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Enantiomeric discrimination in solid-state cyclodextrin complexes

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Summary – Cyclodextrins were used to prepare inclusion complexes of a volatile chiral compound, 1,7-dioxaspiro[5.5]undecane **1**, a pheromone of *Dacus oleae*. The included pheromone was recovered from the inclusion complexes. Cyclodextrins that were unsymmetrically substituted with at least one unit different from the others could form inclusion complexes preferentially with the *S* enantiomer of the pheromone.

cyclodextrin / heptakis(2,6-di-*O*-methyl)-β-cyclodextrin / heptakis(2,3,6-tri-*O*-methyl-β-cyclodextrin / pheromone / inclusion complex / 1,7-dioxaspiro[5.5]undecane

Cyclodextrins (CDs) [1] have a natural chirality due to both the intrinsic chirality of the sugar and the conformation of the cyclodextrin cycle. Despite the large number of chiral centers and the overall chiral conformation, an effective enantiomeric discrimination by solid-state complexation cannot be assured in general. On the other hand, successful chiral resolution is obtained by the use of chromatography on cyclodextrin or modified cyclodextrin stationary phases [2]. Cyclodextrins have also been used in capillary electrophoresis to achieve chiral separation on an analytical scale [3]. Recently [4], a peroctylated cyclodextrin was used in a potentiometric method to measure the enantiomeric purity of ephedrinium salts.

The presence of an aromatic ring and a substituent on a chiral center of the guest that can form at least one strong interaction with the hydroxyl groups of the CD cavity are usually considered as the basic requirements for chiral discrimination. Diastereomeric inclusion complexes have been described by inclusion of each enantiomer of fenoprofen (2-(3-phenoxyphenyl)propanoic acid) in β-CD. However, when the inclusion complex was prepared from racemic fenoprofen both enantiomers were found at different positions in the crystal [5].

The problem is considerably more difficult in the case of chemically inert molecules. These lack the possibility of hydrogen-bond anchoring, which can be determinant of the preferential fixation of one of the enantiomers. However, numerous non-bonding interactions were recently shown to allow discrimination, at low temperature, of the chiral conformers of *cis*-decalin [6].

We are currently studying the preparation of cyclodextrin inclusion complexes of pheromones, which are generally chemically inert. These complexes of pheromones are of practical interest because they can provide a continuous source of pheromones which are usually too volatile for large-scale use in agriculture. 1,7-Dioxaspiro[5.5]undecane **1** (fig 1a) is the main component of the *Dacus oleae* pheromone. Both enantiomers are active pheromones but they have been reported to exhibit different qualitative and quantitative biological behaviors : *R*(−) **1** si probably a long-range attractant for males; and *S*(+) **1** might be an arrester for females [7]. However, the exact pheromone activities are not yet clear and further studies are needed. This molecule has a twofold symmetry axis [8] and presents an intrinsic chirality. It is currently the object of intensive studies [9] in both laboratory and field experiments.

We have recently reported [10] the first resolution of a racemic mixture by formation of an inclusion complex of **1** in a partially methylated CD derivative **2**. The X-ray crystal study of the complex revealed several original features. The host is a pentadeca-*O*-methyl cyclodextrin (fig 1b). Two glycosidic residues differ from those of heptakis(2,6-di-*O*-methyl)-βCD (DIMEB) : unit A is trimethylated; and unit G is dimethylated in positions 3 and 6. The guest is the *S*(+) enantiomer (enantiomeric excess (ee) : 96%).

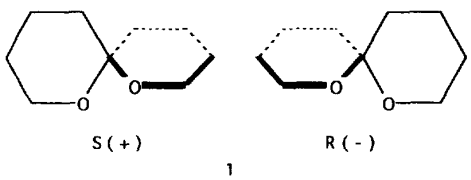

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Fig 1a. Enantiomers of 1,7-dioxaspiro[5.5]undecane **1**.

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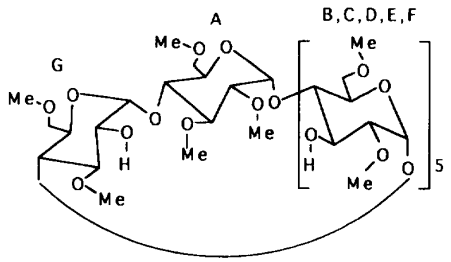

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Fig 1b. Numbering of residues of **2**.

