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Optically Active trans-Bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane and Its Derivatives As Chiral Shift Reagents for the Determination of Enantiomeric Purity and Absolute Configuration

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Abstract: The title compounds were found to be useful as chiral shift reagents for the determination of enantiomeric purity and absolute configuration of amines, cyanohydrins, and amino acid esters.

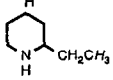
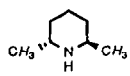
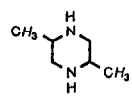
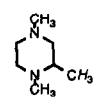
The asymmetric compounds such as 2,2'-dihydroxy-1,1'-binaphthyl (**1**),[1] 10,10'-dihydroxy-9,9'-biphenanthryl (**2**),[1] 4,4',6,6'-tetrachloro-2,2'-bis(hydroxydiphenylmethyl)biphenyl (**3**),[2] and 1,6-bis(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**4**)[1] have been known as chiral shift reagents for the determination of enantiomeric purity[1,2] and absolute configuration.[3] We report that the title optically active compound (**5a**)[4] and its derivatives (**5b**[2] and **5c**[2]) are also useful as chiral shift reagents for the determination of enantiomeric purity and absolute configuration of amines, cyanohydrins, and amino acid esters.[5]

All the measurements of ^{1}H NMR spectra were carried out for a solution of sample (10 mg) in $CDCl_3$ (0.4 ml) in the absence and presence of 1/2, 1.0, and 2.0 equimolar amounts of **5**.

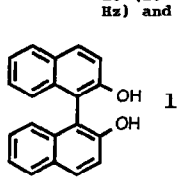
In the case of acyclic amines (**6-9**), the α-methine proton of (*S*)-enantiomer appeared at higher magnetic field than did that of (*R*)-one. In the case of cyclic amines (**10-16**), however, the β-methyl proton of (*R*)-enantiomer appeared at higher magnetic field than did that of (*S*)-one. Therefore, (-)-enantiomer of **11** which shows the β-methyl proton signal at relatively higher megnetic field may have (*R*)-configuration (Table 1).

The α-methine protons of the cyanohydrins (**17-25**) which were derived from aldehydes are split in the presence of **5a** (Table 2). However, the β-methyl protons of the cyanohydrins (**26-28**) derived from ketones are split (Table 2).

Table 1. Relationship Between Chemical Shift Value and Molar Ratio of 5a to Amine

Amine		Chemical shift (ppm)[c] Molar ratio of 5a to amine 0	1/2	1	2	Absolute configuration
Ph-*C*HCH$_3$ NH$_2$	(6)	4.25	3.92 3.91	3.76 3.73	3.63 3.60	(*R*)-(+)- (*S*)-(−)-
Ph-*C*HCH$_2$CH$_3$ NH$_2$	(7)	3.94	3.58 3.56	3.42 3.39	3.28 3.25	(*R*)-(+)- (*S*)-(−)-
Ph-*C*HCH$_2$Ph NH$_2$	(8)	4.29	4.09 4.07	4.00 3.97	3.89 3.84	(*R*)-(−)- (*S*)-(+)-
Ph-*C*HCH$_3$ N(CH$_3$)$_2$	(9)[a]	3.32	3.25	3.22 3.20	3.18 3.15	
	(10)	1.09	0.97 0.94	0.91[d] 0.85	0.85 0.78	(*S*)-(+)- (*R*)-(−)-
	(11)[b]	1.02	0.94 0.92	0.88 0.85	0.80 0.76	(+)- (−)-
	(12)[a]	1.13	——	0.94[d] 0.91	0.87 0.81	
	(13)[a]	1.04		0.98 0.94		
	(14)	1.07	0.93 0.92	0.87 0.82	0.72 0.67	(*S*)-(+)- (*R*)-(−)-
	(15)[a]	1.10	0.90 0.87	0.84 0.78	0.75 0.67	
	(16)[b]	1.08	——	0.98 0.95	0.96 0.89	(+)- (−)-

[a] Assignment of the signal is not determined. [b] Absolute configuration is not known. [c] Of proton italicized. [d] Linewidth of the original signal of 10 (1.0 Hz) and 12 (0.9 Hz) turned to that of split signal of 10 (1.6 Hz) and 12 (1.4 Hz) in the presence of equimolar amount of 5a.



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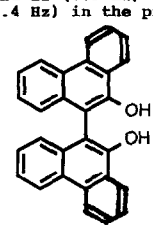

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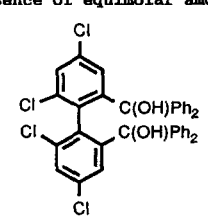

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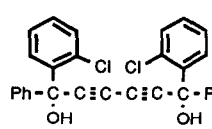

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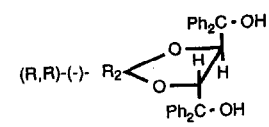

5

a: R_2=Me$_2$

b: R_2= 

c: R_2= 

Table 2. Relationship Between Chemical Shift Value and Molar Ratio of 5a to Cyanohydrin

