

Lanthanide-induced Shifts in Proton Magnetic Resonance; Studies on the Conformations of Thujane Derivatives

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Dedicated to Professor František Šorm on his 60th birthday

The conformations of (+)-3-thujanol (1), (-)-3-neoisothujanol (2), (+)-*trans*-sabinol (3), and (-)-*cis*-sabinol (4) have been studied by NMR-spectroscopy. The observed coupling constants as well as europium-induced chemical shifts provide evidence for boat-like conformations in these thujane derivatives. A method is described which compensates for experimental errors in shift reagent work.

NMR-studies of the thujyl alcohols and of the thujones have shown that these compounds possess a boat-like conformation.¹ This postulation appears to be universal for all derivatives of the bicyclo[3,1,0]hexane series.²⁻¹¹ Recently, however, Hach *et al.*¹² have reported some IR data which they interpret as evidence against boat-like conformations in (+)-3-thujanol (1) and (-)-3-neoisothujanol (2).**

A correct assignment of the conformation of bicyclo[3,1,0]hexane derivatives is important for the interpretation of kinetic data in rearrangement reactions⁴ and also of ORD and CD data associated with conjugated cyclopropyl chromophores¹³ in these systems. We therefore decided to reinvestigate the conformations of (+)-3-thujanol (1) and of (-)-3-neoisothujanol (2). This study also includes NMR investigations of (+)-*trans*-sabinol (3) and (-)-*cis*-sabinol (4).^{14,15}

The NMR-spectra of (+)-3-thujanol (1), (-)-3-neoisothujanol (2), (+)-*trans*-sabinol (3) and (-)-*cis*-sabinol (4) have previously, been studied.^{1,15} The relationships between the thujanols, thujones, and sabinols are given in Fig. 1. The NMR data obtained in the present investigation are presented in Tables 1, 2 and 3 in which the assignments of the various signals and signal patterns in principle are consistent with previous investigations.

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** Revised nomenclature according to Ref. 9.

Table 1. Chemical shifts of protons in sabinols and thujanols (τ -values, TMS internal standard).

	C(2 α)-H	C(2 β)-H	C(3)-H	C(4)-H	C(5)-H	C(6 α)-H	C(6 β)-H	C(7)-H	C(8)-H ₃	C(9)-H ₃	C(10)-H _{2,3}
(+)-3-Thujanol (1) CCl ₄	8.04 ^a	8.44 ^g	6.82 ^c	8.11	^e	9.82	9.85	8.68 ^e	9.07 ^b	9.15 ^b	9.00 ^b
(-)-3-Neoisothujanol (2) CCl ₄	8.17 ^a	8.53 ^g	6.20 ^c	7.96	9.19 ^{d,e}	9.7	9.8	^e	9.03 ^b	9.13 ^b	9.14 ^b
(+)-trans-Sabinol (3) CCl ₄ CDCl ₃	8.34 ^a 8.31 ^a	8.05 ^c 7.98 ^c	5.68/ 5.67/	—	8.46 ^a 8.36 ^c	8.93 ^d 8.93 ^d	9.25 ^h ^e	^e ^e	9.05 ^b 9.07 ^b	9.10 ^b 9.12 ^b	5.15 ^h 5.02 ^h 5.17 ^h 5.07 ^h
(-)-cis-Sabinol (4) CCl ₄ CDCl ₃	7.88 ^a 7.77 ^a	8.48 ^a 8.46 ^a	5.94 ^c 5.82 ^c	—	8.40 ^{d,e} 8.33 ^{a,e}	9.45 9.2 — 9.6	9.45	8.65 ^e 8.69 ^e	9.06 ^b 9.06 ^b	9.12 ^b 9.09 ^b	5.16 ^b 5.05 ^b 5.21 ^b 5.15 ^b

^a Quartet. ^b Doublet. ^c Multiplet. ^d Triplet. ^e Uncertain due to overlapping signals. ^f Broadened doublet. ^g Broadened quartet. ^h Broadened singlet.

