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Chirality Recognition by 1,1'-Binaphthyl-2,2'-diyl Phosphoryl Chloride—Determination of Configuration of Asymmetric Carbon Atom Attached to the Hydroxy Methylene Group

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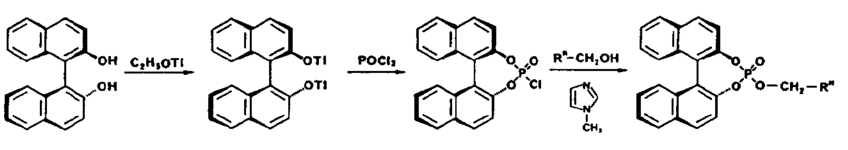
Abstract: Chirality of the asymmetric carbon atom attached to the hydroxy methylene group can be determined with high sensitivity by derivation into the 1,1'-binaphthyl-2,2'-diyl phosphate [(*R*,*S*)-BNP ester] . Consistent result with the sign of the CD spectra and the chirality of the asymmetric carbon atom was obtained by the introduction of a novel sequence rule.

Over the past few decades, useful methods have been developed for the determination of the absolute stereochemistry on organic compound.[1] Recently we presented a novel method, according to which the chirality on the carbon atom of the secondary alcohols could be determined with high sensitivity by derivation into a 1,1'-binaphthyl-2,2'-diyl phosphate (abbreviated to BNP ester).[2] However, the chemical and spectroscopic methods determining the chirality of an asymmetric carbon attached to the hydroxy methylene group have not yet been reported

We wish to report that the chiral 1,1'-binaphthyl-2,2'-diyl phosphoryl chloride [abb. (*R*)- or (*S*)-(BNP)Cls] discriminates sensitively the chirality of the asymmetric carbon atom. The primary alcohols are derived into BNP esters by treatment with the racemic (BNP)Cl [abb. (*R*,*S*)-(BNP)Cl] prepared from C_2 symmetry dithallous 1,1'-bi-2-naphthoxide and $POCl_3$ *in situ* as well as in the case of the secondary alcohols (Scheme 1).[2,3] The obtained BNP esters exhibit differential Cotton effects with Davydov splitting (maxima at 225 and 213 nm) based on the kinetic reaction with either (*R*)- or (*S*)-(BNP)Cls (Figure 1, Table 1).[4,5] As is distinct from the result of the secondary alcohol, Cotton sign of the BNP-primary alcohol derivatives exhibites inconsistency with the chirality of the asymmetric carbon atom attached to the hydroxy methylene group. If the reagent recognizes the chirality of the carbon atom in accordance with some rule, the inconsistent result should be reinvestigated by novel sequence rule different from Cahn-Ingold-Prelog (C-I-P) nomenclature[6]



Scheme 1. Preparation of (*R*)-(BN)Tl2, (*R*)-(BNP)Cl, and (*R*)-BNP chiral alcohol derivatives [(*S*)- and (*R*,*S*)-BNP derivatives obtained by the same procedure]

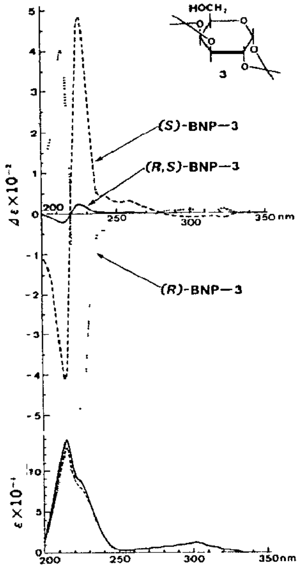
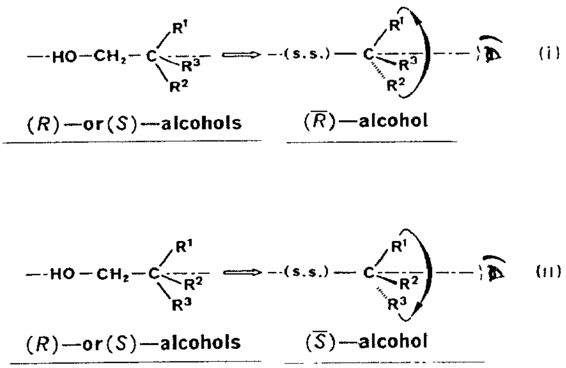


Figure 1. CD and UV spectra of (*R*)-, (*S*)-, and (*R*,*S*)-BNP-3 derivatives.



