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^{13}C NMR OF CARBONYL COMPOUNDS — 4. SOLUTION CONFORMATION OF β-IONONE AND RELATED DIENONES

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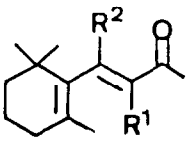
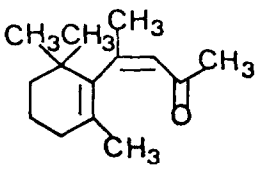
Abstract The steric factors relevant for the conformations of β-ionone and structurally related compounds were studied by dynamic n.m.r. and $^1H,^1H$-NOE measurements.

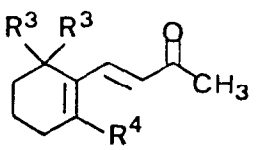
Extensive photochemical studies on conjugated dienones revealed that the behaviour of, e. g. β-ionone (1) depends on the mode of alkyl substitution[2,3] and, thus, on the prevailing conformations. These findings prompted us to investigate the solution conformations of β-ionone (1)[4-6] and its analogues 2-7 using n.m.r. spectroscopy. Our approach appeared particularly promising since 1 is closely related to the retinal chromophore[7] whose binding within the rhodopsin is known to be conformation-dependent.[8]



1 (R^1=R^2=H)
2 (R^1=CH_3, R^2=H)
3 (R^1=H, R^2=CH_3)



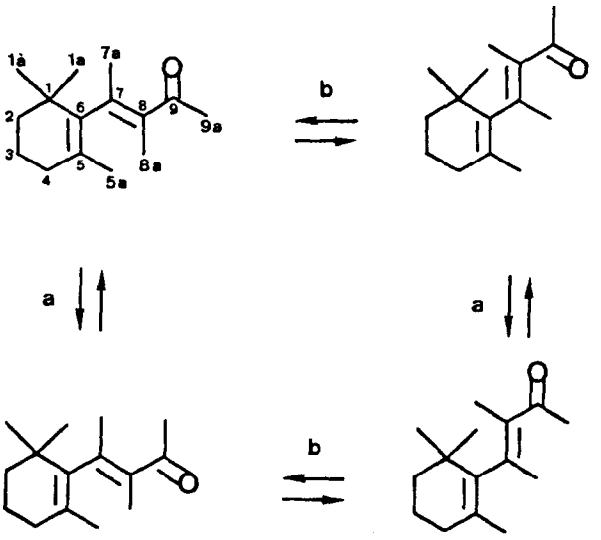
4



5 (R^3=CH_3, R^4=H)
6 (R^3=H, R^4=CH_3)
7 (R^3=R^4=H)

The choice of the title compounds is governed by the following considerations. β-Ionone can undergo three types of conformational interconversions: rotation about the enone single bond (process a) and diene single bond (process b) (see Scheme) and cyclohexene ring inversion (the latter isomerism being rapid on the n.m.r. time scale at temperatures in excess of -100°C). The energy profile of process b controls the relative orientation of ring and side chain . Methyl substitution at C-7 or C-8 (compounds 2[9], 3[3]) affects both (a) and (b), while

SCHEME



a successive removal of the methyl groups from C-1 and C-5 of 1 (compounds 5-7[10-12]) influences only process b.

8-Methyl-ß-ionone (2) was obtained by isomerization of 8-methyl-α-ionone with 86% H_2SO_4.[9] The (E/Z)-7-methyl-ß-ionones 3 and 4 were synthesized in 66% overall yield by reaction of ß-ionone (1) with lithium dimethyl cuprate, trapping of the intermediate enolate with benzeneselenylbromide and subsequent oxidation with H_2O_2.[3] The (E/Z)-iosomers were easily separable by column chromatography. Compounds 5[10] and 7[12] were synthesized via reaction of 2,2-dimethylcyclohexanone and cyclohexanone, respectively, with the Grignard reagent prepared from 3-butin-2-ol analogous to a procedure by Weedon et al..[13] The related system 6[11] was readily obtained by an aldol condensation of 2-methylcyclohexenylcarbaldehyde[14] with acetone.

