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ASSIGNMENT OF RELATIVE CONFIGURATIONS TO DIASTEREOMERIC CARBINOLS WITH LANTHANIDE SHIFT REAGENT[Eu(fod)$_3$]

APPLICATION TO 1-MESITYL-2-METHYL-3-PHENYL-1-PROPANOL†

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Abstract—Assignment of relative configurations to the diastereomeric racemates (1*R*2*R*, 1*S*2*S*) and (1*R*2*S*, 1*S*2*R*) of 1-mesityl-2-methyl-3-phenyl-1-propanol was carried out, by studing the chemical shifts induced by Eu(fod)$_3$ an the signal of the Me group in position 2, taking into account a prior estimate of the populations of significant forms in both diastereomers.

Following the discovery of some coordination complexes of lanthanide elements as shifting inducing reagents (LSR) in ^{1}H and ^{13}C NMR, numerous studies of Lanthanide Induced Shifts (LIS) have been performed in organic compounds. In these heteroatoms that can intervene as coordinating atoms in the formation of complexes with these reagents must be present.[1,2] These studies include establishment of the molecular shape of such complexes in structurally rigid systems,[2–4] identification of isomers,[2] determination of the composition of mixture,[2,5] determination of the optical purity of enantiomers,[6–8] conformational analysis of simple cyclic[9] and acyclic systems[10]—conformers *s-cis* and *s-trans* of aldehydes, ketones, esters and amides of the α, β-unsaturated type.[10] The procedure has been applied also to mixtures of epimers of acyclic secondary alcohols having an asymmetrical C atom,[11] cyclic secondary alcohols[12] and primary carbinols having the asymmetrical C atom in position 2,[13] through prior formation of their diastereomeric 2-methoxy-α-trifluoromethylacetates (MTPA), on the basis of the LIS values of the MTPA OMe group in both diastereomers and of the application of McConnell-Robertson's equation.[14]

Assignment of relative configurations to diastereomeric secondary acyclic carbinols with two asymmetrical C atoms has been done for the first time in this work, by studying the Eu(fod)$_3$ induced chemical shifts on the signal of the protons of the Me group in position 2 of the (1*R*2*R*, 1*S*2*S*) and (1*R*2*S*, 1*S*2*R*) diastereomeric racemates of 1-mesityl-2-methyl-3-phenyl-1-propanol, taking into account a prior estimate of the significant conformational populations in both diastereomers.

Conformational analysis

After careful examination of the Dreiding models of all possible alternating conformations of both diastereomers and the semi-quantitative determination of their relative conformational free energies we selected the significant conformers of each diastereomer: I, II, III and IV for isomer 1*S*2*S* and V, VI and VII for isomer 1*R*2*S* (Fig. 1).

The semi-quantitative calculation of the populations of these conformers has been carried out by means of an evaluation of their relative conformational free energy values and applying the method already described,[15] computing the differential steric interactions and estimating their energy content. The results are collected in Table 1.

EXPERIMENTAL

M.ps are uncorrected. IR spectra have been recorded between NaCl windows in the case of liquid products or in KBr tablet for solids, in a Perkin–Elmer 257 spectrophotometer. The ^{1}H NMR spectra have been recorded with a Varian A-60 spectrometer, using TMS as internal reference.

The α and β diastereomeric racemates of 1-mesityl-2-methyl-3-phenyl-1-propanol were obtained by reduction of (±) 1-mesityl-2-methyl-3-phenyl-1-propanone with LAH (unpublished results). Separation was performed by careful fractional crystallization of their 3,5-dinitro-benzoates (DNB) in EtOH.

DNB-α: m.p. = 158–9° (Found: C, 67.46; H, 5.17; N, 5.97. Calc. for $C_{26}H_{26}N_2O_6$: C, 67.51; H, 5.66; N, 6.05%). IR (KBr), ν_{max} = 1730 cm^{-1}. ^{1}H NMR (CDCl$_3$), δ: 0.75 (d, 3H, J = 6Hz); 2.15 (s, 3H); 2.45 (s, 6H); 1.70–3.06 (m, 3H); 6.15 (d, 1H, J = 10 Hz); 6.65 (s, 2H); 6.70–7.03 (m, 5H); 8.55–8.80 (m, 3H).