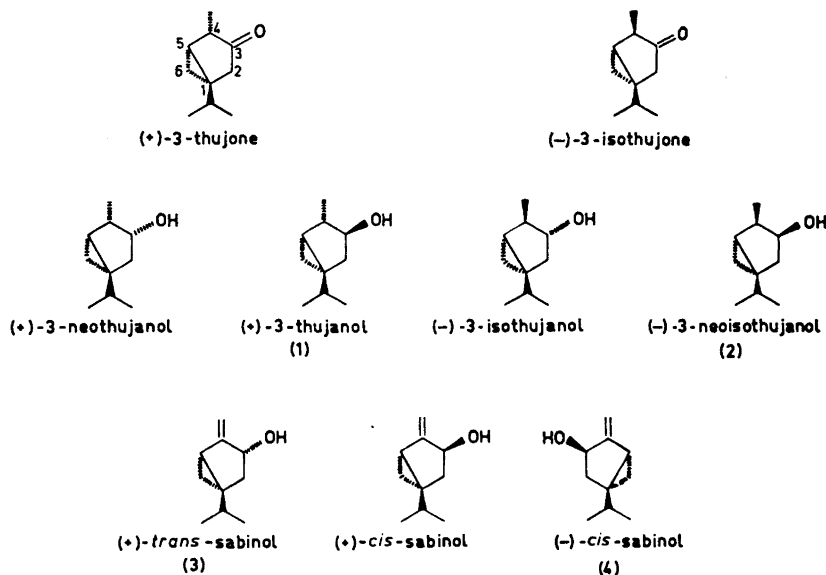


Fig. 1. Steric relationship of thujyl alcohols and related compounds.

Table 2. Apparent coupling constants (Hz) in sabinols and in thujanols.

	$J_{2\alpha,2\beta}$	$J_{2\alpha,3}$	$J_{2\beta,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,10}$	$J_{5,6\beta}$	$J_{5,6\alpha}$	$J_{6\alpha,6\beta}$	$J_{2\beta,6\beta}$	$J_{3,10}$
(+)-3-Thujanol (1)											
Eu(dpm) ₃ -CCl ₄	12.1	6.6 ^b	8.5 ^b	8.2	3.8	6.2	8.0	4.0	4.9		—
(-)-3-Neoisothujanol (2)											
CCl ₄	12.0	7.4 ^b	9.3 ^b	6.5	~0	7.0	8.5	4.0	~5	0.5	—
Eu(dpm) ₃ -CCl ₄	12.0	7.3	9.3		~0	7.2	8.4	3.8	5.0		—
(+)-trans-Sabinol (3)											
CCl ₄	13.3	1.5	6.7	—	—	—	~8	3.3	~4	~2	~0
CDCl ₃	13.6	1.3	6.6	—	—	—	~8	~4	~4	1.6	~0
Eu(dpm) ₃ -CCl ₄	13.5	~0	7.0	—	—	—	~8	3.2	~4	~2	~0
(-)-cis-Sabinol (4)											
CCl ₄	12.0	7.8	8.2	—	—	—		11 ^a		~0	~2
C ₆ D ₅ N	11.9	7.7	8.6	—	—	—	7.3	~4			~2
C ₆ D ₆	~12	~8	~8	—	—	—		11.2 ^a			~2
CDCl ₃	12.0	7.7	8.2	—	—	—	~7	~4			~2
Eu(dpm) ₃ -CCl ₄	12.0	7.5	~8	—	—	—	8.3	3.3	~4		~2

^a Sum of $J_{5,6\beta}$ and $J_{5,6\alpha}$. ^b Previous values of H-C(2)-C(3)-H vicinal coupling constants ($J_{2,3}$) in (+)-3-thujanol (1) and in (-)-3-neoisothujanol (2) have been interchanged (cf. Table 3 in Ref. 1).

Table 3. Absolute values of observed and predicted $\text{Eu}(\text{dpm})_3$ -induced shifts, $|\Delta_{\text{Eu}}|$, assuming a linear dependence of $\log |\Delta_{\text{Eu}}|$ upon $\log R$, where R is the distance between oxygen and hydrogen atoms.

		(+) -3-Thujanol (1)		(-) -3-Neoisothujanol (2)		(+)-trans-Sabinol (3)		(-)-cis-Sabinol (4)	
		boat ^a	chair	boat ^a	chair	boat ^a	chair	boat ^a	chair
C(2 α)-H	obs	12.71	—	12.5	—	20.78	—	11.50	—
	pred	13.84	9.92	12.40	9.14	19.55	18.49	13.52	10.46
C(2 β)-H	obs	20.76	—	19.4	—	10.07	—	20.09	—
	pred	21.21	18.14	18.68	17.43	10.67	13.24	19.83	18.86
C(3)-H	obs	29.40	—	26.6	—	29.28	—	25.57	—
	pred ^b	—	—	—	—	—	—	—	—
C(4 α)-H	obs	—	—	12.6	—	—	—	—	—
	pred	—	—	12.40	9.14	—	—	—	—
C(4 β)-H	obs	21.31	—	—	—	—	—	—	—
	pred	21.21	18.14	—	—	—	—	—	—
C(5)-H	obs	6.80	—	5.8	—	8.09	—	6.83	—
	pred	5.21	7.43	4.85	6.71	6.20	5.94	5.63	7.89
C(6 α)-H	obs	6.74	—	5.13	—	20.98	—	5.76	—
	pred	7.59	5.07	8.46	4.45	26.55	8.64	7.35	5.43
C(6 β)-H	obs	4.25	—	3.46	—	7.76	—	4.28	—
	pred	3.68	3.47	3.47	2.97	7.98	4.84	4.11	3.76
C(7)-H	obs	^c	—	^c	—	4.43	—	4.63	—
	pred	—	—	—	—	—	—	—	—
C(8)-H ₃	obs	3.32	—	3.46	—	2.74	—	3.88	—
	pred	3.68	9.66	3.47	8.88	3.24	4.99	4.33	10.20
C(9)-H ₃	obs	2.25	—	2.63	—	2.50	—	2.73	—
	pred	2.68	3.35	2.57	2.86	3.09	4.02	2.76	3.89
C(10)-H _A	obs	—	—	—	—	11.17	—	19.65	—
	pred	—	—	—	—	9.82	16.86	17.84	9.64
C(10)-H _B	obs	—	—	—	—	7.73	—	9.07	—
	pred	—	—	—	—	6.07	7.95	7.54	6.04
C(10)-H ₃	obs	10.18	—	13.9	—	—	—	—	—
	pred	9.34	6.03	13.23	12.17	—	—	—	—

