CONFORMATIONAL ANALYSIS OF THE PYRROLIDINE RING OF THE N-METHYLTHIOHYDANTOIN OF 2-METHYLPROLINE

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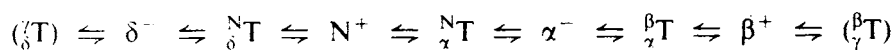*Rijksuniversiteit-Gent, Krijgslaan 281 (S-4), B-9000 Gent, Belgium*

Dedicated to the memory of Dr Karel Bláha.

The conformational analysis of the pyrrolidine ring in 2-methylproline-N-methylthiohydantoin was achieved from the vicinal proton spin spin coupling constants obtained from the 360 MHz ^{1}H NMR spectrum in hexadeuterobenzene solution. Two descriptions are consistent with the experimental data. One is a large amplitude torsional oscillation centered between a β-*endo* envelope (C_s) and a β-*endo*-α-*exo* twist (C_2). The other is a 3 : 1 dynamic equilibrium between two fixed states: a (major) β-*exo* envelope and a minor N-*endo* envelope with N-*endo*-δ-*exo* twist character. The effect of the 2-methyl group on the pyrrolidine ring conformation is evaluated and discussed.

In the preceding paper[1] we have studied by ^{1}H NMR methods the conformation of the pyrrolidine ring in some N-alkyl-thiohydantoins of proline (*I*), applying the "Haasnoot"-empirical generalization[2] of the Karplus equation and assuming two stable states[3] (N and S) each characterized by a phase angle (*P*) and a puckering amplitude (χ_m) of pseudorotation[4]. The annelation of the pyrrolidine ring and the hydantoin ring excludes conformers outside the following range of the pseudorotational circuit[6].

$$({}^{\gamma}_{\delta}T) \;\leftrightarrows\; \delta^- \;\leftrightarrows\; {}^{N}_{\delta}T \;\leftrightarrows\; N^+ \;\leftrightarrows\; {}^{N}_{\alpha}T \;\leftrightarrows\; \alpha^- \;\leftrightarrows\; {}^{\beta}_{\alpha}T \;\leftrightarrows\; \beta^+ \;\leftrightarrows\; ({}^{\beta}_{\gamma}T)$$

Envelopes are represented by the symbols α, β, γ, δ or N (indicating the position of the flap) followed by the superscript " + " if the flap is pointing towards the same side (*endo*) as the α-carboxamide group, or a " − " if *exo*. A twist form with e.g. the nitrogen atom *endo* and the δ carbon *exo* is denoted as ${}^{N}_{\delta}T$. A 4 : 1 dynamic equilibrium was found for *I*, of a β$^+$ conformer (type N, with $P_N = -13°$) and a δ$^-$ form (type S; P_S 242°). These forms are separated by a difference in phase angle $\Delta P = P_N - P_S$ of 103°, with a postulated barrier in the N$^+$-α$^-$ region.

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The biasing effect of a polar γ-substituent on the N $\rightleftharpoons$ S equilibrium of the pyrrolidine ring has been well established in the closely related hydantoin bicyclic system (*II*), i.e. in *trans*-γ-hydroxyproline hydantoin[3,7] (*IIb*) and in *trans*-γ-fluoroproline hydantoin[8] (*IIa*).