DNB-β: m.p. = 147–8° (Found: C, 67.23; H, 5.29; N, 5.86. Calc. for $C_{26}H_{26}N_2O_6$: C, 67.51; H, 5.66; N, 6.05%). IR (KBr), ν_{max} = 1730 cm^{-1}. ^{1}H NMR (CDCl$_3$), δ: 1.03 (d, 3H, J = 6 Hz); 2.20 (s, 3H); 2.53 (s, 6H); 1.70–3.36 (m, 3H); 6.15 (d, 1H, J = 10 Hz); 6.65 (s, 2H); 6.38–7.16 (m, 5H); 8.80 (s, 3H).

The pure α and β diastereomeric racemates were obtained by saponification of the separated DNBs, by reflux heating for 75 hr of a mixture containing amounts proportional to 1.8 mmoles of

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†Part VI *Conformational study of diastereomers*. Part V of this series: Ref. 15 in this paper.

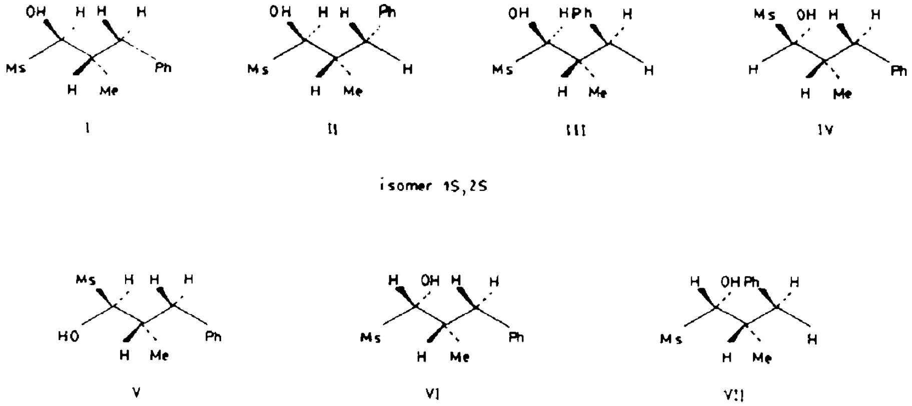

Fig. 1.

ester, 8 mmoles of NaOH, 8 mmoles of KOH, 20 ml of distilled water and 20 ml of EtOH. The mixture was then extracted with ether and the usual working technique was followed, yield: 100%. They were purified through percolation in a silica gel column using CH_2Cl_2 as elution solvent, and obtaining two viscous liquids. Purity was verified by gas chromatography (stationary phase 10% APIEZON on 1/8 in. 2 m W-AW Chromosorb, column temp. 240°C, flow rate 50 ml/min) and the standard spectroscopy methods.

^1H NMR *spectra*. The ^1H NMR spectra of the α and β isomers were recorded using an A-60 Varian spectrometer. Solns of the racemic carbinols 13% by volume in CCl_4 at 303°K were used, with TMS as internal reference.

Weighed amounts of $Eu(fod)_3$ were then added in increments to achieve different lanthanide/carbinol molar ratios (l_0/s_0). Tables 2 and 3 show the results.

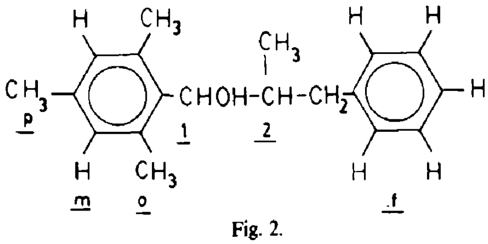

Fig. 2.