Scheme 2 In the chirality recognition reaction, the hydroxy methylene group on the alcohol is replaced to the smallest substituent group [abb (s.s)-] , and hence the primary alcohols having the priolity sequence, $R^1 > R^2 > R^3$, are reassigned to ($\overline{R}$)- or ($\overline{S}$)-alcohols (i and ii)

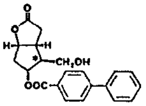
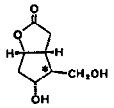
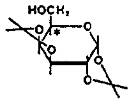
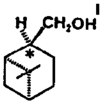
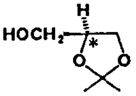
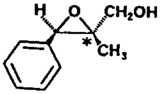
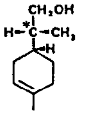
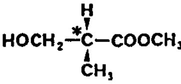
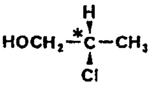
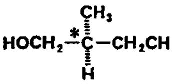
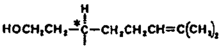
We assume that, in the enantiomer discrimination reaction, the atomic group participating directly in the bond-formation reaction is regarded as the ligand of lowest precedence within the ligands on the chiral carbon atom (Scheme 2). Thus, the other three ligands are put into a priority sequence[7] and, according to whether the path turns right or left looked at from the opposite side of the hydroxy methylene group, they are assigned the replaced chiral label, ($\overline{R}$) or ($\overline{S}$). The chirality on the remarked carbon atom of the primary alcohols can be reassigned in accordance with the novel sequence rule as shown in Table 1. Thus, plus or minus Cotton signs at 225 nm of all the BNP derivatives are identical to the replaced chirality ($\overline{S}$) or ($\overline{R}$), respectively.[8]

The enatiomer discrimination ability of the BNP reagent is revealed on the reaction with the primary alcohol residue on cyclic and acyclic structures, **1**-**6** and **7**-**9**. The neighboring large substituent group does not affect the discriminating reaction, **1** and **2**. And the absolute configuration can be determined not only on the secondary chiral carbon atom, but on the tertiary carbon atom attached to the primary alcohol group **6**. However, it seems difficult that the (BNP)Cl reagent distinguishs the difference of a methylene group between alkyl substituent groups, **10**, and recognizes the chirality of the carbon atom partitioned off by the two methylene groups, **11**

The ^{1}H NMR spectrum of the (*R*,*S*)-BNP derivatives shows a superimposed spectrum of these of (*R*)-and (*S*)-BNP derivatives. Therefore, an excess of (*R*)-BNP — ($\overline{R}$)-primary alcohol or (*S*)-BNP — ($\overline{S}$)-primary alcohol diastereomers can be calculated from an integrated area of each shifted signal and represents as (*R*)-($\overline{R}$) or (*S*)-($\overline{S}$) diastereomeric excess (de) in Table 1.

Acknowledgment. We gratefully acknowledge the use of the instrumental facilities of the Analytical Center of Faculty of Pharmacy, Meijo University, for the perform of this work, and are indebted for skilled assistance to Mr K. Masuda and Miss. T. Sakai, the Analytical Center.

Table 1. CD spectral data and chirality identification of BNP-alcohol derivatives.

Compound[a]					BNP derivative: $\Delta\varepsilon$(λ,[b] nm), [α_D,[c] deg]			
Structure	No.	$[\alpha]_D$,deg	Chirality of *C	Replaced chirality	R,S	R	S	de,[d] %
	1	-84	*S*	$\bar{S}$	+17 (225) -23 (214) [-59]	-498 (225) +399 (214) [-248]	+536 (225) -436 (214) [+143]	-[f] (S-$\bar{S}$)
	2	-43.8	*S*	$\bar{S}$	+17 (225) -14 (214) [+14]	-392 (225) +313 (214) [-299]	+451 (225) -370 (214) [+299]	-[f] (S-$\bar{S}$)
	3	-52.6	*R*	$\bar{S}$	+78 (225) -65 (214) [+2]	-494 (225) +399 (214) [-324]	+487 (225) -406 (214) [+241]	25(S-$\bar{S}$)
	4	-28	*S*	$\bar{R}$	-4 (225) +3 (214) [+14]			3(R-$\bar{R}$)
	5	+15.2	*S*	$\bar{R}$	-5[g](225) +7 (214) [+0.5]	-495 (225) +402 (214) [-366]	+521 (225) -436 (214) [+399]	3(R-$\bar{R}$)
	6	+15	*R*	$\bar{S}$	+13 (225) -8 (214) [+24]			10(S-$\bar{S}$)
	7	+99	*R*	$\bar{S}$	+3[g](225) -5 (214) [+28]	-544 (225) +432 (214) [-317]	+489 (225) -402 (214) [+470]	-[f] (S-$\bar{S}$)
 $HOCH_2-\overset{H}{\underset{CH_3}{\overset{*}{C}}}-COOCH_3$	8	-26	*R*	$\bar{R}$	-15 (225) +9 (214) [-2]	-538 (225) +419 (214) [-384]	+579 (225) -373 (214) [+409]	5(R-$\bar{R}$)
 $HOCH_2-\overset{H}{\underset{Cl}{\overset{*}{C}}}-CH_3$	9	+17.5	*S*	$\bar{S}$	+13 (225) -7 (214) [+18]	-524 (225) +422 (214) [-364]	+580 (225) -447 (214) [+440]	6(S-$\bar{S}$)
 $HOCH_2-\overset{CH_3}{\underset{H}{\overset{*}{C}}}-CH_2CH_3$	10	-5.8	*S*	$\bar{R}$	0 (225) 0 (214) [0]			0
 $HOCH_2CH_2-\overset{H}{\underset{CH_3}{\overset{*}{C}}}-CH_2CH_2CH=C(CH_3)_2$	11	+5.3	*R*	-[h]	0 (225) 0 (214) [0]			0

