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DETERMINATION OF ENANTIOMERIC PURITY OF GLYCOLS RCHOHCH$_2$OH

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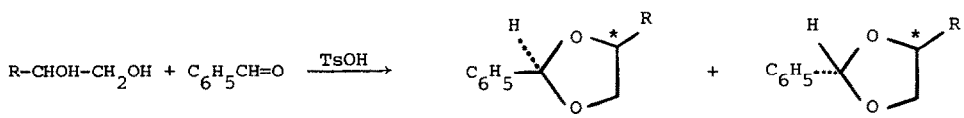
Abstract. The enantiomeric purity of primary-secondary glycols, RCHOHCH$_2$OH, is conveniently determined by conversion to a pair of epimeric 1,3-dioxolanes through condensation with benzaldehyde, followed by nmr spectroscopy in presence of a chiral shift reagent with observation of the benzylic protons.

Chiral glycols are sometimes of interest as synthetic intermediates. Recently, a synthesis of chiral primary-tertiary glycols, RR'COHCH$_2$OH, has been described;[1-3] their enantiomeric purity was readily determined[3] by conversion to diastereomeric esters (at the primary alcohol function) using a chiral acid, such as Mosher's acid,[4] $C_6H_5C(OCH_3)CF_3CO_2H$, and determining the composition of the resulting esters by proton nmr. Alternatively, the enantiomeric purity can be determined directly[3] by means of chiral europium shift reagents in proton nmr.[5]

Similar methodology fails for primary-secondary glycols, RCHOHCH$_2$OH. Esterification using chiral acids is equivocal, since either the primary or the secondary alcohol function or both may react.[6] The use of chiral shift reagents is virtually precluded by the complexity of the ABC spin system of the glycol.

We have found that the enantiomeric purity of such glycols can be conveniently determined by chiral shift reagents after first converting the glycols to 2-phenyl-1,3-dioxolanes by condensation with benzaldehyde. Treatment of the glycol with benzaldehyde and a trace of acid for a very short time (<15 mins) leads to a mixture of cis and trans isomers of dioxolanes (in unequal amounts) as shown in Scheme 1. The benzylic protons in these 2-phenyldioxolanes are



Scheme 1

easily seen in the proton nmr at low field (δ 5.6-6.2 ppm), two distinct signals being discerned for the two diastereomers (Table 1). The cis or trans configuration of the two dioxolanes was deduced from the relative shift of H(2) (Table 1) by analogy with earlier results,[7] from the upfield C-13 shift of C(2) in the trans isomers by similar analogy,[8] and from the fact that the cis isomer has a more open face than the trans as evidenced by the

better resolution (Table 1) in the cis series on complexing (believed to be stronger in this series) and by the fact that the cis isomer has the longer retention time in column chromatography, i.e. is more strongly adsorbed. Upon addition of a chiral shift reagent

Table 1

Benzaldehyde Derivatives of Glycols,

$RCHOHCH_2OH$ in Absence and Presence of $Eu(hfc)_3$

R in Glycol (Scheme 1)	d.e.%[a]	δ[b] A	δ[b] B	Mole ratio[c]	Δδ[d] A	Δδ[d] B	e.e.%[e]
CH_3		5.94	5.80	0.17	0.13	0.14	0[f]
$\underline{n}$-C_6H_{13}	35,85,99[g]	5.91	5.78	0.08	0.11	0.16	36,84,98[g]
n-C_8H_{17}		5.83	5.71	0.22	0.09	0.11	0[f]
$(CH_3)_2CHCH_2$		5.87	5.73	0.13	0.08	0.12	0[f]
$(CH_3)_2CH$	78	5.89	5.78	0.28	0.06	0.08	78[h]
cyclo-C_6H_{11}	96,94[g]	5.87	5.76	0.14	0.04	0.08	95,94[g,i]
$(CH_3)_3C$	91	5.88	5.61	0.18	0.08	0.15	93
C_6H_5		6.16	5.97	0.10	0.02	0.06	0[f]

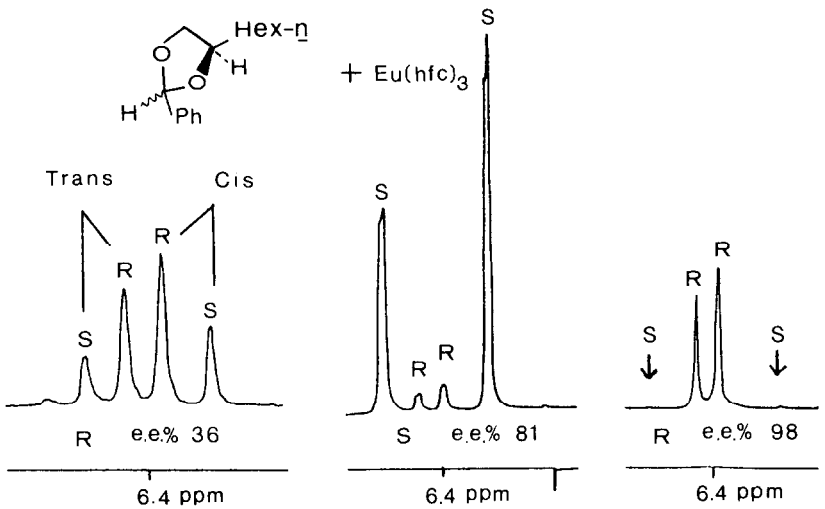
[a]Diastereomer excess in glycol precursor. [b]Shift (ppm from TMS) of H(2) in 2-phenyldioxolanes in absence of shift reagent: A, trans isomer; B cis isomer. [c]Mole ratio of $Eu(hfc)_3$ to glycol. The optimal ratio should be determined by trial and error, since it seems to depend not only on the nature of the glycol, but also on the presence, if any, and nature of impurities (which may also complex). [d]Differential shift (ppm) for the two enantiomers of diastereomers A and B, respectively, in the presence of the amount of $Eu(hfc)_3$ indicated. [e]Average of two determinations (for the cis- and trans-2-phenyl-4-alkyl-1,3-dioxolanes). Generally these determinations were within 1% of each other. Absolute accuracy is estimated as ±2%. [f]Racemic diol. [g]Samples of different diastereomeric (or enantiomeric) purity. [h]Since the "inner" peaks (Fig.1) originating from the two diastereomers (A,B) were not well resolved, the e.e. was calculated from the ratio of the sum of the inner peaks (from major enantiomer) to the sum of the outer peaks (from minor enantiomer). [i]Also a sample with 68±1% e.e. as determined by Meyers' method[9] analyzed for 66% e.e.