α-Isomer. δ 0.45 (d, 3H; J = 6 Hz); 2.14 (s, 3H); 2.30 (s, 6H); 1.76–3.43 (m, 3H); 4.6 (d, 1H, J = 9 Hz); 6.60 (s, 2H); 7.06 (m, 5H).

β-Isomer. δ 0.91 (d, 3H; J = 6 Hz); 2.13 (s, 3H); 2.26 (s, 6H); 1.2–3.0 (m, 3H); 4.56 (d, 1H; J = 8 Hz); 6.53 (s, 2H); 6.87 (m, 5H).

DISCUSSION OF RESULTS

The assignment of relative configurations (*RR*, *SS*) and (*RS*, *SR*) to the diastereomeric racemates of 1-mesityl-2-methyl-3-phenyl-1-propanol has been performed according to the McConnell–Robertson equation[14] (eqn 1). This correlates the limiting chemical shift Δ_l (Limit LIS) with a geometric factor of the molecule (G) and a constant (K) related to the ability of formation of the lanthanide-substrate association complex, which is characteristic for each compound:

$$\Delta_l = K.G;\ G = \frac{3\cos^2\theta - 1}{r^3}. \qquad (1)$$

In (1) r stands for the modulus of the vector linking the paramagnetic centre (lanthanide) to the nucleus considered, θ for the angle defining that vector with respect to the z axis, taking the lanthanide nucleus as co-ordinate origin.

The limiting chemical shifts Δ_l for the different protons in the molecule are the slopes of the straight lines resulting from the diagramm of $\Delta\delta$ vs the molar ratios[2] l_0/s_0. The results of a linear multiple regression are presented in Table 4.

The assignment of absolute configurations to enantiomeric carbinols having an asymmetrical C atom has been discussed in the literature,[11–13] on the basis of the limit LIS values induced by $Eu(fod)_3$ on the signal of the OMe group of the diastereomeric MTPA esters obtained from each one of the enantiomeric carbinols. The authors correlate different limit LIS values with different K constants (eqn 1) considering that the geometric factor G is the same for both isomers. The different values values of the constant K corresponding to the $Eu(fod)_3$ association are a function of the different steric hindrance exerted by the groups of the chiral centre (*R* or *S*) of the original carbinol.

In the present case, the above methodology can not be applied since the geometric factor G corresponding to the protons whose signals have different Δ_l values for each one of the diastereomers (Me group bound to C_2) is different for each isomer. Therefore, the assignment of relative configurations has been based upon the fact that the constant K is the same for both diastereomers because the limit [LIS] values observed for the protons of the p-Me of the mesityl group and the H atom bound to C_1 (Table 4), as well as their geometric factors are identical for both diasteremers. Therefore, the limit LIS, Δ_l, for other signals shall be directly proportional to the geometric factor G, so that different values of the parameter Δ_l should correspond to different shapes, that is to say, to different relative positions of the grouping considered and of the lanthanide in each diastereomer.

According to the former consideration, the assignment of relative configurations to the α and β isomers of 1-mesityl-2-methyl-3-phenyl-1-propanol must be based upon the different values observed for parameter Δ_l of the Me group linked to C_2 in each diastereomer: 9.19 for isomer α; and 3.23 for isomer β (Table 4).

Assignment of relative configurations.

Due to the molecular complexity of the compounds studied in this work, the determination of the geometric parameter θ and r for the various protons in the mole-

Table 1. Steric 1,3-parallel interactions present in selected conformers and tentative conformational populations of (1*S*, 2*S*) and (1*R*, 2*S*)-1-mesityl-2-methyl-3-phenyl-1-propanol