a Chiral compounds were supplied by Aldrich Chemical Co., Ltd.

b. CD measurement was performed with a Jasco J-600 spectropolarimeter in EtOH. Cotton effects showed intense peaks only separated by Davydov splitting.

c. Specific rotation was measured using a Jasco DIP-181 digital polarimeter in $CHCl_3$.

d. Diastereomeric excess (de) was calculated from integrated area of the isolated signals on NMR spectra (Jasco GX-270, CDCl3-TMS) of the (*R,S*)-BNP derivatives. The ratio of each diastereomer was calculated by the area of the isolated signals as showed; 3. δ 1.44 (*S*, 0.571H_3, s, Me), 1 45 (*R*, 0.429H_3, s, Me); 4: δ 0.81 (*S*, 0.492H_3, s, 7-Me), 0 85 (*R*, 0.508H_3, s, 7-Me); 5 δ 1 40 (*S*, 0.492H_3, s, Me), 1.41 (*R*, 0.508H_3, s, Me); 6· δ 1 12 (*R*, 0.474H_3, s, 2-Me), 1 17 (*S*, 0.526H_3, s, 2-Me); 8:δ 1,22 (*R*, 0 513H_3, d, J=7.06Hz, 2-Me), 1.23 (*S*, 0.487H_3, d, J=7.05Hz, 2-Me); 9.δ 1.53 (*S*, 0 515H3, d, J=6.72Hz, 2-Me), 1.54 (*R*, 0.485H_3, d, J=6.72Hz, 2-Me). *R* and *S* in parentheses indicated the signals assigned to the (*R*)- and (*S*)-BNP derivatives, respectively It should be noted that low de values ($<$ 10%) included an uncertainty with respect to the integrated area of the peaks

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f. Signals of (*R*)- and (*S*)-BNP derivatives almost always overlapped each other on the NMR spectrum

g The strongest Cotton at 214 nm may be resulted by overlapping with noise, which was stronger at shorter wave lengths.

h. It is not clear whether the novel chirality rule is applicable to the chiral carbon atom partitioned off by the two methylene groups.

References and Footnotes

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2. Kato, N. *J. Amer. Chem. Soc.* **1990**, *112*, 254-257.
3. A typical procedure of (*R,S*)-BNP-primary alcohol derivative. The (*R,S*)-(BNP)Cl solution (0.2 mmol, CH_2Cl_2) prepared from Tl_2 1,1'-bi-2-naphthoxide and $POCl_3$ *in situ* was poured into a mixture of Corey lactone **1** (35.2 mg, 0.1 mmol), 1-methylimidazole (82 mg, 1 mmol), and dimethyl aminopyridine (cat.). After stirring for 4 hr, the solution was worked up in the usual manner followed by purification on TLC. The (*R,S*)-BNP-Corey lactone derivative was easily purified on the repeated TLC (EtOAc-n-hexane) and obtained as an amorphous powder (67 mg, 98% yield). The esters gave satisfactory spectroscopic (NMR, UV) and elemental analysis data.
4. (*R*)-(-)- and (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphates exhibit extremely intense and oppositly splitting Cotton effects at 225 ($\Delta\varepsilon$ -746) and 213 ($\Delta\varepsilon$ +562) nm and 225 ($\Delta\varepsilon$ +720) and 213 ($\Delta\varepsilon$ -538) nm, respectively, attributed to the identical intramolecular charge-transfer absorption at 218 (log ε 5.01) nm. The BNP-primary alcohol derivatives showed the splitting Cotton effects at 225 and 214 nm, which were the differential CD spectra resulting from the BNP moiety, and exhibited the extremely strong absorption at about 218 (log ε ca. 5) nm.
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7. Cram, D.J.; Elhafez, F.A.A. *J Amer. Chem. Soc.* **1952**, *74*. 5828-5835.
8. The correlation for the Cotton sign at 225 nm and the chirality was followed to the exciton chirality method (cf. Ref. 5b).