Liquid Chromatographic Resolution of Racemic 2-Phenyl-1,1-cyclopropanedicarbonitrile and its Analogues on Chiral Stationary Phase

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Abstract: Excellent resolution of racemic 2-phenyl-1,1-cyclopropanedicarbonitrile and its nine analogues was accomplished using 100-5CHI-TBB chiral stationary phase under normal-phase HPLC conditions. The influence of mobile phase and the optimum conditions for the resolution of optically active enantiomers were investigated.

Keywords: HPLC, chiral stationary phase, 2-phenyl-1,1-cyclopropanedicarbonitrile (PCN), chromatographic resolution.

Introduction

Liquid chromatographic resolution of enantiomers on chiral stationary phases is now employed as the most convenient and accurate means of determining enantiomeric composition of chiral compounds[1,2]. There are reports on the resolution of chiral cyclopro-pane compounds[3,4], but the resolution of the title compounds has not been reported. We have synthesized the racemic and optically active enantiomers of 2-(X-phenyl)-1,1-cyclopropanedicarbonitrile(X-PCN) and 2 α -, and 2 β -naphthyl-1,1-cyclopropanedicarbo-nitrile(α -NCN and β -NCN) *via* the reaction of 2-bromo-1-(X-phenyl)ethylidenemalono-nitrile(X-BPM)and 2-bromo-(α -naphthyl)ethylidenemalono-nitrile(α -BNM) and 2-bromo-(β -naphthyl)ethylidenemalononitrile(β -BNM) with coenzyme NADH models, BNAH[5] and (S_S)-1-benzyl-3-(p-tolylsulfinyl)-1,4-dihydropy-ridine[6] , respectively (**Scheme 1**). The resolution of enantiomers of X-PCN, α -, and β -NCN was achieved using TBB chiral stationary phase and optimizing the resolution conditions by changing the composition of mobile phase.

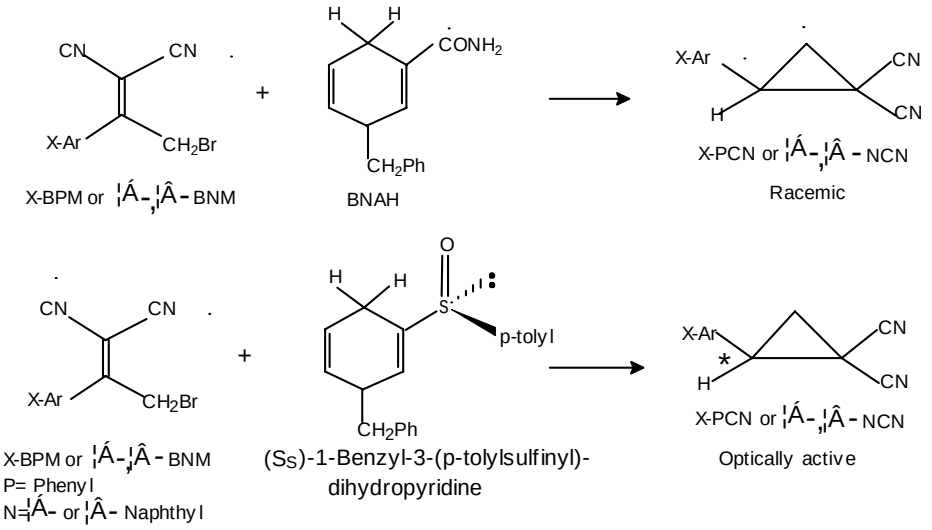
Experimental

1. Materials

n-Hexane and isopropyl alcohol(IPA) were of HPLC grade. All the racemates and

optically active enantiomers were synthesized in this laboratory and characterized by ^1H NMR, MS, IR and elemental analysis.

Scheme 1



2. Apparatus

Waters 600E multisolvent delivery system, Waters 2487 dual absorbance UV detector, Waters Millennium32 chromatography software, 100-5CHI-TBB chiral column of Eka Chemicals AB (The chiral monomer is 0,0'-bis (4-tert-butylbenzoyl)-N,N-diallyl-L-tartar diamide. The monomers are reacted with a multifunctional hydrosilane yielding a network polymer).

2.Chromatography

The mobile phase was n-hexane-isopropyl alcohol. The flow-rate was 1ml/min. The column temperature was kept at 20℃. The dual λ UV detection wavelength was set at 223 nm. The samples were injected through a Rheodyne 7725i manual injector, which was equipped with a 10μl loop. Void volume of the column was determined with acetophenone.

Results and discussion

Data in **Table 1** show the effect of the ratio of isopropyl alcohol in mixed solvents on chromatographic behavior. The capacity factors k', selectivity factors α and resolution factors R_S are used to evaluate the separation of enantiomers.

