Chromatographic Resolution of Racemic Compounds Containing Phosphorus or Sulfur Atom as Chiral Center

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Synopsis. Racemic compounds containing a phosphorus or a sulfur atom as a chiral center were resolved by high-performance liquid chromatography on optically active (+)-poly(triphenylmethyl methacrylate). The resolved compounds include insecticides such as *O*-ethyl *O*-(4-nitrophenyl) phenylphosphonothionate (EPN), *O*-(4-cyanophenyl)-*O*-ethyl phenylphosphonothionate (cyanofenfos), and 2-methoxy-4*H*-1,3,2-benzo-dioxaphosphorin 2-sulfide (salithion).

Optically active poly(triphenylmethyl methacrylate) (PTrMA)[1] has been used as an effective chiral packing material for liquid chromatographic resolution of various racemic compounds,[2-9] most of which possess an asymmetric carbon. Here, we wish to report the resolution of racemic compounds containing a phosphorus or a sulfur atom as the asymmetric center using high-performance liquid chromatography (HPLC) with a (+)-PTrMA column.

Recently, Pirkle and coworkers successfully resolved racemic sulfoxides on their chiral HPLC column.[10] However, liquid chromatographic resolution of racemic phosphoric compounds has not so far been reported.

Experimental

The synthesis of compounds **1**—**5** in Table 1 has been carried out in the following manner. **1**: Preparation procedures were similar to those in a literature.[11] Methyl methyl(phenyl)phosphinate was reacted with benzylmagnesium chloride in diethyl ether to give a crude product which was purified by chromatography (silica gel) to give white solid **1**; ^{31}P NMR ($CDCl_3$ with external standard of 85% H_3PO_4) δ= 35.2 (single peak). ^{1}H NMR ($CDCl_3$) δ=1.60 (d, J=12 Hz, 3H), 3.20 (d, J=15 Hz, 2H), 6.83—7.75 (m, 10H). IR (Nujol) 1297, 1175, 1115, 920, 897, 770, 740 cm^{-1}. TLC (acetone) R_f= 0.5. **2**: Similarly, methyl methyl(phenyl)phosphinate was allowed to react with 1-naphthylmagnesium bromide, giving rise to a solid product **2** after purification by chromatography. **3**: The hydrolysis of a spirophosphonane, 5-phenyl-1,4,6-trioxa-5-phosphaspiro[4.4]nonan-7-one, gave 2-hydroxyethyl (2-carboxyethyl)phenylphosphinate (mp 75—76 °C) whose esterification with diazomethane produced **3**. **4**: Phenylphosphonic dichloride was treated with an equimolar amount of ethanol in the presence of triethylamine in benzene followed by a further reaction with an equimolar amount of methanol in the presence of triethylamine in benzene to give **4**, bp 69—72 °C/0.2 mmHg**. **5**: Phenylphosphonic dichloride was subjected to reaction with an equimolar amount of cyclohexanol and then with methanol (equimol.) in the presence of pyridine in benzene to give **5**, bp, 105—110 °C/0.2 mmHg. ^{31}P NMR ($CDCl_3$) δ=19.1 (single peak). ^{1}H NMR ($CDCl_3$) δ=1.00—2.05 (m, 10H), 3.60(d, J=11 Hz, 3H), 4.33 (br, 1H), 7.28—7.95 (m, 5H). IR (neat) 2930, 2850, 1440, 1245, 1130, 1050, 990, 800, 557 cm^{-1}. TLC (diethyl ether) R_f=0.6.

Compounds **6**—**9** were commercially obtained.

The preparations of (+)-PTrMA[12] and the packing material[4] for HPLC were described previously. The resolution was accomplished with a JASCO TRIROTOR II chromatograph equipped with a UV detector at 15 °C, methanol (0.5 ml/min) being used as eluent.

Results and Discussion

Figure 1 shows the chromatograms of the resolution of 2-hydroxyethyl [2-(methoxycarbonyl)ethyl] phenylphosphinate (**3**), *O*-ethyl *O*-(4-nitrophenyl) phenylphosphonothionate (EPN, **6**), and 2-methoxy-4*H*-1,3,2-benzo-dioxaphosphorin 2-sulfide (salithion, **8**) on (+)-PTrMA columns; the results are summarized in Table 1 together with the data for the resolution of other racemic compounds. Most compounds in Table 1 were resolved on (+)-PTrMA. The separation factor α was increased by the addition of water to the eluent, suggesting that the chiral recognition ability of (+)-PTrMA is enhanced in a polar medium, probably due to the stronger hydrophobic interaction between the polymer and enantiomers. Phosphinate **3** was resolved most effectively. Insecticides, **6**, *O*-(4-cyanophenyl) *O*-ethyl phenylphosphonothionate (cyanofenfos, **7**), and **8** were also resolved. Although optically active isomers of **6** and **7** have already been prepared and the difference of the biological activities between the optical an-

