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DETERMINATION OF ENANTIOMERIC COMPOSITION OF CHIRAL 2-SUBSTITUTED-1,2-GLYCOLS VIA ^{13}C-NMR and HPLC

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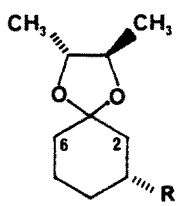
Summary: By use of ^{13}C analyses and/or HPLC, the diastereomers derived from acetal formation of S(+)-2-propylcyclohexanone and 1,2-glycols may be quantitatively determined.

The advent of successful asymmetric synthetic procedures has necessitated analytical methods to determine the degree of enantiomeric excesses. Several techniques have proven very valuable in this regard, namely chiral shift reagents[3], Mosher esters[4], and chromatographic methods on chiral columns[5]. In 1977, Wynberg reported[6] the enantiomeric purity of 3-substituted cyclohexanones as their cyclic acetals, 1, by observing diastereomeric ^{13}C signals at



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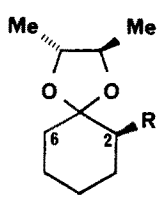

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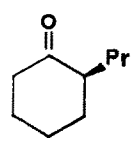

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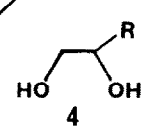

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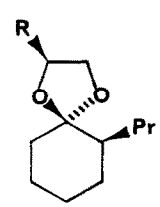

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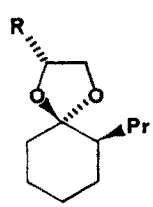

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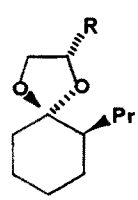
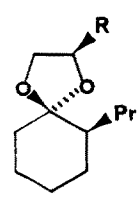


5C



5D

C-2 and C-6. More recently, we have utilized this method to determine the enantiomeric purity of 2-substituted cyclohexanones, 2[7]. In the latter study, enantiomeric excesses of ketones were achieved up to 99% in many cases. Because S(+)-2-propylcyclohexanone 3[7] could be conveniently prepared in multi-gram quantities and exhibited excellent stability toward racemization, we felt it would have the potential for assessing enantiomeric purities of 1,2-glycols, 4[8]. This, indeed turned out to be correct and the glycols could be analyzed for enantiomeric purity using either ^{13}C-spectroscopy or HPLC techniques. When 3 was heated with various racemic or enantiomerically enriched glycols in dry, distilled methylene chloride in a flask fixed with a Dean Stark trap containing a small amount of $MgSO_4$ to azeotropically remove water, the acetals 5A-5D were formed (4-18 h as determined by GLC)[9]. Due to the fact that the acetal carbon represents a new chiral center, four diastereomers were produced. However the racemic

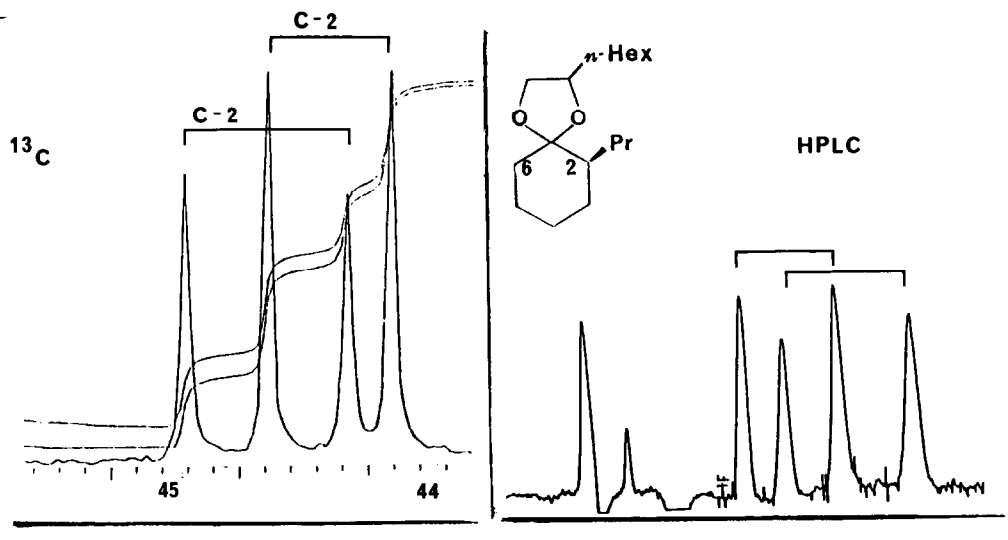
TABLE 1. Percent Enantiomers of 5 Using Both ^{13}C-NMR or HPLC