Ia , R = Me
Ib , R = Aryl

IIa , X = F
IIb , X = OH

III
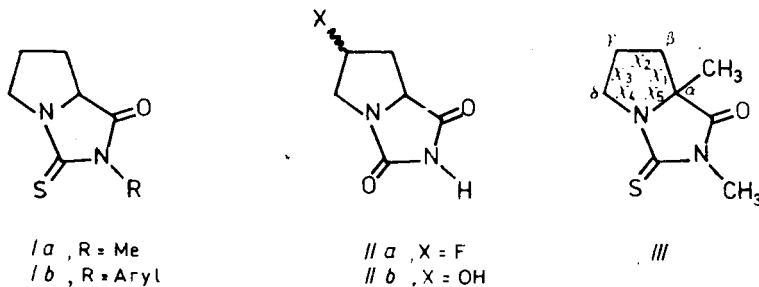
The present study evaluates the effect of α-branching on the pyrrolidine ring conformation in the α-methyl-N-methyl thiohydantoin of proline *III*. The vicinal proton–proton coupling constants of the title compound have been measured accurately in hexadeuterobenzene solution, and a detailed pseudorotational analysis was performed (along the lines advocated by the Altona group[2-5]) for the fixed single state, for the bistable state and for a simple oscillating single state model. It is found in the present study that the bistable state model reproduces the experimental coupling constants with a root-mean--square deviation (rms) of 0.55 Hz (compared to an rms value of 1.22 for the fixed single state model). The introduction of the α-methyl group significantly displaces the N and S conformers towards each other on the phase angle axis ($P_N = -19$ and $P_S = 262°$; $\Delta P = 79°$), but hardly affects their relative population, when compared to the proline thiohydantoin itself. A simple oscillating single state model, characterized by a broad and shallow energy minimum with a relatively large amplitude of libration, fits the experimental values comparably well (rms = 0.70 Hz).

EXPERIMENTAL

included) were freely iterated simultaneously to an rms deviation between experimental and calculated transitions reduced to 0.15 Hz, as determined on 173 lines assigned out of 223 theoretical transitions with minimum intensity 0.01.

The analysis according to the bistable state model was realized with the computer program CONFIT[10], which combines a generalized Karplus equation[2], the concept of pseudorotation[4], and a least-squares iteration procedure[11]. CONFIT, created by one of us (J.J.M.S.) in 1981–1982, is equivalent to the computer program PSEUROT[12] now available as QCEP No. 463.

In the oscillating single state model[13] used here, a harmonic dependency of the potential energy $E(P)$ on the phase angle P is assumed: $E(P) = 0.5\,V_1\,(1 - \cos(P - P_0))$. The V_1 parameter determines how broad and shallow the energy minimum is. Coupling constants $J(P)$, calculated from the generalized Karplus equation[2] (χ_m was fixed to a value of $45.7°$) were averaged assuming a continuous Boltzmann distribution. The rms deviation of experimental and "averaged" coupling constants was then calculated for chosen combinations of P_0 and V_1. The results are pictured in a contour plot of the rms deviation in the V_1, P_0 plane in Fig. 3.

RESULTS

Table I contains the coupling constants and chemical shifts of the N-methylthiohydantoin of 2-methylproline *III* in benzene solution, and compares these to the corresponding data of the 2-*des*methyl derivative *Ia*. The 360 MHz ^{1}H NMR spectrum of *III* in C_6D_6 solution is presented in Fig. 1.

TABLE I

^{1}H NMR chemical shifts and coupling constants of α-methylproline-N-methylthiohydantoin (*III*) in hexadeuterobenzene and of proline-N-methylthiohydantoin (*Ia*) in octadeuterotoluene

Com- pound	Chemical shifts[a]							
	N-Me	α	β^c	β^t	γ^c	γ^t	δ^c	δ^t
III	3.164	1.396	1.730	1.861	2.152	2.202	4.013	3.520
Ia	2.945	3.189	0.731	1.319	1.243	1.100	3.556	2.878

	Coupling constants, Hz										
	^2J (geminal)			^3J (vicinal)[b]							
	$\beta^c\,\beta^t$	$\gamma^c\,\gamma^t$	$\delta^c\,\delta^t$	$\beta^c\,\gamma^c$	$\beta^c\,\gamma^t$	$\beta^t\,\gamma^c$	$\beta^t\,\gamma^t$	$\gamma^c\,\delta^c$	$\gamma^c\,\delta^t$	$\gamma^t\,\delta^c$	$\gamma^t\,\delta^t$
III	−12.62	−13.29	−11.98	8.78	10.65	2.35	7.50	8.83	3.95	7.89	9.40
Ia	−12.35	−12.85	−11.48	7.86	10.96	2.40	6.96	7.90	3.31	8.78	8.86

[a] In ppm downfield relative to TMS internal; coding of protons with superscript c (or t) if proton on the same (or opposite) side of the ring, with reference to the α-carboxamide substituent; [b] for *Ia* additional couplings: $^3J(\alpha\beta^t) = 7.01$ Hz; $^3J(\alpha\beta^c) = 10.33$ Hz; for *III*: $^4J(\beta'\delta^c) \sim 0.7$ Hz.