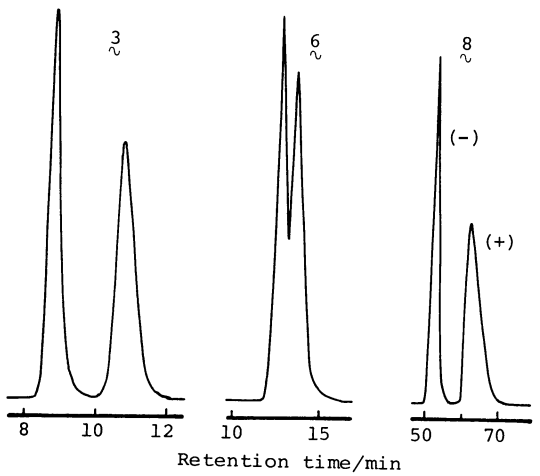
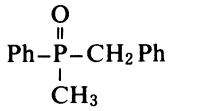
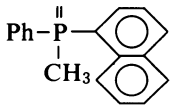
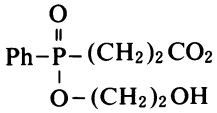
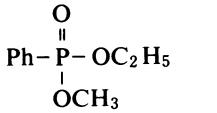
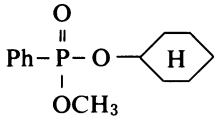
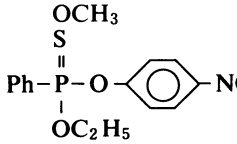
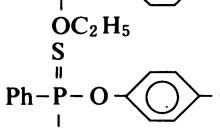
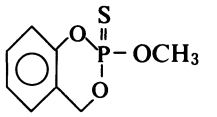
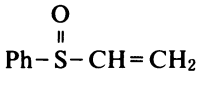


Fig. 1. Chromatograms of the resolution of **3**, **6**, and **8** on (+)-PTrMA columns. (Column: 25 cm×0.46 (id) cm for **3** and **6**; 50 cm×0.72 (id) cm for **8**, dead times of two columns were 6.4 and 30 min, respectively).

** 1 mmHg≈133.322 Pa.

*** **Note added in proof.** After submission of this Note, the optical isomers of **8** and their insecticidal activity were reported. A. Hirashima and M. Eto, *Agric. Biol. Chem.*, **47**, 2831 (1983).

Table 1. Resolution of racemic compounds on (+)-PTrMA columns[a]

Entry	Compound	k_1'[b]	α[c]	R_s[d]
1		0.62 1.68[e](+) 10[f]	≈1 1.09[e] 1.14[f]	≈0.4[e] 0.84[f]
2		0.78(−)	1.14	≈0.5
3		0.41(−)[g]	1.79	2.33
4		0.43	≈1	
5		1.85	1.11	0.80
6		1.03(+)	1.14	0.77
7		1.09(+) 17[e]	1.10 1.13[e]	≈0.3 0.67[e]
8		0.35[h](−)	1.45[h]	1.95[h]
9		0.20(−) 0.74[e](−)	≈1 1.19[e]	0.87[e]

a) Column: 25 cm×0.46(id)cm. b) k' (capacity factor to less retained enantiomer)=(retention time of less retained enantiomer−dead time)/dead time; the sign in parenthesis is that of the optical rotation at 365 nm. c) α (separation factor)=(capacity factor to more retained enantiomer)/k_1'. d) Resolution factor=2×(difference of retention times of more and less retained enantiomers)/(sum of the band width of the two enantiomer peaks). e) Eluent: CH_3OH-H_2O(80:20). f) Eluent: CH_3OH-H_2O(60:40). g) Elipticity of the CD spectrum at 263 nm. h) Column (50 cm× 0.72(id)cm).

tipodes has been studied,[13,14] optical isomers of **8** and their activity have not yet been reported.*** These isomers are expected to show different biological activity.

Phenyl vinyl sulfoxide (**9**) was not separated with methanol as eluent but was resolved with methanol-water (80:20).

These results suggest that the (+)-PTrMA column is useful for the resolution of racemic compounds having heteroatoms.

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