Conformer	1,3-parallel interactions[a]	Contribution of the ortho-methyl groups of mesityl (kJ.mol^{-1}).[b]	Energy value (kJ. mol^{-1})	N_i
I	(OH-H) + 2(Ph-H)	8.8	22.7	0.74
II	(OH-H) + 3(Ph-H)	8.8	29.0	0.06
III	(OH-Ph) + (Ph-H)	8.8	28.1	0.08
IV	2(OH-H) + 2(Ph-H)	12.1	27.3	0.12
V	(OH-H) + 2(Ph-H)	8.8	22.7	0.76
VI	2(OH-H) + 2(Ph-H)	12.1	27.3	0.12
VII	2(OH-H) + 2(Ph-H)	12.1	27.3	0.12

a) The energy contents of these interactions were taken from the literature (15) : (OH-H) = 1.3 kJ mol^{-1}; (Ph-H) = 6.3 kJ.mol^{-1}; (Ph-OH) = 13.0 kJ.mol^{-1}.

b) The energy content of 1,3-parallel esteric interactions between the mesityl group, Ms, and the remaining groups, X, in accordance with a precedent in the literature[16], has been estimated as the sum of a 1,3-parallel esteric interaction type (Ph-X) and the contribution of the o-methyl groups, for which a minimum content has been considered, for a value of 60° of the dihedral angle defined by the plane of the aromatic ring of the mesityl group and the C_1-OH bond.

Table 2. Chemical shifts (δ) and Lanthanide Induced Shifts ($\Delta\delta \equiv$ LIS) of the methyl group of C2, in the α and β diastereomers, for various molar ratio (I_0/s_0)

	α Diastereomer		β Diastereomer	
I_o/s_o	δ	$\Delta\delta$	δ	$\Delta\delta$
0	0.45	0	0.91	0
0.22	2.96	2.51	1.33	0.42
0.29	3.56	3.11	1.66	0.75
0.37	4.26	3.81	2.05	1.14
0.42	4.48	4.03	2.13	1.22
0.52	5.23	4.78	2.56	1.65

Table 3. Chemical shifts (δ) an Lanthanide Induced Shifts ($\Delta\delta \equiv$ LIS) of commons resonance signals in both diastereomers, for various molar ratio (l_0/s_0)

l_0/s_0	p-CH$_3$ (a		o$_1$-CH$_3$ (a		o$_2$-CH$_3$ (a		m-H (a		H$_1$ (b		H$_f$ (c	
	δ	$\Delta\delta$	δ	$\Delta\delta$	δ	$\Delta\delta$	δ	$\Delta\delta$	δ	$\Delta\delta$	δ	$\Delta\delta$
0	2.13	0	2.26	0	2.26	0	6.50	0	4.56	0	6.87	0
0.22	2.30	0.17	3.03	0.77	3.26	1.00	7.03	0.53	5.96	1.40	7.25	0.38
0.29	2.43	0.30	3.40	1.44	3.63	1.37	7.25	0.75	6.70	2.14	7.35	0.48
0.37	2.53	0.40	3.76	1.50	4.05	1.79	7.45	0.95	7.16	2.60	7.48	0.61
0.42	2.55	0.42	3.85	1.59	4.15	1.89	7.50	1.00	7.30	2.74	7.60	0.73
0.52	2.66	0.53	4.23	1.97	4.53	2.27	7.73	1.23	8.13	3.57	7.70	0.83

a) Signals of the different types of protons of the mesityl group: p-CH$_3$: methyl group at para; o$_1$-CH$_3$ and o$_2$-CH$_3$: methyl groups at ortho; m-H: hydrogen atoms at meta.

b) Signal of hydrogen atom linked to C$_1$.

c) Signal corresponding to the multiplet of the five hydrogen atoms of the phenyl group linked to C$_3$ (measured at the centre of gravity).

Table 4. Limiting Chemical Shifts (Δ_l) for the different protons in the *α* and *β* diastereomers of the 1-mesityl-2-methyl-3-phenyl-1-propanol

	α Diastereomer	β Diastereomer	α and β diastereomer					
	CH_3 bound to C_2	CH_3 bound to C_2	H_1	p-CH_3	O_1-CH_3	O_2-CH_3	m-H	H_f
Δ_l	9.195	3.234	6.832	1.050	3.856	4.448	2.390	1.633
Ordinate at the origin	0.251	-0.118	0.003	-0.015	-0.008	0.037	0.018	0.005
Correlation coefficient	0.991	0.983	0.996	0.991	0.997	0.996	0.997	0.996

Table 5.