[$Eu(hfc)_3$], both benzylic proton signals are seen to double, since each enantiomer (at the starred chiral center) of each diastereomer will give its own signal in presence of the chiral complexing agent.

Typical results (for $\underline{n}$-$C_6H_{13}CHOHCH_2OH$) are shown in Fig. 1. It is evident that two ratios (for the two diastereomers) are obtained in each experiment, thus affording an internal consistency check.

In Table 1 are shown chemical shift data for the 2-phenyldioxolanes derived from various glycols (Scheme 1) in the absence and presence of $Eu(hfc)_3$. In the case of the optically active compounds, the glycols were synthesized from precursors of known stereoisomeric purity,[9] so that, assuming absence of racemization, their enantiomeric purity should be estimated.

Pertinent figures are included in the Table; clearly, there is good agreement between the stereoisomeric purity of the precursors and that of the glycols determined by the method here described.



250-MHz spectra of three $Eu(hfc)_3$ doped samples of 2-phenyl-4-n-hexyl-1,3-dioxolanes in $CDCl_3$.

Fig. 1

A.I. Meyers and coworkers have elaborated an independent method for the determination of enantiomeric purity of glycols $RCHOHCH_2OH$, described in the adjoining letter.[10] In one case where both methods were applied (cyclohexylethylene glycol), their results were 68±1% and ours 66±2%, in good agreement. The 2-n-propylcyclohexanone ketal method[10] has the advantage that the enantiomeric excess of the glycol may be determined by hplc as well as by nmr; the hplc determination is more accurate. The advantage of the benzaldehyde acetal - europium shift reagent method is that all necessary reagents are readily available; the required ratio of shift reagent to glycol is 10-30 mol%.

Experimental: The preparation and analysis of 4-n-hexyl-2-phenyl-1,3-dioxolane is described as being typical.

A mixture of 1,2-octanediol (120 mg, 0.82 mmol), benzaldehyde (105 mg, 20% excess) and p-TsOH (~5 mg) in dry benzene (50 mL) was refluxed under nitrogen for 10-15 min in a flask equipped with a Dean and Stark trap. The solution was cooled, washed, successively, with 10 mL of 2% Na_2CO_3 solution, 10 mL of water, 20 mL of 35% $NaHSO_3$ and 10 mL of water, dried (Na_2SO_4) and concentrated. The residue was Kugelrohr distilled (0.05 mmHg 120-125°) to give 180 mg (94% yield) of 1,3-dioxolanes, consisting of cis and trans isomer in a 55:45 ratio. ^{13}C NMR ($CDCl_3$) for cis δ 138.2, 129.2, 128.3, 126.7, 104.0, 77.5, 70.2, 33.5, 31.8, 29.3, 25.8, 22.6, 14.0, for trans[10] 129.0, 128.3, 126.4, 103.1, 76.0, 70.8, 33.4, 31.8, 29.3, 25.8, 22.6, 14.1. Anal.calc'd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.40. Found: C, 76.75; H, 9.39.

To ca. 50 mg of the above dioxolane mixture in ca. 0.6 ml of $CDCl_3$ in a 5-mm nmr tube portions of $Eu(hfc)_3$ were added in 5 mg increments until separation of the four peaks (Fig. 1) was satisfactory. The separation of the peaks was monitored in a 60-MHz instrument; but for accurate measurements the solution was suitably diluted and the relative peak areas determined in a Bruker WM-250 FT nmr spectrometer at 250 MHz. It is desirable to work out the procedure with racemic material before applying it to resolved or partly resolved dioxolanes. Results are shown in Table 1. (Assignment of R and S configuration was made independently from optical rotation measurements.[12])

In the case of one of the samples of chiral 1,2-octanediol, $n\text{-}C_6H_{13}CHOHCH_2OH$, a check for possible racemization during dioxolane formation was performed by hydrogenolysing the dioxolane (Scheme 1, R = $n\text{-}C_6H_{13}$) back to the original glycol by means of hydrogen over palladium on charcoal. The rotation of the recovered glycol was, within experimental error, the same as that of the starting glycol, indicating that no racemization had occurred.

References and Footnotes

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