Stereospecific Inclusion in Cycloamyloses: Partial Resolution of Isopropyl Methylphosphinate and Related Compounds

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Summary Stereospecific inclusion of the (−)-enantiomer of isopropyl methylphosphinate (I) in cyclohepta-amylose affords (−)-(I) and (+)-(I) with optical purities of 66% and 17%, respectively.

IN preceding communications, the isolation[1] and stereospecific free-radical reactions[2] of an optically pure epimer of menthyl methylphosphinate were described. We now report the partial resolution of alkyl alkylphosphinates, $R^1O(R^2)P(O)H$ (R^1,R^2 = symmetric alkyl), by means of stereospecific inclusion in cycloamyloses(cyclodextrins, CD). The resolution of chiral compounds *via* diastereoisomeric inclusion complexes of cyclohepta-amylose(β-CD) was first explored by Cramer and Dietsche.[3] Recently, Van Hooidonk *et al.*[4] showed that, in aqueous alkaline solution, the (*S*)-(+)-enantiomer of isopropyl methylphosphonofluoridate(Sarin) is preferentially included in cyclohexa-amylose(α-CD), prior to phosphonylation of the latter compound.

Optimal conditions for stereospecific inclusion were determined for the system β-CD–isopropyl methylphosphinate(I)–water and led to the following procedure. A stirred suspension of β-CD·12H_2O[5] (11·7 g, 8·7 mmol) in (I) (6·7 g, 54·9 mmol) and water (1·9 ml) almost solidifies in the course of a few minutes. After being kept for 24 h at room temperature, the mixture is treated with ether. Filtration yields the precipitated inclusion complex (12·2 g), containing β-CD, (I), and water in a molar ratio of 1·0 : 1·0 : 8·7 (based on elemental analysis). Trituration of this inclusion complex with methylene chloride–water (25/1, v/v) released (−)-(I) quantitatively into the liquid phase.† Filtration, drying on molecular sieves, and distillation afforded (−)-(I) (1·0 g) with α_D^{25} −17·30°,‡ optical purity 66·5% (see Table 2). Distillation of the filtrate from the work-up of the inclusion procedure, after drying on molecular sieves, gave a non-included residue of (+)-(I) (4·7 g) with α_D^{25} +4·42°,§ optical purity 17·0%. By repeating the inclusion procedure twice, (+)-(I) (2·1 g) was obtained with α_D^{25} +12·92°, optical purity 49·6%. A fourth inclusion, coinciding with a change of the molar

TABLE 1

Stereospecific inclusion of $(R^1O)(R^2)P(X)H$ *in* α-CD *and* β-CD

	Phosphinate[b]			α-CD				β-CD			
				Residue		Included[a]		Residue		Included[a]	
	R^1	R^2	X	α_D^{25}	Optical purity[c] (%)	α_D^{25}	Optical purity[c] (%)	α_D^{25}	Optical purity[c] (%)	α_D^{25}	Optical purity[c] (%)
(I)	Pr^i	Me	O	+1·20	4·6	—	—	+ 4·42 +12·92[d]	17·0 49·6[d]	−17·30 −21·86[e]	66·5 84·0[e]
(II)	Pr^i	Me	S	−2·30	—	+14·92[f]	—	0·00	0·0	—	—[g]
(III)	Pr^i	Et	O	+1·72	6·8	—	—	+ 4·10	16·2	−15·18	60·0
(IV)	Et	Et	O	+1·04	4·9	− 5·06	23·8	+ 0·61	2·9	—	—
(V)	Et	Ph	O	−2·27	5·4	+12·08	28·8	0·00	0·0	—	—[h]

[a]The molar ratio CD : phosphinate in the inclusion complex was 1·0 : (1·0 ± 0·1), except when otherwise stated. [b]Compounds (I–V) were prepared according to standard procedures described in the literature and were vacuum-distilled through a spinning band column, purities ≥99% (g.l.c.). [c]See Table 2 for the calculation of optical purities. [d]After three inclusion procedures. [e]Treatment of the inclusion complex from the first inclusion procedure with anhydrous methylene chloride gave a small yield of (−)-(I) with α_D^{25} −0·58°. Subsequent trituration with methylene chloride–water (25/1, v/v) gave (−)-(I) with α_D^{25} −21·86°. [f]Molar ratio α-CD : (II) = 2·0 : 1·0. [g]Molar ratio β-CD : (II) = 2·5 : 1·0. [h]Molar ratio β-CD : (V) = 6·1 : 1·0.