	CH_3 bound to C 2							
	α Diastereomer	β Diastereomer	H_1	O_2-Me	O_1-Me	m-H	H_f	p-Me
Δ_l	9,19	3,23	6,83	4,45	3,86	2,39	1,63	1,05
r' (Å)	2,9	3,7	2,0	3,1	4,0	5,2	6,0	6,5

cule and for each one of the significant alternating conformations of each isomer is not possible in practice, and therefore a simplified expression for the geometric factor G has been admitted (eqn 2), whose validity for solving stereochemical problems is already justified in the literature.[2,17]

$$G = 1/r^3. \tag{2}$$

According to this simplification and to eqn (1), we can state eqn (3) introducing the numerical values observed for parameter Δ_1 of the Me group linked to C_2 in each of the isomers.

$$\Delta_1{}^{\alpha}/\Delta_1{}^{\beta} = r_\beta{}^3/r_\alpha{}^3 = 2.84. \tag{3}$$

That is to say, $r_\beta = 1.42\, r_\alpha$, so that the distance between the Europium nucleus in the Eu(fod)$_3$-carbinol complex and the C_2 Me group must be larger in the β isomer than in the α isomer. In this manner, based upon the previous conformational analysis which allows to affirm that in the (*RS, SR*) isomer all significant conformers present a sinclinal relative orientation between the C_2 Me group and the OH group, while in the (*RR, SS*) isomer the relative orientation of both groups is antiperiplanar in 90% of the conformers, it can be unmistakably affirmed that isomer α has a relative configuration (*RS, SR*) and isomer β (*RR, SS*).

Additional considerations

The differentiation of the two *o*-Me groups from the mesityl rest by means of the parameters Δ_1 (Table 4; entries o_1-Me and o_2-Me) can only be justified on the basis of a restricted rotation of the mesityl group. This assumption is qualitatively confirmed by the conformational analysis with Drieding models, allowing to determine an approximative angle of 60° between the plane of the aromatic ring of the mesityl group and the C_1–OH band.

On the other hand, parameters Δ_1 corresponding to the protons o_1-Me, o_2-Me, *m*-H and H_f are identical for the two diastereomeric racemates, this being justified since the spatial arrangement of each of these protons with respect to the hydroxyl group is identical in both diastereomers.

Finally, we have verified the consistency of the experimental results obtained through a semi-quantitative determination of the slope and the ordinate value at the origin for eqn (4):

$$\log \Delta_1 = \log K - a \log r' \tag{4}$$

resulting from the simplification already proposed in the literature[2] for the logarithmic form of the simplified McConnell–Robertson equation (eqn 5):

$$\log \Delta_1 = \log K - 3 \log r \tag{5}$$

where a must be equal to or smaller than 3, r′ being the distance of the nucleus in question to the coordination centre, measured on Dreiding models[2] (Table 5).

The diagram representing these data by means of a least square linear regression is a straight line having a slope of 1.64; ordinate value at the origin 1.49, corresponding to a K value of 30.8, and a correlation coefficient $r = 0.913$. If proton H_1 having the lowest r' value and hence the largest influence on the angular term of G is disregarded, the experimental results conform to a straight line having a slope of 2.10; an ordinate value at the origin of 1.81, corresponding to $K = 64.1$; and a correlation coefficient $r = 0.950$. The values found for the slope are of the same order than those formerly described in the literature.[2]

The fact that the experimental values obtained conform to a straight line, irrespective of the alternative selected, confers validity to the two fundamental hipothesis on which the assignment of configurations performed above is based: one common constant K for both diastereomeric racemates, and the simplification of McConnell–Robertson's equation (eqns 2 and 5).

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