Cyanohydrin[a]		Chemical shift (ppm)[c] Molar ratio of 5a to cyanohydrin 0	1/2	1	2	Enantiomerism
CH_3-*C*HCN, OH	(17)	4.55	4.41 4.34	4.28[d] 4.21	3.97 3.89	(+)- (−)-
CH_3-*C*HCN, OH	(18)[b]	4.58	4.37 4.33	4.12 4.07	——	
CH_3, CH_3, *C*HCHCN, OH	(19)	4.29	4.07 4.03	3.90 3.83	——	(+)- (−)-
Ph-*C*HCN, OH	(20)	5.60	5.35 5.32	5.19[d] 5.14	5.01 4.94	(+)- (−)-
CH_3, *C*HCN, OH	(21)	5.66	5.49 5.48	5.37 5.34	5.19 5.15	(+)- (−)-
CH_3, *C*HCN, OH	(22)	5.56	5.37 5.34	5.21 5.16	5.05 4.97	(+)- (−)-
CH_3, *C*HCN, OH	(23)	5.55	5.33 5.29	5.19 5.15	4.99 4.93	(+)- (−)-
PhO, *C*HCN, OH	(24)[b]	5.52	5.33 5.30	5.20 5.16	5.06 4.98	
*C*HCN, OH	(25)	6.17	5.97 5.94	5.84 5.80	5.70 5.62	(+)- (−)-
CH_3, CH_3, *C*HC-CN, CH_3, OH	(26)	1.63	1.54	1.48 1.46	1.41 1.39	(+)- (−)-
CH_3, CH_3, CH_3-C-*C*-CN, CH_3, OH	(27)	1.62	1.54	1.50 1.49	1.42 1.40	(+)- (−)-
CH_3, Ph-*C*-CN, OH	(28)[b]	1.96	1.86	1.80 1.79	1.74 1.73	

[b]Absolute configuration is not known in all cases. [b]Assignment of the signal is not determined. [c]Of proton italicized. [d]Linewidth of the original signal of 17 (1.0 Hz) and 20 (1.2 Hz) turned to that of split signal of 17 (1.4 Hz) and 20 (1.4 Hz) in the presence of 5a.

In all the cases of amino acid esters tested except **32**, the α-metine proton is split, although the γ-methyl protons of **31** are also split (Table 3). In the case of **32**, only the γ-methyl protons are split. In the cases of **30**, **31**, and **33**, the methine proton signal of (*R*)-enantiomer appeared at higher magnetic field, although the α-methine proton signal of (*S*)-enantiomer of **34** appeared at higher magnetic field (Table 3).

5b and **5c** also worked as chiral shift reagents for the determination of enantiomeric purity and absolute configuration efficiently.

Table 3. Relationship Between Chemical Shift Value and Molar Ratio of 5a to Amino Acid Ester

Amino acid ester		Chemical shift (ppm)[c] Molar ratio of 5a to amino acid ester 0	1/2	1	2	Absolute configuration
CH_3-C*H*CO_2CH_3 (NH$_2$)	(29)[a]	3.53		3.26 3.23		
Ph-C*H*CO_2CH_3 (NH$_2$)	(30)	4.65	4.47	4.35 4.31	4.20 4.16	(*S*)-(+)- (*R*)-(−)-
CH_3, CH_3-C*H*-C*H*CO_2CH_3 (NH$_2$)	(31)	3.34	3.17 3.16	3.06 3.04	2.91 2.87	(*S*)-(+)- (*R*)-(−)-
CH_3, CH_3-C*H*-C*H*CO_2CH_3 (NH$_2$)	(31)	1.00	0.94	0.90 0.88	0.84 0.81	(*S*)-(+)- (*R*)-(−)-
CH_3CH_2, CH_3-C*H*-C*H*CO_2CH_3 (NH$_2$)	(32)[b]	0.99	0.92	0.87 0.85	0.84 0.82	(+)- (−)-
Ph-C*H*$CO_2CH_2CH_3$ (NH$_2$)	(33)	4.66	4.52	4.43 4.40	4.30 4.26	(*S*)-(+)- (*R*)-(−)-
CH_3-C*H*$CO_2CH(CH_3)_2$ (NH$_2$)	(34)	3.59	3.34	3.19 3.17	3.01 2.98	(*R*)-(−)- (*S*)-(+)-

[a]Assignment of the signal is not determined. [b]Absolute configuration is not known. [c]Of proton italicized.

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References and Notes

1. F. Toda, K. Mori, J. Okada, M. Node, A. Itoh, K. Oomine, and K. Fuji, Chem. Lett., **1988**, 131.
2. F. Toda, R. Toyotaka, and H. Fukuda, Tetrahedron Asymm., **1**, 303 (1990).
3. F. Toda, K. Mori, and A. Sato, Bull.Chem. Soc. Jpn., **61**, 4167 (1988).
4. F. Toda and K. Tanaka, Tetrahedron Lett., **29**, 551 (1988).
5. In the preparation of this paper, Seebach and his co-workers reported that **5a** is useful as chiral shift reagent for determination of enantiomeric purity of some alcohols, methylcyanohydrin, and phenetylamine; C. von Bussche-Hunnefeld, A. K. Beck, U. Lengweiler, and D. Seebach, Helv. Chim. Acta, **75**, 438 (1992).