Fig. 2 compares the experimental and simulated individual spin multiplets in expansions.

In Table II we report the pseudorotation parameters for the N and S forms in the bistable state model, the individual pyrrolidine ring torsion angles and the rms deviation on ^3J. In Fig. 3 the rms deviation between experimental and calculated couplings obtained with the oscillating single state model is pictured. Scheme 1 summarizes the conformational features obtained with the different physical models, i.e. the fixed single state, the oscillating single state and the bistable state.

DISCUSSION

The fixed single state model, coupled to the pseudorotational equation and the generalized Karplus equation, iterates to a χ_m of $38 \cdot 4$ and a P of $-29 \cdot 7$. The rms deviation of $1 \cdot 25$ Hz (Table III) indicates that this model is inferior, relative to the oscillating single state (rms error $0 \cdot 70$ Hz) and the bistable state model,
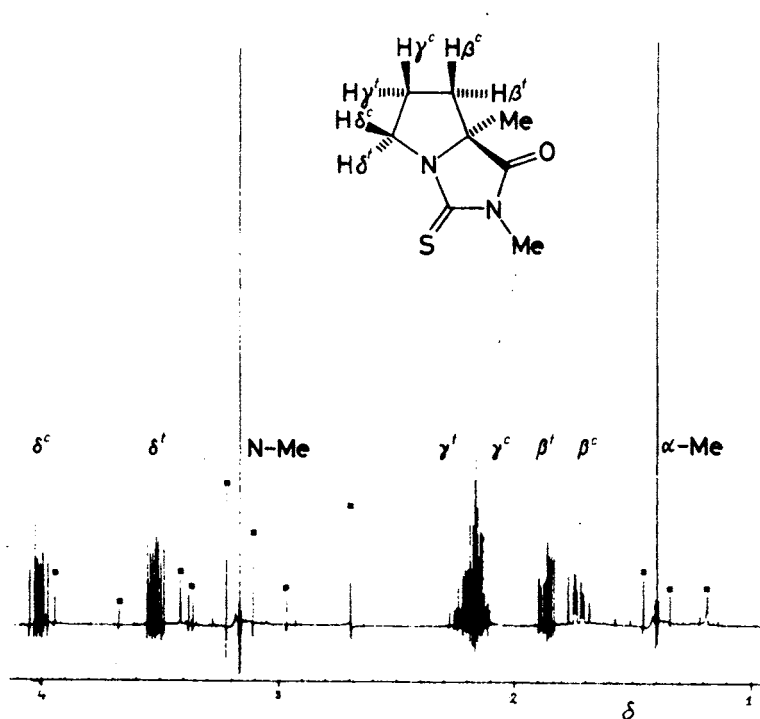

FIG. 1

^{1}H NMR spectrum at 360 MHz of α-methylproline-N-methylthiohydantoin (*III*) in C$_6$D$_6$ with TMS as internal standard. Signals due to impurities and side-bands are marked by black squares
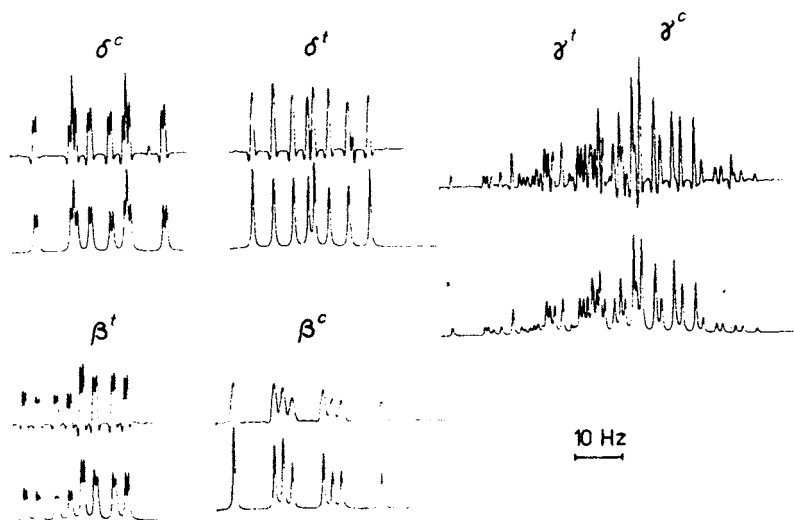
FIG. 2