TABLE 2

Optical purities of $R^1O(R^2)P(O)H$, *determined by stereospecific conversion*[a] *into* $R^1O(R^2)P(O)SR^3$

	R^1	R^2	R^3	$R^1O(R^2)P(O)H$ α_D^{25}	$R^1O(R^2)P(O)SR^3$	Optical purity (%)
(I)	Pr^i	Me	Me	+3·67	−16·48 (117·0)[b]	14·1
(III)	Pr^i	Et	Me	+2·20	− 8·18 (94·2)[b]	8·7
(IV)	Et	Et	Et	+0·83	− 2·82 (72·5)[c]	3·9
(V)	Et	Ph	Me	−1·11	+ 2·78 (104·7)[b]	2·7

[a]Addition of sulphur, followed by alkylation with methyl or ethyl iodide: see ref. 1. [b]Values between brackets refer to the rotations of the optically pure products. These values were obtained by complete resolution of the acids $R^1O(R^2)P(S)OH$ according to the method of Boter *et al.* (H. L. Boter and D. H. J. M. Platenburg, *Rec. Trav. chim.*, 1967, **86**, 399), and subsequent methylation with methyl iodide. [c]The rotation of the optically pure product is based on data from the literature (J. Michalski and A. Ratajczak, *Roczniki Chem.*, 1963, **37**, 1185).

† Included (I) is stable against oxidation by air for at least 3 months.

‡ In this paper, all optical rotations were measured on neat products (l = 1 dm.).

§ The rotation (α_{578}^{25}) of an optically active sample of (+)-(I) gradually changed from +3·91° to +3·46° on standing for 10 weeks at room temperature in an atmosphere of carbon dioxide.

ratio β-CD : (I) in the inclusion complex from 1·0 : 1·0 to 1·7 : 1·0, gave no further optical enrichment of (+)-(I).

Addition of the aforementioned *small* amount of water to the system β-CD–(I) is essential for an optimal stereospecific inclusion, since: (i) inclusion of (I) in a saturated aqueous solution of β-CD, containing *ca.* 1·5% β-CD (w/v), was non-stereospecific; (ii) inclusion of (I) in β-CD·0H_2O under anhydrous conditions gave a non-included residue of (+)-(I) with α_D^{25} +0·19°, optical purity 0·7%.

Results concerning the partial resolutions of (I) and four related compounds (II—V) with α-CD and with β-CD are summarized in Table 1. Optical purities were calculated according to Table 2. The resolutions with β-CD were performed as described for (I), using β-CD·12H_2O, phosphinate, and water in a molar ratio of 1 : 6·3 : 12. Similar stereospecific inclusions in α-CD were obtained by mixing anhydrous α-CD, phosphinate, and water in a molar ratio of 1 : 6·3 : 17. It is evident from Table 1 that a large variety of phosphinates can be resolved to a considerable extent, using either α-CD (II, IV, and V) or β-CD (I and III), although the obtained optical purities vary in a rather unpredictable way with the ring size of the CD and with the structure of the phosphinate.

In principle, the simple and highly reproducible partial resolution of compounds (I—V) overcomes previous difficulties with regard to stereochemical investigations of the optically active functional group >P(O)H, *i.e.* low rotations in the case of secondary phosphine oxides,[6,7] and the possibility of asymmetric induction in an epimer of menthyl methylphosphinate,[1] owing to the presence of additional chiral centres.

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