assumed to be present in the free base of III and IV. This conclusion does not agree with the recent statement of Bohlmann *et al.*[4] who reported that compound III has the IB configuration and used this finding as one of the arguments to confirm the boat conformation of ring C in the sparteine molecule. According to our views, the existence of the N-oxide III does not prove that I has a IB configuration since rapid configurational changes may occur within the sparteine molecule during oxidation. For the same reason it is not possible to decide on the most stable sparteine configuration by means of structure V, which is deduced from our investigations. The problem of the configuration of III and IV is of great interest not only because these structures were unexpected theoretically, but also because there are in existence N-oxides of a number of sparteine and α-isosparteine monolactams which are stable in the form of free bases. In contrast to III and IV however, these compounds exhibit normal chemical and physico-chemical N-oxide properties.

EXPERIMENTAL

Apparatus and materials. The NMR spectra were recorded using a Varian Associates A-60 spectrometer and 0·8M solns of perchlorate salts in DMSO-d_6 (isotopic purity 99·5 atom % D), supplied by Merck Sharp and Dohme of Canada Ltd.) In the case of V and VI additional spectra of saturated solns in $CDCl_3$ were obtained. TMS was used as an internal reference.

M.ps (uncorrected) were determined on a Kofler hot stage.

Potentiometric titrations were carried out in 80% methoxyethanol using a Radiometer (Copenhagen) Titrator TTT1.

N,N,N′,N′-Tetramethyldiaminoethane and N,N,N′,N′-tetramethyldiaminomethane were obtained from the Ames Laboratories, Inc., N,N,N′,N′-tetramethyldiaminopropane was obtained from the J. T. Baker Chemical Co., and other substituted diamines were supplied by K and K Laboratories, Inc.

Standard method for preparation of mono- and diperchlorates of substituted diamines. The free bases of diamines were stored over solid KOH and purified by refluxing over KOH or BaO and distillation. Amounts of ca. 1 g of the free bases were dissolved in 10 ml MeOH and a stoichiometric volume of perchloric acid in MeOH was added to obtain the mono- or disalts. In most cases the salts crystallized from MeOH. If crystallization from that solvent could not be achieved, the solvent was evaporated, and after drying the salt under reduced press in the presence of P_2O_5, crystallization was attempted using such solvents as EtOH, isopropanol or t-butanol. Each salt was recrystallized twice from the most suitable solvent, and the crystals were dried for several days over P_2O_5 (10^{-1} torr).

The salts were analyzed by potentiometric titration and good agreement between the measured acid/base ratio and the theoretically expected acid/base ratio was found in each case.

In the NMR spectra of mono- and diperchlorates of substituted diamines (0·8M in DMSO-d_6) the following N^+H proton signal positions were found:

N,N,N′,N′-tetramethyl-diaminomethane	$\cdot H^+ = 5{\cdot}33\ \tau$,	$\cdot 2H^+ = 3{\cdot}84\ \tau$,
N,N,N′,N′-tetramethyldiaminoethane	$\cdot H^+ = 2{\cdot}50\ \tau$,	$\cdot 2H^+ = 1{\cdot}37\ \tau$,
N,N,N′,N′-tetramethyl-1,3-diaminopropane	$\cdot H^+ = 2{\cdot}93\ \tau$,	$\cdot 2H^+ = 1{\cdot}30\ \tau$,
N,N,N′,N′-tetramethyl-1,4-diaminobutane	$\cdot H^+ = 2{\cdot}09\ \tau$,	$\cdot 2H^+ = 0{\cdot}62\ \tau$,
N,N-dimethyl-1,3-diaminopropane	$\cdot H^+ = 4{\cdot}08\ \tau$,	$\cdot 2H^+ = 1{\cdot}57\ \tau$,
N,N-dimethyl-1,4-diaminobutane	$\cdot H^+ = 2{\cdot}67\ \tau$,	$\cdot 2H^+ = 2{\cdot}00\ \tau$,
N,N-dimethyl-1,5-diaminopentane	$\cdot H^+ = 3{\cdot}17\ \tau$,	$\cdot 2H^+ = 1{\cdot}75\ \tau$.

Perchlorates of sparteine (I), *α-isosparteine* (II) *and their monolactams.* The alkaloids were largely samples used in previous investigations by one of us, and were purified by distillation or sublimation under reduced press (10^{-3} torr). Immediately after purification the perchlorate salts were prepared using the same procedure as for the diamine perchlorates. Potentiometric titrations again gave the expected acid/base ratios. The following m.ps and N^+H proton signal positions (0·8 in DMSO-d_6) were obtained:

sparteine monoperchlorate	m.p. 169°,	$N^+H = 3{\cdot}45\ \tau$,
sparteine diperchlorate	m.p. 265°,	$N^+H \simeq 1{\cdot}80\ \tau$,
α-isosparteine monoperchlorate	m.p. 157°,	$N^+H \simeq 3{\cdot}70\ \tau$,
α-isosparteine diperchlorate	m.p. 264°,	$N^+H = 2{\cdot}00\ \tau$,
lupanine perchlorate	m.p. 214°,	$N^+H \simeq 0{\cdot}85\ \tau$,
α-isolupanine perchlorate	m.p. 249°,	$N^+H = 2{\cdot}97\ \tau$,
17-oxosparteine perchlorate	m.p. 247°,	$N^+H \simeq 0{\cdot}40\ \tau$.

Perchlorates of N-*oxides of sparteine* (III) *and α-isosparteine.* The salts described in a previous paper[8] were used.

Acknowledgement—This work was supported financially by the National Research Council of Canada. One of us (J. S.) expresses his appreciation for the award of a postdoctoral fellowship.