Table 1 The effect of the percentage of isopropyl alcohol in the mobile phase on separation

IPA %	Para-meters	A PCN	B *p*-F-PCN	C *p*-Br-PCN	D *p*-MeOPCN	E *o*-F-PCN	F *o*-Cl-PCN	G *o*-Br-PCN	H *o*-MeO PCN	I α-Naph. NCN	J β-Naph. NCN
	k_1'	2.03	4.15	5.30	2.85	2.68	3.27	3.49	1.46	2.83	3.46
1.0	α	1.12	1.18	1.21	1.13	1.11	1.11	1.11	1.09	1.18	1.24
	R_S	2.82	4.75	5.62	3.35	2.76	2.92	3.09	1.99	4.47	5.84
	k_1'	2.74	5.64	6.79	5.44	3.25	4.08	4.13	2.17	3.64	4.44
2.0	α	1.14	1.20	1.23	1.18	1.11	1.13	1.12	1.11	1.20	1.24
	R_S	3.49	5.34	6.32	5.05	2.99	3.50	3.36	2.77	5.01	6.22
	k_1'	1.91	3.62	4.42	2.42	2.41	2.95	3.13	1.35	2.44	3.07
3.0	α	1.14	1.20	1.20	1.15	1.11	1.11	1.11	1.09	1.18	1.24
	R_S	3.09	4.99	5.34	3.57	2.68	2.84	3.01	1.89	4.21	5.76
	k_1'	1.78	3.32	4.01	2.33	2.14	2.61	2.77	1.23	2.32	2.76
4.0	α	1.14	1.20	1.19	1.15	1.11	1.11	1.11	1.11	1.18	1.24
	R_S	3.05	4.95	5.03	3.54	2.55	2.73	2.92	1.78	4.11	5.64
	k_1'	1.60	2.96	3.59	2.15	2.02	2.44	2.59	1.16	2.14	2.55
5.0	α	1.14	1.18	1.20	1.15	1.11	1.11	1.12	1.11	1.17	1.23
	R_S	2.92	4.39	5.12	3.46	2.55	2.81	3.00	1.77	4.01	5.36

Figure 1 Plot of capacity factors *vs.* the percentage of isopropyl alcohol

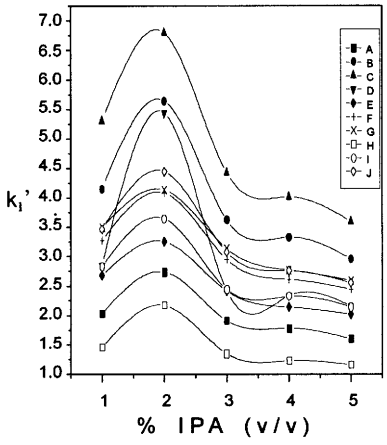
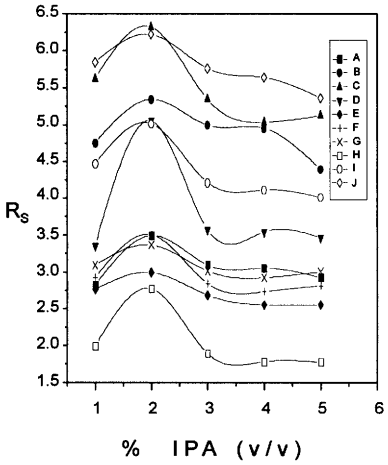


Figure 2 Plot of resolution factors *vs.* the percentage of isopropyl alcohol

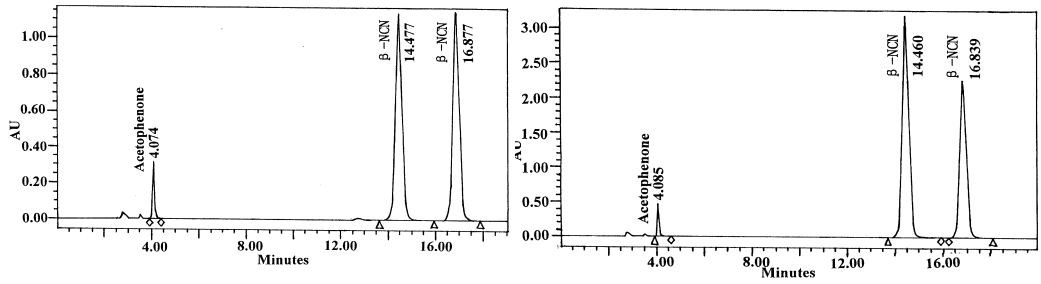


It is seen from **Figure. 1** and **Figure. 2** that, regardless of the compound studied, the selectivity factor α remained almost unchanged. However, the capacity factor k' and resolution factor R_S for each compound varied considerably and became the highest when the percentage of isopropyl alcohol in mobile phase was two percent, that was the optimum conditions.

The enantiomers interacted with the chiral stationary phase, while the mobile phase also interacted with the enantiomers. There was a competition between the two interactions. The chiral recognition process was the summation of all of the possible

chiral interactions, *i.e.*, dipole-dipole, hydrogen bond-hydrogen bond and π - π interactions.[7] On the other hand, the enantiomeric resolution ability of the racemates was strongly dependent on the site and the property of substituents on the benzene ring or naphthalene ring. Finally, we have optimized the resolution conditions and applied it to the identification of optically active enantiomers(**Figure 3**).

Figure 3 The enantiomeric resolution of racemic and optically active β -NCN



β -NCN (Racemate)

β -NCN (Optically active enantiomers)

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