Comparison of the experimental spectrum (upper trace) of *III* with the calculated (bottom) as simulated by PANIC
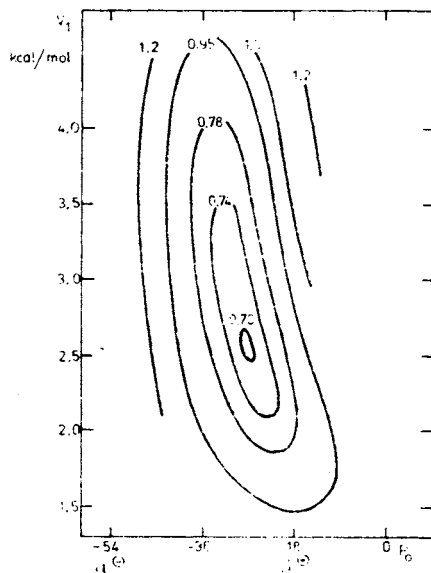

FIG. 3

Contour plot representation of the rms deviation in Hz between experimental and "averaged" coupling constants in the V_1, P_0 plane, for the oscillating single state model

in explaining the experimental set of 8 vicinal coupling constants. The lowest rms deviation (0·55 Hz) is obtained for a mixture consisting of 73.5% of a β^+ (envelope) form and 26·5% of a conformation that can be described as an N^+ envelope with $^N_\delta T$ twist character. These results can be compared to a similar pseudorotational analysis performed on the ten vicinal coupling constants of the

TABLE II

Conformational description[a,b] of the "N-" and "S-type" forms of the pyrrolidine ring of α-methylproline-N-methylthiohydantoin (III) in benzene in the two-state approximation[c]

Form	Phase angle P	Maximal puckering amplitude χ_m	Mol-fraction x	Endocyclic ring torsion angles				
				χ_1	χ_2	χ_3	χ_4	χ_5
"N-type"	−19·0 (8·1)	45·6 (4·4)	0·736 (0·05)	−44	43	−26	−1	27
"S-type"	+262 (22·5)	40·1 (15·2)	0·264 (0·05)	−19	−5	28	−39	36

[a] Via the pseudorotation equation[4]: $\chi_i = \chi_m \cos(P + 4\pi(i - 2)/5)$ in which $i = 1,2,3,4,5$; [b] values in brackets are standard deviations; [c] bistable state model; rms deviation = 0·55 Hz.
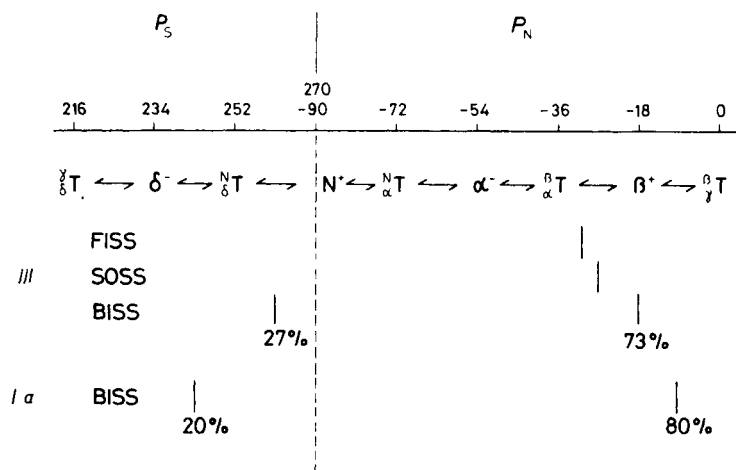
SCHEME 1