	^{13}C-NMR (90.5 MHz)		HPLC	
R	δC-2 (%)	δC-6 (%)[a]	T_R (min)	% A-D (% AB,CD)
(±)-Me	45.12 44.73	36.52 36.26 (50±1)	9.80	29[b]
	44.32 --	35.40 34.95 (50±1)	12.3	71[b]
(+)-Me (62.3% ee)	45.14 44.71	36.52 36.68 (82.2) (17.8)	b	
	44.32	35.41 34.91 (80.6) (19.4)		
(±)-n-Bu	45.09 44.36 (50±2)	36.48 36.14 (50±1)	6.45 7.10	20.6 28.5 (49.1)
	44.70 44.21 (50±2)	35.12 34.78 (50±1)	7.90 8.90	20.9 29.8 (51.7)
(±)-n-Hex	44.99 44.26 (50±1)	36.38 36.09 (50±1)	6.40 7.90	20.8 31.8 (52.6)
	44.65 44.16 (50±1)	35.12 34.73 (50±1)	7.05 9.10	23.1 31.2 (54.3)
(±) CH_2CH_2OMe	45.02 44.07 (50±1)	36.40 36.09 (50±1)	c	
	44.33 44.19 (50±1)	35.11 34.75 (50±2)		
(+) Cyclohex (66% ee)	d	d	8.8 9.9	6.9 9.0 (15.9)
			9.4 10.5	36.0 48.1 (84.1)

a) From peak integration. b) Only two pairs of diastereomers are observed, 5A,5B and 5C,5D. It is not known which pair is the faster eluting. c) Not completely resolved into the four diastereomers. d) Not attempted.

diols, 5A and 5B (and 5C and 5D) showed 1:1 peak height in the ^{13}C spectrum or the HPLC trace. The ratios of (5A, 5B) to (5C, 5D) were usually different due to the thermodynamic stability of each pair (usually ∿65:35). Since all four peaks (5A-5D) were base line separated, integration of the areas was a simple matter either by NMR and/or HPLC methods. Table 1 reveals the data via both techniques which allowed assessment of the enantiomeric composition. From Table 1 it is seen that all the acetals were cleanly separated in the ^{13}C-NMR either at C-2 or C-6 to give the expected ratios, 50 ± 1-2% for racemates. In the case of 62.3% enantiomerically enriched S(+)-propylene glycol (obtained 99+% ee from Aldrich and diluted to 62.3% with racemate) the NMR ratios corresponding to 61-64% ee was observed. The latter acetal could not be separated on HPLC showing only two peaks corresponding to two pairs of diastereomers. Similarly the 2-methoxyethyl acetal failed to completely resolve into the four diastereomers on HPLC. Another enantiomerically enriched acetal, derived from 1-cyclohexyl-1,2-diol in 66% ee, separated cleanly on HPLC to give four diastereomers which integrated to 84.1:15.9 or 68% ee, in good agreement with the prepared mixture[10]. Thus, successful analyses were performed using one or both of these methods. A typical HPLC and ^{13}C trace utilizing this technique is given in Fig. 1 for the acetal of racemic 1,2-octane-diol. Note that both analytical methods show diastereomeric ratios of ∿6:4 for 5A,B and 5C,D.

FIG. 1



Finally, the tertiary glycol, 1-methyl-1-phenyl-1,2-ethanediol was examined in its racemic form and the resulting acetal showed four clearly separated ^{13}C signals for C-2 at 35.12, 34.87 (50 ± 3%) and 34.44 and 34.29 (50 ± 2%). This indicates that tertiary glycols, in addition to the secondary mentioned above, also may be analyzed with regard to enantiomeric purity.

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REFERENCES AND NOTES

1. Taken, in part, from the doctoral dissertation of SKW (1983).

2. National Institutes of Health Research Fellow, 1982-1984.

3. Determination of Optical Purity by Nuclear Magnetic Resonance has been summarized in part: Kagan,H. B.; Gaudemer, A.; in "Stereochemistry: fundamental and methods," Vol. 1, p. 117; Georg Thieme Publishers, Stuttgart, Germany, 1977.

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6. Hiemstra, H.; Wynberg, H.; Tetrahedron Letters, 2183, 1977.

7. Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S. K.; Druelinger, M.; J. Amer. Chem. Soc. 103, 3081, 1981. Acetal formation was shown to proceed without racemization of the 2-alkylcyclohexanones.

8. For another useful technique using benzylidene acetals of glycols and chiral LISR reagents, see E. L. Eliel and K.-Y. Ko, accompanying paper in this issue.

9. An excess of the ketone was used. Thus, 1.5-1.7 equiv of ketone were used to completely convert the diol to its acetal. After heating the dichloromethane solution, the excess ketone was removed by distillation or rotary evaporation and the ^{13}C ($CDCl_3$) or HPLC (ZORBAX Sil, 1% ether - 99% hexane, ref. index detector) analysis performed. It is also possible to use 3-5% anhydrous TSOH as a catalyst to speed up the acetal formation.

10. 1-cyclohexyl-1,2-ethanediol (66% ± 2 ee) was kindly furnished by Professor Ernest Eliel to test our method. Satisfactory agreement between this technique and that of Eliel's[8] was therefore established.

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