We report here results concerning eight cyclodextrin derivatives (fig 2). We prepared the inclusion complexes of **1** with symmetrical and unsymmetrical cyclodextrins : β-CD **3**, heptakis (2,6-di-*O*-methyl)-βCD, (DIMEB) **4**, mono(6-azido-6-deoxy) β-CD **5**, mono(6-azido-6-deoxy-2-*O*-methyl)hexakis (2,6-di-*O*-methyl)-β-CD **6**, mono(6-amino-6-deoxy-2-*O*-methyl)hexakis(2,6-di-*O*-methyl)-β-CD **7**, mono (6-acetylamino-6-deoxy-2-*O*-methyl)hexakis (2,6-di-*O*-methyl)-β-CD **8**, heptakis (2,3,6-tri-*O*-methyl)-β-CD (TRIMEB) **9** and 2-hydroxypropyl-β-CD (HPCD) **10**. Compound **8** was obtained by acetylation of **7** [12]. Heptakis(2,6-di-*O*-methylated)-β-CD **5** was prepared according to Szejtli [13]. This compound is always contaminated by different methylated derivatives. The purity is determined by NMR spectroscopy. A

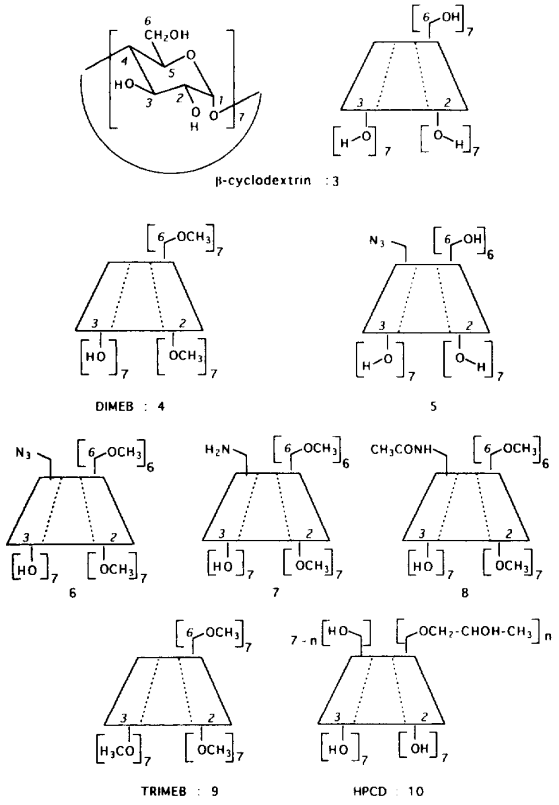

Fig 2. Cyclodextrins used for the complexation of **1**.

pure DIMEB was obtained by recrystallization from methanol. TRIMEB **9** [13] was prepared by methylation of β-CD with dimethyl sulfate in the presence of potassium *tert*-butoxide as base and Aliquat 336 as catalyst. Commercially available HPCD was used. The average degree of substitution was determined by ^{1}H NMR and appeared to be of 3.6 hydroxypropyl groups per cyclodextrin.

The preparation of crystalline inclusion complexes of **1** was attempted with **3-10**. The inclusion complexes of **1** with β-CD **3**, mono(6-azido-6-deoxy)β-CD **5** and HPCD **10** were prepared in water. The inclusion complexes of **1** with **4** and **6-9** were obtained in methanol. The ^{1}H NMR spectra of the isolated complexes prepared in methanol always showed a 1:1:1 complex of a cyclodextrin derivative, a pheromone, and one molecule of methanol. This proportion was observed previously in the case of the complex between **1** and **2**. In this last case, the molecule of methanol was shown by the X-ray diffraction diagram to be located outside of the cavity between the CD units [10]. The pheromone was extracted from the solid inclusion complexes upon heating in water. The results are gathered in table I.

Table I. Results of complexation of **1** with cyclodextrins **2-10**. Isolated yields of complexes are based on the amount of cyclodextrins.