^a Conformations with "flap angles" of 25°. Staggered conformations of the isopropyl group were assumed. ^b Not included in the calculations (cf. Ref. 17). ^c Obscured by other signals.

Dihedral angles were estimated from a Dreiding model where the "flap angle" (angle between the C(1),C(2),C(4),C(5) plane and the C(2),C(3),C(4) plane) of the five membered ring was 20–30°. The observed spin-spin splittings of the compounds (1), (2), (3), and (4) satisfy the Karplus equation only if the molecules exist mainly in boat-like conformations with coupling constants between the C(2) and C(3) protons as indicated in Fig. 2.

Allylic coupling is observed in (-)-cis-sabinol but not in (+)-trans-sabinol. Estimated from a Dreiding model in a boat-like conformation, the

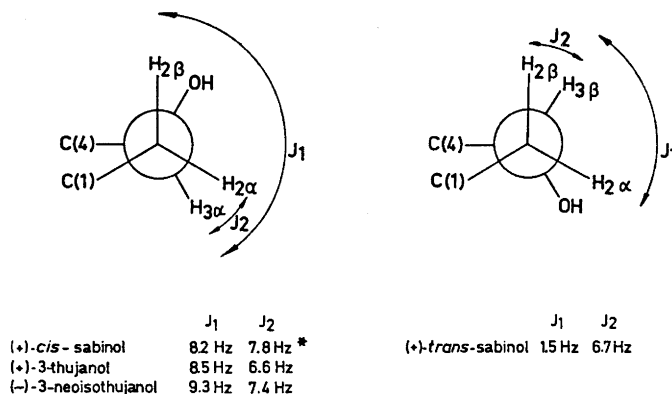


Fig. 2. Newman projection of C(2)-C(3) in boat-like conformation with observed coupling constants C(2)-H-C(3)-H (* the coupling constants were determined on the enantiomer (-)-*cis*-sabinol).

C(3)-H bond in (+)-*trans*-sabinol is only *ca.* 30° out of the allylic plane. This bond in (-)-*cis*-sabinol is almost perpendicular to the allylic plane in the boat-like conformation and should therefore give rise to a significant allylic coupling (*cf.* Ref. 15).

Europium-induced chemical shifts* for the protons of (+)-3-thujanol, (-)-3-neoisothujanol, (+)-*trans*-sabinol and (-)-*cis*-sabinol are given in Table 3. The induced paramagnetic shift is largest for protons near the coordination site in the direction of the Eu-O bond.¹⁷⁻¹⁹ The europium complex induced a large paramagnetic shift of the 6-endo proton signal in (+)-*trans*-sabinol but not in (-)-*cis*-sabinol, (+)-3-thujanol and (-)-3-neoisothujanol. Furthermore, vicinal protons *cis* to the hydroxyl groups are more shifted than vicinal protons in the *trans*-positions. These induced shifts confirm previous configurational assignments of the sabinols and of the thujanols.

The observed coupling constants in the NMR-spectra of the various compounds were practically (± 0.5 Hz) not affected by the addition of europium complex (see Table 2). Thus the addition of the complex apparently has no significant influence on the conformations of the molecules. The paramagnetic induced chemical shifts, Δ_{Eu} , defined as $\tau_{Eu(dpm), n=1} - \tau_{Eu(dpm), n=0}$ were obtained from the slope of the plot of chemical shift ($\tau_{Eu(dpm), n}$) against the molar ratio (n), shift reagent/substrate.¹⁷

Log $|\Delta_{Eu}|$ was then plotted against log R , where R is the distance between the oxygen atom of the hydroxyl group and the proton in question. A good linear correlation is observed only for boat-like conformations. Observed and predicted Δ_{Eu} -values are given in Table 3 and correlation coefficients in Table 4. The flap angles, *i.e.* the angles between the C(1),C(2),C(4),C(5)- and the C(2),C(3),C(4)-planes in boat and chair conformations were assigned to be 25°. Distances were measured in Dreiding models.

