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Hydroxypinanone : Solute/solute Interactions and Non-linear Chiroptical Properties.

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Abstract : *The non-linear behaviour of the optical rotation in* $CHCl_3$ *and EtOH of a rigid hydroxyketone often used as chiral auxiliary in enantioselective syntheses is described. It is also shown that ethanol in spite of its ability to disrupt solute/solute interactions through H-bond formation leads also to significant discrepencies.* © 1997 Elsevier Science Ltd.

During work concerning the use of hydroxypinanone 1 as chiral auxiliary[1] we have noted larger than expected variations of the optical rotation between samples prepared (by the usual MnO_4K oxidation[2]) from α-pinene samples of known different enantiomeric purities. A close examination of the crystallographic data[3] showed a "zig-zag chain" arrangement of the molecules through strong H-bonds (O-H...O ; $l_{(O...O)}$ = 2.84 Å) suggesting that solute/solute interactions could still be present in solution, thus explaining the observed variations.

This effect of solute/solute interaction on chiroptical properties, discovered by Krow in 1968,[4] was, since the work of Horeau,[5] widely accepted and used in the cases of acids, amino acids and/or amides but otherwise underestimated and not even considered.

We report here the non-linear behavior of an hydroxyketone often used as chiral auxiliary in enantioselective syntheses, the hydroxypinanone 1.

Variations of $[\alpha]_D^{24}$ (equat. 1), $[\alpha]_D^{24}$ Max (equat. 2) and E% (equat. 3) as a function of the concentration have been studied for samples of different and known enantiomeric purities.

(1) $[\alpha_o]_D^{24}$ or $[\alpha]_D^{24} = \alpha_D^{24} / l.c$ (l in dm, c in g/mL)
(2) $[\alpha]_D^{24}\text{Max} = [\alpha]_D^{24} / \text{e.e.}$ with e.e. = R - S / R + S (from GC results)
(3) $\text{E \%} = [\alpha_o]_D^{24} - [\alpha]_D^{24}\text{Max} / [\alpha_o]_D^{24}$ (deviation from linearity, *cf.* ref. 5)
(4) $\text{o.p.\%} = 100 \,.\, [\alpha]_D^{24} / [\alpha_o]_D^{24}$

The results are gathered in Tables 1 and 2.

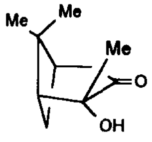
The concentrations have been obtained by dilution (at ~24°C) from a starting 5% concentrated solution obtained from 1.25 ± 0.005 g. of hydroxypinanone 1 of the desired enantiomeric purity and 25 ± 0.04 mL of the desired solvent (of spectroscopic purity). The optical rotations (measured at 24°C on an electronic polarimeter) were in the range 2° to 0.3° ± 0.002°. The errors on $[\alpha]_D$ have been calculated to be in the range 0.6-0.9% for [c]=5% and in the range 2.3-2.7% for [c]=2%.The enantiomeric purities of the hydroxypinanone samples were determined by GC (on a CP-chirasyl-DEX CB column) to be : **I**(-) = 100% ; **II**(+) = 90% and **III**(+) = 70% (± 0.05%).

Although the variations of $[\alpha_o]_D^{24}$ (Table 1) and of $[\alpha]_D^{24}$ (Table 2, lines 2 and 6) are within experimental errors, the values of $[\alpha]_D^{24}$Max calculated using the GC-determined enantiomeric purities (equat. 2) exhibit noticeable deviations and are either over-estimated (compare line 1 with line 3 in Table 2) or under-estimated (compare line 1 with line 7 in Table 2). The Horeau's effect, E% (equat. 3), is thus negative for sample **II**(+)-90% e.e. in $CHCl_3$ and positive for sample **III**(+)-70% e.e. in $CHCl_3$ and EtOH.

Table 1 : $[\alpha_o]_D^{24}$ of Hydroxypinanone 100% e.e. (**I(-)**)

[c]^a	$[\alpha_o]_D^{24}$ in $CHCl_3$	$[\alpha_o]_D^{24}$ in EtOH
5	-40.8 ± 0.25	-21.4 ± 0.15
4	-41.4 ± 1.20	-22.5 ± 0.65
3	-41.4 ± 1.45	-22.9 ± 0.80
2	-41.1 ± 0.95	-22.6 ± 0.60

a) in g/100 mL



1 (+)-*RRR*

Table 2 : $[\alpha]_D^{24}$, $[\alpha]_D^{24}$Max, E% and optical purities for **II(+)**-90% ee and **III(+)**-70% ee.

		[c] in $CHCl_3$ ^{a}				[c] in EtOH ^{a}			
e.e. ^{b}		5	4	3	2	5	4	3	2
100%^{c}	$[\alpha_o]_D^{24}$	+ 40.8	+ 41.4	+41.4	+ 41.1	+ 21.4	+ 22.5	+ 22.9	+ 22.6
II (+) **90%**	$[\alpha]_D^{24}$	+ 38.7	+ 39.8	+ 40.1	+ 39.6	+ 19.2	+ 21.2	+ 19.5	+ 18.7
	$[\alpha]_D^{24}$Max	+ 43.0	+ 44.2	+ 44.5	+ 44.0	+ 21.3	+ 23.5	+ 21.7	+ 20.8
	E%	-5.5	-7	-7.5	-7	+ 0.5	- 4.5	+ 1	+ 8
	o.p.%	95	96	97	96	90	94	85	83
III (+) **70%**	$[\alpha]_D^{24}$	+ 24.6	+ 25.2	+ 25.0	+ 25.0	+ 13.1	+ 13.0	+ 13.9	+ 13.1
	$[\alpha]_D^{24}$Max	+ 35.1	+ 36.0	+ 35.7	+ 35.7	+ 18.7	+ 18.5	+ 19.8	+ 18.7
	E%	+ 14	+ 13.0	+ 13.0	+ 13	+ 12.5	+ 18	+ 13.5	+ 17
	o.p.%	60	61	60	61	68	61	71	70

a) in g/100 mL ; errors on [α] follow the same trend as in Table 1. b) e.e. determined by GC (*cf.* text). c) obtained from the values of the (-) enantiomer,Table 1.

Most important are the ***calculated optical purities****, o.p.%, which are, in both solvents,* ***significantly different from the enantiomeric excesses*** *(determined by chromatography) and are* ***unpredictably either overestimated or underestimated.***

One must note also that ***EtOH is not as good a solvent as expected on the basis of its ability to provide, through H-bonds, solute/solvent interactions strong enough to reach the rotation of the solvated substrate-monomer.*** *And it is worth noting that dilution would lead to still worse results because of experimental errors on determination of [α] which take over.*

This new example acts as a reminder and note that, in asymmetric and total syntheses' papers, ***when using specific rotations, the conclusions concerning enantiomeric purities are nothing but indicative and rotations values should be given without decimals.***

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