Neither the chemical shift of the carbonyl carbons [δ_C (1, 5-7) 198.6 ± 0.1] nor the shift difference between the carbons C-7 and C-8[15] are reliable criteria for describing the conjugation between the enone side chain and the ring double bond and, thus, the diene conformation. Instead, we shall invoke: (i) the dynamic behaviour, (ii) nuclear Overhauser effects, and (iii) $^1H,^1H$-longe range coupling constants as more direct probes for this problem.

Below ca. -130°C the signal of C-1a, C-1a' in 1 broadens and, finally, splits [$T_{coal.}$ = -145°C (100 MHz)] into two signals of equal intensity. Compounds 2 and 3 exhibit the same line broadening effects, although at significantly higher temperatures [2: $T_{coal.}$ = -41°C (20 MHz); 3: $T_{coal.}$ = +25°C (20 MHz)]. One concludes that in 2 and 3 process b is highly hindered. [2: $\Delta G^{\ddagger}_{coal.}$ = 12.3 ± 0.5 kcal/Mol; 3: $\Delta G^{\ddagger}_{coal.}$ = 15.1 ± 0.5 kcal/Mol] and interconverts diene conformations with nearly orthogonal arrangements (torsional angle φ = ± 90°) of ring and side chain. It should be noted in this context that 1 undergoes rapid α-pyran formation

upon photochemical E/Z-isomerization[2] while the Z-isomer of 2 forms the pyran more slowly, and that of 3 fails to undergo the ring closure. In fact, compound 4, the Z-isomer of 3, was isolated by us, and its methyl groups 1a and 1a' remain inequivalent even at 100°C (20 MHz).

In a previous ^{13}C NMR study of 1 and related acyclic dienones (with $R^1 = R^2 = H$) we succeeded in slowing down the enone rotation at very low temperatures and in separately detecting the s-cis and s-trans enone conformers.[16] As this is not possible for the diene mobility of 1 we are restricted to a consideration of the equilibrium mixture in the fast-exchange domain of the dynamic process b. The Table lists the nuclear Overhauser enhancements [%] observed for the protons H-7 and H-8 of 1, 5 and 6 upon irradiation with the resonance frequency of the methyl protons 5a and 1a, 1a', respectively. An interpretation is straightforward assuming the steric interactions associated with the nuclei involved (see Scheme). In the parent compound 1 the s-cis diene conformation is obviously preferred. This is in accord with results of Sykes and Karplus who estimated a torsional angle of 30-40°.[5] The most serious non-bonded interaction occurs between H-8 and the methyl groups at C-1 within a planar s-trans diene conformation. Not surprisingly, therefore, compound 6 -without geminal methyl groups at C-1- appears to exist in an s-trans diene conformation based on the observed Overhauser enhancements.

Table Overhauser enhancements [%] observed for the resonances of H-7 and H-8 in 1, 5 and 6 (400 MHz, CD_2Cl_2, 25°C)

		1	5	6
Irradiation of:				
H-1a, 1a'	H-7	15	13	
	H-8	10	12	
H-5a (H-5)	H-7	7	6	21
	H-8	9	10	3
H-9a	H-7	13	10	14
	H-8	9	7	9

The longe range coupling constants between protons of the ring and of the side chain were determined by an exact analysis [^5J (H-4, H-7) = 1.60 (1)[5]; 1.13 (5); < 0.5 Hz (6); 0.64 (7), ^6J (H-4, H-8) = 0.75 (5), 0.88 (7) Hz]. Particularly significant for the conformational problem is the homoallylic coupling ^5J (H-4, H-7) since it is positive and its $^{\pi}J$-term proportional to $\sin^2 \varphi$.[5] While a differentiation of the s-cis and s-trans isomers is not straightforward it is obvious from the data that upon going from 1 to 6 and 7 a coplanar arrangement of ring and side chain becomes more favorable. Compound 6 is best described (see below) as adopting a more or less planar s-trans conformation.

To conclude, the dominance of a (twisted) s-cis diene conformation in 1 results from a

subtle balance of non-bonded H-H-interactions: the enone side chain fits into the pocket formed by the methyl groups at C-1 and C-5. "Successive" demethylation of β-ionone or methyl substitution in the side chain systematically affect the diene conformation. This must also hold for the corresponding retinal analogues in which the "longitudinal restriction" for the opsin formation[8] (i.e. the distance between the lipophilic cyclohexene ring and the hydrophilic oxygen) is expected to vary drastically.

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