* Paramagnetic shift reagent, Eu(dpm)₃, tris(dipivalomethanato)europium(III).

Table 4. Correlation coefficients and slopes from the plot $\log |\Delta_{Eu}|$ against $\log R$.

Compound	Conformation	Corr. coefficient	Slope
(+) -3-Thujanol (1)	boat	0.983	-2.44
	chair	0.797	-2.28
(-) -3-Neoisothujanol (2)	boat	0.984	-2.34
	chair	0.849	-2.44
(+) - <i>trans</i> -Sabinol (3)	boat	0.968	-2.29
	chair	0.752	-1.91
(-) - <i>cis</i> -Sabinol (4)	boat	0.977	-2.19
	chair	0.741	-2.23

The precision in molar ratio (n) was as high (0.5–5 %) as the precision of the τ -values, if aliquots of the substrate solution were added to a solution of shift reagent and substrate. If, however, the spectrum was shifted downfield by adding small amounts of shift reagent to the substrate solution, errors were larger. In such cases, it is convenient to determine a concentration independent parameter by plotting the $\tau_{Eu(dpm), n=x}$ -values of a proton for arbitrary molar ratios against the corresponding $\tau_{Eu(dpm), n=x}$ -value for a second proton ("reference proton"), the chemical shift of which can be determined with high precision, e.g. the carbinylic proton, C(3)–H.

The least-square derived slope (k) of such a plot is linearly correlated to the Δ_{Eu} -value: $k = \Delta_{Eu} [\Delta_{Eu, \text{reference proton}}]^{-1} = \Delta_{Eu} \text{ const.}$ Therefore, k -values may be used instead of Δ_{Eu} -values in the pseudocontact shift equation.¹⁷ After the completion of this work, Kelsey²⁰ reported a similar method of using internal proton standards in shift reagent work. These procedures are apparently alternatives to the method of compensating for experimental errors in shift reagent work described by ApSimon and Beierbeck.²¹

It is of interest to note that such a simple approximation,¹⁷ which does not take into account the true geometric factors,^{18,19} is nonetheless sufficiently accurate to predict the conformations. A refined calculation using a computer program has also been used for this problem.²² The geometric factor $(3 \cos^2 \theta - 1)r^{-3}$ has been determined. Such calculations could only with slightly higher accuracy confirm the results of the more simple and approximate method presented in this paper.

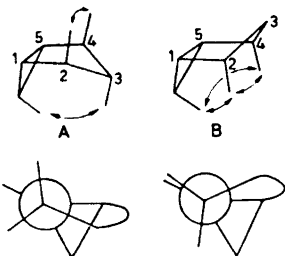


Fig. 3. Steric interactions in the bicyclo[3,1,0]hexane system. Newman projections of C(2)-C(1).

An approximate conformational analysis of the bicyclo[3,1,0]hexane system shows that the strong 1,3-interactions of the chair-like conformer (B) are relieved in favor of only one 1,4-interaction of similar magnitude by forcing the molecule into a boat-like conformation (A). Furthermore, the chair-like conformer (B) exhibits eclipsed C(1)–C(2) and C(4)–C(5) conformations (*cf.* Newman projection Fig. 3). The boat-like structure (A) is in the more favoured staggered conformation.

EXPERIMENTAL

NMR spectra were recorded on a 60 Mc/s Perkin-Elmer R-12 instrument. Chemical shifts are given in τ -units, ppm relative to tetramethylsilane (TMS).

(–)-*cis*-Sabinol was a gift from Dr. E. Klein (Dragoco) and exhibited, after recrystallisation from light petroleum (b.p. 30–40°), m.p. 45–46°, $[\alpha]_D - 131^\circ$ (c 1.0 CHCl₃) (*cf.* Ref. 14).

(+)-*trans*-Sabinol was obtained from (+)-sabinylacetate previously described.²³ (+)-*trans*-Sabinol had $[\alpha]_D + 21.7^\circ$ (c 2.1 CHCl₃). (–)-3-Neoisothujanol (*cf.* Ref. 1) had m.p. 66–68°, $[\alpha]_D - 24^\circ$ (c 2.0 in EtOH). (+)-3-Thujanol (*cf.* Ref. 1) had $[\alpha]_D + 106^\circ$ (c 1.5 CHCl₃).

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