Cyclodextrin	Solvent	Isolated yield of complexes (%)	Pheromone Yield (%)	Isolated ee
2	CH_3OH	[a]8	63	96 [9]
3	H_2O	35	49	0
4	CH_3OH	77	49	0
5	H_2O	25	44	0
6	CH_3OH	71	55	0
7	CH_3OH	34	60	0
8	CH_3OH	69	66	12
9	CH_3OH	34.5	71	0
10	H_2O	27	34	0

[a] Calculated on the amount of β-CD used in the methylation.

No significant ee could be detected for **1** extracted from the inclusion complexes prepared from **3-7**, **9** and **10**. On the contrary, a low but significant 12% ee of the *S*-enantiomer was measured when **1** was extracted from its inclusion complex with **8**.

In conclusion, the enantiomeric discrimination by inclusion into chathrates is more difficult to achieve for hydrophobic molecules than for hydrophilic ones. As it could be expected, experimental evidence suggests that unsymmetrical modifications of β-CD enhance the chirality of the host and are favorable for chiral discrimination.

The modification of the primary side, which is easier to perform, seems less efficient for chiral discrimination than the modification of the secondary side.

An amplification of ee can be expected from successive recrystallizations. It can be noticed that **1** and numerous chemically inert compounds structurally related to **1** are endowed with other types of biological activities [14].

Unsymmetrical CDs might be useful tools for chiral resolution. The resolution of racemates by the formation

of diastereomeric inclusion complexes could offer major advantages. It could have wide range of uses which may not be limited to enantiomers but may also involve a diastereomeric salt or an ester with the chiral resolving agent. This type of complex may also allow an easy recovery of the resolving agent.

Experimental section

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 270 MHz apparatus using TMS as an internal standard.

Purification of heptakis(2,6-di-O-methyl)-β-cyclodextrin **4**

DIMEB was prepared by Szejtli's method [13] and purified by three successive recrystallizations from methanol.

Preparation of mono(6-acetylamino-6-deoxy-2-O-methyl)hexakis(2,6-di-O-methyl)-β-cyclodextrin **8**

A solution of mono(6-amino-6-deoxy-2-*O*-methyl)hexakis (2,6-di-*O*-methyl)-β-CD [12] (13.15 g, 10 mmol) in 20 mL methylene chloride was cooled to 5°C. Triethylamine (2.30 g, 20 mmol) was added and after a few minutes stirring, a solution of acetyl chloride (1.2 mL, 15 mmol) in 3 mL methylene chloride was also added. The mixture was shaken 2 h at room temperature. A 1 N solution of sodium hydroxide was added and the mixture was stirred at room temperature for 30 min. The methylene chloride solution was separated, dried and evaporated. Compound **3** was recrystallized from methanol : 7.20 g, yield = 53%.

^{1}H NMR ($CDCl_3$) : δ 2.32 (s, 3H, CH_3CO); 3.31 (s, 18H, C_6-OCH_3); 3.60 (m, 21H, C_2OCH_3); 4.90-5.10 (m, 7H, HC_1).

^{13}C NMR ($CDCl_3$) : 20.6; 52.7; 57.0; 68.45; 71.3; 80.17; 81.6; 99.3; 170.7.

Anal calc : C 56.20; H 8.13; N 1.15. Found : C 55.85; H 8.44; N 1.08.

Preparation of heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin **9**

A mixture of cyclodextrin hydrate (13.5 g, 10 mmol), finely ground potassium hydroxide (17 g, 300 mmol), neutral alumina (10 g) and aliquat 336 (1 g) was vigorously shaken at room temperature for 10 min. A solution of dimethyl sulfate (25.2 g, 21 mmol) in toluene (50 mL) was added dropwise. The reaction was exothermic, stirring was continued for 1 h. Water 50 mL was added dropwise and after 1 h stirring, the mixture was extracted with methylene chloride. The solvent was eliminated under vacuum and the same process was repeated once more on the crude mixture.

The resulting oil was dissolved in 100 mL of diethyl ether. Crystals of permethyl-β-cyclodextrin **6** separated as needles on standing overnight at 0°C : 6.57 g, yield = 46%.