Schematic representation of the conformational features of α-methylproline-N-methylthiohydantoin (III) and proline-N-methylthiohydantoin (Ia) obtained from the different models. FISS fixed single state; SOSS simple oscillating single state; BISS bistable state

corresponding 2-*des*methyl derivative (*Ia*; R = CH$_3$) (i.e. proline-N-methylthio-hydantoin). This reveals a considerable lowering of the separation of the two states on the phase angle axis, i.e. from $\Delta P = 103$ in *Ia* (R = CH$_3$) to 79 in *III* ($\Delta P = P_N - P_S$). The analysis of the 2-*des*methyl derivative (*Ia*; R = CH$_3$) spans a temperature interval of c. 100 C and provides evidence for an equilibrium between two states.

Apparently, introduction of the 2-methyl group (see Scheme 1) destabilizes more the β^+ form (gauche butane interaction in C$_\gamma$—C$_\beta$—C$_\alpha$—CH$_3$ fragment) and the δ^- form (α-methyl group involved in eclips situation) than the in-between conformers (N$^+$–α^-). The conformational adaptation of the pyrrolidine ring (vide supra) is at the expense of increased Pitzer strain in the C$_\beta$ C$_\gamma$ C$_\delta$ region. This results in a decreased barrier between the "North-" and "South-type" pyrrolidine ring conformations. Therefore the physical meaning of the existence of two distinct forms (i.e. separated by an energy barrier) that approach each other with a phase angle difference of only 79 can be questioned. A single, but shallow and broad energy minimum, with a large amplitude of libration might better approach physical reality in the present particular case. A similar situation was described for cyclo-triproline ($\Delta P = 70$)[13].

TABLE III

Observed and calculated vicinal coupling constants and rms deviation for α-methylproline-N--methylthiohydantoin (*III*)

J	Experimental[a]	Calculated[b]		
		FISS	BISS	SOSS
β' γ'	8·78	8·57	8·02	8·27
β γ'	10·65	11·31	10·16	9·97
β' γ	2·35	0·23	1·83	1·47
β' γ'	7·50	8·29	7·82	8·22
γ δ'	8·83	10·11	8·78	8·50
γ' δ'	3·95	1·86	3·24	3·04
γ δ	7·89	7·58	7·20	7·32
γ δ	9·40	10·36	8·95	8·68
rms deviation		1·25	0·54	0·70

[a] Values apply to benzene solution and are iterated with the PANIC spin simulation program; [b] FISS = fixed single state model: $\chi_m = 38\cdot4°$; $P = -29\cdot7°$; BISS = bistable state model: $\chi_m^N = 45\cdot5°$; $P_N = -19\cdot0$; $\chi_m^S = 40\cdot1$; $P_S = 262\cdot1$; $x_N = 0\cdot735$; SOSS = simple oscillating single state model: $\chi_m = 45\cdot6°$; $P_n = -28°$; $V_1 = 2\cdot5$ kcal mol.

The results of an analysis based on a simple (harmonic) oscillating single state model[13] are pictured in Fig. 3 for the presently studied molecule. With χ_m not optimized and in the "harmonic" approximation (although the BISS-model suggests skewness of the potential energy profile) rms deviations on ^3J as low as 0.70 Hz are readily obtained. Such value surpasses the rms error of the two-state model by only 0.15 Hz, which is an insignificant difference since the rms deviation of the iterative spin-simulation itself is 0.15 Hz. Clearly, the vicinal coupling data set of the title compound can not distinguish the bistable state from the large-amplitude torsional oscillation model as proper conformational descriptions for the pyrrolidine ring in the present hydantoin derivative.

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