^{1}H NMR ($CDCl_3$), δ : 3.13 (d×d, J_{1-2} = 3.5, J_{2-3} = 9.5, 7H, H_2); 3.32 (s, 21H, C_6-OCH_3); 3.43 (t, J_{2-3} = J_{3-4} = 9.5, 7H, H_3); 3.45 (s, 21H, C_3-OCH); 3.52 (d broad, 7H, H_5); 3.56 (t, J_{3-4} = J_{4-5} = 9.5, 7H, H_4); 3.59 (s, 21H, C_2-OCH_3); 3.76 (m, 14H, H_6); 5.06 (d, J_{1-2} = 3.5, 7H, H_1).

Anal calc : C 52.94; H 7.84. Found : C 52.78; H 8.09.

Preparation of the complex of **1** *with β-CD* **3**, *mono-(6-azido-6-deoxy)β-cyclodextrin* **5** *and HPCD* **10**

1,7-Dioxaspiro[5.5]undecane **1** (2.17 g, 16 mmol) in methanol (5 mL) was added dropwise to the solutions of the cyclodextrins (4 mmol) in water (50 mL) heated at 70°C. After stirring for 5 min, the hot solution was introduced in a Dewar. After 36 h the crystals were separated by filtration.

Preparation of the inclusion complexes of **1** *in* **3**, **5** *and* **6**

The cyclodextrins (4 mmol) were dissolved in CH_3OH (36 mL) and 1,7-dioxaspiro[5.5]undecane (2.17 g, 16 mmol) was added. The solution was boiled for a few minutes. The hot solution was immediately placed in a Dewar. After 36 h the crystals were separated by filtration.

Recovery of the pheromone from the inclusion complexes

The crystals corresponding to 1 mmol of complex were dissolved (or suspended) in water (10 mL) and introduced in a micro-distillation apparatus. About half of the solution was distillated under partial vacuum (150 mm). The distillates were extracted by diethyl ether (2 × 5 mL) dried on sodium sulfate and evaporated under vacuum without heating. The isolated pheromone was dissolved in pentane for the measurement of the optical activity.

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References and notes

1 Szejtli J, *Cyclodextrin Technology*, Kluwer, Dordrecht, 1988; Duchene D, *Cyclodextrin and their Industrial Uses*, Editions de la Santé, Paris, 1987

2 Armstrong DW, *J Liq Chromatography* (1976) 7, S-2, 353

3 Nielen MW, *Anal Chem* (1993) 65, 885

4 Bates PS, Kataky R, Parker D, *J Chem Soc Chem Commun* (1992) 153

5 Hamilton JA, Chen L, *J Am Chem Soc* (1988) 110, 4379

6 Dodziuk H, Sitkowski J, Stefaniak L, Jurczak J, Sybilska D, *J Chem Soc Chem Commun* (1992) 207

7 Haniotis G, Francke W, Mori K, Redlich M, Schurig V, *J Chem Ecol* (1986) 12, 1559

8 Baker R, Herbert R, Howses PE, Jones OT, Francke W, Reith W, *J Chem Soc Chem Commun* (1980) 52

9 Mazomenos BE, Haniotakis GE, *J Chem Ecol* (1985) 11, 397

10 Galons H, Gnaïm J, Rysanek N, Le Bas G, Villain F, Tsoucaris G, *Tetrahedron-Asymmetry* (1993) 4, 181; Rysanek N, Le Bas G, Vilain F, Tsoucaris G, *Acta Cryst* (1992) C48, 1466

11 Iwata C, Fujita M, Kuroki T, Hattori K, Uchida S, Imanishi T, *Chem Pharm Bull* (1988) 36, 3257

12 Parrot-Lopez H, Galons H, Dupas S, Miocque M, Tsoucaris G, *Bull Soc Chim Fr* (1990) 127, 568

13 Szejtli J, Liptàk A, Jodàl I, Fugedi P, Nànàsi P, Neszmélyl A, *Stärke* (1980) 32, 145; Rao CT, Pitha J, *Carbohydrate Res* (1991) 220, 209; Casu B, Reggiani G, Gallo G, Vigevani A, *Tetrahedron* (1968) 24, 803

14 Prudhomme M, Dauphin C, Jeminet G, *J Chem Res* (1987) 420